Nonlinear Analysis: Modelling and Control
ISSN: 1392-5113
ISSN: 2335-8963
nonlinear@mii.vu.lt
Vilniaus Universitetas
Lituania

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Nonlinear Analysis: Modelling and Control, vol. 26, núm. 1, 2021

Vilniaus Universitetas, Lituania

Disponible en: https://www.redalyc.org/articulo.oa?id=694172828001

DOI: https://doi.org/10.15388/namc.2021.26.

Article

Mathematical analysis of an HTLV-I infection model with the mitosis of CD4+ T cells and delayed CTL immune response

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Nonlinear Analysis: Modelling and Control, vol. 26, núm. 1, 2021

Vilniaus Universitetas, Lituania

Recepción: 05 Septiembre 2019
Revisado: 23 Mayo 2020
Publicación: 01 Enero 2021

DOI: https://doi.org/10.15388/namc.2021.26.

Redalyc: https://www.redalyc.org/articulo.oa?id=694172828001

Abstract: In this paper, we consider an improved Human T-lymphotropic virus type I (HTLV-I) infection model with the mitosis of CD4. T cells and delayed cytotoxic T-lymphocyte (CTL) immune response by analyzing the distributions of roots of the corresponding characteristic equations, the local stability of the infection-free equilibrium, the immunity-inactivated equilibrium, and the immunity-activated equilibrium when the CTL immune delay is zero is established. And we discuss the existence of Hopf bifurcation at the immunity-activated equilibrium. We define the immune-inactivated reproduction ratio .0 and the immune-activated reproduction ratio .1. By using Lyapunov functionals and LaSalle's invariance principle, it is shown that if .0 < 1, the infection-free equilibrium is globally asymptotically stable; if .1 < . < *R*0, the immunity- inactivated equilibrium is globally asymptotically stable; if .1 > 1, the immunity-activated equilibrium is globally asymptotically stable when the CTL immune delay is zero. Besides, uniform persistence is obtained when .1 > 1. Numerical simulations are carried out to illustrate the theoretical results.

Keywords: HTLV-I infection, the mitosis of CD4. T cells, delayed CTL immune response, the reproduction ratio, Lyapunov functionals, Hopf bifurcation.

1 Introduction

Human T-lymphotropic virus type I (HTLV-I) is a pathogenic retrovirus. About 10 million to 20 million people worldwide are infected [1, 13, 19]. It is closely linked to two main types of viral diseases: adult T cell leukaemia/lymphoma (ATL), an aggressive blood can- cer; and HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP), a pro- gressive neurological and inflammatory disease [8,9,20,21]. However, there is no definite mechanism for the development of HTLV-I related diseases and no effective treatment. Besides, most of the infected persons are asymptomatic carriers, and only 0.1–4 % of the infected persons develop from long-term asymptomatic carriers to ATL or HAM/TSP [21].

Similar to Human Immunodeficiency Virus (HIV), the target cell of HTLV-I is CD4+ T cells. For the infected CD4+ T cells, a hypothesis was put forward by Asquith and Bangbam that only a small part of infected

CD4+ cells express Tax [5]. Based on this, the infected CD4+ T cells were divided into actively infected CD4+ T cells and latently in- fected CD4+ T cells according to whether Tax is expressed or not [5]. And the hypothesis of dynamic interaction between CD4+ T cells without Tax expression and CD4+ T cells with Tax expression proposed by Asquith and Bangbam explains that HTLV-I infected individuals have a sustained activation of the specific immune response to HTLV-I, while the viral load increases [3]. Therefore, it is very important to distinguish latently infected CD4+ T cells from actively infected CD4+ T cells. For mitosis, it should be pointed out that although mitosis is a natural process that occurs in all CD4+ T cells, normal homeostatic mitosis occurs at a much slower rate than that of actively infected CD4+ T cells proliferation. To avoid unnecessarily complicating the mathematical analysis, the mitosis of the healthy and latently CD4+ T cells is ignored [15].

Based on the above discussion, in order to explore the dynamic interaction between latently infected CD4+ T cells and actively infected CD4+ T cells in HTLV-I infection, in [15], Lim and Li proposed the following mathematical model:

$$\begin{aligned} x'(t) &= \lambda - dx - \beta xy, \\ u'(t) &= \delta\beta xy + \epsilon ry\left(1 - \frac{x+u}{k}\right) - (\mu+\sigma)u, \\ y'(t) &= \sigma u - ay, \end{aligned} \tag{1}$$

where $x(t)$ denotes the concentration of healthy CD4+ T cells, which are produced at rate λ and die at rate d, $u(t)$ denotes the concentration of latently infected CD4+ T cells, and $y(t)$ denotes the concentration of actively infected CD4+ T cells; β is the transmission coefficient; a and μ represent the death rates of actively infected CD4+ T cells and latently infected CD4+ T cells, respectively; σ is the rate at which latently infected CD4+ T cells translate into actively infected CD4+ T cells. $\delta\beta xy$ and #ry(1 (x + u)/k) are used to describe the newly infected CD4+ T cells entering the latently infected CD4+ T cells compartment through infection and mitosis or vertical transmission, respectively.

In model (1), logistic growth term ry(1 (x + u)/k) is used to describe the mitosis of actively infected CD4+ T cells. However, the numerical results show that there is no qualitative difference between exponential growth term and logical growth term in the behaviour of trajectories [17]. Therefore, in order to avoid the complication of the model equation, it is reasonable to assume that x(t)+u(t)/k, the proliferation of actively infected CD4+ T cells follows an exponential growth term ry instead of logical growth term ry(1 (x+u)/k). The exponential growth term ry has been used by Lim and Maini [17].

In the process of HTLV-I infection, a strong cytotoxic T lymphocyte (CTL) immune response was established to fight infection [5, 12]. In the most virus infections, CTL immune response can lower the proviral load and consequently lower the risk of disease [1]. However, experiments have shown that the cytotoxicity of CTL ultimately leads to demyelination of HAM/TSP central nervous system and the development of HAM/TSP disease [16]. It can be seen that the effect of CTL immune response on HTLV-I infection is much more complicated. Therefore, the consideration of CTL immune response in the HTLV-I infection model is of great significance to the study of the development and treatment of ATL or HAM/TSP.

Since antigenic stimulation to generate HTLV-I specific CTLs involves a series of events that require a time delay [7]. Therefore, it is necessary to consider the effect of time delay in the model, and the form of CTL immune function f (y, z) = cy(t τ) has been used in [14]. Motivated by the works of Li and Shu [16], Lim and Maini [17], in this paper, we consider the following HTLV-I infection model with actively infected CD4+ T cells mitosis and delayed CTL immune response:

$$
\begin{aligned}
x'(t) &= \lambda - dx - \beta xy, \\
u'(t) &= \beta xy + ry - (\mu + \sigma)u, \\
y'(t) &= \sigma u - ay - pyz, \\
z'(t) &= cy(t-\tau)z(t-\tau) - bz,
\end{aligned} \tag{2}
$$

where z(t) denotes the concentration of the specific CD8+ CTLs, b is the death rate of specific CD8+ CTLs; pyz describes actively infected CD4+ T cells being lysed by specific CD8+ CTLs, cy(t τ)z(t τ) represents that the CTLs produced at time t depends on the concentration of CTLs and actively infected CD4+ T cells at time t τ [16, 23]. Experiments have shown that the mitosis of actively CD4+ T cells is usually lower than the removal rate caused by natural death [17], hence, in the following, we assume that a > r.

The initial condition for system (2) takes the form

$$
\begin{aligned}
&x(\theta) = \phi_1(\theta), \qquad u(\theta) = \phi_2(\theta), \qquad y(\theta) = \phi_3(\theta), \qquad z(\theta) = \phi_4(\theta), \\
&\phi_i(\theta) \geqslant 0, \quad \theta \in [-\tau, 0), \qquad \phi_i(0) > 0 \quad (i = 1, 2, 3, 4),
\end{aligned}
$$

where (ϕ1(θ), ϕ2(θ), ϕ3(θ), ϕ4(θ)) ∈ C([−τ, 0], R4), here R4 = {(x1, x2, x3, x4):

xi ≥ 0, i = 1, 2, 3, 4}.

This paper is organized as follows. In Section 2, we show the positivity and bound-edness of solutions to system (2). In Section 3, the existence of feasible equilibria, the local stability of the infection-free equilibrium, the immunity-inactivated equilibrium, and the immunity-activated equilibrium (when $\tau = 0$) is established. And we discuss the existence of Hopf bifurcation at the immunity-activated equilibrium. In Section 4, by constructing suitable Lyapunov functionals and using LaSalle's invariance principle, the global stability of the infection-free equilibrium, the immune-inactivated equilibrium, and the immune-activated equilibrium (when $\tau = 0$) is established. In Section 5, we analyze the uniform persistence of system (2) when the immune-activated reproduction ratio is greater than one. In Section 6, we give some numerical simulations to illustrate the theoretical results. Finally, a brief remark is given in Section 7 to conclude this work.

2 The positivity and boundedness of solutions

Theorem 1. Any solution of system (2) with the initial condition (3) is defined on [0, +∞) and remains positive for all t > 0.

Proof. Let (x(t), u(t), y(t), z(t)) be any solution of system (2) with the initial condi- tion (3). First, by the first equation of system (2) we have x˙ x=0 = λ > 0. This implies that x(t) > 0 for all t > 0 as long as x(0) = ϕ1(0) > 0.

Next, we show that u(t) > 0 for all t > 0. Notice that u0 = ϕ2(0) > 0 if there exists a t0 such that u(t0) = 0, then t0 > 0. Assume that t0 is the first time such that u(t) = 0, that is, t0 = inf t > 0: u(t0) = 0 . Then u˙(t0) = (βx(t0) + r)y(t0) ≤ 0.

Hence, y(t0) ≤ 0. By the third equation of system (2) we have

$$y(t) = \left(\phi_3(0) + \sigma \int\limits_0^t u(s)\mathrm{e}^{\int_0^s (a+pz(v))\,\mathrm{d}v}\,\mathrm{d}s\right)\mathrm{e}^{-\int_0^s (a+pz(s))\,\mathrm{d}s}.$$

Thus, we have y(t0) > 0. The contradiction shows that u(t) > 0 for all t > 0. Similarly, we can obtain y(t) > 0 for all t > 0. Furthermore, by the fourth equation of system (2) we have

$$z(t) = \left(\phi_4(0) + c\int\limits_0^t y(s-\tau)z(s-\tau)\mathrm{e}^{bs}\,\mathrm{d}s\right)\mathrm{e}^{-bt}.$$

When t [0, τ), we have z(t τ) = ϕ4(t τ) > 0. Hence, according to (2), we have z(t) > 0 for t [0, τ). Similarly, when t [τ, 2τ), we can obtain that z(t) > 0. By using mathematical induction method we have z(t) > 0 for all t > 0. This completes the proof.

Theorem 2. There is a positive constant M such that for any positive solution (x(t), u(t), y(t), z(t)) of system (2) with the initial condition (3),

$$\limsup_{t\to+\infty} x(t) < M, \qquad \limsup_{t\to+\infty} u(t) < M,$$
$$\limsup_{t\to+\infty} y(t) < M, \qquad \limsup_{t\to+\infty} z(t) < M.$$

Proof. Let (x(t), u(t), y(t), z(t)) be any positive solution of system (2) with the initial condition (3). Define

$$N(t) = x(t) + u(t) + y(t) + \frac{p}{c}z(t+\tau).$$

Calculating the derivative of N (t) along positive solution of system (2), it follows that

$$\begin{aligned}\dot{N}(t) &= \lambda - dx(t) - \mu u(t) - (a-r)y(t) - \frac{bp}{c}z(t+\tau)\\ &\leqslant \lambda - mN(t),\end{aligned}$$

yielding lim sup$_{t\to+\infty}$ N (t) ≤ λ/m, where m = min{d, μ, a − r, b}.

Therefore, the following set is positively invariant for system (2):

$$\Omega = \left\{(x,u,y,z) \in \mathbb{R}^4_+ \colon\ 0 \leqslant x(t) + u(t) + y(t) + \frac{p}{c}z(t+\tau) \leqslant \frac{\lambda}{m}\right\}.$$

If we choose M = (λ/m) min{1, c/p}, then Theorem 2 follows.

3 Equilibria, local stability, and Hopf bifurcation

In this section, we study the existence of feasible equilibria, the local stability of the infection-free equilibrium, the immunity-inactivated equilibrium, and the immunity-acti- vated equilibrium (when τ = 0) of system (2) by analyzing the distributions of roots of the corresponding characteristic equations, and we show the existence of Hopf bifurcation at the immunity-activated equilibrium.

System (2) always has an infection-free equilibrium E0(λ/d, 0, 0, 0). We can obtain the immune-inactivated reproduction ratio by using the method of the next generation matrix [24]:

$$R_0 = \rho\left(FV^{-1}\right) = \frac{(\beta\lambda + rd)\sigma}{ad(\mu + \sigma)},$$

where ρ(FV −1) is the spectrum radius of FV −1. R0 represents the expected number of newly infected cells generated by a single infected cell in its life span. If R0 > 1, in addition to the infection-free equilibrium, system (2) has an immunity-inactivated equilibrium E1(x1, u1, y1, 0), where

$$x_1 = \frac{a(\mu + \sigma) - r\sigma}{\beta\sigma}, \qquad u_1 = \frac{a^2 d(\mu + \sigma)(R_0 - 1)}{\beta\sigma[a(\mu + \sigma) - r\sigma]},$$
$$y_1 = \frac{ad(\mu + \sigma)}{\beta[a(\mu + \sigma) - r\sigma]}(R_0 - 1).$$

Further, by calculation we obtain the immune-activated reproduction ratio

$$R_1 = \frac{\sigma[\beta\lambda c + r(\beta b + cd)]}{a(\mu + \sigma)(\beta b + cd)}.$$

If R1 > 1, in addition to E0 and E1, system (2) has an immunity-activated equilibrium E#(x#, u#, y#, z#), where

$$x^* = \frac{\lambda c}{\beta b + cd}, \qquad u^* = \frac{ab}{\sigma c}R_1, \qquad y^* = \frac{b}{c}, \qquad z^* = \frac{a}{p}(R_1 - 1).$$

Theorem 3. If R0 < 1, the infection-free equilibrium E0 of system (2) is locally asymp- totically stable; if R0 > 1, E0 is unstable.

Proof. The characteristic equation of system (2) at the equilibrium E0 is

$$(s + b)(s + d)\left[s^2 + (a + \mu + \sigma)s + (1 - R_0)\right] = 0. \tag{4}$$

Clearly, (4) has negative real roots s1 = b, s2 = d, and other roots of (4) are determined by the following equation:

$$f(s) := s^2 + (a + \mu + \sigma)s + (1 - R_0) = 0.$$

(5)

If R0 < 1, it is easy to show that all roots of (5) have only negative real parts.

Therefore, the equilibrium E0 is locally asymptotically stable.

If R0 > 1, we have f (0) < 0, f (s) + (s +). Hence, (5) has at least one positive real root. Accordingly, E0 is unstable.

Theorem 4. If R1 < 1 < R0, the immunity-inactivated equilibrium E1 of system (2) is locally asymptotically stable; if R1 > 1, E1 is unstable.

Proof. The characteristic equation of system (2) at the equilibrium E1 is

$$g(s)h(s) = 0,$$

(6)

where

$$\begin{aligned} g(s) &= s + b - cy_1 e^{-s\tau}, \\ h(s) &= (s + d + \beta y_1)\left(\frac{s}{\mu + \sigma} + 1\right)\left(\frac{s}{a} + 1\right) \\ &\quad + \beta y_1 - (s + d + \beta y_1) - \frac{\beta y_1 r \sigma}{a(\mu + \sigma)}. \end{aligned}$$

We first claim that all roots of the following transcendental equation

$$s + b - cy_1 e^{-s\tau} = 0$$

(7)

have negative real parts. Otherwise, there exists a root s1 = a1 + ib1 with a1 ≥ 0. If

R1 < 1 < R0, we have

$$|s_1 + b| \geqslant b, \qquad \left|cy_1 e^{-s\tau}\right| \leqslant |cy_1| < b.$$

It follows that

$$\left|s_1 + b\right| > \left|cy_1 \mathrm{e}^{-s_1\tau}\right|,$$

which contradicts (7). Hence, all roots of (7) have negative real parts, and other roots of (6) are determined by the following equation:

$$(s + d + \beta y_1)\left(\frac{s}{\mu+\sigma} + 1\right)\left(\frac{s}{a} + 1\right) + \beta y_1 \\ = (s + d + \beta y_1) + \frac{\beta y_1 r\sigma}{a(\mu+\sigma)}. \tag{8}$$

Now, we claim that all roots of (8) have negative real parts. Otherwise, there exists a root

s2 = a2 + ib2 with a2 ≥ 0. In this case, we have

$$\left|\frac{s_2}{\mu+\sigma} + 1\right| > 1, \qquad \left|\frac{s_2}{a} + 1\right| > 1, \qquad \left|\beta y_1\right| > \left|\beta y_1 \frac{r\sigma}{a(\mu+\sigma)}\right|.$$

It follows that

$$\left|(s_2 + d + \beta y_1)\left(\frac{s_2}{\mu+\sigma} + 1\right)\left(\frac{s_2}{a} + 1\right) + \beta y_1\right| \\ > \left|(s_2 + d + \beta y_1) + \frac{\beta y_1 r\sigma}{a(\mu+\sigma)}\right|,$$

which contradicts (8). Therefore, if R1 < 1 < R0, all roots of (8) have negative real parts. Further, all roots of (6) have negative real parts. Accordingly, E1 is locally asymptotically stable.

If R1 > 1, it only needs to consider (7), it is clear that g(0) = b cy1 < 0, g(s) = s + b cy1e−sτ + (s +∞). Therefore, (6) has at least one positive real root. Accordingly, E1 is unstable.

The characteristic equation of system (2) at the immunity-activated equilibrium E# is

$$s^4 + p_3 s^3 + p_2 s^2 + p_1 s + p_0 + \left(q_3 s^3 + q_2 s^2 + q_1 s + q_0\right)\mathrm{e}^{-s\tau} = 0. \tag{9}$$

where

$$
\begin{aligned}
p_0 &= \beta^2 x^* y^* b\sigma,\\
p_1 &= b(d+\beta y^*)(a+pz^*+\mu+\sigma)+\beta^2 x^* y^* \sigma,\\
p_2 &= (d+\beta y^*)(a+pz^*+b+\mu+\sigma)+b(a+pz^*+\mu+\sigma),\\
p_3 &= a+pz^*+d+\beta y^*+b+\mu+\sigma,\\
q_0 &= -b\big[\beta^2 x^* y^* \sigma-(d+\beta y^*)(\mu+\sigma)pz^*\big],\\
q_1 &= -b\big[(\mu+\sigma)(d+\beta y^*)+(a+pz^*)(d+\beta y^*)-pz^*(\mu+\sigma+d+\beta y^*)\big],\\
q_2 &= -b(a+d+\beta y^*+\mu+\sigma),\\
q_3 &= -b.
\end{aligned}
$$

When τ = 0, (9) reduces to

$$
\begin{aligned}
s(s+d+\beta y^*)(s+\mu+\sigma)(s+a+pz^*)+s\beta^2 x^* y^* \sigma\\
+(s+d+\beta y^*)(s+\mu+\sigma)pbz^*\\
=s(s+d+\beta y^*)(a+pz^*)(\mu+\sigma).
\end{aligned}
$$

Now, we claim that all roots of (10) have negative real parts. Otherwise, (10) has at least one root s1 = x1 + iy1 with x1 ≥ 0. Noting that

$$
\begin{aligned}
\big|s_1(s_1+d+\beta y^*)(s_1+\mu+\sigma)(s_1+a+pz^*)+s_1\beta^2 x^* y^* \sigma\\
+(s_1+d+\beta y^*)(s_1+\mu+\sigma)pbz^*\big|\\
>\big|s_1(s_1+d+\beta y^*)(a+pz^*)(\mu+\sigma)\big|,
\end{aligned}
$$

which contradicts (10). Thus, all roots of (10) have negative real parts. Hence, when τ = 0, the equilibrium E# is locally asymptotically stable.

When τ > 0, substituting s = iω (ω > 0) into (9) and separating real and imaginary parts, we have

$$
\begin{aligned}
\omega^4-p_2\omega^2+p_0=(q_3\omega^3-q_1\omega)\sin\omega\tau+(q_2\omega^2-q_0)\cos\omega\tau,\\
p_3\omega^3-p_1\omega=(q_2\omega^2-q_0)\sin\omega\tau-(q_3\omega^3-q_1\omega)\cos\omega\tau.
\end{aligned}
\tag{11}
$$

Squaring and adding the two equations of (11), it follows that

$$
\omega^8+C_3\omega^6+C_2\omega^4+C_1\omega^2+C_0=0,
\tag{12}
$$

where

$$C_0 = p_0^2 - q_0^2, \qquad C_1 = p_1^2 - 2p_0p_2 - q_1^2 + 2q_0q_2,$$
$$C_2 = p_2^2 + 2p_0 - 2p_1p_3 + 2q_1q_3 - q_2^2, \qquad C_3 = p_3^2 - 2p_2 - q_3^2.$$

Let z = ω2. Equation (12) becomes

$$h(z) := z^4 + C_3z^3 + C_2z^2 + C_1z + C_0 = 0. \tag{13}$$

Clearly, if C0 < 0, we have h(0) = C0 < 0, limz→+∞ h(z) = +∞ Therefore, (13) has at least one positive root. From (13) we have

$$h'(z) = 4z^3 + 3C_3z^2 + 2C_2z + C_1.$$

Denote

$$P = \frac{8C_2 - 3C_3^2}{16}, \qquad Q = \frac{C_3^3 - 4C_3C_2 + 8C_1}{32}, \qquad D_0 = \frac{Q^2}{4} + \frac{P^3}{27},$$

and

$$z_1^* = -\frac{C_1}{4} + \sqrt[3]{-\frac{Q}{2} + \sqrt{D_0}} + \sqrt[3]{-\frac{Q}{2} - \sqrt{D_0}} \quad \text{if } D_0 > 0,$$
$$z_2^* = \max\left\{-\frac{C_1}{4} - 2\sqrt[3]{\frac{Q}{2}}, -\frac{C_1}{4} + \sqrt[3]{\frac{Q}{2}}\right\} \quad \text{if } D_0 = 0,$$
$$z_3^* = \max\left\{-\frac{C_1}{4} + 2\,\mathrm{Re}\{\alpha\}, -\frac{C_1}{4} + 2\,\mathrm{Re}\{\alpha\varepsilon\}, -\frac{C_1}{4} + 2\,\mathrm{Re}\{\alpha\bar{\varepsilon}\}\right\} \quad \text{if } D_0 < 0,$$

where α is one of cubic roots of the complex number Q/2+√D0, and ε = 1/2+√3/2i. By [27] we have the following result.

Lemma 1. (See [27].)

i. (i) If C0 < 0, then (13) has at least one positive root.
   (ii) Assume that C0 ≥ 0, then (13) has no positive roots if one of the following conditions holds:

a) (a) D0 > 0 and z1# < 0;
   (b) D0 = 0 and z2# < 0;
   (c) D0 < 0 and z3# < 0.

(iii) Assume that C0 ≥ 0, then (13) has at least one positive root if one of the following conditions holds:

$$\begin{aligned}&\text{(a)}\ \ D_0>0,\ z_1^*>0,\ and\ h(z_1^*)<0;\\&\text{(b)}\ \ D_0=0,\ z_2^*>0,\ and\ h(z_2^*)<0;\\&\text{(c)}\ \ D_0<0,\ z_3^*>0,\ and\ h(z_3^*)<0.\end{aligned}$$

Without loss of generality, we assume that (13) has positive real roots zk (k = 1, 2, Importar imagen . . . , k¯)

Without loss of generality, we assume that (13) has positive real roots zk (k = 1, 2, . . . , k¯), where 1 ≤ k¯ ≤ 4. Then (12) has positive roots ωk = √zk (k = 1, 2, . . . , k¯).

From (11) we have

$$\begin{aligned}&\text{(a)}\ \ D_0>0,\ z_1^*>0,\ and\ h(z_1^*)<0;\\&\text{(b)}\ \ D_0=0,\ z_2^*>0,\ and\ h(z_2^*)<0;\\&\text{(c)}\ \ D_0<0,\ z_3^*>0,\ and\ h(z_3^*)<0.\end{aligned}$$

Without loss of generality, we assume that (13) has positive real roots zk (k = 1; 2;: : : ; k), where 1 6 k 6 4. Then (12) has positive roots !k =pzk (k = 1; 2; : : : ; k).From (11) we havewhere k = 1; 2; : : : ; k, j = 1; 2; : : : . Then !k is a pair of purely imaginary roots of(12) with = (j)k .Denote 0 = mink2f1;2;:::;kgf (0)k g, !0 = !k0. Let s( ) = ( ) + i!( ) be a rootof (9) satisfying ((j)k) = 0, !((j)k) = !k. Differentiating (9) with respect , we have

$$\tau_k^{(j)}=\frac{1}{\omega_k}\arccos\left[\frac{(\omega_k^4-p_2\omega_k^2+p_0)(q_2\omega_k^2-q_0)-(p_3\omega_k^3-p_1\omega_k)(q_3\omega_k^3-q_1\omega_k)}{(q_3\omega_k^3-q_1\omega_k)^2+(q_2\omega_k^2-q_0)^2}+2\pi j\right],$$

where k = 1; 2; : : : ; k, j = 1; 2; : : : . Then !k is a pair of purely imaginary roots of(12) with = (j)k .

Denote 0 = mink2f1;2;:::;kgf (0)k g, !0 = !k0. Let s( ) = ( ) + i!( ) be a rootof (9) satisfying ((j)k) = 0, !((j)k) = !k. Differentiating (9) with respect , we have

$$\left(\frac{\mathrm{d}s}{\mathrm{d}\tau}\right)^{-1}=-\frac{4s^3+3s^2p_3+2sp_2+p_1)}{s(s^4+p_3s^3+p_2s^2+p_1s+p_0)}+\frac{3q_3s^2+2q_2s+q_1}{s(q_3s^3+q_2s^2+q_1s+q_0)}-\frac{\tau}{s}.$$

Therefore, we obtain from (11) and (14) that

$$\operatorname{sign}\left\{\frac{\mathrm{d}(\operatorname{Re} s)}{\mathrm{d}\tau}\right\}_{\tau=\tau_0} = \operatorname{sign}\frac{h'(\omega_0^2)}{(q_3\omega_0^2 - q_1)^2 + (q_0 - q_2\omega_0^2)^2}.$$

From what has been discussed above we have the following result [22, 26].

Theorem 5. For system (2), we have

i. (i) If Eq. (13) has no positive roots, then the equilibrium E# is locally asymptotically stable.
   If Eq. (13) has at least one positive root, and h′ (ω 2) = 0, then the equilibrium E# is locally asymptotically stable for τ [0, τ0) and unstable for τ > τ0. Further, system (2) undergoes a Hopf bifurcation at E# when τ = τ0.

4 Global stability

In this section, we study the global stability of the infection-free equilibrium, the immune- inactivated equilibrium, and the immune-activated equilibrium (when τ = 0) of sys- tem (2) by using Lyapunov functionals and LaSalle's invariance principle.

Theorem 6. If R0 < 1, the infection-free equilibrium E0(x0, 0, 0, 0) of system (2) is globally asymptotically stable.

Proof. Let (x(t), u(t), y(t), z(t)) be any positive solution of system (2) with the initial condition (3). Define

$$\begin{aligned} W_0(t) = {} & x(t) - x_0 - x_0\ln\frac{x(t)}{x_0} + u(t) + \frac{\mu+\sigma}{\sigma}y(t) \\ & + \frac{p(\mu+\sigma)}{c\sigma}z(t) + \frac{p(\mu+\sigma)}{\sigma}\int_{t-\tau}^{t} y(s)z(s)\,\mathrm{d}s, \end{aligned}$$

where x0 = λ/d. Calculating the derivative of W0(t) along positive solution of system (2) yields

$$\begin{aligned} \dot{W_0}(t) &= \left(1 - \frac{x_0}{x}\right)(\lambda - dx) + \beta x_0 y + ry - \frac{\mu+\sigma}{\sigma}ay - \frac{p(\mu+\sigma)}{c\sigma}bz \\ &= -\frac{d(x-x_0)^2}{x} + \left(\frac{\beta\lambda}{d} + r - \frac{a(\mu+\sigma)}{\sigma}\right)y - \frac{p(\mu+\sigma)}{c\sigma}bz \\ &= -\frac{d(x-x_0)^2}{x} + \frac{a(\mu+\sigma)}{\sigma}(R_0 - 1)y - \frac{p(\mu+\sigma)}{c\sigma}bz. \end{aligned}$$

It follows that W˙0(t) ≤ 0, W˙0(t) = 0 if and only if x = x0, u = 0, y = 0, z = 0. The maximal variant set in (x(t), u(t), y(t), z(t)) Ω: W˙0(t) = 0 is the singleton E0 . From Theorem 3, E0 is locally asymptotically stable. Accordingly, the global stability

of E0 follows from LaSalle's invariance principle.

Theorem 7. If R1 < 1 < R0, the immunity-inactivated equilibrium E1(x1, u1, y1, 0) of system (2) is globally asymptotically stable.

Proof. Let (x(t), u(t), y(t), z(t)) be any positive solutions of system (2) with the initial condition (3). Define

$$\begin{aligned} W_1(t) &= x(t) - x_1 - x_1 \ln\frac{x(t)}{x_1} + u(t) - u_1 - u_1 \ln\frac{u(t)}{u_1} + \frac{p(\mu+\sigma)}{c\sigma} z(t) \\ &\quad + \frac{\mu+\sigma}{\sigma}\left(y(t) - y_1 - y_1 \ln\frac{y(t)}{y_1}\right) + \frac{p(\mu+\sigma)}{\sigma}\int_{t-\tau}^{t} y(s)z(s)\,\mathrm{d}s. \end{aligned}$$

Calculating the derivative of W1(t) along positive solution of system (2), it follows that

$$\begin{aligned} \dot{W}_1(t) &= \lambda\left(1 - \frac{x_1}{x}\right) - dx + dx_1 + \beta x_1 y + ry - (\beta xy + ry)\frac{u_1}{u} \\ &\quad + (\mu+\sigma)u_1 - \frac{a(\mu+\sigma)}{\sigma} y - (\mu+\sigma)u\frac{y_1}{y} + \frac{\mu+\sigma}{\sigma} a y_1 \\ &\quad + p y_1 z \frac{\mu+\sigma}{\sigma} - \frac{p(\mu+\sigma)}{c\sigma} bz. \end{aligned}$$

On substituting

$$\lambda = dx_1 + \beta x_1 y_1, \qquad \beta x_1 y_1 + r y_1 = (\mu+\sigma)u_1, \qquad \sigma u_1 = a y_1$$

into (15), we obtain

$$\begin{aligned} \dot{W}_1(t) &= dx_1\left(2 - \frac{x_1}{x} - \frac{x}{x_1}\right) + \beta x_1 y_1 - \beta x_1 y_1 \frac{x_1}{x} - \beta x_1 y_1 \frac{x y u_1}{x_1 y_1 u} + \beta x_1 y_1 + r y_1 \\ &\quad + \beta x_1 y_1 + r y_1 - r y_1 \frac{y u_1}{y_1 u} + p y_1 z \frac{\mu+\sigma}{\sigma} - \frac{p(\mu+\sigma)}{c\sigma} bz - (\beta x_1 y_1 + r y_1)\frac{u y_1}{u_1 y} \\ &= dx_1\left(2 - \frac{x_1}{x} - \frac{x}{x_1}\right) + \beta x_1 y_1\left(3 - \frac{x_1}{x} - \frac{x y u_1}{x_1 y_1 u} - \frac{u y_1}{u_1 y}\right) \\ &\quad + r y_1\left(2 - \frac{y u_1}{y_1 u} - \frac{u y_1}{u_1 y}\right) + \frac{p(\mu+\sigma)^2(\beta b + ad)}{\beta\sigma c[a(\mu+\sigma) - r\sigma]}(R_1 - 1)z. \end{aligned}$$

It follows that W˙1(t) ≤ 0. Clearly, we obtain that W˙1(t) = 0 if and only if x = x1 Z=0,

$$3 - \frac{x_1}{x} - \frac{xyu_1}{x_1y_1u} - \frac{uy_1}{u_1y} = 0, \qquad 2 - \frac{yu_1}{y_1u} - \frac{uy_1}{u_1y} = 0.$$

It follows from x(t) = x1 that x˙(t) = 0. According to the first equation of system (2), we have

$$0 = \dot{x}(t) = \lambda - dx_1 - \beta x_1 y(t),$$

which yields y(t) = y1. In addition, according to (4), we have u(t) = u1. Hence, W˙1(t) = 0 if and only if x = x1, u = u1, y = y1, z = 0. Hence, the maximal variant set in (x(t), u(t), y(t), z(t)) Ω: W˙1(t) = 0 is the singleton E1 . Note that E1 is locally asymptotically stable. From LaSalle's invariance principle we conclude that E1 is Importar imagen globally asymptotically stable.

Theorem 8. If R1 > 1, the immunity-activated equilibrium E#(x#, u#, y#, z#) of sys- tem (2) is globally asymptotically stable when τ = 0.

Proof. Let (x(t), u(t), y(t), z(t)) be any positive solution of system (2) with the initial condition (3). Define

$$\begin{aligned} W_2(t) &= x(t) - x^* - x^* \ln\frac{x(t)}{x^*} + u(t) - u^* - u^* \ln\frac{u(t)}{u^*} \\ &\quad + \frac{\mu+\sigma}{\sigma}\left(y(t) - y^* - y^* \ln\frac{y(t)}{y^*}\right) + \frac{p(\mu+\sigma)}{c\sigma}\left(z(t) - z^* - z^* \ln\frac{z(t)}{z^*}\right). \end{aligned}$$

Calculating the derivative of W2(t) along positive solution of system (2), it follows that

$$\begin{aligned} \dot{W}_2(t) &= \left(1 - \frac{x^*}{x}\right)(\lambda - dx - \beta xy) + \left(1 - \frac{u^*}{u}\right)[\beta xy + ry - (\mu+\sigma)u] \\ &\quad + \frac{\mu+\sigma}{\sigma}\left(1 - \frac{y^*}{y}\right)(\sigma u - ay - pyz) + \frac{p(\mu+\sigma)}{c\sigma}\left(1 - \frac{z^*}{z}\right)(cyz - bz). \end{aligned} \tag{16}$$

On substituting

$$\lambda = dx^* + \beta x^* y^*, \qquad \beta x^* y^* + r y^* = (\mu + \sigma)u^*,$$
$$\sigma u^* = a y^* - p y^* z^*, \qquad c y^* = b$$

into (16), we obtain

$$\begin{aligned}\dot{W}_2(t) &= \left(1-\frac{x^*}{x}\right)(\lambda - dx - \beta xy) + \left(1-\frac{u^*}{u}\right)[\beta xy + ry - (\mu+\sigma)u] \\ &\quad + \frac{\mu+\sigma}{\sigma}\left(1-\frac{y^*}{y}\right)(pyz^* - pyz) + \frac{p(\mu+\sigma)}{c\sigma}\left(1-\frac{z^*}{z}\right)(cyz - bz) \\ &\quad + \frac{\beta x^* y^* + ry^*}{\sigma u^*}\left(1-\frac{y^*}{y}\right)\left(\sigma u - \sigma u^* \frac{y^*}{y}\right) \\ &= dx^*\left(2 - \frac{x^*}{x} - \frac{x}{x^*}\right) + \beta x^* y^*\left(3 - \frac{x^*}{x} - \frac{xyu^*}{x^*y^*u} - \frac{uy^*}{u^*y}\right) \\ &\quad + ry^*\left(2 - \frac{yu^*}{y^*u} - \frac{uy^*}{u^*y}\right).\end{aligned}$$

It follows that W˙2(t) ≤ 0. Clearly, we obtain that W˙2(t) = 0 if and only if x = x#,

$$3 - \frac{x^*}{x} - \frac{xyu^*}{x^*y^*u} - \frac{uy^*}{u^*y} = 0, \qquad 2 - \frac{yu^*}{y^*u} - \frac{uy^*}{u^*y} = 0.$$

It follows from x(t) = x# that x˙(t) = 0. According to the first equation of system (2), we have

$$0 = \dot{x}(t) = \lambda - dx^* - \beta x^* y(t),$$

which yields y(t) = y#. In addition, according to (4), we have u(t) = u#. Furthermore, we have z(t) = z#. Hence, we have W˙2(t) = 0 if and only if x = x#, u = u#, y = y#, z = z#. Hence, the maximal variant set in (x(t), u(t), y(t), z(t)) Ω: W˙2(t) = 0 is the singleton E# . Noting that E# is locally asymptotically stable. From LaSalle's invariance principle we see that E# is globally asymptotically stable when τ = 0.

5 Uniform persistence

In this section, we verify the uniform persistence of system (2) when R1 > 1.

Assume that T (t) is a C0 semigroup of X satisfying

$$T(t) : X^0 \to X^0,\ X_0 \to X_0.$$

Let T∂(t) = T (t) X0 , A∂ be the global attractor for T∂(t). The following results was developed in [10].

Lemma 2. (See [10].) Suppose that T (t) satisfies (17) and that the following conditions are valid:

i. (i) There is a t0 ≥ 0 such that T (t) is compact for t > t0.
 (ii) T (t) is point dissipative in X.
 (iii) A˜∂ = ∪ ω (x) (x ∈ A∂) is isolated and has an acyclic covering M˜ , where M˜ = {M1, M2, . . . , Mn}.
 (iv) Ws(Mi) ∩ X0 = ϕ, i = 1, 2, . . . , n.

Then T (t) is uniformly persistent in the sense that there is an ε > 0 such that, for any x ∈ X0,

$$\liminf_{t\to+\infty} d(T(t)x, X_0) \geqslant \varepsilon,$$

where d is the distance of T (t)x from X0.

Theorem 9. If R1 > 1, system (2) is uniformly persistent.

Proof. Let X = R4+, X0 = U1 [U2, where U1 = f(x; u; y; z) 2 R4+: u 0; y 0g,U2 = f(x; u; y; z) 2 R4+: z 0g. Let X0 = X nX0, where X0 is a positive invariant setfor system (2), X0 is a positive invariant set for system (2) when any initial component iszero. Therefore, X satisfies (17). DenoteProof. Let X = R4 , X0 = U1 ∪ U2, where U1 = {(x, u, y, z) ∈ R4 : u ≡ 0, y ≡ 0},

$$\phi_0 = \big(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)\big),$$
$$T(t)_{\phi_0} := \big(x(t), u(t), y(t), z(t)\big) \quad (t \geqslant 0),$$

where (x(t), u(t), y(t), z(t)) is a positive solution of system (2) with the initial condi- tion (3). Then T (t) t≥0 is a C0 semigroup generated by (2). It is easy to prove that conditions (i)–(iv) of Lemma 2 is satisfied when R1 > 1. Therefore, all solutions of system (2) in X0 are uniform repellers with respect to X0 [25]. In other words, there is an ε0 > 0 such that for any solution Φ(t) := (x(t), u(t), y(t), z(t)) of system (2) with initial condition in X0, we have

$$\liminf_{t\to+\infty} d\big(\varPhi(t), X_0\big) \geqslant \varepsilon_0,$$

where d is the distance of Φ(t) from X0. Thus, there exists an ε1 > 0 such that

$$\liminf_{t\to+\infty}\big(y(t)+u(t)\big)\geqslant\varepsilon_1,\qquad \liminf_{t\to+\infty}z(t)\geqslant\varepsilon_1$$

for any solution of system (2) with the initial condition in X0. We obtain from the first equation of system (2) that

$$x'=\lambda-dx-\beta xy\geqslant\lambda-(d+\beta M)x.$$

By comparison we have $x(t) > \lambda/2(d + \beta M)$ for sufficiently large t, for any solution of system (2) with initial condition in X0.

Let $y_\infty = \liminf_{t\to+\infty} y(t)$, $u_\infty = \liminf_{t\to+\infty} u(t)$. By the fluctuations lemma in [11] there exists a sequence τ_n , $y(\tau_n)\ y_\infty$ and $y'(\tau_n) = 0$. By the third equation of system (2) we have

$$0=\sigma\lim_{n\to\infty}u(\tau_n)-ay_\infty-py_\infty\lim_{n\to\infty}z(\tau_n),$$

and hence

$$\frac{a+pM}{\sigma}y_\infty+y_\infty\geqslant u_\infty+y_\infty\geqslant\varepsilon_1.$$

Therefore, $y_\infty \geq \varepsilon_1\sigma/(a + pM + \sigma)$. Similarly, there exists a sequence $\tau_n \to \infty$, $u(\tau_n) \to u_\infty$ and $u'(\tau_n) = 0$. Then by the second equation of system (2) we have

$$\begin{aligned}(\mu+\sigma)u_\infty&=\beta\lim_{n\to\infty}x(\tau_n)y(\tau_n)+r\lim_{n\to\infty}y(\tau_n)\\&\geqslant\left(\frac{\beta\lambda}{2(d+\beta M)}+r\right)y_\infty.\end{aligned}$$

Hence,

$$u_\infty\geqslant\frac{[\beta\lambda+2r(d+\beta M)]\varepsilon_1\sigma}{2(d+\beta M)(a+pM+\sigma)(\mu+\sigma)}:=\varepsilon_2.$$

Let " = minf=(d + M); "2; "1=(a + pM +); "1g. We have

$$\liminf_{t\to+\infty} x(t) \geqslant \varepsilon, \qquad \liminf_{t\to+\infty} u(t) \geqslant \varepsilon,$$

$$\liminf_{t\to+\infty} y(t) \geqslant \varepsilon, \qquad \liminf_{t\to+\infty} z(t) \geqslant \varepsilon,$$

for any solution of system (2) with the initial condition in X0. Hence, system (2) is uniformly persistent.

6 Numerical simulation

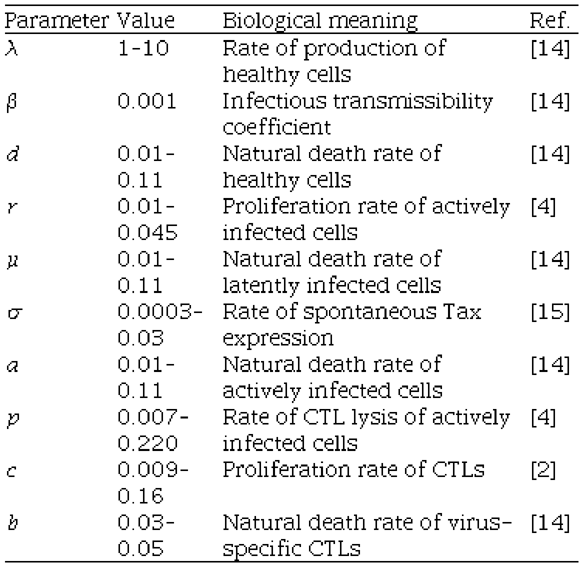
In this section, we carry out numerical simulations to illustrate our analytical results. The relevant parameters are listed in Table 1. Here, we choose the initial condition as (850, 1, 0.5, 1) [6].

We choose λ = 1, β = 0.001, r = 0.02, σ = 0.003, p = 0.029, a = μ = d = 0.03,

c = 0.036, b = 0.04. By calculation we obtain that R0 = 10/93 < 1. System (2) has an infection-free equilibrium E0(100/3, 0, 0, 0). From Theorem 3 the equilibrium E0 is locally asymptotically stable (see Fig. 1).

Table 1

Table of biologically relevant parameter ranges



Parameter	Value	Biological meaning	Ref.
λ	1-10	Rate of production of healthy cells	[14]
β	0.001	Infectious transmissibility coefficient	[14]
d	0.01-0.11	Natural death rate of healthy cells	[14]
r	0.01-0.045	Proliferation rate of actively infected cells	[4]
μ	0.01-0.11	Natural death rate of latently infected cells	[14]
σ	0.0003-0.03	Rate of spontaneous Tax expression	[15]
a	0.01-0.11	Natural death rate of actively infected cells	[14]
p	0.007-0.220	Rate of CTL lysis of actively infected cells	[4]
c	0.009-0.16	Proliferation rate of CTLs	[2]
b	0.03-0.05	Natural death rate of virus-specific CTLs	[14]

(values)

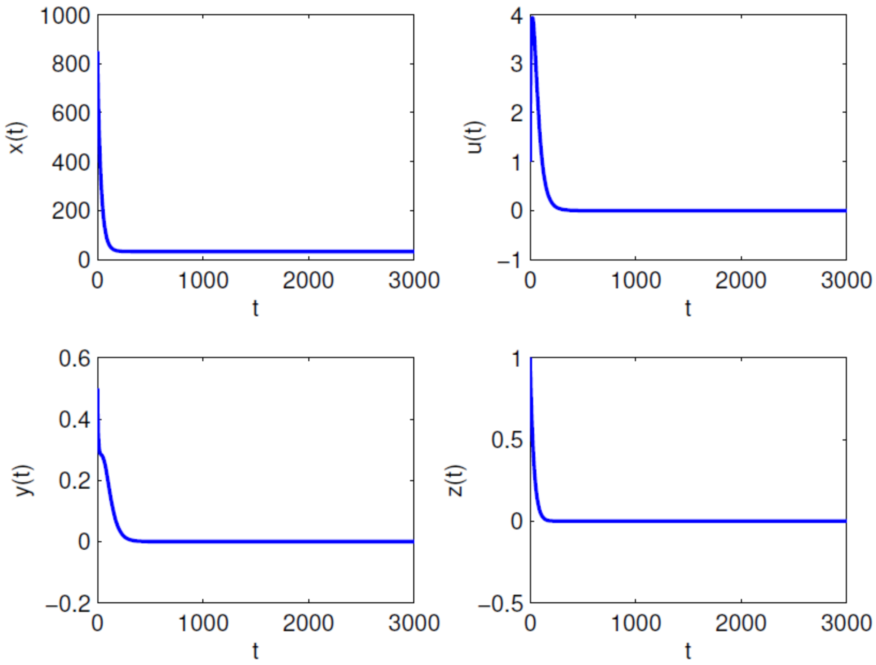


Figure 1

When R0 < 1, E0(100/3, 0, 0, 0) is locally asymptotically stable.

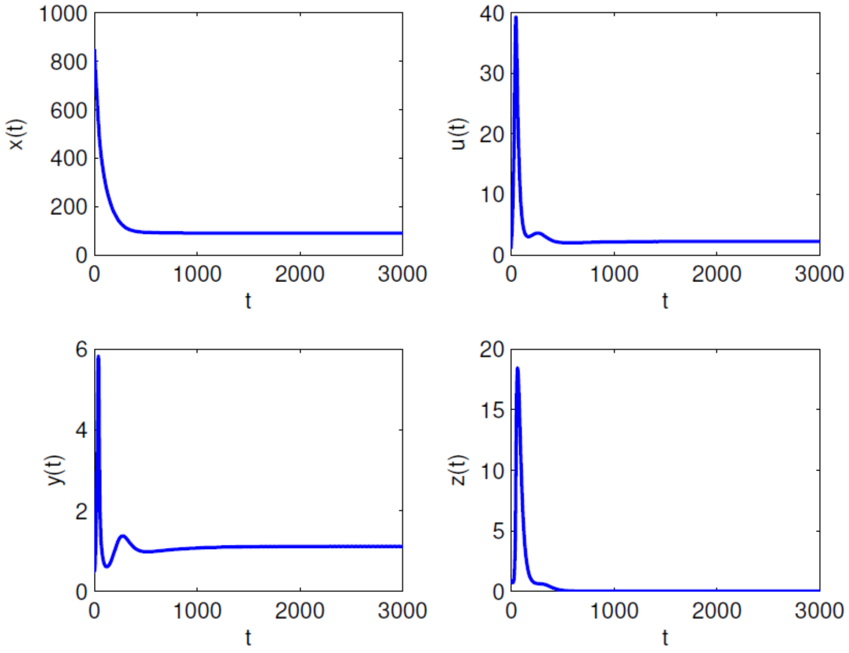


Figure 2

When R1 < 1 < R0, E1(30, 40/3, 40/3, 0) is locally asymptotically stable.

We choose $\lambda = 1$, $d = 0.01$, $\beta = 0.001$, $r = 0.03$, $\mu = \sigma = 0.03$, $a = 0.06$, $p = 0.029$, $c = 0.036$, $b = 0.05$. It is easy to show $R1 = 161/164 < 1 < 10/9 = R0$. System (2) has an immunity-inactivated equilibrium E1(90, 20/9, 10/9, 0). From Theorem 4 the equilibrium E1 is locally asymptotically stable. Numerical simulation illustrates this fact (see Fig. 2).

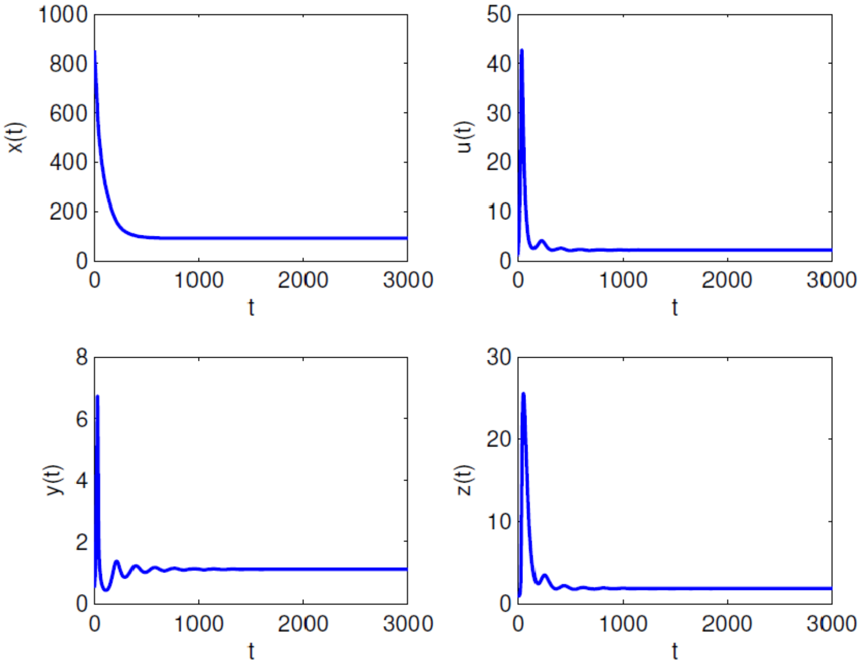


Figure 3
When R1 > 1, τ = 0.2 < τ0, E#(90, 110/54, 10/9, 25/29) is locally asymptotically stable.

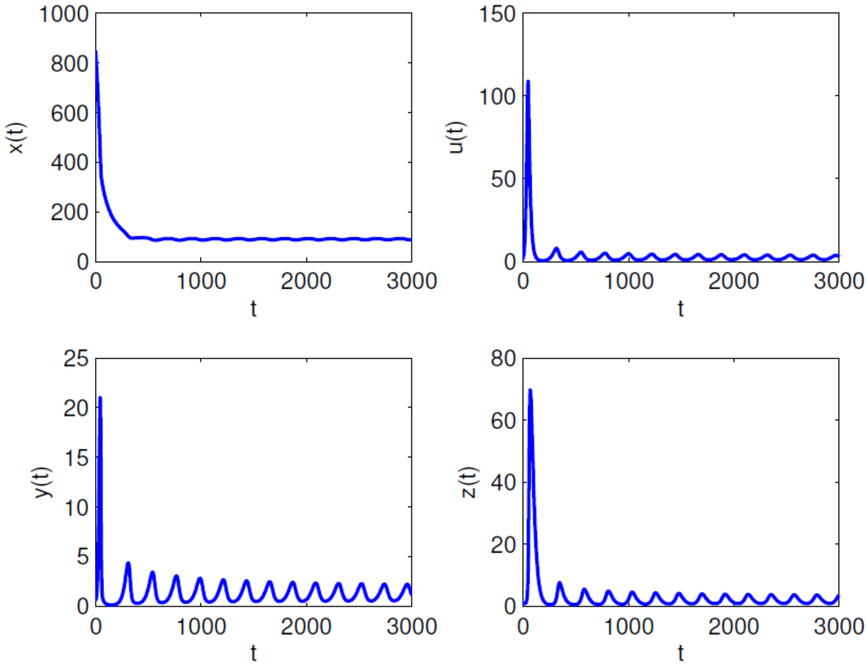
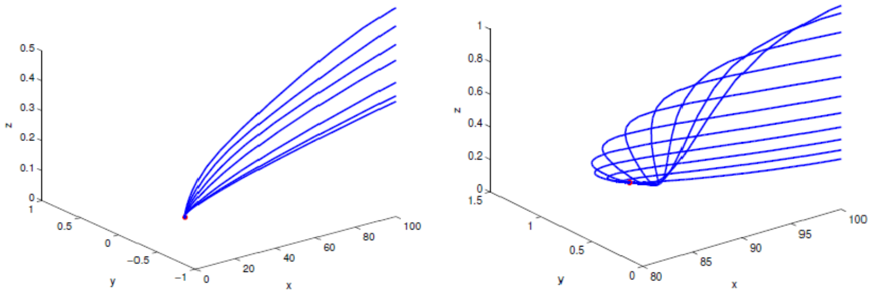


Figure 4
When R1 > 1, τ = 8.5 > τ0, E#(90, 110/54, 10/9, 25/29) is unstable

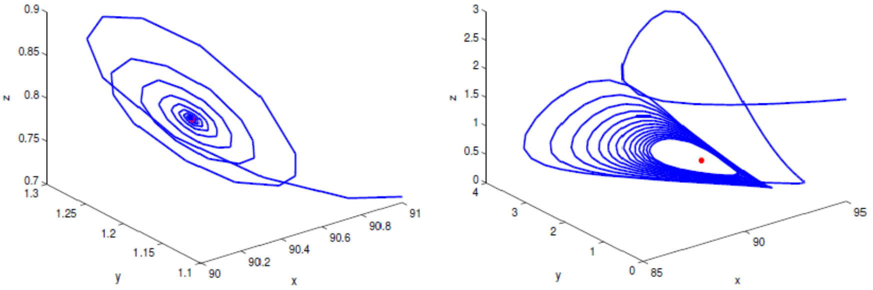
We choose λ = 1, β = 0.001, r = 0.02, d = 0.01, p = 0.029, a = σ = μ = 0.03,

c = 0.036, b = 0.04. It is easy to show R1 = 11/6 > 1. System (2) has an immunity- activated equilibrium E#(90, 110/54, 10/9, 25/29). From Theorem 5 the equilibrium E# is locally asymptotically stable when τ <

τ0, E# is unstable when τ > τ0. Numerical simulation illustrates this fact (see Figs. 3 and 4).



(a) $R_0 < 1$ (b) $R_1 \leqslant 1 < R_0$



(c) $R_1 > 1, \tau = 0.2 < \tau_0$ (d) $R_1 > 1, \tau = 8.5 > \tau_0$

Figure 5
Phase trajectory of the feasible equilibria of system (2)

In order to see the behavior of the solution of system (2), we obtain the phase trajectory of the feasible equilibria of system (2) (see Fig. 5). From Figs. 5(a) and 5(b) we see that the infection-free equilibrium E0 and the immunity-inactivated equilibrium E1 are locally asymptotically stable for any τ ≥ 0. Besides, the immunity-activated equilibrium E# is locally asymptotically stable when τ < τ0, a periodic oscillation exists when τ > τ0 (see Figs. 5(c) and 5(d)). Besides, we obtain the bifurcation diagram of system (2) (see Fig. 6).

LHS allows an un-biased estimate for each parameter of R0 and R1, a probability density function is defined and divided into N equal probability intervals. N represents the sample size. The choice for N should be at least k + 1, where k is the parameters varied, but usually much larger to ensure accuracy. A single value is then selected ran- domly from every interval [18]. In this way, an input value from each sampling interval is used only once in the analysis, but the entire parameter space is equitably sampled in an efficient manner.

Through analysis of the sample derived from LHS, we can obtain large efficient data in respect to different parameters of R0 and R1. Figure 7 shows that r, σ are both positive correlative variables with R0 and R1. It is clear that σ contributes more to R0 and R1 than r, hence, σ is a more important factor.

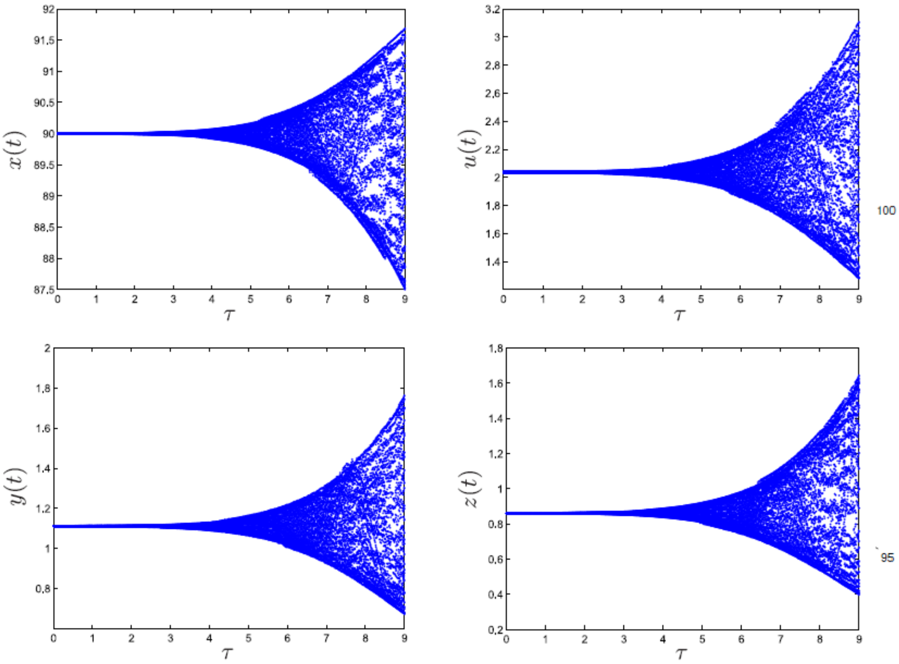


Figure 6

The bifurcation diagram of system (2) plotted for increasing values of the time delay.

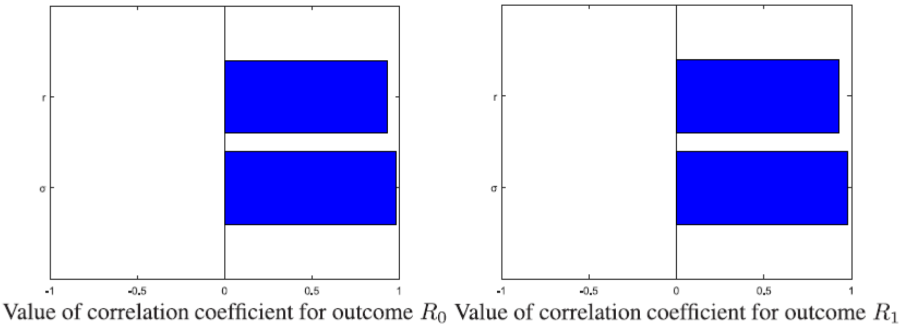


Figure 7

Tornado plot of partial rank correlation coefficients in respect to R0, R1.

7 Conclusions

In this paper, we considered an improved HTLV-I infection model with CD4+ T cells mitosis and delayed cytotoxic T-lymphocyte (CTL) immune response. Through a rigorous mathematical analysis, the threshold dynamical of the model was established, and it can be determined by the immune-inactivated reproduction ratio R0 and the immune-activated reproduction ratio R1. If R0 < 1, the infection-free equilibrium is globally asymptotically stable; if R1 < 1 < R0, the immunity-inactivated equilibrium is globally asymptotically stable; if R1 > 1, the immunity-activated equilibrium is globally asymptotically stable when $\tau = 0$. Besides, we established the existence of Hopf bifurcation at the immunity- activated equilibrium. By Theorem 5 we found that when the delay varies, the immunity- activated steady state loses its stability and Hopf bifurcation occurs. That is to say, the time delay can destabilize the immunity-activated equilibrium and lead to periodic oscillation through Hopf bifurcation. Numerical simulations showed the occurrence of bifurcating periodic oscillation when the delay passes the critical value. Sensitivity anal- ysis showed that σ has a great influence on the threshold parameter R0 and R1, which can provide some suggestions for clinical treatment of HTLV-I related diseases.

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Notes

1 Corresponding author This research was supported by the National Natural Science Foundation of China (Nos. 11871316, 11801340, 11371368), the Natural Science Foundation of Shanxi Province (Nos. 201801D121006, 201801D221007).