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A DELAY-DIFFERENTIAL EQUATION MODEL OF HIV INFECTION OF CD4$^+$ T-CELLS

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Abstract. In this paper, we introduce a discrete time to the model to describe the time between infection of a CD4$^+$ T-cells, and the emission of viral particles on a cellular level. We study the effect of the time delay on the stability of the endemically infected equilibrium, criteria are given to ensure that the infected equilibrium is asymptotically stable for all delay. We also obtain the condition for existence of an orbitally asymptotically stable periodic solution.

1. Introduction

Mathematical modelling has proven to be valuable in understanding the dynamics of HIV-1 infection. By direct application of models to data obtained from experiments in which antiretroviral drugs were given to perturb the dynamical state of infection in HIV-1 infected patients, minimal estimates of the death rate of productively infected cells, the rate of viral clearance and the viral production rate have been obtained [1–6]. Those models gave so accurate depiction of the virus load which are almost consistent with the actual data. The research of mathematical models is very helpful for the clinical treatment. Especially, the models of combination therapy provide very important meaning for the cure of HIV. However, infection by *HIV-1* and *HCV* has *many puzzling* quantitative features. For example, there is an average 10 years between infection with the virus and the AIDS in adults. The reason for this time lag remains largely unknown, although it seems tied to changes in the number of circulating CD4$^+$ T cells. The major target of HIV infection

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is a class of lymphocytes, or white blood cells, known as $CD4^+$ T cells. These cells secrete growth and differentiation factors that are required by other cell populations in the immune system, and hence these cells are called "helper T cells".

When the $CD4^+$ T cell count, which is normally around 1000 mm^{-3}, reaches 200 mm^{-3} or below in an HIV-infected patient, then that person is classified as having AIDS. The reason for fall in the T cell count is unknown.

Over the past decade, a number of models have been developed to describe the immune system, its interaction with HIV and HCV, and the decline in $CD4^+$ T cells. These models typically consider the dynamics of the $CD4^+$ and virus populations as well as the effects of drug therapy (see survey [6] and its references). There are also some models which include an intracellular delay [7–14]. HIV infects cells that carry the $CD4^+$ cell surface protein as well as other receptors called coreceptors. Cells that are susceptible to HIV infection are called target cells. The major target of HIV infection is $CD4^+$ T cells. After becoming infected, such cells can produce new HIV virus particles, or virions. Thus, we introduce a population of uninfected target cells, T, and productively infected cells, I, the virus concentration, V.

To account for the time between viral entry into a target cell and the production of new virus particles, models that include delays have been introduced [7–14]. The first model that included this type of 'intracellular' delay was developed by Herz et al.[7] and assumed that cells became productively infected τ time units after initial infection. Thus, the model incorporated a fixed, discrete, delay. While their model was non-linear in that it incorporated a bilinear term for the rate of target cell infection by free virus, the authors assumed therapy was 100% effective and thus set this non-linear term to zero when analyzing drug perturbation experiments, reducing the problem to a linear one. They reported that including a delay changed the estimated value of the viral clearance rate, c, but did not change the productively infected T cell loss rate, δ. Mittler et al.[10] examined a related model but assumed that the intracellular delay, rather than being discrete, was continuous and varied according to a gamma distribution. Fitting the model to experimental data, they obtained new estimates for the viral clearance rate constant, c [13]. As did Herz et al., they assumed the drug to be completely effective and observed no change in the estimated value for δ. Grossman et al.[9] developed a related non-linear delay model, in which the assumption that a productively infected cell died by a first order process, was replaced by introducing a delay in the cell death process. Patrick et al.[14] extend the development of delay models of HIV-1 infection and treatment to the general case of combination antiviral therapy that is less than completely efficacious.

In this paper, we shall investigate the viral models with delay. The model can be written as the following form:

$$\begin{aligned} \dot{T} &= s - dT + aT(1 - T/T_{\max}) - \beta TV \\ \dot{I} &= \beta_1 T(t-\tau)V(t-\tau) - \delta I \\ \dot{V} &= pI - cV, \end{aligned} \tag{1.1}$$

where T is the number of target cells, I is number of infected cells, V is the viral load of the virions, s represents the rate at which new T cells are created from sources within the body, such as the thymus, a is the maximum proliferation rate of target cells. $T_{\max}$ is the T population density at which proliferation shuts off. In model (1.1), d is death rate of the T cells, $\beta_1 = \beta e^{-m\tau}$, β is the infection rate constant, the term $e^{-m\tau}$ accounts for cells that are infected at time t but die before becoming productively infected τ time units later. δ is the death rate of infective cells, p is the reproductively rate of the infected cell, and p/δ is the total number of virions produced by a productively infected cell during its lifetime, c is the clearance rate constant of virions.

This paper is organized as follows. In the following three sections, we always assume that $\beta_1 = \beta$. In section 2, we obtain the existence and local stability of boundary and positive equilibria, and determine conditions for which the system enters a Hopf-type bifurcation. Section 3 gives the global stability of boundary equilibria and permanence of system. In section 4, we obtain the condition for the existence of the periodic solution of system. In section 5, we try to interpret our mathematical results in terms of their biological implication and formulate our conclusion. We also point out some future research directions.

2. Equilibria, local stability, and Hopf bifurcation

We begin by presenting certain notations that will be used throughout this paper. Let $C([-\tau,0],R^3_+)$ denote the set of continuous functions mapping $[-\tau,0]$ into R^3_+. For vectors x and y in R^3_+, the inequality $x \le y$ means that $x_i \le y_i$ holds for all i. For elements φ and ψ in $C([-\tau,0],R^3_+)$, the inequality $\varphi \le \psi$ means that $\varphi_i(\theta) \le \psi_i(\theta)$, $\theta \in [-\tau,0]$, for all i. For biological reason, we always assume that the initial data (ψ, ϕ_1, ϕ_2) for system (1.1) satisfy $(\psi, \phi_1, \phi_2) \in C([-\tau, 0], R^3_+)$. If $(T(t), I(t), V(t))$ is a solution of system (1.1) through (ψ, ϕ_1, ϕ_2) at $t = 0$ with $\psi(0) > 0, \phi_1(0) > 0, \phi_2(0) > 0$, it is easy to verify $(T(t), I(t), V(t))$ is positive on the maximum existence interval of solution. Such solution will be called as positive solutions.

We consider the following model with time delay

$$\begin{aligned} \dot{T} &= s - dT + aT(1 - T/T_{\max}) - \beta TV \\ \dot{I} &= \beta T(t-\tau)V(t-\tau) - \delta I \\ \dot{V} &= pI - cV \end{aligned} \tag{2.1}$$

The possible non-negative equilibia of system (2.1) are $E_1(\hat{T}, 0, 0)$, $E_2(\bar{T}, \bar{I}, \bar{V})$, where

$$\hat{T} = \frac{T_{\max}}{2a}\left[a - d + \sqrt{(a-d)^2 + 4as/T_{\max}}\right], \quad \bar{T} = \frac{c\delta}{p\beta}, \quad \bar{T} < \hat{T}$$

$$\bar{I} = \frac{1}{\delta}[s - d\bar{T} + a\bar{T}(1 - \bar{T}/T_{\max})], \quad \bar{V} = \frac{p}{c\delta}[s - d\bar{T} + a\bar{T}(1 - \bar{T}/T_{\max})]$$

Let

$$R_0 = \frac{\hat{T}}{\bar{T}}$$

It is well-known the importance of the value, R_0, which is called as the basic reproductive ratio of system (2.1). Thus, the basic reproductive ratio, R_0 determines the dynamical properties of system (2.1) over a long period of time.

Now, we will begin to analysis the geometric properties of the equilibria of system (2.1).

Let $E^*(T^*, I^*, V^*)$ be any arbitrary equilibrium. Then the characteristic equation about E^* is given by

$$\det \begin{vmatrix} a - d - 2aT^*/T_{\max} - \beta V^* - \lambda & 0 & -\beta T^* \\ \beta V^* e^{-\lambda\tau} & -\delta - \lambda & \beta T^* e^{-\lambda\tau} \\ 0 & p & -c - \lambda \end{vmatrix} = 0. \tag{2.2}$$

For equilibrium $E_1(\hat{T}, 0, 0)$, (2.2) reduces to

$$\left(\lambda + \sqrt{(a-d)^2 + 4as/T_{\max}}\right)(\lambda^2 + (c+\delta)\lambda + c\delta - \beta p\hat{T}e^{-\lambda\tau}) = 0. \tag{2.3}$$

When $\tau = 0$, $E_1(\hat{T}, 0, 0)$ is asymptotically stable for $R_0 < 1$, is a saddle with $\dim W^s(E_1) = 2$, $\dim W^u(E_1) = 1$ for $R_0 > 1$. We also obtain: If $R_0 < 1$, for any time delay τ, $E_1(\hat{T}, 0, 0)$ is asymptotically stable; If $R_0 > 1$, $E_1(\hat{T}, 0, 0)$ is unstable.

For equilibrium $E_2(\bar{T}, \bar{I}, \bar{V})$, (2.2) reduces to

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 e^{-\lambda\tau} + b_4\lambda e^{-\lambda\tau} + b_5 = 0, \tag{2.4}$$

where

$$\begin{aligned} b_1 &= d - a + 2a\bar{T}/T_{\max} + \beta\bar{V} + c + \delta, \\ b_2 &= c\delta + (c+\delta)(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V}), \\ b_3 &= p\beta^2\bar{T}\bar{V} - p\beta\bar{T}(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V}), \\ b_4 &= -p\beta\bar{T}, \\ b_5 &= c\delta(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V}). \end{aligned}$$

When $\tau = 0$, (2.4) become as

$$\lambda^3 + b_1\lambda^2 + \bar{b}_2\lambda + \bar{b}_3 = 0,$$

where $\bar{b}_2 = (c+\delta)(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V})$, $\bar{b}_3 = p\beta^2\bar{T}\bar{V}$. At steady state,

$$s - d\bar{T} + a\bar{T}(1 - \bar{T}/T_{\max}) - \beta\bar{T}\bar{V} = 0,$$

then

$$d - a + 2a\bar{T}/T_{\max} + \beta\bar{V} = s/\bar{T} + a\bar{T}/T_{\max} > 0.$$

Hence, $b_1 > 0, \bar{b}_2 > 0, \bar{b}_3 > 0$,

$$\begin{aligned} b_1\bar{b}_2 - \bar{b}_3 = {} & (c+\delta)(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) \\ & - p\beta^2\bar{T}\bar{V}. \end{aligned}$$

If $\tau = 0$, by Routh-Hurwitz Criterion, we have the following theorem.

THEOREM 2.1. *If $\tau = 0$, $R_0 > 1$ and*

$$(c+\delta)(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) > p\beta^2\bar{T}\bar{V}, \tag{2.5}$$

then the positive equilibrium $E_2(\bar{T}, \bar{I}, \bar{V})$ is asymptotically stable.

For the parameters

$$\begin{aligned} & d = 0.01,\ \delta = 0.5,\ c = 10,\ a = 6.8, \\ & T_{\max} = 1300,\ s = 5,\ \beta = 0.0002,\ p = 1000, \end{aligned}$$

and the initial values are $T_0 = 1000, I_0 = 1, V_0 = 1$. The steady state becomes $E_2 = (25.00000000, 342.9615384, 34296.15384)$, which is asymptotically stable. When $\tau \neq 0$, we have the following Theorem 2.2

THEOREM 2.2. *Suppose that*
(i) $R_0 > 1$,
(ii) $(c+\delta)(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) > p\beta^2\bar{T}\bar{V}$,
(iii) $\beta\bar{V} > 2(s/\bar{T} + a\bar{T}/T_{\max})$.

Then as τ increases from zero, there is a value τ_0 such that the unique infected equilibrium E_2 is locally asymptotically stable when $\tau \in [0, \tau_0)$ and unstable when $\tau > \tau_0$. Further, system (2.1) undergoes Hopf bifurcation at E_2 when $\tau = \tau_0$.

Proof. If $\tau = 0$, we know that E_2 is asymptotically stable. Next we show that there is a unique pair of purely imaginary roots $\pm i\omega_0$ for characteristic equation (2.4) at positive equilibrium E_2.

If $\lambda = i\omega$, $\omega > 0$ is a root of (2.4), separating real and imaginary parts, we have the following:

$$\begin{aligned} b_1\omega^2 - b_5 &= b_3 \cos\omega\tau + b_4\omega \sin\omega\tau, \\ \omega^3 - b_2\omega &= -\, b_3 \sin\omega\tau + b_4\omega\cos\omega\tau. \end{aligned} \tag{2.6}$$

Squaring and adding both equation of (2.6) we finally have

$$\omega^6 + (b_1^2 - 2b_2)\omega^4 + (b_2^2 - 2b_1b_5 - b_4^2)\omega^2 + b_5^2 - b_3^2 = 0, \tag{2.7}$$

where

$$\begin{aligned} b_1^2 - 2b_2 &= (d - a + 2a\bar{T}/T_{\max} + \beta\bar{V})^2 + c^2 + \delta^2 > 0, \\ b_2^2 - 2b_1b_5 - b_4^2 &= (c^2 + \delta^2)(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V})^2 > 0, \\ b_5^2 - b_3^2 &= c^2\delta^2\beta\bar{V}[2(s/\bar{T} + a\bar{T}/T_{\max}) - \beta\bar{V}] < 0. \end{aligned}$$

Hence the conditions of the theorem imply that there is a unique positive ω_0 satisfying Eq.(2.7), that is, the characteristic equation (2.4) has a pair of purely imaginary roots of the form $\pm i\omega_0$. From (2.6) we know that τ_{0n} corresponding to ω_0 is

$$\tau_{0n} = \frac{1}{\omega_0} \arccos \frac{b_4\omega_0^4 + (b_1b_3 - b_2b_4)\omega_0^2 - b_3b_5}{b_3^2 + b_4^2\omega_0^2} + \frac{2n\pi}{\omega_0}, \quad n = 0, 1, 2, \cdots.$$

For $\tau = 0, E_2$ is stable. Hence by Butler's Lemma [15], E_2 remains stable for $\tau < \tau_0$, where $\tau_0 = \tau_{0n}$ as $n = 0$. We have now to show that

$$\left.\frac{d(Re\lambda)}{d\tau}\right|_{\tau=\tau_0} > 0.$$

This will signify that there exists at least one eigenvalue with positive real part for $\tau > \tau_0$. Moreover, the conditions for Hopf bifurcation [16] are then satisfied yielding the required periodic solution. Now differentiating (2.4) with respect τ, we get

$$[3\lambda^2 + 2b_1\lambda + b_2 - b_3\tau e^{-\lambda\tau} + b_4e^{-\lambda\tau} - b_4\tau\lambda e^{-\lambda\tau}]\frac{d\lambda}{d\tau} = e^{-\lambda\tau}(b_3\lambda + b_4\lambda^2).$$

This gives

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1} &= \frac{3\lambda^2+2b_1\lambda+b_2+e^{-\lambda\tau}[b_4-\tau(b_4\lambda+b_3)]}{\lambda(b_4\lambda+b_3)e^{-\lambda\tau}}\\ &= \frac{3\lambda^2+2b_1\lambda+b_2}{(b_4\lambda+b_3)\lambda e^{-\lambda\tau}}+\frac{b_4}{\lambda(b_4\lambda+b_3)}-\frac{\tau}{\lambda}\\ &= \frac{3\lambda^2+2b_1\lambda+b_2}{-\lambda(\lambda^3+b_1\lambda^2+b_2\lambda+b_5)}+\frac{b_4}{b_3\lambda}-\frac{b_4^2}{b_3(b_4\lambda+b_3)}-\frac{\tau}{\lambda}.\end{aligned}$$

Thus,

$$\begin{aligned}&\operatorname{sign}\left\{\frac{d(Re\lambda)}{d\tau}\right\}_{\lambda=i\omega_0}\\ &= \operatorname{sign}\left\{Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\right\}_{\lambda=i\omega_0}\\ &= \operatorname{sign}\left\{Re\left[\frac{3\lambda^2+2b_1\lambda+b_2}{-\lambda[\lambda^3+b_1\lambda^2+b_2\lambda+b_5]}\right]_{\lambda=i\omega_0}\right.\\ &\qquad\left.+Re\left[-\frac{b_4^2}{b_3(b_4\lambda+b_3)}\right]_{\lambda=i\omega_0}\right\}\\ &= \operatorname{sign}\left[\frac{(b_2-3\omega_0^2)(b_2-\omega_0^2)+2b_1(b_1\omega_0^2-b_5)}{(b_2\omega_0-\omega_0^3)^2+(b_1\omega_0^2-b_5)^2}-\frac{b_4^2}{b_3^2+b_4^2\omega_0^2}\right]\\ &= \operatorname{sign}\left[\frac{P}{Q}\right],\end{aligned}$$

where

$$\begin{aligned}P &= 2b_4^2\omega_0^6+(3b_3^2+b_4^2(b_1^2-2b_2))\omega_0^4+2b_3^2(b_1^2-2b_2)\omega_0^2\\ &\quad+b_3^2(b_2^2-2b_1b_5)-b_4^2b_5^2,\\ Q &= (b_3^2+b_4^2\omega_0^2)[(b_2\omega_0-\omega_0^3)^2+(b_1\omega_0^2-b_5)^2].\end{aligned}$$

Since

$$b_1^2-2b_2>0,\ b_3^2(b_2^2-2b_1b_5)-b_4^2b_5^2>b_5^2(b_2^2-2b_1b_5-b_4^2)>0,$$

we have

$$\left.\frac{d(Re\lambda)}{d\tau}\right|_{\tau=\tau_0,\omega=\omega_0}>0.$$

Therefore, the transversality condition holds and hence Hopf bifurcation occurs at $\omega=\omega_0, \tau=\tau_0$. This completes the proof. □

REMARK. It must be pointed out that Theorem 2.2 cannot determine the stability of bifurcation periodic orbits, that is, the periodic solutions may exist either for $\tau > \tau_0$ or for $\tau < \tau_0$, near τ_0. Further, we can investigate the stability of bifurcating periodic orbits by analyzing higher-order terms. The calculation is very complex and the method is trivial, so we omit it. The time delay induces instability and bifurcation but there is no switching of stability.

For the parameters

$$d = 0.01, \ \delta = 0.4, \ c = 3, \ a = 0.8,$$
$$T_{\max} = 1300, \ s = 4, \ \beta = 0.0002, \ p = 1000.$$

Hence, the conditions of Theorem 2.2 are satisfied, and

$$E_2 = (6.000000000, 21.79461538, 7264.871795),$$
$$\omega_0 = 0.2257505045, \ \tau_0 = 8.624589426.$$

(a) $\tau = 8.5, \tau < \tau_0$. In this case, E_2 is a stable spiral point.

(b) By Theorem 2.2, a Hopf bifurcation occurs when $\tau = \tau_0$, the equilibrium E_2 loses its stability and a periodic solution bifurcates from the equilibrium E_2 exists for $\tau > \tau_0$. We let $\tau = 8.7$. Two trajectories are shown, one with increasing and the other with decreasing amplitude, hence the bifurcation is supercritical and the bifurcating periodic solution is orbitally asymptotically stable.

By a similar arguments as those in the proof of Theorem 2.2 we obtain

THEOREM 2.3. *Suppose that*

(i) $R_0 > 1$,

(ii) $(c+\delta)(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) > p\beta^2\bar{T}\bar{V}$,

(iii) $\beta\bar{V} < 2(s/\bar{T} + a\bar{T}/T_{\max})$.

Then the infected steady state E_2 of the system (2.1) *is absolutely stable; that is, E_2 is asymptotically stable for all $\tau \geq 0$.*

For the parameters $d = 0.01, \delta = 1, c = 10, a = 9, T_{\max} = 1300, s = 4, \beta = 0.00002, p = 1000$, we can obtain that the infected steady state E_2 of the system (2.1) is absolutely stable; that is, E_2 is asymptotically stable for all $\tau \geq 0$.

3. Global stability results and permanence

Standard and simple arguments shows that solution of the system (2.1) always exist and stay positive. Indeed, as is obvious for system

(2.1), we have

$$\lim_{t\to+\infty} \sup T(t) \le \hat{T} = \frac{T_{\max}}{2a}\left[a - d + \sqrt{(a-d)^2 + 4as/T_{\max}}\right].$$

Then there is a $t_1 > 0$ such that for any sufficiently small $\epsilon > 0$, we have

$$T(t) \le \hat{T} + \epsilon, \quad \text{for } t > t_1.$$

THEOREM 3.1. *There is an $M > 0$ such that, for any positive solution $(T(t), I(t), V(t))$ of system (2.1),*

$$I(t) < M, \quad V(t) < M, \quad \textit{for all large } t.$$

Proof. Set $V_1(t) = T(t-\tau) + I(t)$. Calculating the derivative of V_1 along the solutions of system (2.1), we find

$$\begin{aligned}\dot{V}_1(t) &= s - dT(t-\tau) + aT(t-\tau)(1 - T(t-\tau)/T_{max}) - \delta I \\ &= -dT(t-\tau) - \delta I + aT(t-\tau) - a/T_{max}T^2(t-\tau) + s \\ &\le -hV_1(t) + M_0,\end{aligned}$$

where $M_0 = (T_{\max}a^2 + 4as)/4a$, $h = \min(d, \delta)$. Recall that $T(t) \le \hat{T} + \epsilon$ for all $t > t_1$. Then there exists an M_1, depending only on the parameters of system (2.1), such that $V_1(t) < M_1$, for $t > t_1$. Then $I(t)$ has an ultimately above bound. It follows from the third equation of (2.1) that $V(t)$ has an ultimately above bound, say, their maximum is an M. Then the assertion of Theorem 2.1 now follows and the proof is complete. This shows that system (2.1) is dissipative.

Define

$$\Omega = \{(T, I, V) : 0 \le T \le \hat{T}, 0 \le I, V \le M\}.$$

In the following we shall prove that the unstability of E_1 implies that system (2.1) is permanent. Before starting our theorem, we give some definitions:

DEFINITION 3.1. System (2.1) is said to be uniformly persistent if there is an $\eta > 0$ (independent of the initial data) such that every solution $(T(t), I(t), V(t))$ with initial condition of system (2.1) satisfies

$$\lim_{t\to+\infty} \inf T(t) \ge \eta, \quad \lim_{t\to+\infty} \inf I(t) \ge \eta, \quad \lim_{t\to+\infty} \inf V(t) \ge \eta.$$

DEFINITION 3.2. System (2.1) is said to be permanent if there exists a compact region $\Omega_0 \in \text{int}\Omega$ such that every solution of (2.1) with initial condition will eventually enter and remain in region Ω_0.

Clearly for a dissipative system uniform persistence is equivalent to permanence.

THEOREM 3.2. *System* (2.1) *is permanent provided* $R_0 > 1$.

In order to prove Theorem 3.2, We present the persistence theory for infinite dimensional system from paper [17]. Let X be a complete metric space. Suppose that $X^0 \subset X, X_0 \subset X, X^0 \cap X_0 = \emptyset$. Assume that $Y(t)$ is a C_0 semigroup on X satisfying

$$\begin{aligned} Y(t) &: X^0 \to X^0, \\ Y(t) &: X_0 \to X_0. \end{aligned} \tag{3.1}$$

Let $Y_b(t) = Y(t)|_{X_0}$ and let A_b be the global attractor for $Y_b(t)$.

LEMMA 3.1. *Suppose that* $Y(t)$ *satisfies* (3.1) *and we have the following :*

(i) *there is a* $t_0 \geq 0$ *such that* $Y(t)$ *is compact for* $t > t_0$*;*
(ii) $Y(t)$ *is point dissipative in* X*;*
(iii) $\overline{A}_b = \cup_{x\in A_b}\omega(x)$ *is isolated and has an acyclic covering* $\overline{M}$, *where*

$$\overline{M} = \{M_1, M_2, \cdots, M_n\};$$

(iv) $W^s(M_i) \cap X^0 = \emptyset$, *for* $i = 1, 2, \cdots, n$.

Then X_0 *is a uniform repellor with respect to* X^0, *i.e., there is an* $\epsilon > 0$ *such that for any* $x \in X^0$, $\liminf_{t\to+\infty} d(Y(t)x, X_0) \geq \epsilon$, *where* d *is the distance of* $Y(t)x$ *from* X_0.

We are now able to prove Theorem 3.2.

Proof of Theorem 3.2. We begin by showing that the boundary planes of R^3_+ repel the positive solutions of system (2.1) uniformly. Let us define

$$C_0 = \{(\psi, \phi_1, \phi_2) \in C([-\tau, 0], R^3_+) : \psi(\theta) \neq 0, \\ \phi_1(\theta) = \phi_2(\theta) = 0, \theta \in [-\tau, 0]\}.$$

If C^0=int$C([-\tau, 0], R^3_+)$, it suffices to show that there exists an $\epsilon_0 > 0$ such that for any solution u_t of system (2.1) initiating from C^0, $\lim_{t\to+\infty}$int$d(u_t, C^0) \geq \epsilon_0$. To this end, we verify below that the conditions of Lemma 3.1 are satisfied. It is easy to see that C^0 and C_0 are positively invariant. Moreover, conditions (i) and (ii) of Lemma 3.1 are clearly satisfied. Thus we only need to verify the conditions (iii) and (iv). There is a constant solution E_1 in C_0, to $T(t) = \hat{T}, I(t) = V(t) = 0$. If $(T(t), I(t), V(t))$ is a solution of system (2.1) initiating from C_0 then $T(t) \to \hat{T}, I(t) \to 0, V(t) \to 0$, as $t \to +\infty$. It is obvious that E_1 is isolated invariant. Now, we show that $W^s(E_1) \cap C^0 = \emptyset$. Assuming the contrary, then there exists a positive solution $(\tilde{T}(t), \tilde{I}(t), \tilde{V}(t))$ of system (2.1) such that

$$(\tilde{T}(t), \tilde{I}(t), \tilde{V}(t)) \to (\hat{T}, 0, 0) \quad \text{as} \quad t \to +\infty.$$

Choosing $\xi > 0$ small enough such that

$$\hat{T} - \xi > \bar{T}.$$

Let $t_0 > 0$ be sufficiently large such that

$$\hat{T} - \xi < \tilde{T}(t) < \hat{T} + \xi, \quad \text{for} \quad t \geq t_0 - \tau.$$

Then we have, for $t \geq t_0$,

$$\begin{aligned} \tilde{I}'(t) &\geq \beta(\hat{T} - \xi)\tilde{V}(t - \tau) - \delta \tilde{I}(t), \\ \tilde{V}'(t) &= p\tilde{I}(t) - c\tilde{V}(t). \end{aligned} \tag{3.2}$$

Let us consider the matrix A_ξ define by

$$A_\xi = \begin{pmatrix} -\delta & \beta(\hat{T} - \xi) \\ p & -c \end{pmatrix}.$$

Since A_ξ admits positive off-diagonal elements, Perron-Frobenius theorem implies that there is a positive eigenvector v for the maximum eigenvalue α of A_ξ. Moreover, by a simple computation we see that the maximum eigenvalue α is positive, since we have $p\beta(\hat{T} - \xi) > c\delta$. Let us consider

$$\begin{aligned} \dot{I}(t) &= \beta(\hat{T} - \xi)V(t - \tau) - \delta I(t), \\ \dot{V}(t) &= pI(t) - cV(t). \end{aligned} \tag{3.3}$$

Let $v = (v_1, v_2)$ and $l > 0$ be small enough such that

$$\begin{aligned} lv_1 &< \tilde{I}(t_0 + \theta) \quad \text{for} \quad \theta \in [-\tau, 0], \\ lv_2 &< \tilde{V}(t_0 + \theta) \quad \text{for} \quad \theta \in [-\tau, 0]. \end{aligned}$$

If $(I(t), V(t))$ is a solution of system (3.3) satisfying $I(t) = lv_1, V(t) = lv_2$, for $t_0 - \tau \leq t \leq t_0$, since the semiflow of (3.3) is monotone and $A_\xi v > 0$, it follows from papers [18, 19] that $I(t)$ and $V(t)$ are strictly increasing and $I(t) \to +\infty, V(t) \to +\infty$ as $t \to +\infty$. Note that $\tilde{I}(t) \geq I(t), \tilde{V}(t) \geq V(t)$ for $t > t_0$. We have $\tilde{I}(t) \to +\infty, \tilde{V}(t) \to +\infty$ as $t \to +\infty$. This contradicts Lemma 2.3. The above assertion is thus proved. At this time, we are able to conclude from Theorem 3.1 that C_0 repels the positive solutions of (2.1) uniformly. Incorporating into Lemma 3.1 and Theorem 3.1, we know that system (2.1) is permanent. □

By a similar arguments as those in the proof of Theorem 3.2 we obtain

THEOREM 3.3. *Assume* $R_0 < 1$ *in system* (2.1). *Then the equilibrium* $E_1(\hat{T}, 0, 0)$ *is globally asymptotically stable.*

4. Existence of a stable periodic orbit

Our main result below gives sufficient conditions that almost every solution is asymptotically periodic.

THEOREM 4.1. *Suppose that*

(i) $R_0 > 1, \tau = 0$,

(ii) $(c+\delta)(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) < p\beta^2\bar{T}\bar{V}$.

Then the system (2.1) *exists an orbitally asymptotically stable periodic solution.*

Proof. A change of variables $z_1 = -T, z_2 = I$ and $z_3 = -V$ transforms system (2.1) into

$$\begin{aligned} \dot{z}_1 &= -s - dz_1 + az_1(1 + z_1/T_{\max}) + \beta z_1 z_3, \\ \dot{z}_2 &= \beta z_1 z_3 - \delta z_2, \\ \dot{z}_3 &= -pz_2 - cz_3. \end{aligned} \tag{4.1}$$

If we write (4.1) as $\dot{z} = f(z)$, Jacobian matrix of f at z is as follows

$$J(z) = \begin{pmatrix} -d + a + 2a/T_{\max}z_1 + \beta z_3 & 0 & \beta z_1 \\ \beta z_3 & -\delta & \beta z_1 \\ 0 & -p & -c \end{pmatrix}$$

If $E = \{(z_1, z_2, z_3) : z_1 < 0, z_2 > 0, z_3 < 0\}$, $J(z)$ has non-positive off-diagonal elements at each point of E. Let $z_1^* = -\bar{T}, z_2^* = \bar{I}$ and $z_3^* = -\bar{V}$. It is obvious that (z_1^*, z_2^*, z_3^*) is the unique equilibrium of system (4.1). Since the inequality (2.5) is reversed, the analysis above shows that (z_1^*, z_2^*, z_3^*) is unstable and $\det J(z^*) < 0$. Moreover, since system (2.1) is permanent, there exists a compact subset B of E such that for each $z_0 \in E$, there exists a $t(z_0) > 0$ such that $z(t, z_0) \in B$ for all $t \geq t(z_0)$. Consequently, by Theorem 1.2 of paper [20], system (2.1) has an orbitally asymptotically stable periodic solution. The assertion of Theorem 4.1 now follows and proof is completed.

EXAMPLE. Let us consider the following model

$$\begin{aligned} \dot{T} &= 5 - 0.01T + 8T(1 - T/1300) - 0.0002TV \\ \dot{I} &= 0.0002TV - 0.5I \\ \dot{V} &= 1000I - 9V \end{aligned} \tag{4.2}$$

By applying Theorem 4.1 to system (4.2) we see that there exists an orbitally asymptotically stable periodic solution.

5. Discussion

We obtained a restriction on the number of viral particles released per infectious cell in order for infection to be sustained. Under this restriction, the system has a positive equilibrium-the infected steady state. By stability analysis we obtained sufficient conditions on the parameters for the stability of the infected steady state. We also obtained the conditions for the system exists an orbitally asymptotically stable periodic solution. Biologically, it implies that the some parameter values can cause the cell and virus population to fluctuate.

We introduced a time delay into the model which describes the time between infection of a $CD4^+$ T-cell and the emission of viral particles on the cellular level. The same restriction on the number of viral particles released per infectious cell is required. By analyzing the transcendental characteristic equation, we analytically derived stability conditions for the infected steady state in terms of the parameters and independent of the delay. Using the given parameters values, we found that all the conditions are satisfied. Thus, the infected steady state is stable, independent of the size of the delay, though the time delay does cause transient oscillations in all components. Biologically, it implies that the intercellular delay can cause the cell and virus population to fluctuate in the early stage of infection, in a longer term they will converge to the infected steady state values.

To incorporate the intracellular phase of the virus life-cycle, we assume that virus production lags by a delay τ behind the infection of a cell. This implies that recruitment of virus-producing cells at time t is not given by the density $\beta T(t-\tau)V(t-\tau)$ of newly infected cells as in (2.1), but rather by the density of cells that were newly infected at time $t-\tau$ and are still alive at time t. If we assume a constant death rate m for infected but not yet virus-producing cells, the probability of surviving from time $t-\tau$ to time t is just $e^{-m\tau}$. Thus the refined model can be written as (1.1). Hence, we have the following system

$$
\begin{aligned}
\dot{T} &= s - dT + aT(1 - T/T_{\max}) - \beta TV, \\
\dot{I} &= \beta e^{-m\tau} T(t-\tau)V(t-\tau) - \delta I, \qquad (5.1)\\
\dot{V} &= pI - cV.
\end{aligned}
$$

In the following, we always assume $\beta_1 = \beta e^{-m\tau}$ and $R_0 > 1$. We should study the stability of positive equilibrium as τ increase. We know that $\bar{T}, \bar{I}, \bar{V}$ are dependent on τ, the characteristic equation (2.4) gives the form of the following:

$$P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0, \tag{5.2}$$

where

$$\begin{aligned}
P(\lambda, \tau) &= \lambda^3 + b_1(\tau)\lambda^2 + b_2(\tau)\lambda + b_5(\tau),\\
Q(\lambda, \tau) &= b_3(\tau) + b_4(\tau)\lambda,\\
b_1(\tau) &= d - a + 2a\bar{T}/T_{\max} + \beta\bar{V} + c + \delta,\\
b_2(\tau) &= c\delta + (c + \delta)(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V}),\\
b_3(\tau) &= p\beta\beta_1\bar{T}\bar{V} - p\beta_1\bar{T}(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V}),\\
b_4(\tau) &= -p\beta_1\bar{T},\\
b_5(\tau) &= c\delta(d - a + 2a\bar{T}/T_{\max} + \beta\bar{V}).\\
\bar{T} &= \frac{c\delta}{p\beta_1}, \quad \bar{I} = \frac{\beta_1}{\beta\delta}[s - d\bar{T} + a\bar{T}(1 - \bar{T}/T_{\max})],\\
\bar{V} &= \frac{p\beta_1}{\beta c\delta}[s - d\bar{T} + a\bar{T}(1 - \bar{T}/T_{\max})].
\end{aligned}$$

Because realistically constructing model often leads to intractable mathematics, there are a few results on this kind of transcend equation (5.2) which only obtained a region in parameters space where all roots have negative real parts. This effectively means that one cannot compute exactly the values of τ at which stability switches occur. Beretta and Kuang[21] have developed a systematic approach to studying the difficult characteristic equations arising from such system. Their approach is a computationally assisted one, requiring the plotting of accurate graphs of certain functions. One cannot in practice compute the stability switches analytically. We will summarize their technique as it applies to our particular problem in the future work.

By analogous analysis, we know that except for the dynamical behavior of positive equilibrium, other results such as boundedness of solution, global stability of boundary equilibrium and permanence on system (1.1) with $\beta_1 = \beta e^{-m\tau}$ are the same as those on system (2.1).

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