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The qualitative properties of mathematical models for HIV infection

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Qualitative analysis for the model of HIV infection *in vivo* presented by Perelson and Nelson are developed. The local stability analysis is done for the interior equilibrium, and it is shown that, for some paramter value, the interior equilibrium can be unstable and a Hopf bifurcation can occur. It is shown that the boundary equilibrium is globally asymptotically stable. Last, it is shown that this system is permanent.

Keywords: HIV, Mathematical model, Stability, Liapunov function

1 Introduction

Dynamics of Human immunodeficiency virus (HIV) *in vivo* has been studied using mathematical models in the form of ordinary differential equations. Many new insights about AIDS are found by researches using mathematical models (for example, Ho *et al.*[2], Wei *et al.*[7]).

In a review paper by Perelson and Nelson [5], the researches of Perelson and his colleague are reviewed. A model which describes the state before therapy and two models under the treatment by the drug therapies, reverse transcriptase (RT) inhibitor and protease (PT) inhibitor, are presented and these models are analyzed. These models are non-linear and of three or fourth order, and it is difficult to write down solutions analytically. They assume that the density of uninfected cells for a short period are constant. Under this assumption, the systems are linear, and it is possible to write the solutions explicitly. They estimate the parameters in the systems using the above approximation. They state only a little concerning the analysis in the general situation that the density of uninfected T cells is not constant.

In this paper, we study the qualitative property of the models in Perelson *et al.* [5]. Especially we investigate the local stability of the equilibrium, the global stability of the boundary equilibrium, the existence of the attractor and permanence. There exist two equilibria for the model in this paper. One is the boundary equilibrium, whose components are zero except T component, and this expresses the disease free state. Another is the interior equilibrium, whose components are all positive, and this expresses the state at which the disease is persistent. By the analysis of the boundary equilibrium we can obtain the condition that virus are eliminated by the drug therapy. The analysis of the global stability of the interior equilibrium is difficult, in general. Instead of global stability, we can show that the disease does not die out under the condition that the interior equilibrium exists in the interior of the first quadrant.

2 The models

We consider the model which describes the state before treatment, the model which describes the effect of the treatment by the RT inhibitor and the model which describes the effect of the treatment by the PT inhibitor.

For the convenience of the stability analysis of

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these models, we present a model of HIV infection following [5] which can be applicable to all three models by the choice of the parameters.

We call $CD4^+T$ cell T cell later. The model contains three variables: the density T of T cells, the density T^* of infected T cells and the density V of virus in blood.

For modeling, we assume as follows:

- The rate constant at which thymus produces T cells is constant.
- T cells proliferate. The rate constant at which T cells proliferate decrease following a linear function of T.
- The death rate of T-cells is proportional to the density of T cells.
- The probability that a virion contact a T-cell is proportional to the product of them.
- The death rate of infected cells is proportional to the density T^* of infected cells.
- The virus clearance rate is proportional to the density V of virus.

By these assumptions, we can write the model which describe the dynamics of T, T^*, and V ([5]):

$$\begin{aligned} \frac{dT}{dt} &= s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T - \alpha V T, \\ \frac{dT^*}{dt} &= \alpha V T - \delta T^*, \\ \frac{dV}{dt} &= \beta T^* - cV, \end{aligned} \tag{1}$$

where s denotes the rate at which thymus produces T cell, p denotes the rate at which T cells proliferate, $T_{\max}$ denotes the value of the density of T at which the proliferation of T cells stop, d_T denotes the death rate of T cells, α denotes the rate constant of infection, β denotes the rate constant of virus generation from infected cells and c denotes the clearance rate of virus in blood.

First we consider the state befere therapy. We suppose that the interior equilibrium exists. Put

$$\alpha = k, \qquad \beta = N\delta,$$

where k denotes the rate constant of infection before therapy, N denote the number of virion which each infected cell produces during its lifespan. Then (1) describes the state before therapy,

Next, we consider the state under the therapy by RT inhibitor. RT inhibitor blocks the new infection of virus on uninfected cells. the constant $\eta_{RT}(0 < \eta_{RT} \leq 1)$ denotes the effect of RT inhibiter. Putting

$$\alpha = (1 - \eta_{RT})k, \quad \beta = N\delta$$

in (1), the model expresses the state under the therapy by reverse transcriptase. We call this RT model.

Last we consider the state ounder the therapy by PT inhibitor. When PT inhibitor is treated, the infected cells produce non infectious virus instead of normal infectious virus. The virus created before therapy are infectious. V_I denotes the density of infectious virus, and V_{NI} denotes the density of non-infectious virus. A positive constant $\eta_{PI}(0 < \eta_{PI} \leq 1)$ expresses the efficiency of PT inhibitor. The model is expressed as follows ([5]):

$$\begin{aligned} \frac{dT}{dt} &= s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T - \alpha T V_I, \\ \frac{dT^*}{dt} &= \alpha T V_I - \delta T^*, \\ \frac{dV_I}{dt} &= \beta T^* - cV_I, \\ \frac{dV_{NI}}{dt} &= \gamma T^* - cV_{NI}, \end{aligned}$$

where

$$\alpha = k, \quad \beta = (1 - \eta_{PI})N\delta, \quad \gamma = \eta_{PI} N\delta.$$

We call this PT model. The variable V_{NI} is not contained without in the last equation. We may consider the reduced system containing only the equations for T, T^*, and V_I, and the qualitative analysis follows from that of system (1). We note that non-infectious virus are ultimately eliminated if infectious cells die out.

3 The local stability of the equilibrium

It is sufficient to investigate the system (1). The model (1) has the boundary equilibrium X $(\bar{T}, 0, 0)$ and the interior equilibrium Y $(T_{SS}, \bar{T}^*, \bar{V})$ where

$$\bar{T} = \frac{T_{\max}}{2p}\left\{p - d_T + \sqrt{(p - d_T)^2 + \frac{4sp}{T_{\max}}}\right\},$$

$$
\begin{aligned}
T_{\mathrm{SS}} &= \frac{\delta c}{\alpha\beta}, \\
\bar{V} &= \frac{s}{\alpha T_{\mathrm{SS}}} + \frac{p\left(1-\dfrac{T_{\mathrm{SS}}}{T_{\max}}\right) - d_T}{\alpha}, \qquad (2) \\
\bar{T}^* &= \frac{c\bar{V}}{\beta}.
\end{aligned}
$$

The equilibrium X is asymptotically stable if $\delta c - \alpha\beta\bar{T} > 0$, and unstable if $\delta c - \alpha\beta\bar{T} < 0$ ([5]).

For RT model, the boundary equilibrium is asymptotically stable if and only if

$$\eta_{RT} > 1 - \frac{c}{kN\bar{T}}.$$

For model PT model, the boundary equilibrium is asymptotically stable if and only if

$$\eta_{PI} > 1 - \frac{c}{kN\bar{T}}.$$

We investigate the stability of the interior equilibrium. The interior equilibrium exists in the interior of the first quadrant if and only if $0 < T_{\mathrm{SS}} < \bar{T}$, which means $\bar{V} > 0$. The characteristic equation of Jacobi matrix at the interior equilibrium point is

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0,$$

where

$$
\begin{aligned}
A &= \delta + c + \left(\frac{2pT_{\mathrm{SS}}}{T_{\max}}\right) - (p - d_T) + \alpha\bar{V} \\
B &= (\delta + c)\left\{\frac{2pT_{\mathrm{SS}}}{T_{\max}} - (p - d_T) + \alpha\bar{V}\right\} \\
C &= c\delta\alpha\bar{V}.
\end{aligned}
$$

By (2)

$$\alpha\bar{V} = \frac{s}{T_{\mathrm{SS}}} + p\,(1 - T_{\mathrm{SS}}T_{\max}) - d_T,$$

and using this we have,

$$
\begin{aligned}
A = &\quad \delta + c + \frac{pT_{\mathrm{SS}}}{T_{\max}} + \frac{s}{T_{\mathrm{SS}}}, \\
B = &\quad (\delta + c)\left(\frac{pT_{\mathrm{SS}}}{T_{\max}} + \frac{s}{T_{\mathrm{SS}}}\right). \\
C = &\quad c\delta\left(\frac{s}{T_{\mathrm{SS}}} + p\left(1 - \frac{T_{\mathrm{SS}}}{T_{\max}}\right) - d_T\right),
\end{aligned}
$$

By the Routh-Hurwitz criterion, if $A > 0$, $C > 0$ and $AB - C > 0$ then the real parts all roots of the characteristic polynomial are negative. Clearly, $A > 0$ and $C > 0$.

We calculate $AB - C$:

$$
\begin{aligned}
& AB - C \\
= \; & (\delta + c)^2\left(\frac{s}{T_{\mathrm{SS}}} + \frac{pT_{\mathrm{SS}}}{T_{\max}}\right) \\
& \cdot(\delta + c)\left(\frac{s}{T_{\mathrm{SS}}} + \frac{pT_{\mathrm{SS}}}{T_{\max}}\right)^2 \\
& - c\delta\left(\frac{s}{T_{\mathrm{SS}}} + p\left(1 - \frac{T_{\mathrm{SS}}}{T_{\max}}\right) - d_T\right) \\
= \; & (\delta^2 + c^2)\left(\frac{s}{T_{\mathrm{SS}}} + p\left(\frac{Tss}{T_{\max}}\right)\right) \\
& + (\delta + c)\frac{s^2}{T_{\mathrm{SS}}^2} + 2(\delta + c)\frac{ps}{T_{\max}} + \frac{(\delta + c)p^2(T_{\mathrm{SS}}^2)}{T_{\max}^2} \\
& + \frac{\delta cs}{T_{\mathrm{SS}}} + c\delta d_T + c\delta p\left(3\frac{T_{\mathrm{SS}}}{T_{\max}} - 1\right)
\end{aligned}
$$

Only the last term can be negative.

The following is an example of realistic parameter values (Perelson *et al.*[5])

$$
\begin{aligned}
& s = 10.0\mathrm{day}^{-1} \qquad p = 0.03\mathrm{day}^{-1} \\
& T_{\max} = 1500\mathrm{mm}^{-1} \qquad d_T = 0.02\mathrm{day}^{-1} \\
& \delta = 0.24\mathrm{day}^{-1} \qquad c = 2.4\mathrm{day}^{-1} \\
& k = 2.4 \times 10^{-5}\mathrm{mm}^3\mathrm{day}^{-1} \qquad N = 500 \quad (3)
\end{aligned}
$$

We use this parameter in system (1). We set $\alpha = k$ and $\beta = N\delta$. When the parameter values are near (3), $AB - C$ is positive. We indicate the graph of a numeric solution of (1) for the parameter at (3) in Fig 1. In this case, the interior equilibrium is asymptotically stable.

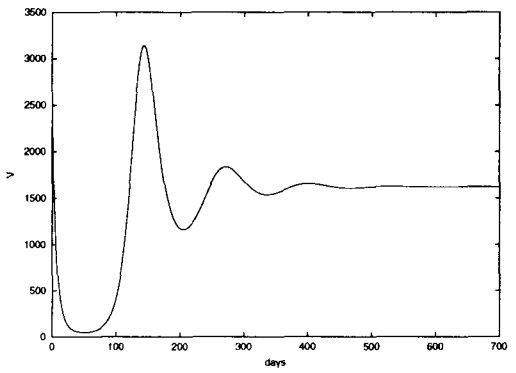

Figure 1: The graph of V at the parameter (3)

In Perelson *et al.* [5], the authors state that the interior equilibrium of this model is always asymptotically stable if it exists, but this statement is not correct. When we set $s = 0$ and $d_T = 0$ and then we have,

$$\begin{aligned} &AB - C \\ &= p\left(\left(\frac{Tss}{T_{\max}}\right)\right. \\ &\cdot \left.\left((\delta^2 + c^2) + (\delta + c)p\left(\frac{T_{\rm SS}}{T_{\max}}\right) + 3\delta c\right) - \delta c\right). \end{aligned}$$

We can conclude that $AB-C$ can be negative when $\frac{T_{\rm SS}}{T_{\max}}$, s and d_T are positive and sufficiently small. By the Theorem in Liu [3] a Hopf bifurcation occurs and the interior equilibrium becomes unstable. For a numerical analysis, we set

$$\begin{aligned} &s = 0.00001\text{day}^{-1} \qquad p = 1.0\text{day}^{-1} \\ &T_{\max} = 1500\text{mm}^{-1} \qquad d_T = 0.1\text{day}^{-1} \\ &\delta = 1.0\text{day}^{-1} \qquad c = 1.0\text{day}^{-1} \\ &k = 0.9\text{mm}^3\text{day}^{-1} \qquad N = 500. \end{aligned} \tag{4}$$

We use this parameter in system (1). We set $\alpha = k$ and $\beta = N\delta$. We indicate the graph of a numeric solution for the parameters (4) in fig 2, and the

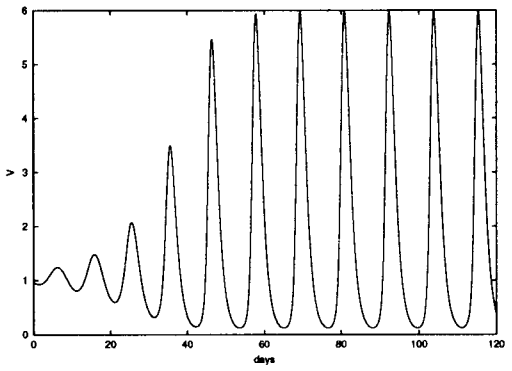

Figure 2: The graph of V at the parameter (4)

trajectory of the solution in T-V plane in Fig 3. These figure assure that this solution approach the limit cycle.

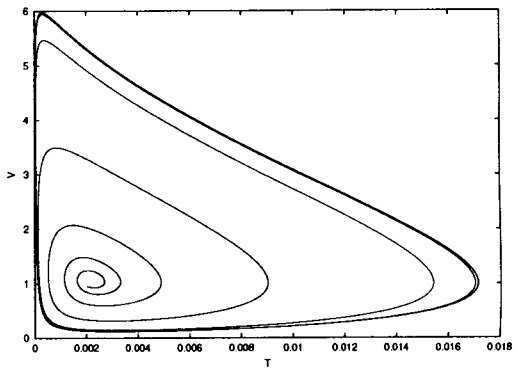

Figure 3: The graph in T-V plane at the parameter (4)

4 The global stability of the boundary equilibrium

In Section 3, we investigate the local stability of the equilibria. When an equilibrium is locally asymptotically stable, a solution approach the equilibrium if the initial point is located near to the equilibrium. But when the initial point is far from the equilibrium, we can not conclude that the solution approach the equilibrium from the local stability analysis. In this section, we prove that the boundary equilibrium is globally asymptotically stable, and show that if the boundary equilibrium is asymptotically stable, the virus are eliminated.

First, we show that there exists a compact region such that each solution is contained in it when t is sufficiently large. We sya that such a system has a compact attractor.

We fix initial values. The quadratic equation

$$s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T = 0$$

with respect to T has a positive solution $\bar{T}$ and a negative solution $-U$. Since $VT > 0$, we have

$$\frac{dT}{dt} < -p(T - \bar{T})(T + U).$$

Then there exists $M_1 > 0$ and t_1 such that we have $T(t) \leq M_1$ for every $t \geq t_1$. The constant M_1 is independent of initial values. Using this, if $t \geq t_1$ we have

$$s + pT\left(1 - \frac{T}{T_{\max}}\right) \leq M_2.$$

We add the equations of T and that of T^*, and hence we have

$$\frac{dT}{dt} + \frac{dT^*}{dt} = s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T - \delta T^*.$$

Putting $K = \min(d_T, \delta)$, for $t \geq t_1$ we have

$$\frac{dT}{dt} + \frac{dT^*}{dt} \leq M_2 - K(T + T^*).$$

Then there exists M_3 and $t_2 (> t_1)$ such that for every $t \geq t_2$ we have

$$T + T^* \leq M_3.$$

Then we have $T^* \leq M_3$ for $t \geq t_2$, and the constant M_3 is independent of the initial values. Last, for $t \geq t_2$ we have

$$\frac{dV}{dt} \leq M_3 - cV.$$

There exists $M_4 > 0$ and $t_3 (> t_2)$ such that for every $t \geq t_3$, we have $V(t) \leq M_4$, where the constant M_4 is independent of the initial values. But we note that t_3 does depend on the initial values.

Putting $M = \max(M_1, M_2, M_3, M_4)$ we have the following theorem.

Theorem

For the system (1), there exists a positive constant M which is independent of the choice of the initial values in the first quadrant such that

$$\limsup_{t\to\infty} T(t) \leq M, \tag{5}$$

$$\limsup_{t\to\infty} T^*(t) \leq M, \tag{6}$$

$$\limsup_{t\to\infty} V(t) \leq M. \tag{7}$$

We state the global stability of the boundary equilibrium for RT model and PT model.

(i) RT model:

$$\begin{aligned} \frac{dT}{dt} &= s + pT\left(1 - \frac{T}{T_{\max}}\right) \\ &\quad - d_T T - (1 - \eta_{RT})kTV \\ \frac{dT^*}{dt} &= (1 - \eta_{RT})kTV - \delta T^* \\ \frac{dV}{dt} &= N\delta T^* - cV. \end{aligned} \tag{8}$$

In this model, if $\eta_{RT} > 1 - \frac{c}{N k \bar{T}}$ the boundary equilibrium $(T, T^*, V) = (\bar{T}, 0, 0)$ is asymptotically stable. We construct a Liapunov function. We define W as follows:

$$W = \frac{T}{\bar{T}} - 1 - \log\frac{T}{\bar{T}} + w_1 T^* + w_2 V,$$

where w_1 and w_2 are positive number to be specified later.

We put $f(x) = x - 1 - \log x$. Then we have $f(1) = 0$ and

$$\begin{aligned} \frac{df(x)}{dx} &= 1 - \frac{1}{x} > 0 \qquad (x > 1), \\ \frac{df(x)}{dx} &= 1 - \frac{1}{x} < 0 \qquad (x < 1) \end{aligned}$$

and hence we have $f(x) \geq 0$. The equation $f(x) = 0$ holds if and only if $x = 1$. Using this we have

$$W \geq 0,$$

and $W = 0$ if and only if $(T, T^*, V) = (\bar{T}, 0, 0)$.

We differentiate W along the system (8), then we have

$$\begin{aligned} \frac{dW}{dt} &= \frac{T - \bar{T}}{T\bar{T}}\left\{s + pT\left(1 - \frac{T}{T_{\max}}\right)\right. \\ &\quad \left. - d_T T - (1 - \eta_{RT})kTV\right\} \\ &\quad + w_1\{(1 - \eta_{RT})kTV - \delta T^*\} \\ &\quad + w_2(N\delta T^* - cV). \end{aligned} \tag{9}$$

Since

$$s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T = -\frac{p}{T_{\max}}(T - \bar{T})(T + U),$$

we have

$$\begin{aligned} \frac{dW}{dt} &= -\frac{p}{T\bar{T}T_{\max}}(T - \bar{T})^2(T + U) \\ &\quad + kAVT + BT^* + CV, \end{aligned}$$

where

$$\begin{aligned} A &= w_1(1 - \eta_{RT}) - \frac{1 - \eta_{RT}}{\bar{T}} \\ B &= w_2 N\delta - w_1\delta \\ C &= (1 - \eta_{RT})k - cw_2. \end{aligned}$$

We determine w_1 and w_2 such that $\frac{dW}{dt} < 0$ holds for $(T, T^*, V) \neq (\bar{T}, 0, 0)$. We assume $A = 0$. Then we have

$$w_1 = \frac{1}{\bar{T}}. \tag{10}$$

Moreover we assume $B < 0$, $C < 0$, then we have

$$\frac{(1-\eta_{RT})k}{c} < w_2 < \frac{1}{\bar{T}N}. \tag{11}$$

Since $\eta_{RT} > 1 - \frac{c}{Nk\bar{T}}$, we may take w_2 satisfying (11). For such a choice of w_1 and w_2, we have

$$\frac{dW}{dt} \leq 0$$

and $\frac{dW}{dt} = 0$ if and only if $(T, T^*, V) = (\bar{T}, 0, 0)$. Therefore if $\eta_{RT} > 1 - \frac{c}{Nk\bar{T}}$, the equilibrium $(\bar{T}, 0, 0)$ is globally asymptotically stable.

(ii) PT inhibitor model:

$$\begin{aligned}
\frac{dT}{dt} &= s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T - kTV_I, \\
\frac{dT^*}{dt} &= kTV_I - \delta T^*, \\
\frac{dV_I}{dt} &= (1-\eta_{PI})N\delta T^* - cV_I, \\
\frac{dV_{NI}}{dt} &= \eta_{PI} N\delta T^* - cV_{NI}.
\end{aligned} \tag{12}$$

If $\eta_{PI} > 1 - \frac{c}{kN\bar{T}}$, the boundary equilibrium $(T, T^*, V_I, V_{NI}) = (\bar{T}, 0, 0, 0)$ is locally asymptotically stable. As in RT model, we construct Liapunov function. We put

$$W = \frac{T}{\bar{T}} - 1 - \log\frac{T}{\bar{T}} + w_1 T^* + w_2 V_I + w_3 V_{NI} \quad (w_1 > 0, w_2 > 0, w_3 > 0).$$

As in RT model, we have

$$W \geq 0,$$

and we have $W = 0$ only at the disease free equilibrium.

We differentiate W along (12), and we have

$$\begin{aligned}
\frac{dW}{dt} &= -\frac{P}{T\bar{T}T_{\max}}(T-\bar{T})^2(T+U) \\
&\quad + kAV_I T + BT^* + CV_I + DV_{NI},
\end{aligned}$$

where

$$\begin{aligned}
A &= w_1 - \frac{1}{\bar{T}} \\
B &= w_2(1-\eta_{PI})N\delta - w_1\delta + w_3\eta_{PI}N\delta \\
C &= k - cw_2 \\
D &= -w_3 c.
\end{aligned}$$

We determine w_1, w_2 and w_3 such that $\frac{dW}{dt} < 0$ for (T, T^*, V_I, V_{NI}). We assume $A = 0$, $D = 0$. Then we have

$$w_1 = \frac{1}{\bar{T}}, \quad w_3 = 0. \tag{13}$$

Moreover we assume $B < 0$, $D < 0$

$$\frac{k}{c} < w_2 < \frac{1}{(1-\eta_{PI})\bar{T}N}. \tag{14}$$

Since $c > (1-\eta_{PI})k\bar{T}$, we can choose w_2 satisfying (14). If w_1 and w_2 satisfy (13), (14) and w_3 is a sufficiently small positive number, we have

$$\frac{dW}{dt} \leq 0,$$

and $\frac{dW}{dt} = 0$ if and only if $(T, T^*, V_I, V_{NI}) = (\bar{T}, 0, 0, 0)$.

Then, if $c > (1-\eta_{PI})k\bar{T}$, the disease free equilibrium $(\bar{T}, 0, 0, 0)$ is globally asymptotically stable in the first quadrant.

5 Permanence

When the boundary equilibrium becomes unstable, the interior equilibrium appears and is asymptotically stable in many cases. But it is not easy to show that the interior equilibrium is globally asymptotically stable in general. The interior equilibrium can be unstable, and then the solution can oscillate.

But, it is important to consider the condition that the disease does not die out, which is called permanence of the system.

For the system

$$\begin{aligned}
\frac{dT}{dt} &= s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T - \alpha VT, \\
\frac{dT^*}{dt} &= \alpha VT - \delta T^*, \\
\frac{dV}{dt} &= \beta T^* - cV,
\end{aligned} \tag{15}$$

if we can take $\varepsilon > 0$ such that for every initial value in the first quadrant, we have

$$\begin{aligned}
\liminf_{t\to\infty} T(t) &\geq \varepsilon, \\
\liminf_{t\to\infty} T^*(t) &\geq \varepsilon, \\
\liminf_{t\to\infty} V(t) &\geq \varepsilon,
\end{aligned}$$

we call this system permanent (or uniformly persistent).

Some conditions which guarantee permanence are known. The review paper [1] is a good reference to permanence. We use a Theorem in Thieme [6] using acyclicity condition. The system has a compact attractor, as shown in Section (4), and there exists only one equilibrium in the boundary of the first quadrant. When the interior equilibrium exits, we can show that the boundary equilibrium is a repeller by the argument using Liapunov function. Then we have the following theorem.

Theorem
If the interior equilibrium exists, the system (15) is permanent.

6 Concluding remarks

In this paper, we investigate the qualitative property of the models presented in Perelson *et al.* [5]. We study the local stability of the equilibria, the global stability of the boundary equilibrium, and permanence.

We treat three model in Perelson *et al.* [5] in a unified form. In Perelson *et al.* [5], the local stability of the interior equilibrium of their models is not studied rigorously, and the authors state that the interior equilibrium is asymptotically stable if itexists. We show that the interior equilibrium is asymptotically stable for a set of realistic parameter set and it can be unstable for some parameter set. We show that a Hopf bifurcation can occur and show numerically that a solution approach the limit cycle. It is known that the interior equilibrium at the model where $p = 0$ is locally asymptotically stable if it exists. It is interesting that the dynamics of the proliferation of uninfected cells affect the stability of the interior equilibrium.

We show that the boundary equilibrium is globally asymptotically stable when the interior equilibrium does not exits. This means that the disease die out if the efficiency of the treatment becomes higher than some threshold value. Last, we show that the system is permanent if the boundary equilibrium is unstable, and that the disease does not die out.

In this paper, we do not analyze the effect of time delay from the infection of HIV into T a cell to the lysis of the T cell. The effect of the time delay is interesting, and we study this in future.

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