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GLOBAL STABILITY FOR A DYNAMIC MODEL OF HEPATITIS B WITH ANTIVIRUS TREATMENT

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Abstract An epidemic model on the basis of therapy of chronic Hepatitis B with antivirus treatment was introduced in this paper. By applying a comparison theorem and analyzing the corresponding characteristic equations, we obtain sufficient conditions on the parameters for the global stability of the disease-free state. It's proved that if the basic reproduction number $R_0 < 1$, the disease-free equilibrium is globally asymptotically stable. If $R_0 > 1$, the disease-free equilibrium is unstable and the disease is uniformly permanent. Moreover, if $R_0 > 1$, sufficient conditions are obtained for the global stability of the endemic equilibrium.

Keywords Global stability, comparison theorem, characteristic equations, basic reproduction number.

MSC(2000) 35Q, 34D, 92B.

1. Introduction

Immune system plays an important role in the process of anti-HBV infection. Many models considering immune response have been developed (see [11, 14]). An immune-response model is described by the following system:

$$\begin{aligned} \frac{dT}{dt} &= \lambda - (1-\eta)\beta TV - d_1 T, \\ \frac{dI}{dt} &= (1-\eta)\beta TV - \gamma IU - d_2 I, \\ \frac{dV}{dt} &= (1-\epsilon)pI - d_3 V, \\ \frac{dU}{dt} &= s + \alpha IU - d_4 U. \end{aligned} \tag{1.1}$$

As science develops, some kinds of drug have been introduced into the treatment of chronic hepatitis B. In this paper, we study the model considering antivirus treatment. The model is described below by the following system [3]:

$$\begin{aligned} \frac{dT}{dt} &= \lambda - (1-\eta(t))\beta TV - d_1 T, \\ \frac{dI}{dt} &= (1-\eta(t))\beta TV - \gamma IU - d_2 I, \\ \frac{dV}{dt} &= (1-\epsilon(t))pI - d_3 V, \\ \frac{dU}{dt} &= \frac{\sigma c(t)}{c(t)+Kc(t)} s + \alpha IU - d_4 U, \end{aligned} \tag{1.2}$$

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where

$$\eta(t) = \frac{c(t)}{c(t) + IC_{50}}, \quad \epsilon(t) = \frac{c(t)}{c(t) + M}$$

and

$$c(t) = \begin{cases} c(\tau) + \frac{t}{t_p}(c_{max} - c(\tau)), & 0 \le t < t_p, \\ c_{max}e^{-\omega(t-t_p)}, & t_p \le t \le \tau. \end{cases}$$

The parameters are described as follows:

$T(t)$-the density of uninfected target cells;
$I(t)$-the density of infected cells;
$V(t)$-the density of free virions;
$U(t)$-the density of immune cells;
λ-the generation rate of target cells;
$\eta(t)$-the efficacy of the drug in blocking new infection at t;
β-the rate of infection of new target cells;
d_1 - the death rate of each target cell;
γ-the rate that immune cells killing infected cells;
d_2-the death rate of infected cells;
$\epsilon(t)$-the efficacy of the drug in blocking viral production at t;
d_3-the natural death rate of virions;
σ-the effect that drug concentration has on the production of immune cells;
$c(t)$-the drug concentration at t;
M-the control variable;
K-the control variable;
p-the average rate of each infected cell producing virions;
α-the efficacy of infected cells in damaging immune cells;
IC_{50}-the drug concentration that makes the virus replication reduced to 50;
τ-the period of taking drugs;
t_p- the time when the blood concentration reaches a maximum;
c_{max}-the maximum value of the blood concentration;
ω-the rate of reduced blood concentration;
d_4-the natural death rate of immune cells;
s-the generation rate of immune cells.

The global stability of the disease-free equilibrium has been obtained in [6]. In this article, we prove the global stability of the disease-free equilibrium in another way introduced in [5]. The article is organized as follows. In section 2, we discuss the model under the assumption that the conditions are completely ideal. In section 3, we obtain some basic results and establish a comparison principle which play important roles in the discussion of global stability. In section 4, we introduce auxiliary systems and the corresponding characteristic equations. With the help of information of eigenvalues and Semigroup theory, we obtain the global stability of the disease-free equilibrium. In the last section, we find sufficient conditions for the global stability of the endemic equilibrium.

2. The Model

Assume that the conditions are completely ideal. That is the drug concentration being constant, then the model is described by the following system:

$$\begin{aligned} \frac{dT}{dt} &= \lambda - \beta TV - d_1 T, \\ \frac{dI}{dt} &= \beta TV - \gamma IU - d_2 I, \\ \frac{dV}{dt} &= pI - d_3 V, \\ \frac{dU}{dt} &= s + \alpha IU - d_4 U, \end{aligned} \tag{2.1}$$

with boundary conditions

$$T(0) \geq 0,\ U(0) \geq 0,\ I(0) \geq 0,\ V(0) \geq 0.$$

For system (2.1), it is straightforward to see the existence of a disease-free equilibrium

$$E_0(T_0, 0, 0, U_0) = (\frac{\lambda}{d_1}, 0, 0, \frac{s}{d_4}).$$

Next in order to find the positive endemic equilibrium state, we consider the following equations:

$$\begin{aligned} &\lambda - \beta TV - d_1 T = 0, \\ &\beta TV - \gamma IU - d_2 I = 0, \\ &pI - d_3 V = 0, \\ &s + \alpha IU - d_4 U = 0. \end{aligned} \tag{2.2}$$

From the third equation of (2.2), we have

$$V = \frac{pI}{d_3}. \tag{2.3}$$

Substitute (2.3) into the first equation of (2.2), we have

$$T = \frac{\lambda d_3}{\beta pI + d_1 d_3}. \tag{2.4}$$

From the last equation, we have

$$U = \frac{s}{d_4 - \alpha I}. \tag{2.5}$$

Substitute (2.3), (2.4) and (2.5) into the second equation of (2.2), then we have

$$f(I) := d_2 p\alpha\beta I^2 + \omega_1 I + \omega_2 = 0, \tag{2.6}$$

where

$$\begin{aligned} \omega_1 &= -\lambda p\alpha\beta - pd_2 d_4\beta + d_1 d_2 d_3\alpha - \gamma sp\beta, \\ \omega_2 &= \lambda pd_4\beta - d_1 d_3(d_2 d_4 + \gamma s). \end{aligned}$$

It is obvious that there exists a positive enedmic equilibrium if and only if there exists a positive solution on $(0, \frac{d_4}{\alpha})$. Note that

$$f(\frac{d_4}{\alpha}) = -\frac{\gamma s(pd_4\beta + d_1 d_3\alpha)}{\alpha} < 0,$$

we know when $\lambda > \frac{d_1 d_3(d_2 d_4+\gamma s)}{p d_4 \beta}$, (2.6) has a unique positive solution on $(0, \frac{d_4}{\alpha})$, and the equilibrium $E^*(T^*, I^*, V^*, U^*)$ satisfies (2.3), (2.4), (2.5), (2.6) and $0 < I^* < \frac{d_4}{\alpha}$. Furthermore, when $\lambda < \frac{d_1 d_3(d_2 d_4+\gamma s)}{p d_4 \beta}$, the positive solution does not exist.

Define the basic reproduction number R_0 as follows

$$R_0 = \frac{\lambda p d_4 \beta}{d_1 d_3(d_2 d_4 + \gamma s)}.$$

Next we will study the global stability of the disease-free equilibrium state.

3. Basic Results

Let us begin with considering the following linear non-autonomous ODE system

$$\dot{u} = A(t)u, \qquad u \in \mathbb{R}^n, \tag{3.1}$$

where $A(t) = [a_{ij}(t)]_{n\times n}$ for $t \in [0,T]$ and $a_{ij} \in L^1([0,T],\mathbb{R})$ and satisfies the conditions

$$a_{ij}(t) \geq 0 \ \text{ for } \ i \neq j, \ t \in [0,T]. \tag{3.2}$$

It is well known that (3.1) is a monotone system under the condition (3.2). That is let $u(t,u_0)$ be a solution of (3.1) with $u(0,u_0) = u_0$. Then for any $u \in \mathbb{R}^n, \bar{u}_0 \in \mathbb{R}^n, u_0 \geq \bar{u}_0 \longrightarrow u(t,u_0) \geq u(t,\bar{u}_0)$ for all $t \in [0,T]$. Through out this and next sections, for $u = (u_1 \cdots u_n)^T \in \mathbb{R}^n,\ v = (v_1 \cdots v_n)^T \in \mathbb{R}^n$, we write $u \geq v (u > v)$ if $u_i \geq v_i$ for $i = 1 \cdots n$ (if $u \geq v$ and $u \neq v$). In particular, if $a_{ij}(t)$ is strictly positive for $i \neq j$, then $u(t,u_0) > u(t,\bar{u}_0)$ for all $t \in [0,T]$.

Lemma 3.1. *(see [5]) Let $U(t), t \in [0,T]$ be the fundamental solution matrix of (3.1). That is, $U(0) = I$, where I is the identity matrix and $\dot{U}(t) = A(t)U(t)$. Then $U(t) : \mathbb{R}^n \to \mathbb{R}^n$ is a monotone operator for all $t \in [0,T]$.*

Let $F : \mathbb{R}^n \to \mathbb{R}^n$ such that $F(\cdot) \in L^1(\mathbb{R}^n, \mathbb{R}^n)$, and $F(\cdot)$ is continuous and increasing.

Let $g_i : \mathbb{R}^+ \to \mathbb{R}^n$ such that $g_i(\cdot) \in L^1(\mathbb{R}^+, \mathbb{R}^n)$ and $g_i(\cdot)$ is continuous.

Theorem 3.1. *(see [5]) Let $W_i : i = 1, 2$, be the solutions of the systems*

$$\begin{aligned} &\tfrac{dW_i(t)}{dt} = A(t)W_i(t) + F(W_i(t)) + g_i(t), \\ &W_1(0) \geq W_2(0) = P_0 \in \mathbb{R}^n. \end{aligned} \tag{3.3}$$

Suppose that $A(t)$ satisfies the assumptions (3.2) and $g_1(t) \geq g_2(t)$ for $t \geq 0$. Then

$$W_1(t) \geq W_2(t), \ \textit{for } t \geq 0.$$

Lemma 3.2. *(see [3]) Assume that $f : [0,+\infty] \to \mathbb{R}$ is bounded and $K \in L^1(0,+\infty)$, then*

$$\lim_{t\to+\infty} sup\{|\int_0^t K(s)f(t-s)ds|\} \leq |f|^\infty \, \|K\|_{L^1(0,+\infty)},$$

where

$$|f|^\infty = \lim_{t\to\infty} sup\{|f|\}.$$

Lemma 3.3. *All solutions of system* (2.1) *with initial value* $(T(0), I(0), V(0), U(0))$ *are positive for* $t > 0$*, where* $(T(0), I(0), V(0), U(0))$ *is nonnegative.*

Proof. Since $I = V = 0$ is a constant solution of the second and the third equations of system (2.1), by the uniqueness and continuity of the solutions for initial conditions, we get $I(t) > 0$ and $V(t) > 0$ for all $t > 0$. We prove that $T(t) > 0$. If it is not true, let τ be the first time such that $T(\tau) = 0$. From the first equation, we obtain $T'(\tau) = \lambda > 0$. This means $T(t) < 0$ for $t \in (\tau - \epsilon, \tau)$, where ϵ is the positive constant which is arbitrarily small. This is a contradiction. As the same reason, we get $U(t) > 0$ for all t. □

Theorem 3.2. *There exists an* $M > 0$*, such that all solutions of system* (2.1) *satisfy* $T(t), I(t), V(t), U(t) \leq M$ *for all large* t*.*

Proof. By Lemma 3.3 and the first equation of (2.1), we have

$$T' = \lambda - \beta TV - d_1 T \leq \lambda - d_1 T.$$

Therefore, there exists a t_1 and an $M_1 > 0$, such that $T \leq M_1$ for $t > t_1$.

Let $W = T + I$. Calculating the time derivative along system (2.1), we have

$$W' \leq \lambda - dW, \text{ where } d = \min\{d_1, d_2\}.$$

So there exists a t_2 and an M_2 such that

$$T + I \leq M_2, \text{ for } t > t_2.$$

Since $T \leq M_1$ for $t > t_1$, there exists an $M_3 > 0$, such that $I \leq M_3$ for $t > t_3$ where $t_3 = \max\{t_1, t_2\}$. Then $I(t)$ has an ultimately above bound. It follows from the last two equations of system (2.1) that $V(t)$ and $U(t)$ have ultimately above bounds. That is, there exists t_4, t_5 and $M_4 > 0, M_5 > 0$, such that $V(t) \leq M_4$ for $t > t_4$, $U(t) \leq M_5$ for $t > t_5$.

Let $M = \max\{M_1, M_2, M_3, M_4, M_5\} > 0,\ t = \max\{t_1, t_2, t_3, t_4, t_5\}$. Then we complete the proof. □

Remark 3.1. Theorem 3.2 shows that system (2.1) is dissipative.

Define

$$D = \{(T, I, V, U) \in \mathbb{R}^4_+,\ 0 \leqslant T, I, V, U \leqslant M\}.$$

Hence D is a positively invariant for system (2.1).

4. Global stability of the infection-Free Equilibrium

Let us consider an auxiliary system:

$$\begin{aligned} \tfrac{dT_*}{dt} &= \lambda - d_1 T, \\ \tfrac{dU_*}{dt} &= s - d_4 U, \end{aligned} \tag{4.1}$$

with boundary conditions

$$T_*(0) = T(0) \geq 0, \qquad U_*(0) = U(0) \geq 0. \tag{4.2}$$

It is easy to obtain the solutions of (4.1) and (4.2). That is

$$\begin{aligned} T_*(t) &= \tfrac{\lambda}{d_1} + (T(0) - \tfrac{\lambda}{d_1})e^{-d_1 t}, \\ U_*(t) &= \tfrac{s}{d_4} + (U(0) - \tfrac{s}{d_4})e^{-d_4 t}. \end{aligned} \tag{4.3}$$

Hence we obtain that

$$\begin{aligned} \lim_{t\to+\infty} T_*(t) &= T_0, \\ \lim_{t\to+\infty} U_*(t) &= U_0. \end{aligned} \tag{4.4}$$

Lemma 4.1. *Let $(T(t), I(t), V(t), U(t))$ be the nonnegative solution of system* (2.1)*, then there exists an $N > 0$, such that for all $t > N$*

$$T(t) \le T_0, \quad U(t) \ge U_0.$$

Proof. Comparing the equations for $T(t)$ and $U(t)$ in (2.1) with (4.1), and noticing that

$$-\beta TV \le 0, \qquad \alpha IU \ge 0$$

and

$$T_*(0) = T(0), \qquad U_*(0) = U(0).$$

From the comparison theorem - Theorem 3.1, we deduce that

$$T(t) \le T_*(t), \qquad U(t) \ge U_*(t).$$

From (4.4), we get that

$$\begin{aligned} \lim_{t\to+\infty} T(t) &\le \lim_{t\to+\infty} T_*(t) = T_0, \\ \lim_{t\to+\infty} U(t) &\ge \lim_{t\to+\infty} U_*(t) = U_0. \end{aligned}$$

Therefore, there exists an $N > 0$, such that for all $t > N$

$$T(t) \le T_0, \quad U(t) \ge U_0.$$

□

Now let us consider the linear system:

$$\begin{aligned} \tfrac{d\bar{I}}{dt} &= \beta T_0 \bar{V} - (\gamma U_0 + d_2)\bar{I}, \\ \tfrac{d\bar{V}}{dt} &= p\bar{I} - d_3\bar{V}, \end{aligned} \tag{4.5}$$

with boundary conditions

$$\bar{I}(0) = I(0), \qquad \bar{V}(0) = V(0).$$

We let

$$k^* = sup\{Rek : k \text{ is an eigenvalue of } (4.5)\},$$

where the eigenvalue is determined by the following problem:

$$\begin{aligned} \tfrac{d\bar{I}}{dt} &= \beta T_0 \bar{V} - (k + \gamma U_0 + d_2)\bar{I}, \\ \tfrac{d\bar{V}}{dt} &= P\bar{I} - (k + d_3)\bar{V}. \end{aligned} \tag{4.6}$$

Note that the eigenvalue problem corresponds a monotone linear system. Hence k^* is an eigenvalue of the problem (4.6), and the corresponding eigenfunctions are positive. The following theorem gives the necessary and sufficient condition for $k^* < 0$.

Theorem 4.1. *$k^* < 0$ if and only if $R_0 < 1$.*

Proof. By (4.5), we obtain the characteristic equation

$$k^2 + (\gamma U_0 + d_2 + d_3)k + \gamma U_0 d_3 + d_2 d_3 - \beta p T_0 = 0.$$

Note that

$$\gamma U_0 + d_2 + d_3 > 0,$$
$$\gamma U_0 d_3 + d_2 d_3 - \beta p T_0 = \frac{d_1 d_3 (d_2 d_4 + \gamma s) - \lambda p d_4 \beta}{d_1 d_4}.$$

Therefore we can clearly see that $k^* < 0$ if and only if $R_0 < 1$. □

Lemma 4.2. *Suppose that $R_0 < 1$, then all nonnegative solutions $(\bar{I}(t), \bar{V}(t))$ of (4.5) converges to zero as $t \longrightarrow +\infty$.*

Proof. (4.5) is a linear system which generates a strong continuous semigroup $T(t)$ such that

$$\begin{pmatrix} \bar{I}(t) \\ \bar{V}(t) \end{pmatrix} = T(t) \begin{pmatrix} \bar{I}_0 \\ \bar{V}_0 \end{pmatrix}$$

for $\bar{I}(t_0) = \bar{I}_0,\ \bar{V}(t_0) = \bar{V}_0$.

By theorem 3.2 and note that $R_0 < 1$ implies the leading eigenvalue $k^* < 0$. It follows that there are $M > 0$ and $\epsilon > 0$ such that

$$\left\| T(t) \begin{pmatrix} \bar{I}_0 \\ \bar{V}_0 \end{pmatrix} \right\|_{L^1} \leq M e^{-\epsilon t} \left\| \begin{pmatrix} \bar{I}_0 \\ \bar{V}_0 \end{pmatrix} \right\|_{L^1}.$$

Hence

$$\left\| T(t) \begin{pmatrix} \bar{I}_0 \\ \bar{V}_0 \end{pmatrix} \right\|_{L^1} \longrightarrow 0 \text{ as } t \to +\infty.$$

□

Corollary 4.1. *Under the assumption of $R_0 < 1$, if $(T(t), I(t), V(t), U(t))$ is a nonnegative solution of (2.1). Then*

$$\|(I(t), V(t))^T\|_{L^1} \longrightarrow 0 \text{ as } t \to +\infty.$$

Proof. By (4.5), the equation for $I(t), V(t)$ can be written as

$$\frac{dI}{dt} = \beta T_0 V - (\gamma U_0 + d_2) I + \beta(T - T_0))V - \gamma(U - U_0) I,$$
$$\frac{dV}{dt} = pI - d_3 V.$$

Noticing by Lemma 4.1,

$$T(t) \leq T_0, \quad U(t) \geq U_0, \quad \text{for } t > N.$$

Hence for $t > N$,

$$\beta(T - T_0)V - \gamma(U - U_0)I \leq 0.$$

Recall that

$$I(0) = \bar{I}(0), \quad V(0) = \bar{V}(0).$$

Then by applying Theorem 3.1, we conclude that

$$I(t) \leq \bar{I}(t), \quad V(t) \leq \bar{V}(t), \quad \text{for } t > N.$$

Corollary 4.1 immediately follows from Lemma 4.2. □

Next we study the asymptotical behavior of $T(t)$ and $U(t)$ in (2.1). We introduce the transform

$$\begin{aligned} \tilde{T}(t) &= T(t) - T_*(t), \\ \tilde{U}(t) &= U(t) - U_*(t), \end{aligned} \tag{4.7}$$

where T_* and U_* is the solution of (4.1). So T_* and U_* satisfy the equations

$$\begin{aligned} -\dot{T}_* + \lambda - d_1 T_* &= 0, \\ -\dot{U}_* + s - d_4 U_* &= 0. \end{aligned} \tag{4.8}$$

With (2.1), (4.7) and (4.8) we obtain the equations for $\tilde{T}(t)$ and $\tilde{U}(t)$ as

$$\begin{aligned} \tfrac{d\tilde{T}(t)}{dt} &= -d_1\tilde{T}(t) - \beta T(t)V(t), \\ \tfrac{d\tilde{U}(t)}{dt} &= -d_4\tilde{U}(t) + \alpha I(t)U(t), \end{aligned} \tag{4.9}$$

with the boundary condition

$$\tilde{T}(0) = \tilde{U}(0) = 0.$$

If we let $B=\begin{pmatrix} -d_1 & 0 \\ 0 & -d_4 \end{pmatrix}$,

$$W(t) = \begin{pmatrix} \tilde{T}(t) \\ \tilde{U}(t) \end{pmatrix}, \quad H(t) = \begin{pmatrix} -\beta T(t)V(t) \\ \alpha I(t)U(t) \end{pmatrix}.$$

Then we can write (4.9) as

$$\begin{aligned} &\tfrac{dW}{dt} = BW(t) + H(t), \\ &W(0) = 0. \end{aligned} \tag{4.10}$$

Lemma 4.3. *Let $Z(t)$ be the solution of the linear system*

$$\frac{dZ}{dt} = BZ(t), \tag{4.11}$$

with the initial condition $Z(0) = 0$. Then $Z(t) = 0$ for $t \geq 0$.

Now let $\tilde{T}(t) : t \geq 0$ be the semigroup generated by the solutions to the linear system (4.11) i.e.

$$\tilde{T}(t)Z_0 = Z(t, Z_0),$$

where $Z(t, Z_0)$ is the solution of (4.11) and $Z_0 = Z(t_0)$.

Then it is well known that $\tilde{T}(t)$ is strongly-continuous semigroup. Hence, $\tilde{T}(t)$ is uniformly bounded. That is, there is a constant M' such that

$$|\tilde{T}|^{\infty} \leq M', \quad \text{for all } t \geq 0.$$

Theorem 4.2. *Let $W(t)$ be a solution of* (4.10), *then*

$$\|W(t)\|_{L^1} \longrightarrow 0, \ \textit{as } t \to +\infty.$$

Proof. By applying the Variation-of-constant formula to (4.10), we have

$$\begin{aligned} W(t) &= \tilde{T}(t)W(0) + \int_0^t \tilde{T}(t-s)H(s)ds \\ &= \int_0^t \tilde{T}(t-s)H(s)ds. \end{aligned} \tag{4.12}$$

(4.12) and Lemma 3.2 yield that for $t \geq 0$,

$$\begin{aligned} \lim_{t\to+\infty} \|W(t)\|_{L^1} &\leq \lim_{t\to+\infty} sup\{|\int_0^t H(s)\tilde{T}(t-s)ds|\} \\ &\leq |\tilde{T}|^\infty \|H\|_{L^1(0,+\infty)} \\ &\leq M' \|H\|_{L^1(0,+\infty)}. \end{aligned}$$

It is apparent that by Corollary 4.1 and the definition of $H(t)$, we have

$$\lim_{t\to+\infty} \|H(t)\|_{L^1} = 0.$$

Hence, we deduce that

$$\|(\tilde{T}(t), \tilde{U}(t))\|_{L^1} = \|W(t)\|_{L^1} \longrightarrow 0, \text{ as } t \to +\infty.$$

□

Theorem 4.3. *Suppose that $R_0 < 1$, then the disease-free equilibrium $(T_0, 0, 0, U_0)$ of (2.1) is globally stable.*

Proof. Using Corollary 4.1, under the assumption of $R_0 < 1$, if $\big(T(t), I(t), V(t), U(t)\big)$ is a nonnegative solution of (2.1). Then

$$\|(I(t), V(t))^T\|_{L^1} \longrightarrow 0 \text{ as } t \to +\infty$$

and Theorem 4.2 states that if $W(t)$ be a solution of (4.10), then

$$\|(\tilde{T}(t),\ \tilde{U}(t))\|_{L^1} = \|W(t)\|_{L^1} \longrightarrow 0 \text{ as } t \to +\infty,$$

which implies that

$$T \longrightarrow T_*,\ U \longrightarrow U_*,\ \text{since } \tilde{T} = T - T_*,\ \tilde{U} = U - U_*.$$

From (4.4), it's obvious that

$$T \longrightarrow T_0 \text{ and } U \longrightarrow U_0,\ \text{as } t \to +\infty.$$

This proves Theorem 4.3. □

5. Global stability of the positive Equilibrium

By (2.6), it is easy to know that if $R_0 > 1$, there exists a positive equilibrium $E^*(T^*, I^*, V^*, U^*)$ and it is bounded.

Theorem 5.1. *If $R_0 > 1$, the positive equilibrium $E^*(T^*, I^*, V^*, U^*)$ of (2.1) is locally asymptotically stable.*

Proof. Consider the linear system at $E^*(T^*, I^*, V^*, U^*)$,

$$\begin{aligned}
\tfrac{dT}{dt} &= -(\beta V^* + d_1)T - \beta T^* V + (\lambda + \beta T^* V^*),\\
\tfrac{dI}{dt} &= \beta V^* T + \beta T^* V - (\gamma U^* + d_2)I - \gamma I^* U - \beta T^* V^* + \gamma I^* U^*,\\
\tfrac{dV}{dt} &= pI - d_3 V,\\
\tfrac{dU}{dt} &= (\alpha I^* - d_4)U + \alpha U^* I + s - \alpha I^* U^*.
\end{aligned}$$

Constructing a suitable Lyapunov function

$$L = \frac{a_1}{2}(T + bI)^2 + \frac{a_2}{2}V^2 + \frac{a_3}{2}U^2.$$

The derivative of L with respect to t gives

$$\begin{aligned}
L' =& a_1(T + bI)(T' + bI') + a_2 V V' + a_3 U U'\\
=& a_1(T + bI)[-(d_1 + \beta V^* - b\beta V^*)T - (\beta T^* - b\beta T^*)V - b(\gamma U^* + d_2)I - b\gamma I^* U]\\
&+ a_2 V(pI - d_3 V) + a_3 U[(\alpha I^* - d_4)U + \alpha U^* I]\\
=& - a_1[d_1 + (1-b)\beta V^*]T^2 - a_1 b^2(\gamma U^* + d_2)I^2 - a_2 d_3 V^2 - a_3(d_4 - \alpha I^*)U^2\\
&- a_1(1-b)\beta T^* TV - a_1 b[\gamma U^* + d_2 + d_1 + (1-b)\beta V^*]TI - a_1 b\gamma I^* TU\\
&- [a_1 b(1-b)\beta T^* - a_2 p]IV - (a_1 b^2 \gamma I^* - a_3 \alpha U^*)UI.
\end{aligned}$$

Note that $E^*(T^*, I^*, V^*, U^*) \neq 0$ and $E^*(T^*, I^*, V^*, U^*) \in D$, choose $a_1,\ a_2,\ a_3$, b such that they satisfy the following conditions

$$\begin{aligned}
&0 < b < 1,\\
&a_1 b(1-b)\beta T^* - a_2 p \geq 0,\\
&a_1 b^2 \gamma I^* - a_3 \alpha U^* \geq 0,
\end{aligned}$$

then we get $L' < 0$.

By Lyapunov stability theorem, $E^*(T^*, I^*, V^*, U^*)$ is locally asymptotically stable. □

Definition 5.1. The system (2.1) is said to be uniformly persistent in D, if there exists a constant $c > 0$ such that any solution $(T(t), I(t), V(t), U(t))$ of system (2.1) with initial value$(T(t), I(t), V(t), U(t)) \in \text{int}D$ satisfies

$$\min\{\liminf_{t\to+\infty} T(t), \liminf_{t\to+\infty} I(t), \liminf_{t\to+\infty} V(t), \liminf_{t\to+\infty} U(t)\} \geq c.$$

Similar to [1], we can get:

Theorem 5.2. *System is uniformly persistent in intD if and only if* $R_0 > 1$.

Remark 5.1. The uniform persistence of system (2.1) in the bounded set D is equivalent to the existence of a compact $K \subset D$ that is absorbing for (2.1).(see [1])

Next we investigate the global stability of the endemic equilibrium of model (2.1). A geometrical approach developed in [8](see also [1,9]) for proving global stability will be used in our discussion. Now we briefly outline a general mathematical framework developed in [8] for proving the global stability.

Consider the autonomous dynamical system:

$$\frac{dx}{dt} = f(x), \tag{5.1}$$

where $x \longmapsto f(x) \in \mathbb{R}^n$ is a C^1 function about x in $\Omega \subset \mathbb{R}^n$.

Assume that the following hypothesis hold:

(H_1) : Ω is simply connected;

(H_2) : There is a compact absorbing set $K \subset \Omega$;

(H_3) : Differential equation (5.1) has a unique equilibrium x_* in Ω.

Let $x \to P(x)\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 for $x \in \Omega$. Assume that $P^{-1}(x)$ exists and is continuous for $x \in K$.

A quantity q is defined as

$$q = \lim_{t\to\infty} \sup \sup_{x\in K} \frac{1}{t}\int_0^t \mu(B(x(s,x_0)))ds,$$

where $B = P_f P^{-1} + P\frac{\partial f^{[2]}}{\partial x}P^{-1}$, the matrix P_f is

$$(p_{ij}(x))_f = (\partial p_{ij}(x)/\partial x)^T \cdot f(x) = \nabla p_{ij}(x) \cdot f(x)$$

and the matrix $J^{[2]}$ is the second addictive compound matrix of the Jacobian matrix J, i.e. $J(x) = Df(x)$.

The quantity $\mu(B)$ is the *Lozinski* measure of B with respect to a vector norm $|\cdot|$ in $\mathbb{R}^N$, $N = \binom{n}{2}$, defined by

$$\mu(B) = \lim_{h\to 0^+} \frac{|I + hB| - 1}{h}.$$

If the equilibrium x_* is locally stable, then the global stability is assured provided that $(H_1) - (H_3)$ hold and no constant periodic solution of (5.1) exists. Besides, it is remarked that under the assumptions $(H_1) - (H_3)$, $q < 0$ also implies the global stability of x_*. The following global stable result is proved in Theorem 3.5 of [8].

Lemma 5.1. *Suppose that Ω is simply connected and that assumption $(H_1) - (H_3)$ hold, then the unique equilibrium x_* is globally stable in Ω if $q < 0$.*

Now we apply the theory developed in [8], in particular Lemma 5.1, to prove the global stability of E^*.

Theorem 5.3. *If $R_0 > 1$, the endemic equilibrium $E^*(T^*, I^*, V^*, U^*)$ is globally asymptotically stable.*

Proof. Firstly, we consider the sub-system of system (2.1)

$$\begin{aligned} \frac{dT}{dt} &= \lambda - \beta TV - d_1 T, \\ \frac{dI}{dt} &= \beta TV - \gamma IU - d_2 I, \\ \frac{dV}{dt} &= pI - d_3 V. \end{aligned} \tag{5.2}$$

The Jacobian matrix of system (5.2) is

$$J = \begin{pmatrix} -\beta V - d_1 & 0 & -\beta T \\ \beta V & -\gamma U - d_2 & \beta T \\ 0 & p & -d_3 \end{pmatrix}$$

and its second addictive compound matrix is

$$J^{[2]} = \begin{pmatrix} -\beta V - \gamma U - d_1 - d_2 & \beta T & \beta T \\ p & -\beta V - d_1 - d_3 & 0 \\ 0 & \beta V & -\gamma U - d_2 - d_3 \end{pmatrix}.$$

Choose the function $P(x) = P(T, I, V) = \mathrm{diag}(1, \frac{I}{V}, \frac{I}{V})$, then

$$P_f = \mathrm{diag}(0, \tfrac{I'V-IV'}{V^2}, \tfrac{I'V-IV'}{V^2}),$$
$$P_f P^{-1} = \mathrm{diag}(0, \tfrac{I'}{I} - \tfrac{V'}{V}, \tfrac{I'}{I} - \tfrac{V'}{V}),$$
$$PJ^{[2]}P^{-1} = \begin{pmatrix} -\beta V - \gamma U - d_1 - d_2 & \frac{\beta TV}{I} & \frac{\beta TV}{I} \\ \frac{pI}{V} & -\beta V - d_1 - d_3 & 0 \\ 0 & \beta V & -\gamma U - d_2 - d_3 \end{pmatrix}.$$

The matrix $B = P_f P_{-1} + P\frac{\partial f^{[2]}}{\partial x}P^{-1}$ can be written in matrix form

$$B = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix},$$

where

$$B_{11} = -\beta V - \gamma U - d_1 - d_2,$$
$$B_{12} = (\frac{\beta TV}{I}, \frac{\beta TV}{I}), \qquad B_{21} = (\frac{pI}{V}, 0)^T,$$
$$B_{22} = \begin{pmatrix} \frac{I'}{I} - \frac{V'}{V} - \beta V - d_1 - d_3 & 0 \\ \beta V & \frac{I'}{I} - \frac{V'}{V} - \gamma U - d_2 - d_3 \end{pmatrix}.$$

Let (u, v, w) be a vector in $\mathbb{R}^3$, its norm $\|\cdot\|$ is defined as

$$\|(u, v, w)\| = \max\{|u|, |v + w|\}.$$

Let $\mu(B)$ be the *Lozinski* measure with respect to this norm. Then we choose

$$\mu(B) \leq \sup\{g_1, g_2\},$$

where

$$g_1 = \mu_1(B_{11}) + |B_{12}|, \quad g_2 = |B_{21}| + \mu_1(B_{22}).$$

$|B_{12}|$, $|B_{21}|$ are matrix norms with respect to the L_1 vector norm, and μ_1 denotes the *Lozinski* measure with respect to this L_1 norm, then

$$\mu_1(B_{11}) = -\beta V - \gamma U - d_1 - d_2,$$
$$|B_{21}| = \frac{pI}{V}, \qquad |B_{12}| = \frac{\beta TV}{I},$$
$$\mu_1(B_{22}) = \max\{\frac{I'}{I} - \frac{V'}{V} - d_1 - d_3, \frac{I'}{I} - \frac{V'}{V} - \gamma U - d_2 - d_3\} \leq \frac{I'}{I} - \frac{V'}{V} - h - d_3,$$

where

$$h = \min\{d_1, d_2\} > 0.$$

Therefore, we have

$$\begin{aligned} g_1 &= \tfrac{\beta TV}{I} - \beta V - \gamma U - d_1 - d_2, \\ g_2 &\le \tfrac{pI}{V} + \tfrac{I'}{I} - \tfrac{V'}{V} - h - d_3. \end{aligned}$$

From (2.1), we get

$$\begin{aligned} \tfrac{I'}{I} &= \tfrac{\beta TV}{I} - \gamma U - d_2, \\ \tfrac{V'}{V} &= \tfrac{pI}{V} - d_3. \end{aligned}$$

Then we have

$$\begin{aligned} g_1 &= \tfrac{I'}{I} - \beta V - d_1, \\ g_2 &\le \tfrac{I'}{I} - h. \end{aligned}$$

Furthermore, we obtain

$$\mu(B) \le \sup\{g_1, g_2\} \le \frac{I'}{I} - h.$$

Since $I(t) > 0$ for $t > 0$, then for a given $t_0 > 0,\ I(t_0) > 0$. Then we get that

$$\frac{1}{t}\int_0^t \mu(B)ds \le \frac{1}{t}\int_0^t (\frac{I'}{I} - h)ds = \frac{1}{t}\int_0^{t_0} \frac{I'}{I}ds + \frac{1}{t}\ln\frac{I(t)}{I(t_0)} - h,$$

which implies

$$q = \lim_{t\to\infty}\sup\sup_{x\in K}\frac{1}{t}\int_0^t \mu(B(x(s,x_0)))ds \le -\frac{h}{2} < 0.$$

Then based on Theorem 3.5 of [8], we know that the positive equilibrium (T^*, I^*, V^*) is globally asymptotically stable.

Now we consider equation

$$\frac{dU}{dt} = s + \alpha IU - d_4U$$

and its limit system is

$$\frac{dU}{dt} = s + \alpha I^*U - d_4U.$$

We get

$$U(t) = e^{-(d_4-\alpha I^*)t}[U(0) + s\int_0^t e^{(d_4-\alpha I^*)\tau}d\tau],$$

which implies that

$$U(t) \longrightarrow \frac{s}{d_4 - \alpha I^*} = U^*, \qquad t \to \infty.$$

Then we get that E^* is globally asymptotically stable. The proof is completed. □

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