# Dynamical behaviour of an anti-HBV infection therapy model with time-delayed immune response

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Abstract—Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections. In this paper, based on the standard mass action incidence, an anti-HBV therapy model with time-delayed immune response is set up. The time-delay is used to describe the period of time for antigenic stimulation to generate CTLs. The globally asymptotically stable analysis of the infection-free equilibrium is given in the paper. Some conditions for Hopf bifurcation around endemic equilibrium to occur are also obtained by using the time delay as a bifurcation parameter.

# Keywords—Mathematical model; HBV; Immune; Therapy

# I. INTRODUCTION

Chronic hepatitis B caused by the hepatitis B virus (HBV) remains a major global health problem. About 2 billion people have been infected with the virus, with 5 million new cases each year [1]. It is estimated conservatively that there are 350 million persistent carriers of HBV worldwide, 25% of whom have chronic liver disease and cirrhosis, which could progress to hepatocellular carcinoma [2].

Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections. The use of mathematical models to enhance our understanding of the dynamics of chronic viral infections has proven fruitful [3, 4, 5]. The use of mathematical models to interpret experimental and clinical results has made a significant contribution to the fields of anti-HIV, HBV and or HCV infections [6, 7, 8].

It is currently widely accepted that HBV infection is noncytopathic. Note that the immune response after viral infection is universal and necessary to eliminate or control the disease.

Based on bilinear mass action incidences, Nowak and May [9] give the following immune models:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta vx \\ \dot{y} &= \beta vx - ay - pyz \\ \dot{v} &= ky - \mu v \\ \dot{z} &= f(y, z) - bz \end{aligned} \tag{1.1}$$

where *x*, *y*, *v* and *z* are numbers of uninfected (susceptible) cells, infected cells, free virus and CTLs respectively. Uninfected cells are assumed to be produced are the constant rate  $\lambda$ , die at the rate of *dx* and become infected at the rate of  $\beta vx$ . Infected cells are thus produced at the rate of  $\beta vx$  and are assumed to die at the rate *ay*. The infected cells were killed by

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immune response at the rate of pyz. Free virus are assumed to be produced from infected cells at the rate of ky, and are removed at the rate of  $\mu v$ . CTLs immune response to virus activation are described by f(y,z) and are assumed to die at the rate of bz. Here f(y,z) can be cyz, cy or c under different assumption.

Time delays can't be ignored in virus infection immune models. As shown in paper [10] and [11], antigenic stimulation generating CTLs may need a period of time  $\tau$ , i.e., the CTLs response at time t may depend on the population of antigen at a previous time  $t - \tau$ .

On the other hand, there exists cytokine-mediated 'cure' of infected cells during HBV infection [12, 13]. In this paper, based on standard mass action, considering the cytokine-mediated 'cure' of infected cells, we will discuss the following HBV therapy delay immune models:

$$\begin{aligned}
\dot{x} &= \lambda - dx - \frac{\beta vx}{x+y} + \rho y \\
\dot{y} &= \frac{\beta vx}{x+y} - ay - pyz - \rho y \\
\dot{v} &= (k-k_2)y - \mu v \\
\dot{z} &= cy(t-\tau) - bz
\end{aligned}$$
(1.2)

Here infected hepatocytes are 'cured' by noncytolytic processes at a constant rate  $\rho$  per cell,  $k_2$  means the therapy effect of adefovir dipivoxil and  $k_2 < k$ , other parameters are the same as above model (1.2). In the following sections, we let  $\overline{k} = k - k_2$ .

This paper is organized as follows. In Section II, we will give the global stability analysis of infection-free equilibrium and study the dynamical behaviour of the endemic equilibrium of system (1.2). The local stability of the endemic equilibrium and the existence of Hopf bifurcation around the endemic equilibrium were given. At last, this paper ends with a brief conclusion in Section III.

### II. STABLE ANALYSIS

We adopt the following notation to system (1.2): R4 is a four-dimensional real Euclidean space with norm  $|\cdot|$ . For  $\tau > 0$ , we denote by  $C = C([-\tau, 0], R^4)$  the Banach space of continuous

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functions mapping the interval  $[-\tau, 0]$  into R4 with the topology of uniform convergence, i.e., for  $\phi \in C$ , the norm of  $\phi$  is defined as  $\|\phi\| = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|$ . The nonnegative cone of C is defined by  $C^+ = C([-\tau, 0], R^4_+)$ . The initial conditions for system (1.2) is given as

$$x(\theta) = \phi_1(\theta), y(\theta) = \phi_2(\theta), v(\theta) = \phi_3(\theta), z(\theta) = \phi_4(\theta),$$

which  $-\tau \le \theta \le 0$ . For biological meaning, the initial function  $\varphi = (\phi_1, \phi_2, \phi_3, \phi_4)$  belongs to  $C^+$ . From [14] and [15], it is easily seen that the solution (x(t), y(t), v(t), z(t)) with above initial condition exists for all  $t \ge 0$  and is unique. Furthermore, it can also be shown that

$$x(t) > 0, y(t) \ge 0, v(t) \ge 0, z(t) \ge 0.$$
(2.1)

The system (1.2) has two equilibrium points

$$E_0 = (\lambda / d, 0, 0, 0), E_1 = (\overline{x}, \overline{y}, \overline{v}, \overline{z})$$

which represent the infection-free equilibrium and the endemic infection equilibrium respectively, which

$$\overline{x} = \frac{\lambda - a\overline{y} - (pc/b)\overline{y}^2}{d}, \overline{y} = \frac{\overline{k}\overline{y}}{\mu}, \overline{z} = \frac{c\overline{y}}{b},$$

and  $\overline{y}$  is the positive solution of equation:

$$\frac{p^2c^2}{b^2}y^3 + (2\frac{pca}{b} + \frac{pc\rho}{b} - \frac{pc\beta\overline{k}}{b\mu} - \frac{pcd}{b})y^2 + (a^2 + a\rho - da - d\rho - \frac{\beta\overline{k}a}{\mu} - \frac{pc\lambda}{b})y + \frac{\beta\overline{k}\lambda}{\mu} - \lambda(a+\rho) = 0$$

Note that when  $\overline{v} = \overline{ky} / \mu, \overline{z} = c\overline{y} / b$  were substituted into the second equation of (1.2), we can have

$$\frac{\beta \overline{k}}{(a+\rho)\mu} \frac{\overline{x}}{\overline{x}+\overline{y}} = 1 + \frac{pc\overline{y}}{ab}$$

The above equation holds only if  $R_0 = \beta \overline{k} / (a + \rho)\mu > 1$ , which shows the endemic infection equilibrium could only exist when  $R_0 = \beta \overline{k} / (a + \rho)\mu > 1$ . The following of this section is to study the stability of the infection-free equilibrium  $E_0$  and the endemic infection equilibrium  $E_1$  when  $\tau \ge 0$ .

#### A. Boundedness of solutions

First, we will give the boundedness of system (1.2).

**Theorem 2.1.** There is an M > 0, such that, for any positive solution (x(t), y(t), v(t), z(t)) of model (1.2), we have x(t) < M, y(t) < M, v(t) < M, z(t) < M.

Proof. Let

$$N(t) = x(t) + y(t) + \frac{a}{3\overline{k}}v(t) + \frac{a}{3c}z(t+\tau).$$

Calculating the derivative of N(t) along the solutions of the system (1.2) gives

$$\begin{split} \dot{N}(t) &= \lambda - dx(t) - ay(t) - py(t)z(t) + \frac{a}{3}y(t) \\ &- \frac{a\mu}{3\overline{k}}v(t) + \frac{a}{3}y(t) - \frac{ab}{3c}z(t+\tau) \\ &= \lambda - dx(t) - \frac{a}{3}y(t) - py(t)z(t) - \frac{a\mu}{3\overline{k}}v(t) - \frac{ab}{3c}z(t+\tau) \\ &\leq \lambda - dx(t) - \frac{a}{3}y(t) - \frac{a\mu}{3\overline{k}}v(t) - \frac{ab}{3c}z(t+\tau) \\ &= \lambda - qN(t). \end{split}$$

Which  $q = \min\{d, a/3, \mu, b\}$ , so,  $N(t) < \lambda/q + \varepsilon$  for all large t, where  $\varepsilon$  is an arbitrarily small positive constant. Thus, we can get that x(t), y(t), v(t) and z(t) are ultimately bounded by some positive constant M.

# B. Stability of the infection-free equilibrium $E_0$

**Theorem 2.2.** (1) If  $R_0 < 1$ , the infection-free equilibrium point  $E_0$  is locally asymptotically stable for any delay  $\tau \ge 0$ .

(2) If  $R_0 > 1$ , the infection-free equilibrium point  $E_0$  is unstable for any delay  $\tau \ge 0$ .

(3) If  $R_0 = 1$ , it is a critical case.

**Proof.** Let E = (x, y, v, z) be an arbitrary equilibrium of system (1.2), the characteristic equation about E is given by

$$\Delta = \begin{vmatrix} J_{11} & -\frac{\beta vx}{(x+y)^2} - \rho & \frac{\beta x}{(x+y)} & 0 \\ -\frac{\beta vy}{(x+y)^2} & J_{22} & -\frac{\beta x}{(x+y)} & py \\ 0 & -\overline{k} & s+\mu & 0 \\ 0 & -ce^{-s\tau} & 0 & s+b \end{vmatrix} = 0,$$

which

$$J_{11} = s + d + \frac{\beta vy}{(x+y)^2}, J_{22} = s + \frac{\beta vx}{(x+y)^2} + a + \rho + pz.$$

The characteristic equation evaluated at  $E_0$  reduces to

$$\Delta \Big|_{E_0} = \begin{vmatrix} s+d & \rho & \beta & 0\\ 0 & s+a+\rho & -\beta & 0\\ 0 & -\overline{k} & s+\mu & 0\\ 0 & -ce^{-sr} & 0 & s+b \end{vmatrix} = 0.$$
(2.2)

Obviously, (2.2) has the following characteristic roots:

$$s_{1} = -d, \ s_{2} = -b,$$
  
$$s_{3,4} = \frac{-(a+\rho+\mu)\pm\sqrt{(a+\rho+\mu)^{2}-4[(a+\rho)\mu-\beta k]}}{2}.$$

If  $R_0 < 1$ , the four characteristic roots are all negative, so the equilibrium point  $E_0$  is locally asymptotically stable for any delay  $\tau \ge 0$ .

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If  $R_0 > 1$ , the characteristic roots  $s_3$  must be positive, the infection-free equilibrium point  $E_0$  is unstable for any delay  $\tau \ge 0$ .

If  $R_0 = 1$ , the characteristic roots  $s_1$ ,  $s_2$ ,  $s_4$  are negative,  $s_3$  is zero, which implies the trivial solution system of (1.2) is stable for any time delay  $\tau \ge 0$ , this proves the third conclusion.

Now we will give the globally asymptotically stability analysis of the infection-free equilibrium point  $E_0$  of system (1.2). From the first and second equation, we can have  $\dot{x} + \dot{y} \leq \lambda - \min\{a, d\}(x + y)$ , a simple comparison arguments shows that we can have the following lemma.

**Lemma 2.1.** For any solution x(t), y(t), v(t), z(t) of (1.2), we have that

$$\limsup_{t\to\infty}(x(t)+y(t))\leq\frac{\lambda}{\min\{a,d\}}.$$

**Theorem 2.3.** (1) If  $R_0 < 1$ , the infection-free equilibrium  $E_0$  of system (1.2) is globally asymptotically stable for any time delay  $\tau \ge 0$ . (2) If  $R_0 = 1$ , the infection-free equilibrium  $E_0$  of system (1.2) is globally attractive for any time delay  $\tau \ge 0$ .

Proof. Define

$$G = \{ (\phi_1, \phi_2, \phi_3, \phi_4) \in C^+ | \lambda / \min\{a, d\} \ge \phi_1 + \phi_2 \ge 0, \\ \phi_1, \phi_2 \ge 0, \phi_3 \ge 0, \phi_4 \ge 0 \}.$$

Form lemma 1, we can prove *G* is a positively invariant with respect to system (1.2). For any  $\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in G$ , let (x(t), y(t), v(t), z(t)) be the solution of (1.2) with the initial function  $\phi$ , we claim that  $x(t) + y(t) \leq \lambda / \min\{a, d\}$  for any  $t \geq 0$ , In fact, if  $x(t_1) + y(t_1) > \lambda / \min(a, d)$  for any  $t_1$ , then we have

$$\dot{x}(t_1) + \dot{y}(t_1) = \lambda - dx(t_1) - ay(t_1) - py(t_1)z(t_1)$$
  
$$\leq \lambda - \min\{a, d\}(x(t_1) + y(t_1)) - py(t_1)z(t_1) \leq 0$$

which is contradict to  $\dot{x}(t_1) + \dot{y}(t_1) > 0$ . The claim is proved.

If  $R_0 < 1$ , we define a Lyapunov functional W on G as follows:

$$W(\phi) = \frac{\overline{k}}{a+\rho}\phi_2(0) + (1-\frac{\varepsilon}{\overline{k}})\phi_3(0) + \frac{\varepsilon}{c}\phi_4(0) + \varepsilon \int_{-\tau}^0 \phi_2(\xi)d\xi, ,$$

where  $\overline{k} > \varepsilon > 0$  is a positive constant to be chosen later. It is clear that  $W(\phi)$  is continuous on *G*. Calculating the time derivative of *W* along the solution of system (1.2), we obtain

$$\begin{split} \dot{W}\Big|_{(3)} &= \frac{k}{a+\rho} \left(\frac{\beta\phi_1(0)\phi_3(0)}{\phi_1(0)+\phi_2(0)} - a\phi_2(0) - p\phi_2(0)\phi_4(0) - \rho\phi_2(0)\right) \\ &+ \overline{k}\phi_2(0) - \mu\phi_3(0) - \varepsilon\phi_2(0) + \frac{\varepsilon\mu}{k}\phi_3(0) \\ &+ \varepsilon\phi_2(-\tau) - \frac{\varepsilon b}{c}\phi_4(0) + \varepsilon\phi_2(0) - \varepsilon\phi_2(-\tau) \\ &= \frac{\overline{k}\beta\phi_1(0)\phi_3(0)}{(a+\rho)(\phi_1(0)+\phi_2(0))} - \frac{\overline{k}p\phi_2(0)\phi_4(0)}{(a+\rho)} \\ &- \frac{\varepsilon b}{c}\phi_4(0) - \mu\phi_3(0) + \frac{\varepsilon\mu}{k}\phi_3(0) \\ &\leq \frac{\overline{k}\beta\phi_3(0)}{a+\rho} - \mu\phi_3(0) + \frac{\varepsilon\mu}{k}\phi_3(0) - \frac{\overline{k}p\phi_2(0)\phi_4(0)}{a+\rho} - \frac{\varepsilon b}{c}\phi_4(0) \\ &= \mu((\frac{\overline{k}\beta}{(a+\rho)\mu} - 1) + \frac{\varepsilon}{k})\phi_3(0) - \frac{\overline{k}p\phi_2(0)\phi_4(0)}{a+\rho} - \frac{\varepsilon b}{c}\phi_4(0) \end{split}$$

Since  $R_0 = \frac{\kappa \rho}{(a+\rho)\mu} < 1$ , then there must be a positive constant  $\varepsilon > 0$  such that

$$(\frac{\overline{k}\beta}{(a+\rho)\mu}-1)+\frac{\varepsilon}{\overline{k}}<0\,,$$

Thus  $\dot{V} \leq 0$  for any  $\phi \in G$ . This shows that  $w(\phi)$  is a Liapunnov functional on the subset G in  $C^+$ . Define

$$E = \{ \phi \in G \mid \dot{W} \mid_{(3)} = 0 \} ,$$

we have

$$E \subset \{\phi \in G \mid \phi_3(0) = 0, \phi_4(0) = 0\}$$

Let M be the largest set in E which is invariant with respect to (1.2). Clearly, M is not empty since  $(\lambda/d, 0, 0, 0) \in M$ . For any  $\phi \in M$ , let (x(t), y(t), v(t), z(t)) be the solution of (1.2) with the initial function  $\phi$ . From the invariance of M, we have that  $(x(t), y(t), v(t), z(t)) \in M \subset E$ for any  $t \in R$ Thus  $v(t) \equiv 0$ ,  $z(t) \equiv 0$  for any  $t \in R$ . From the third equation of (1.2), we further have  $y(t) \equiv 0$  for any  $t \in R$ . From the first equation of (1.2), we can also have  $x(t) \rightarrow \lambda / d$  as  $t \rightarrow +\infty$ , the invariance of *M* also implies  $x(t) \equiv \lambda / d$  for any  $t \in R$ . Therefore,  $M = (\lambda / d, 0, 0, 0)$ . The classical Liapunov-LaSalle invariance principal [15] shows that  $E_0 = (\lambda / d, 0, 0, 0)$ is globally attractive. Since  $E_0$  is locally asymptotically stable, hence  $E_0$  is globally asymptotically stable for any time delay  $\tau \ge 0.$ 

If  $R_0 = 1$ , we define the following functional on *G*:

$$W(\phi) = \frac{k}{a+\rho}\phi_2(0) + \phi_3(0)$$

It is clear that  $W(\phi)$  is continuous on *G*. Calculating the time derivative of *W* along the solution of system (1.2), we obtain

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$$\begin{split} \dot{W}\Big|_{(3)} &= \frac{\bar{k}}{a+\rho} \left( \frac{\beta \phi_1(0)\phi_3(0)}{\phi_1(0) + \phi_2(0)} - a\phi_2(0) - p\phi_2(0)\phi_4(0) \right. \\ &- \rho\phi_2(0) + \bar{k}\phi_2(0) - \mu\phi_3(0) \\ &= \frac{\bar{k}\beta \phi_1(0)\phi_3(0)}{(a+\rho)(\phi_1(0) + \phi_2(0))} - \frac{\bar{k}p\phi_2(0)\phi_4(0)}{(a+\rho)} - \mu\phi_3(0) \\ &\leq \frac{\bar{k}\beta\phi_3(0)}{a+\rho} - \frac{\bar{k}p\phi_2(0)\phi_4(0)}{a+\rho} - \mu\phi_3(0) \\ &= \left(\frac{\bar{k}\beta}{(a+\rho)} - \mu\right)\phi_3(0) - \frac{\bar{k}p\phi_2(0)\phi_4(0)}{a+\rho} \\ &= -\frac{\bar{k}p\phi_2(0)\phi_4(0)}{a+\rho} \leq 0 \end{split}$$

So  $W(\phi)$  is a Liapunnov functional on the subset *G* in  $C^+$ . Define  $E = \{\phi \in G \mid \dot{W}|_{(3)} = 0\}$ , we have

$$E \subset \{\phi_2(0) = 0 \text{ or } \phi_4(0) = 0\}.$$

Let *M* be the largest set in *E* which is invariant with respect to (1.2). Clearly, *M* is not empty since  $(\lambda / d, 0, 0, 0) \in M$ . For any  $\phi \in M$ , let (x(t), y(t), v(t), z(t)) be the solution of (1.2) with the initial function  $\phi$ . From the invariance of *M*, we have that  $(x(t), y(t), v(t), z(t)) \in M \subset E$  for any  $t \in R$ . If  $\phi_2(0) = 0$ , thus  $y(t) \equiv 0$  for any  $t \in R$ . From the third equation of (1.2), we can have  $v(t) \rightarrow 0$  as  $t \rightarrow +\infty$ , the invariance of *M* implies that  $v(t) \equiv 0$  for any  $t \in R$ . Similarly, we also have  $z(t) \equiv 0$  for any  $t \in R$ . Since  $y(t) \equiv 0$ ,  $v(t) \equiv 0$ , the first equation of (1.2) can also ensure  $x(t) \equiv \lambda / d$ .

If  $\phi_4(0) = 0$ , we have  $z(t) \equiv 0$  for any  $t \in R$ . So the fourth equation of (1.2) can ensure y(t) = 0, by a completely similar proof as for the case  $\phi_2(0) = 0$ , we have that  $v(t) \equiv 0$ ,  $x(t) \equiv \lambda/d$  for any  $t \in R$ . So we have  $M = (\lambda/d, 0, 0, 0)$ . Liapunov-LaSalle invariance principal [15] shows that  $E_0 = (\lambda/d, 0, 0, 0)$  is globally attractive for any time delay  $\tau \ge 0$ .

# C. Stable analysis of the endemic infection equilibrium $E_1$

In this section, we will consider the dynamical behavior of endemic equilibrium  $E_1$ . By using the time delay  $\tau$  as a bifurcation parameter, some conditions for Hopf bifurcation around equilibrium  $E_1$  to occur are obtained.

For endemic equilibrium  $E_1 = (\overline{x}, \overline{y}, \overline{v}, \overline{z})$ , the characteristic equation about (1.2) is given by

$$\Delta = \begin{vmatrix} J_{11} & -\frac{\beta \overline{vx}}{(\overline{x} + \overline{y})^2} - \rho & \frac{\beta \overline{x}}{(\overline{x} + \overline{y})} & 0 \\ -\frac{\beta \overline{vy}}{(\overline{x} + \overline{y})^2} & J_{22} & -\frac{\beta \overline{x}}{(\overline{x} + \overline{y})} & p\overline{y} \\ 0 & -\overline{k} & s + \mu & 0 \\ 0 & -ce^{-s\tau} & 0 & s + b \end{vmatrix} = 0,$$

Which

$$J_{11} = s + d + \frac{\beta \overline{vy}}{(\overline{x} + \overline{y})^2}, J_{22} = s + \frac{\beta \overline{vx}}{(\overline{x} + \overline{y})^2} + a + \rho + p\overline{z}.$$

i.e.,

$$s^{4} + p_{1}s^{3} + p_{2}s^{2} + p_{3}s + p_{4} + (q_{2}s^{2} + q_{3}s + q_{4})e^{-sr} = 0$$
(2.3)

where

$$\begin{split} p_{1} &= b + \mu + \Omega + d + \frac{\beta v y}{(\overline{x} + \overline{y})^{2}} \\ p_{2} &= b(\mu + \Omega) + \mu \Omega + (d + \frac{\beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}})(b + \mu + \Omega) \\ &- \frac{\beta^{2} \overline{v}^{2} \overline{y} \overline{x}}{(\overline{x} + \overline{y})^{4}} - \overline{k} \frac{\beta \overline{x}}{\overline{x} + \overline{y}} - \frac{\rho \beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}} \\ p_{3} &= b \mu (\Omega + d + \frac{\beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}}) + (b + \mu) \frac{\beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}} \Omega \\ &- (b + \mu) \frac{\beta^{2} \overline{v}^{2} \overline{y} \overline{x}}{(\overline{x} + \overline{y})^{4}} - \overline{k} \overline{b} \frac{\beta \overline{x}}{\overline{x} + \overline{y}} - d\overline{k} \frac{\beta \overline{x}}{\overline{x} + \overline{y}} - (b + \mu) \frac{\rho \beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}} \\ p_{4} &= b \mu (d + \frac{\beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}}) \Omega - b \mu \frac{\beta^{2} \overline{v}^{2} \overline{y} \overline{x}}{(\overline{x} + \overline{y})^{4}} - d\overline{k} \overline{b} \frac{\beta \overline{x}}{\overline{x} + \overline{y}} - b \mu \frac{\rho \beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}} \\ q_{2} &= c p \overline{y} \\ q_{3} &= c p \overline{y} (d + \frac{\beta \overline{v} \overline{y}}{(\overline{x} + \overline{y})^{2}}) \mu \\ \Omega &= \frac{\beta \overline{v} \overline{x}}{(\overline{x} + \overline{y})^{2}} + a + \rho + p \overline{z} \end{split}$$

Note that when the delay  $\tau = 0$ , equation (2.3) becomes

$$s^4 + p_1 s^3 + (p_2 + q_2) s^2 + (p_3 + q_3) s + p_4 + q_4 = 0$$

By the Routh-Hurwizt criteria, we can know that all roots of (2.3) would have negative real parts if the following condition holds:

$$\begin{cases} p_{1} > 0, p_{1}(p_{2} + q_{2}) > p_{3} + q_{3}, \\ p_{1}(p_{2} + q_{2})(p_{3} + q_{3}) > p_{1}^{2}(p_{4} + q_{4}) + (p_{3} + q_{3})^{2}, \\ p_{1}p_{2}(p_{1} + p_{3})(p_{4} + q_{4}) > p_{1}^{2}(p_{4} + q_{4})^{2} \\ + (p_{3} + q_{3})(p_{1} + p_{3})(p_{4} + q_{4}). \end{cases}$$

$$(2.4)$$

When  $\tau \neq 0$ , let  $s = \varphi(\tau) + i\psi(\tau)$ , which  $\varphi(\tau), \psi(\tau) \in R$ , rewriting (2.3) in terms of its real and imaginary parts, we can get

$$\phi^{4} - 6\phi^{2}\psi^{2} + \psi^{4} + p_{1}(\phi^{3} - 3\phi\psi^{2}) + p_{2}(\phi^{2} - \psi^{2}) + p_{3}\phi + p_{4} = e^{-\tau\phi} \{ [q_{2}(\psi^{2} - \phi^{2}) - (q_{3}\phi + q_{4})]\cos(\tau\psi) - (2\phi\psi q_{2} + q_{3}\psi)\sin(\tau\psi) \}$$
(2.5)

$$4\phi\psi(\phi^{2} - \psi^{2}) + p_{1}(3\phi^{2}\psi - \psi^{3}) + 2p_{2}\phi\psi + p_{3}\psi$$
  
=  $e^{-\tau\phi} \{ [q_{2}(\phi^{2} - \psi^{2}) + (q_{3}\phi + q_{4})]\sin(\tau\psi)$ (2.6)  
 $-(2\phi\psi q_{2} + q_{3}\psi)c(\tau os\psi) \}$ 

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Let  $\tau$  be such that  $\varphi(\tau) = 0, \psi(\tau) = \psi^*$ , the above equations reduce to

$$\psi^{*4} - p_2 \psi^{*2} + p_4 = (q_2 \psi^{*2} - q_4) \cos(\tau \psi^*) - q_3 \psi^* \sin(\tau \psi^*)$$
  

$$p_1 \psi^{*3} - p_3 \psi^* = (q_2 \psi^{*2} - q_4) \sin(\tau \psi^*) + q_3 \psi^* \cos(\tau \psi^*)$$
(2.7)

Eliminating  $\tau$ , we have

$$\psi^{*8} + (p_1^2 - 2p_2)\psi^{*6} + (p_2^2 + 2p_4 - 2p_1p_3 - q_2^2)\psi^{*4} + (p_3^2 - 2p_2p_4 - q_3^2 + 2q_2q_4)\psi^{*2} + p_4^2 - q_4^2 = 0$$
(2.8)

Suppose that  $\psi_1^*$  is the last positive simple root of equation (2.8), we now show that with this value of  $\psi_1^*$ , there is a  $\tau_1^*$  such that  $\varphi(\tau_1^*) = 0$  and  $\psi(\tau_1^*) = \psi_1^*$ . Given  $\psi_1^*$ , equation (2.7) can be written as

$$U = A\cos(\tau_1^*\psi_1^*) + B\sin(\tau_1^*\psi_1^*)$$
  

$$V = A\sin(\tau_1^*\psi_1^*) - B\cos(\tau_1^*\psi_1^*)$$
(2.9)

where

$$U = p_2 \psi_1^{*2} - \psi_1^{*4} - p_4, V = p_3 \psi_1^{*} - p_1 \psi_1^{*3},$$
  

$$A = q_4 - q_2 \psi_1^{*2}, B = q_3 \psi_1^{*}, U^2 + V^2 = A^2 + B^2 = H^2,$$
  

$$H > 0$$
(2.10)

The equation  $A = H \cos \theta$ ,  $B = H \sin \theta$  Determines a unique  $\theta \in [0, 2\pi]$ , with this  $\theta$ , we have

$$U = H\cos(\tau_1^*\psi_1^*)\cos\theta + H\sin(\tau_1^*\psi_1^*)\sin\theta$$
  

$$V = H\sin(\tau_1^*\psi_1^*)\cos\theta - H\cos(\tau_1^*\psi_1^*)\sin\theta$$
(2.11)

Hence  $U = H \cos(\tau_1^* \psi_1^* - \theta)$ ,  $V = H \sin(\tau_1^* \psi_1^* - \theta)$ , The equation (2.11) determine  $\tau_1^* \psi_1^* - \theta$  uniquely in  $[0, 2\pi)$ , which determine  $\tau_1^* \in [\frac{\theta}{\psi_1^*}, \frac{2\pi + \theta}{\psi_1^*})$  uniquely.

In order to apply the Hopf bifurcation theorem as stated in [16], we need the following lemma:

Lemma 2.2 ([17]) Suppose equation (2.8) has at least one simple positive root and  $\psi_1^*$  is the last such root. Then,  $i\psi(\tau_1^*) = i\psi_1^*$  is a simple root of equation (2.3) and  $\phi(\tau) + i\psi(\tau)$  is differentiable with respect to  $\tau$  in a neighborhood of  $\tau = \tau_1^*$ .

Next, to establish Hopf bifurcation at  $\tau = \tau_1^*$ , we need to verify the transversality condition

$$\left. \frac{d\phi}{d\tau} \right|_{\tau=\tau_1^*} \neq 0 \tag{2.12}$$

Differentiating Eq. (2.5) and (2.6) with respect to  $\tau$ , and setting  $\phi = 0, \psi = \psi_1^*$ , we have

$$\begin{aligned} A_{1} \frac{d\phi}{d\tau} \bigg|_{\tau=\tau_{1}^{*}} &- B_{1} \frac{d\psi}{d\tau} \bigg|_{\tau=\tau_{1}^{*}} \\ &= (\psi_{1}^{*}q_{4} - q_{2}\psi_{1}^{*3})\sin(\tau\psi_{1}^{*}) - q_{3}\psi_{1}^{*2}\cos(\tau\psi_{1}^{*}) \\ B_{1} \frac{d\phi}{d\tau} \bigg|_{\tau=\tau_{1}^{*}} + A_{1} \frac{d\psi}{d\tau} \bigg|_{\tau=\tau_{1}^{*}} \\ &= (\psi_{1}^{*}q_{4} - q_{3}\psi_{1}^{*3})\cos(\tau\psi_{1}^{*}) + q_{3}\psi_{1}^{*2}\sin(\tau\psi_{1}^{*}) \end{aligned}$$

where

$$A_{1} = p_{3} - 3p_{1}\psi_{1}^{*2} + (\tau q_{2}\psi_{1}^{*2} - \tau q_{4} + q_{3})\cos(\tau\psi_{1}^{*}) + (2q_{2}\psi_{1}^{*} - \tau q_{3}\psi_{1}^{*})\sin(\tau\psi_{1}^{*}) B_{1} = 2p_{2}\psi_{1}^{*} - 4\psi_{1}^{*3} + (\tau q_{4} - \tau q_{2}\psi_{1}^{*2} - q_{3})\sin(\tau\psi_{1}^{*}) + (2q_{2}\psi_{1}^{*} - \tau q_{3}\psi_{1}^{*})\cos(\tau\psi_{1}^{*})$$

Solving for  $\frac{d\phi}{d\tau}\Big|_{\tau=\tau_1^*}$  with the help of (2.7), we have

$$\frac{d\phi}{d\tau}\Big|_{\tau=\tau_1^*} = \frac{\psi_1^{*2}}{A_1^2 + B_1^2} \Delta ,$$

where

$$\Delta = 4\psi^{*6} + 3(p_1^2 - 2p_2)\psi^{*4} + 2(p_2^2 + 2p_4 - 2p_1p_3 - q_2^2)\psi^{*2} + (p_3^2 - 2p_2p_4 - q_3^2 + 2q_2q_4)$$

As  $i\psi_1^*$  is a simple root of (2.3), let  $z = \psi_1^{*2}$ , then (2.8) reduce to  $\Phi(z) = 0$ , where

$$\Phi(z) = z^4 + (p_1^2 - 2p_2)z^3 + (p_2^2 + 2p_4 - 2p_1p_3 - q_2^2)z^2 + (p_3^2 - 2p_2p_4 - q_3^2 + 2q_2q_4)z + p_4^2 - q_4^2$$

hence

$$\frac{d\Phi}{dz} = 4z^3 + 3(p_1^2 - 2p_2)z^2 + 2(p_2^2 + 2p_4 - 2p_1p_3 - q_2^2)z + (p_3^2 - 2p_2p_4 - q_3^2 + 2q_2q_4)$$

Since  $\psi_1^*$  is the last positive simple root, then  $\psi_1^{*2}$  must be the last positive simple root of  $\Phi(z) = 0$ , so we must have

$$\left.\frac{d\Phi}{d\tau}\right|_{\tau=\tau_1^*} > 0$$

Therefore

$$\left. \frac{d\phi}{d\tau} \right|_{\tau=\tau_1^*} = \frac{\psi_1^{*2}}{A_1^2 + B_1^2} \frac{d\Phi}{d\tau} \right|_{\tau=\tau_1^*} > 0 \tag{2.13}$$

Now, we summarize the preceding details in the following theorem.

**Theorem 2.4.** Suppose equation (2.8) has at least one simple positive root and  $\psi_1^*$  is the last such root, then, there is a Hopf bifurcation for the system (1.2) as  $\tau$  passes upwards through  $\tau_1^*$  leading to a periodic solution that bifurcates from  $E_1$ .

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Next, by the lemma 2.1 in reference [18], we will give the sensible conditions that the Hopf bifurcation occurs around equilibrium  $E_1$  in the following part.

Define

$$\begin{split} f_1 &= p_1^2 - 2p_2, f_2 = p_2^2 + 2p_4 - 2p_1p_3 - q_2^2, \\ f_3 &= p_3^2 - 2p_2p_4 - q_3^2 + 2q_2q_4, f_4 = p_4^2 - q_4^2, z = \psi^{*2}. \end{split}$$

Then (2.8) reduce to

$$\Phi(z) = z^4 + f_1 z^3 + f_2 z^2 + f_3 z + f_4 = 0$$

Thus we have the following lemma:

**Lemma 2.3.** ([18]) Suppose  $f_4 < 0$ , equation (2.8) has at least one positive root.

Now from lemma 2.2, lemma 2.3 and theorem 2.3, we can get the following results:

**Theorem 2.5.** Suppose  $R_o > 1$ , and (1)  $p_4^2 - q_4^2 < 0$ ; (2) Condition (2.4) holds; then, there is a Hopf bifurcation for the system (1.2) as  $\tau$  passes upwards through  $\tau_1^*$  leading to a periodic solution that bifurcates from  $E_1$ .

#### III. CONCLUSIONS

In this paper, based on standard mass action incidence, we have discussed a HBV infection therapy model with delayed immune response. A detailed analysis of the locally and globally asymptotic stability about the infection-free equilibrium  $E_0$  is carried out. While  $R_0 < 1$ , (hence the endemic equilibrium  $E_1$  is not feasible),  $E_0$  is locally asymptotically stable for any  $\tau \ge 0$ , when  $R_0 = 1$  (the endemic equilibrium  $E_1$  is also not feasible), the system (1.2) at  $E_0$  is stable for any  $\tau \ge 0$ . By Lyapunov-LaSalle type theorem, we have also proved that the infection-free equilibrium  $E_0$  is globally asymptotically stable for any time delay  $\tau \ge 0$  if  $R_0 < 1$ , which shows that the virus could be cleared if therapy effect parameter  $k_2$ , could make the  $R_0 = (k - k_2)\beta / ((a + \rho)u) < 1$  no matter how long the CTL immune response would be stimulated, that is to say the final therapy effect is independent of  $\tau$ . But if the treatment rate  $k_2$  could only make  $R_0 = 1$ , we could prove  $E_0$  is globally attractive, which shows the level of HBV DNA would reduce to very low but couldn't be cleared. On the other hand, if the treatment rate  $k_2$  could only make

$$R_0 = (k - k_2)\beta / ((a + \rho)u) > 1$$
,

the model (1.2) would have endemic equilibrium  $E_1$ . For given parameters, theoretical analysis shows stability in the system would vary as the delay factor  $\tau$  crosses a threshold  $\tau_1^*$  under some conditions. That is to say, if the time needed for the stimulation of immune is less than  $\tau_1^*$ , the system (1.2) would be locally stable, if the immune stimulation time is more than the threshold  $\tau_1^*$ , the HBV load would oscillate near the equilibrium  $E_1$  which is consistent with the phenomena often observed in clinical therapy.

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