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DYNAMICS OF A FRACTIONAL ORDER HBV INFECTION MODEL WITH CAPSIDS AND CTL IMMUNE RESPONSE

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Abstract. In this article, a fractional order model for hepatitis B virus (HBV) infection with capsids and immune response presented by cytotoxic T lymphocyte (CTL) cells is proposed and investigated. The infection transmission is modeled by Hattaf-Yousfi functional response and the fractional derivative is in the Caputo sense. First, the well-posedness of the proposed model is proved in terms of existence, uniqueness, non-negativity and boundness of solutions. The global asymptotic stability of steady states is established by using suitable Lyapunov functionals and applying LaSalle's invariance principle. Numerical simulations are performed to illustrate the analytical results.

Keywords: HBV infection; immunity; fractional derivative; global stability.

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1. Introduction

Hepatitis B is a serious infection caused by the hepatitis B virus (HBV) which is a member of Hepadnaviridae family of viruses that attacks liver cells namely hepatocytes. According to the World Health Organization (WHO), an estimated 257 million people are living with HBV

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infection, and 887000 people are dead in 2015 due to HBV complications including cirrhosis and hepatocellular carcinoma [1]. Therefore, HBV infection still remains a major public health problem globally.

Mathematical modeling using fractional differential equations (FDEs) is a suitable tool to describe the dynamics of HBV infection [2, 3, 4]. Further, the immune response exerted by CTL cells plays an important role in the control of HBV infection. This immune response is called the cellular immunity and is programmed to kill the infected hepatocytes. Motivated by these mathematical and biological reasons, we propose the following fractional order model for HBV infection with cellular immunity:

$$\begin{cases} D^{\alpha}H(t) &= s-\mu H-f(H,V)V, \\ D^{\alpha}I(t) &= f(H,V)V-\delta I-pIZ, \\ D^{\alpha}C(t) &= aI-(\beta+\delta)C, \\ D^{\alpha}V(t) &= \beta C-cV, \\ D^{\alpha}Z(t) &= qIZ-\sigma Z, \end{cases} \tag{1}$$

where $H(t), I(t), C(t), V(t)$ and $Z(t)$ represent the concentrations of uninfected hepatocytes, infected hepatocytes, HBV DNA-containing capsids, virions and CTL cells at time t, respectively. The uninfected hepatocytes are produced from a source at a constant rate s, die at rate μH and become infected by virions at rate $f(H,V)V$. The parameter δ is the death rate for infected hepatocytes and capsids. The parameters a, β and c are, respectively, the production rate of capsids from infected hepatocytes, the rate at which the capsids are transmitted to blood which gets converted to virions, and the clearance rate of virions. The infected hepatocytes are killed by CTL cells at rate p while q and σ denote CTL responsiveness rate and decay rate of CTL cells in absence of antigenic stimulation, respectively. In system (1), the infection transmission is modeled by Hattaf-Yousfi functional response [5] of the form $f(H,V)=\frac{kH}{\alpha_0+\alpha_1 H+\alpha_2 V+\alpha_3 HV}$, where $\alpha_0,\alpha_1,\alpha_2,\alpha_3\geq 0$ are the saturation factors measuring the inhibitory or psychological effect and k is a positive constant rate describing the infection process. Finally, D^{α} is the Caputo fractional derivative and α is a parameter that describes the order of the fractional time-derivative with $\alpha\in(0,1]$.

The aim of this paper is to investigate the dynamical behavior of our FDE model presenting by system (1) that improves and generalizes the mathematical models formulated by ordinary differential equations (ODEs) in [6, 7] and also the FDE models introduced in [2, 3, 4]. So, the rest of the paper is organized as follows. In the next section, we prove the well-posedness of the model and we calculate the threshold parameters for the existence of equilibria. By the method of Lyapunov functionals, we show the global stabilities of the three equilibria in section 3. The illustrative numerical simulations are presented in section 4. Finally, we provide in section 5 some concluding remarks.

2. Well-posedness and threshold parameters

In this section, we establish the existence, uniqueness, non-negativity and boundedness of solutions of our model. For these reasons, we assume that the initial conditions for system (1) satisfy

$$H(0) = H_0 \geq 0, I(0) = I_0 \geq 0, C(0) = C_0 \geq 0, V(0) = V_0 \geq 0, Z(0) = Z_0. \tag{2}$$

Theorem 2.1. *For any initial conditions satisfying (2), there exists a unique solution of system (1) defined on* $[0, +\infty)$. *Moreover, this solution remains non-negative and bounded for all* $t \geq 0$.

Proof. System (1) can be written as follows

$$D^{\alpha} X(t) = F(X),$$

where

$$X(t) = \begin{pmatrix} H(t) \\ I(t) \\ C(t) \\ V(t) \\ Z(t) \end{pmatrix} \text{ and } F(X) = \begin{pmatrix} s - \mu H - f(H,V)V \\ f(H,V)V - \delta I - pIZ \\ aI - (\beta + \delta)C \\ \beta C - cV \\ qIZ - \sigma Z \end{pmatrix}.$$

Let

$$\eta = \begin{pmatrix} s \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \; A_1 = \begin{pmatrix} -\mu & 0 & 0 & 0 & 0 \\ 0 & -\delta & 0 & 0 & 0 \\ 0 & a & -(\beta+\delta) & 0 & 0 \\ 0 & 0 & \beta & -c & 0 \\ 0 & 0 & 0 & 0 & -\sigma \end{pmatrix}$$

and

$$B = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -p \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & q \end{pmatrix}.$$

So, we discuss four cases:

- If $\alpha_0 \neq 0$, then system (1) can be written as follows

$$D^{\alpha}X(t) = \eta + A_1X + \frac{\alpha_0 V}{\alpha_0 + \alpha_1 H + \alpha_2 V + \alpha_3 HV} A_2X + IBX,$$

where

$$A_2 = \begin{pmatrix} \frac{-k}{\alpha_0} & 0 & 0 & 0 & 0 \\ \frac{k}{\alpha_0} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then

$$\|D^{\alpha}X(t)\| \leq \|\eta\| + (\|A_1\| + \|V\| \, \|A_2\| + \|I\| \, \|B\|) \, \|X\|. \tag{3}$$

- If $\alpha_1 \neq 0$, we have

$$D^{\alpha}X(t) = \eta + A_1X + \frac{\alpha_1 H}{\alpha_0 + \alpha_1 H + \alpha_2 V + \alpha_3 HV} A_3X + IBX,$$

where

$$A_3 = \begin{pmatrix} 0 & 0 & 0 & \frac{-k}{\alpha_1} & 0 \\ 0 & 0 & 0 & \frac{k}{\alpha_1} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then

$$\|D^{\alpha}X(t)\| \leq \|\eta\| + (\|A_1\| + \|A_3\| + \|I\|\,\|B\|)\,\|X\|.$$

- If $\alpha_2 \neq 0$, we have

$$D^{\alpha}X(t) = \eta + A_1X + \frac{\alpha_2 V}{\alpha_0 + \alpha_1 H + \alpha_2 V + \alpha_3 HV}A_4X + IBX,$$

where

$$A_4 = \begin{pmatrix} \frac{-k}{\alpha_2} & 0 & 0 & 0 & 0 \\ \frac{k}{\alpha_2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then

$$\|D^{\alpha}X(t)\| \leq \|\eta\| + (\|A_1\| + \|A_4\| + \|I\|\,\|B\|)\,\|X\|.$$

- If $\alpha_3 \neq 0$, we have

$$D^{\alpha}X(t) = \eta + A_1X + \frac{\alpha_3 HV}{\alpha_0 + \alpha_1 H + \alpha_2 V + \alpha_3 HV}A_5 + IBX,$$

where

$$A_5 = \begin{pmatrix} \frac{-k}{\alpha_3} \\ \frac{k}{\alpha_3} \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Then

$$\|D^{\alpha}X(t)\| \leq \|\eta\| + \|A_5\| + (\|A_1\| + \|I\|\,\|B\|)\|X\|.$$

Consequently, the second condition of Lemma 4 in [8] is satisfied and system (1) has a unique solution on $[0,+\infty)$.

On the other hand, we have

$$\begin{aligned} D^{\alpha}H\big|_{H=0} &= s>0,\\ D^{\alpha}I\big|_{I=0} &= f(H,V)V\geq 0, \text{ for all } H,V\geq 0,\\ D^{\alpha}C\big|_{C=0} &= aI\geq 0, \text{ for all } I\geq 0,\\ D^{\alpha}V\big|_{V=0} &= \beta D\geq 0, \text{ for all } D\geq 0,\\ D^{\alpha}Z\big|_{Z=0} &= 0. \end{aligned}$$

It follows from Lemmas 5 and 6 in [8] that the solution of (1) is non-negative.

In order to prove that the solution is bounded, we consider the following function

$$T(t)=H(t)+I(t)+\frac{\delta}{2a}C(t)+\frac{\delta(\beta+\delta)}{4a\beta}V(t)+\frac{p}{q}Z(t).$$

Then we can obtain

$$\begin{aligned} D^{\alpha}T(t) &= s-\mu H(t)-\frac{\delta}{2}I(t)-\frac{\delta(\beta+\delta)}{4a}C(t)-\frac{c\delta(\beta+\delta)}{4a\beta}V(t)-\frac{p\sigma}{q}Z(t)\\ &\leq s-\gamma T(t), \end{aligned}$$

where $\gamma=\min\{\mu,\frac{\delta}{2},\frac{\beta+\delta}{2},c,\sigma\}$. Hence,

$$T(t)\leq T(0)E_{\alpha}(-\gamma t^{\alpha})+\frac{s}{\gamma}\left[1-E_{\alpha}(-\gamma t^{\alpha})\right],$$

where $E_{\alpha}(z)=\sum_{k=0}^{\infty}\frac{z^{\alpha}}{\Gamma(\alpha k+1)}$ is the Mittag-Leffler function of parameter α.
Since $0\leq E_{\alpha}(-\gamma t^{\alpha})\leq 1$, we get

$$T(t)\leq T(0)+\frac{s}{\gamma},$$

which implies that H, I, C, V and Z are bounded. This completes the proof.

Obviously, system (1) has an infection-free equilibrium $E_0(H_0,0,0,0,0)$, where $H_0=\frac{s}{\mu}$. Then we define the first threshold parameter called the basic reproduction number as follows

$$R_0=\frac{\beta ksa}{\delta c(\alpha_0\mu+\alpha_1 s)(\beta+\delta)}.$$

The other equilibria of system (1) satisfy the following equations

$$s-\mu H-f(H,V)V = 0, \tag{4}$$

$$f(H,V)V-\delta I-pIZ = 0, \tag{5}$$

$$aI-(\beta+\delta)C = 0, \tag{6}$$

$$\beta C-cV = 0, \tag{7}$$

$$qIZ-\sigma Z = 0. \tag{8}$$

The last equation (8) implies that either $Z=0$ or $I=\dfrac{\sigma}{q}$. Each of these cases will lead to one of the other equilibria.

First, consider the case $Z=0$. Then by (4)-(7), we have $I=\dfrac{s-\mu H}{\delta}$, $C=\dfrac{a(s-\mu H)}{\delta(\beta+\delta)}$, $V=\dfrac{\beta a(s-\mu H)}{c\delta(\beta+\delta)}$ and

$$f\left(H,\frac{\beta a(s-\mu H)}{c\delta(\beta+\delta)}\right)=\frac{\delta c(\beta+\delta)}{\beta a}. \tag{9}$$

Due to $I\geq 0$, we have $H\leq\dfrac{s}{\mu}$. Define

$$g_1(H)=f\left(H,\frac{\beta a(s-\mu H)}{c\delta(\beta+\delta)}\right)-\frac{\delta c(\beta+\delta)}{\beta a}.$$

We have $g_1(0)=-\frac{\delta c(\beta+\delta)}{\beta a}<0$ and $g_1\left(\frac{s}{\mu}\right)=\frac{\delta c(\beta+\delta)}{\beta a}(R_0-1)$ and

$$g_1'(H)=\frac{\partial f}{\partial H}-\frac{\beta\mu a}{c\delta(\beta+\delta)}\frac{\partial f}{\partial V}>0.$$

When $R_0>1$, we deduce that system (1) admits a unique immune-free infection equilibrium $E_1(H_1,I_1,C_1,V_1,0)$ with $H_1\in\left(0,\dfrac{s}{\mu}\right)$, $I_1=\dfrac{s-\mu H_1}{\delta}$, $C_1=\dfrac{a(s-\mu H_1)}{\delta(\beta+\delta)}$ and $V_1=\dfrac{\beta a(s-\mu H_1)}{c\delta(\beta+\delta)}$.

For the case when $I=\dfrac{\sigma}{q}$, we get $C=\dfrac{\sigma a}{q(\beta+\delta)}$, $V=\dfrac{\beta\sigma a}{cq(\beta+\delta)}$, $Z=\dfrac{q(s-\mu H)-\delta\sigma}{q\sigma}$ and

$$f\left(H,\frac{\beta\sigma a}{cq(\beta+\delta)}\right)=\frac{cq(\beta+\delta)(s-\mu H)}{\beta\sigma a}.$$

Since $Z\geq 0$, we have $H\leq\dfrac{s}{\mu}-\dfrac{\sigma\delta}{q\mu}$. Thus, there does not exist any biologically feasible steady state whenever $H>\dfrac{s}{\mu}-\dfrac{\sigma\delta}{q\mu}$. Let us define the function g_2 defined on the interval $[0,\dfrac{s}{\mu}-\dfrac{\sigma\delta}{q\mu}]$

by

$$g_2(H) = f\left(H, \frac{\beta\sigma a}{cq(\beta+\delta)}\right) - \frac{cq(\beta+\delta)(s-\mu H)}{\beta\sigma a}.$$

Then we can easily obtain that $g_2(0) = -\dfrac{cq(\beta+\delta)(s-\mu H)}{\beta\sigma a} < 0$ and

$$g_2'(H) = \frac{\partial f}{\partial H} + \frac{cq\mu(\beta+\delta)}{\beta\sigma a} > 0.$$

In addition to the threshold parameter R_0, we define the CTL immune response reproduction number R_1 by

$$R_1 = \frac{qI_1}{\sigma}, \tag{10}$$

which describes the average number of CTL immune cells activated by infected hepatocytes in case of successful HBV infection. Here, q denotes the rate of CTL response activation, $\frac{1}{b}$ represents the average life expectancy for CTL cells and I_1 is the number of infected hepatocytes at the immune-free equilibrium E_1.

If $R_1 < 1$, then $I_1 < \frac{\sigma}{q}$, $H_1 > \frac{s}{\mu} - \frac{\sigma\delta}{q\mu}$ and

$$\begin{aligned} g_2\left(\frac{s}{\mu} - \frac{\sigma\delta}{q\mu}\right) &= f\left(\frac{s}{\mu} - \frac{\sigma\delta}{q\mu}, \frac{\beta\sigma a}{cq(\beta+\delta)}\right) - \frac{\delta c(\beta+\delta)}{\beta a} \\ &< f(H_1, V_1) - \frac{\delta c(\beta+\delta)}{\beta a} = 0. \end{aligned}$$

Therefore, there is no biological equilibrium when $R_1 < 1$.

If $R_1 > 1$, then $H_1 < \frac{s}{\mu} - \frac{\sigma\delta}{q\mu}$ and $g_2\left(\frac{s}{\mu} - \frac{\sigma\delta}{q\mu}\right) > 0$. Therefore, there exists a unique infection equilibrium with CTL immune response $E_2(H_2, I_2, C_2, V_2, Z_2)$ with $H_2 \in \left(0, \frac{s}{\mu} - \frac{\sigma\delta}{q\mu}\right)$, $I_2 = \dfrac{\sigma}{q}$, $C_2 = \dfrac{\sigma a}{q(\beta+\delta)}$, $V_2 = \dfrac{\beta\sigma a}{cq(\beta+\delta)}$ and $Z_2 = \dfrac{q(s-\mu H_2) - \delta\sigma}{p\sigma}$.

Summary of the above discussions gives rise to the following theorem.

Theorem 2.2.

(i) When $R_0 \leq 1$, model (1) has a unique infection-free equilibrium $E_0(H_0, 0, 0, 0, 0)$, where $H_0 = \dfrac{s}{\mu}$.

(ii) When $R_1 \leq 1 < R_0$, in addition to E_0, model (1) has a unique immune-free infection equilibrium $E_1(H_1, I_1, C_1, V_1, 0)$, where $H_1 \in \left(0, \frac{s}{\mu}\right)$, $I_1 = \frac{s-\mu H_1}{\delta}$, $C_1 = \frac{a(s-\mu H_1)}{\delta(\beta+\delta)}$ and $V_1 = \frac{\beta a(s-\mu H_1)}{c\delta(\beta+\delta)}$.

(iii) When $R_1 > 1$, besides E_0 and E_1, system (1) has a unique infection equilibrium with CTL immune response $E_2(H_2, I_2, C_2, V_2, Z_2)$, where $H_2 \in \left(0, \frac{s}{\mu} - \frac{\sigma\delta}{q\mu}\right)$, $I_2 = \frac{\sigma}{q}$, $C_2 = \frac{\sigma a}{q(\beta+\delta)}$, $V_2 = \frac{\beta\sigma a}{cq(\beta+\delta)}$ and $Z_2 = \frac{q(s-\mu H_2)-\delta\sigma}{p\sigma}$.

3. Stability analysis

In this section, we analyse the stability of the three equilibria of (1). We first have the following result.

Theorem 3.1. *The infection-free equilibrium E_0 is globally asymptotically stable for $R_0 \leq 1$ and it becomes unstable for $R_0 > 1$.*

Proof. In order to show the first part of this theorem, we consider the following Lyapunov functional

$$L_0(t) = \frac{\alpha_0 H_0}{\alpha_0 + \alpha_1 H_0}\Phi\left(\frac{H}{H_0}\right) + I + \frac{\delta}{a}C + \frac{\delta(\beta+\delta)}{\beta a}V + \frac{p}{q}Z,$$

where $\Phi(x) = x - 1 - \ln(x)$ for $x > 0$. Based on the property of fractional derivatives given in [9], we get

$$D^\alpha L_0(t) \leq \frac{\alpha_0}{\alpha_0 + \alpha_1 H_0}\left(1 - \frac{H_0}{H}\right)D^\alpha H + D^\alpha I + \frac{\delta}{a}D^\alpha C + \frac{\delta(\beta+\delta)}{\beta a}D^\alpha V + \frac{p}{q}D^\alpha Z.$$

By $s = \mu H_0$, we have

$$\begin{aligned} D^\alpha L_0(t) &\leq -\frac{\mu\alpha_0(H-H_0)^2}{(\alpha_0+\alpha_1 H_0)H} + \frac{\delta c(\beta+\delta)}{\beta a}\left(\frac{f(H,V)}{f(H,0)}R_0 - 1\right)V - \frac{p\sigma}{q}Z \\ &\leq -\frac{\mu\alpha_0(H-H_0)^2}{(\alpha_0+\alpha_1 H_0)H} + \frac{\delta c(\beta+\delta)}{\beta a}(R_0-1)V - \frac{p\sigma}{q}Z. \end{aligned}$$

Then $D^\alpha L_0(t) \leq 0$ when $R_0 \leq 1$. Also, the largest invariant set in $\{(H, I, C, V, Z) \mid D^\alpha L_0(t) = 0\}$ is the singleton $\{E_0\}$. By LaSalle's invariance principale [10], we deduce that E_0 is globally asymptotically stable for $R_0 \leq 1$.

It remains to investigate the dynamical property of E_0 in case when $R_0 > 1$. For this purpose, we compute the characteristic equation about E_0 that it is given by

$$(\mu+\xi)(\sigma+\xi)P_0(\xi)=0,$$

where $P_0(\xi)=\xi^3+a_1\xi^2+a_2\xi+a_3$ and

$$\begin{aligned} a_1 &= \beta+c+2\delta, \\ a_2 &= \delta(\beta+\delta)+c(2\delta+\beta), \\ a_3 &= c\delta(\beta+\delta)(1-R_0). \end{aligned}$$

We have $\lim_{\xi\to+\infty} P_0(\xi)=+\infty$ and $P_0(0)=c\delta(\beta+\delta)(1-R_0)$. Then $P_0(0)<0$ when $R_0>1$. Hence, there exists a $\xi_0\in(0,+\infty)$ such that $P_0(\xi_0)=0$, which implies that the characteristic equation at E_0 has a positive root when $R_0>1$. Consequently, E_0 is unstable whenever $R_0>1$. This completes the proof.

Theorem 3.2. *The immune-free infection equilibrium E_1 is globally asymptotically stable for $R_1 \leq 1 < R_0$ and it becomes unstable for $R_1 > 1$.*

Proof. In order to establish the global stability part, we define a Lyapunov functional as follows

$$\begin{aligned} L_1(t) &= \frac{\alpha_0+\alpha_2V_1}{\alpha_0+\alpha_1H_1+\alpha_2V_1+\alpha_3H_1V_1}H_1\Phi\left(\frac{H}{H_1}\right)+I_1\Phi\left(\frac{I}{I_1}\right)+\frac{\delta}{a}C_1\Phi\left(\frac{C}{C_1}\right) \\ &\quad +\frac{\delta(\beta+\delta)}{a\beta}V_1\Phi\left(\frac{V}{V_1}\right)+\frac{p}{q}Z. \end{aligned}$$

The time derivative of $L_1(t)$ along the positive solutions of system (1) satisfies:

$$\begin{aligned} D^\alpha L_1(t) &\leq \left(1-\frac{f(H_1,V_1)}{f(H,V_1)}\right)D^\alpha H+\left(1-\frac{I_1}{I}\right)D^\alpha I+\frac{\delta}{a}\left(1-\frac{C_1}{C}\right)D^\alpha C \\ &\quad +\frac{\delta(\beta+\delta)}{a\beta}\left(1-\frac{V_1}{V}\right)D^\alpha V+\frac{p}{q}D^\alpha Z. \end{aligned}$$

By using $s = \mu H_1 + f(H_1,V_1)V_1$, we get

$$\begin{aligned} D^\alpha L_1(t) \quad \leq \quad & -\frac{\mu\left(\alpha_0+\alpha_2 V_1\right)\left(H-H_1\right)^2}{\left(\alpha_0+\alpha_1 H_1+\alpha_2 V_1+\alpha_3 H_1 V_1\right)H} + \frac{p\sigma}{q}\left(R_1-1\right)Z \\ & + f(H_1,V_1)V_1\left(5-\frac{f(H_1,V_1)}{f(H,V_1)}-\frac{C_1 I}{C I_1}-\frac{f(H,V)}{f(H_1,V_1)}\frac{V I_1}{V_1 I}-\frac{C V_1}{C_1 V}-\frac{f(H,V_1)}{f(H,V)}\right) \\ & - \frac{f(H_1,V_1)V_1(\alpha_0+\alpha_1 H)(\alpha_2+\alpha_3 H)(V-V_1)^2}{(\alpha_0+\alpha_1 H+\alpha_2 V_1+\alpha_3 H V_1)(\alpha_0+\alpha_1 H+\alpha_2 V+\alpha_3 H V)V_1}. \end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean, we have

$$5-\frac{f(H_i,V_i)}{f(H,V_i)}-\frac{C_i I}{C I_i}-\frac{f(H,V)}{f(H_i,V_i)}\frac{V I_i}{V_i I}-\frac{C V_i}{C_i V}-\frac{f(H,V_i)}{f(H,V)} \leq 0, \text{ for } i \in \{1,2\} \tag{11}$$

Therefore, $D^\alpha L_1(t) \leq 0$ if $R_1 \leq 1$. In addition, the largest compact invariant set in $\{(H,I,C,V,Z) \mid D^\alpha L_1(t) = 0\}$ is the singleton $\{E_1\}$. By the LaSalle's invariance principale, E_1 is globally asymptotically stable for $R_1 \leq 1 < R_0$.

On the other hand, the characteristic equation at E_1 is as follows

$$(qI_1 - \sigma - \xi)P_1(\xi) = 0, \tag{12}$$

where

$$P_1(\xi) = \begin{vmatrix} -\mu - V_1\frac{\partial f}{\partial H} - \xi & 0 & 0 & -V_1\frac{\partial f}{\partial V} - f(H_1,V_1) \\ V_1\frac{\partial f}{\partial H} & -\delta & 0 & V_1\frac{\partial f}{\partial V} + f(H_1,V_1) \\ 0 & a & -(\beta+\delta) & 0 \\ 0 & 0 & \beta & -c \end{vmatrix} \tag{13}$$

Clearly, the equation (12) has a root $\xi_1 = qI_1 - \sigma$. Then, when $R_1 > 1$, we have $\xi_1 > 0$. In this case, E_1 is unstable.

Finally, we investigate the global stability of the third equilibrium E_2.

Theorem 3.3. *The infection equilibrium with CTL immune response E_2 is globally asymptotically stable when $R_1 > 1$.*

Proof. Consider the following Lyapunov functional

$$\begin{aligned} L_2(t) &= \frac{\alpha_0+\alpha_2V_2}{\alpha_0+\alpha_1H_2+\alpha_2V_2+\alpha_3H_2V_2}H_2\Phi\left(\frac{H}{H_2}\right)+I_2\Phi\left(\frac{I}{I_2}\right) \\ &\quad +\frac{(\delta+pZ_2)}{a}C_2\Phi\left(\frac{C}{C_2}\right)+\frac{(\delta+pZ_2)(\beta+\delta)}{a\beta}V_2\Phi\left(\frac{V}{V_2}\right) \\ &\quad +\frac{p}{q}Z_2\Phi\left(\frac{Z}{Z_2}\right). \end{aligned}$$

Calculating the time derivative of $L_2(t)$ along the positive solutions of (1), we have

$$\begin{aligned} D^\alpha L_2(t) &\leq \left(1-\frac{f(H_2,V_2)}{f(H,V_2)}\right)D^\alpha H+\left(1-\frac{I_2}{I}\right)D^\alpha I+\frac{(\delta+pZ_2)}{a}\left(1-\frac{C_2}{C}\right)D^\alpha C \\ &\quad +\frac{(\delta+pZ_2)(\beta+\delta)}{a\beta}\left(1-\frac{V_2}{V}\right)D^\alpha V+\frac{p}{q}\left(1-\frac{Z_2}{Z}\right)D^\alpha Z. \end{aligned}$$

By applying the equality $s=\mu H_2+f(H_2,V_2)V_2$, we obtain

$$\begin{aligned} D^\alpha L_2(t) &\leq \frac{-\mu(\alpha_0+\alpha_2V_2)(H-H_2)^2}{(\alpha_0+\alpha_1H_2+\alpha_2V_2+\alpha_3H_2V_2)H_2} \\ &\quad +f(H_2,V_2)V_2\left(5-\frac{f(H_2,V_2)}{f(H,V_2)}-\frac{C_2I}{CI_2}-\frac{f(H,V)}{f(H_2,V_2)}\frac{VI_2}{V_2I}-\frac{CV_2}{C_2V}-\frac{f(H,V_2)}{f(H,V)}\right) \\ &\quad -\frac{f(H_2,V_2)V_2(\alpha_0+\alpha_2H)(\alpha_2+\alpha_3H)(V-V_2)^2}{(\alpha_0+\alpha_1H+\alpha_2V_2+\alpha_3HV_2)(\alpha_0+\alpha_1H+\alpha_2V+\alpha_3HV)V_2}. \end{aligned}$$

From (11), we have $D^\alpha L_2(t)\leq 0$. Observe that $D^\alpha L_2(t)=0$ if and only if $H=H_2$, $I=I_2$, $C=C_2$, $V=V_2$ and $Z=Z_2$. This implies that the largest compact invariant set in $\{(H,I,C,V,Z)\mid D^\alpha L_2(t)=0\}$ is the singleton $\{E_2\}$. If follows from LaSalle's invariance principale that E_2 is globally asymptotically stable.

4. Numerical simulations

In this section, we validate our theoretical results by numerical simulations. We solve numerically the nonlinear fractional model (1) by applying the method developed by Odibat and Momani in [11]. This method is a generalization of the classical Euler's method.

First, we choose $s=5.04\times10^5$, $\mu=0.0039$, $k=3\times10^{-6}$, $\delta=0.00693$, $p=0.00064$, $a=150$, $\beta=0.2$, $c=0.67$, $q=4.4\times10^{-7}$, $\sigma=0.05$, $\alpha_0=1$, $\alpha_1=0.1$, $\alpha_2=0.0001$ and $\alpha_3=0.0000001$. In this case, $R_0=0.9367<1$. According to Theorem 3.1, the infection-free equilibrium $E_0(1.2923\times10^8,0,0,0,0)$ is globally asymptotically stable (see figure 1).

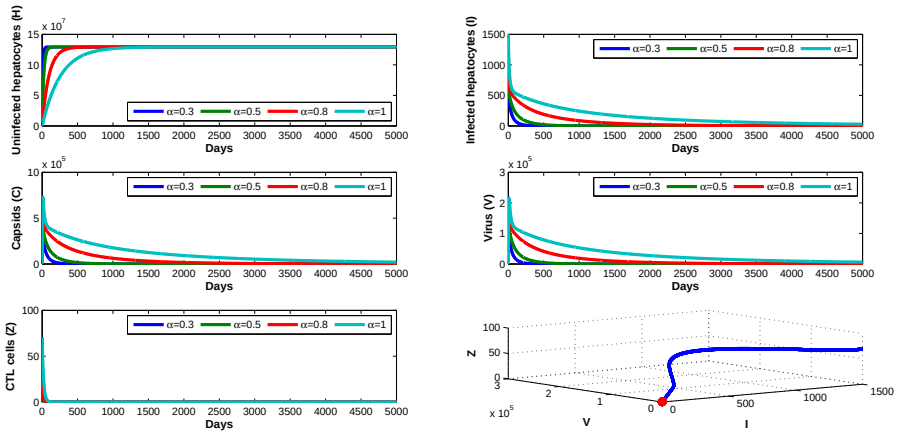

FIGURE 1. Stability of the infection-free equilibrium E_0.

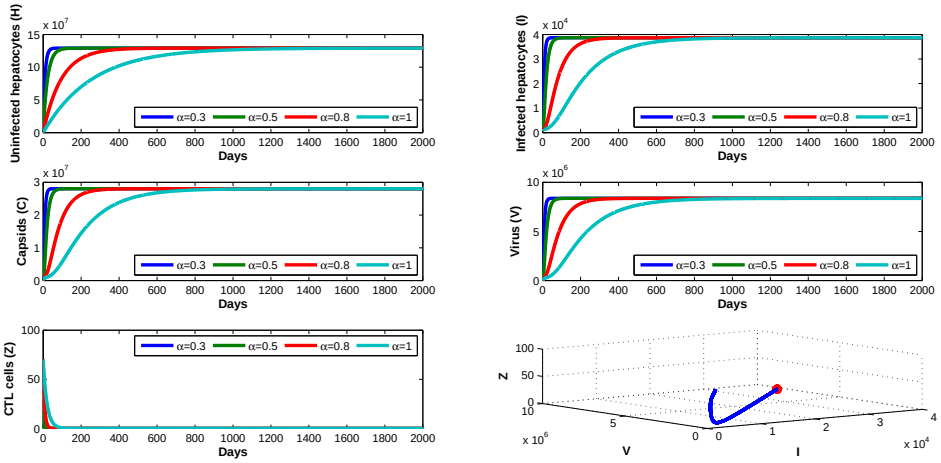

FIGURE 2. Stability of the immune-free infection equilibrium E_1.

Next, we choose $k = 3 \times 10^{-5}$ and do not change the other parameter values. For this case, we obtain $R_0 = 9.3672 > 1$ and $R_1 = 0.3403 < 1$. Applying Theorem 3.2, the immune-free infection equilibrium $E_1(1.2916 \times 10^8, 3.8668 \times 10^4, 2.8030 \times 10^7, 8.3672 \times 10^6, 0)$ is globally asymptotically stable (see figure 2).

Finally, we change $q = 4.4 \times 10^{-6}$ and the other parameters have the same values as in the second case. By calculation, we have $R_1 = 3.4028 > 1$. Then model (1) has an infection equilibrium with CTL immune response $E_2(1.2918 \times 10^8, 1.1364 \times 10^4, 8.2373 \times 10^6, 2.4589 \times 10^6, 18.4959)$ which is globally asymptotically stable. Figure 3 illustrates this result.

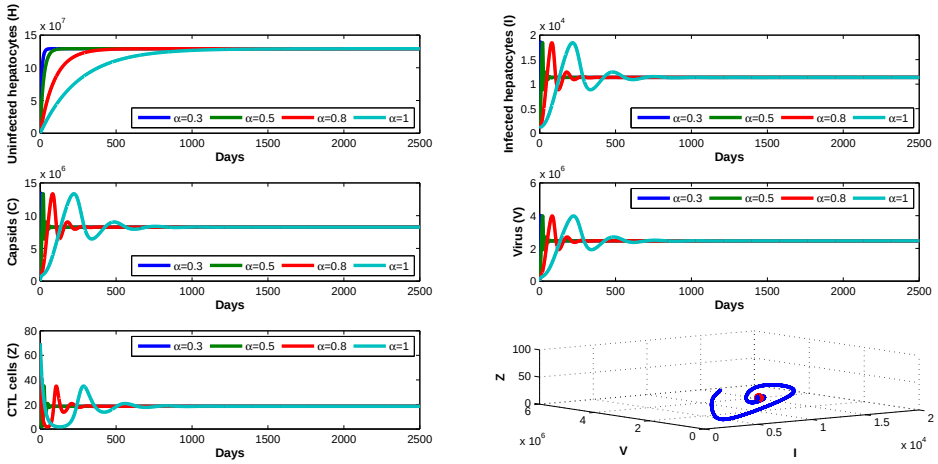

FIGURE 3. Stability of the infection equilibrium with CTL immune response E_2.

5. Conclusions

In this work, we have proposed a fractional order model for HBV infection with capsids, cellular immunity and Hattaf-Yousfi functional response that includes the traditional bilinear incidence rate, the saturated incidence rate, the Beddington-DeAngelis functional response and the Crowley-Martin functional response. We have derived two critical threshold parameters that are the basic reproduction number R_0 and the CTL immune response reproduction number R_1. We have proved that the global dynamical behaviors of the proposed model are completely determined by both threshold parameters. More concretely, the infection-free equilibrium E_0 is globally asymptotically stable when $R_0 \leq 1$ which leads to the eradication of virus in the host. When $R_0 > 1$, two cases arise depending on the value of R_1. For $R_1 \leq 1$, the immune-free infection E_1 becomes globally asymptotically stable and for $R_1 > 1$, the infection equilibrium with CTL immune response E_2 becomes globally asymptotically stable. These results show that the virus persists in the liver despite the activation or not of the CTL immune response. Furthermore, the models and results presented in [6, 7] are extended and improved.

According to the above analytical results, we deduce that the order α of the Caputo fractional derivative does not affect the stability of equilibria. But from the numerical simulations, we observe that when the value of α decreases (long memory), the solutions of the model converge rapidly to the steady states. So, the fractional order can affect the time for arriving to the steady

states and reduces the oscillations (see figures 1, 2 and 3). In addition, we conclude that the activation of CTL immune response is unable to eliminate the virions in the liver, but plays an important role in HBV infection by reducing the viral load, increasing the healthy hepatocytes and decreasing the infected hepatocytes.

Conflict of Interests

The authors declare that there is no conflict of interests.

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