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Modeling the Adaptive Immune Response in an HBV Infection Model with Virus to Cell Transmission in Both Liver with CTL Immune Response and the Extrahepatic Tissue

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Abstract: The objective of this paper is to investigate a mathematical model describing the infection of hepatitis B virus (HBV) in intrahepatic and extrahepatic tissues. Additionally, the model includes the effect of the cytotoxic T cell (CTL) immunity, which is described by a linear activation rate by infected cells. The positivity and boundedness of solutions for non-negative initial data are proven, which is consistent with the biological studies. The local stability of the equilibrium is established. In addition to this, the global stability of the disease-free equilibrium and the endemic equilibrium is fulfilled by using appropriate Lyapanov functions. Finally, numerical simulations are performed to support our theoretical findings. It has been revealed that the fractional-order derivatives have no influence on the stability but only on the speed of convergence toward the equilibria.

1. Introduction

The hepatitis B virus (HBV) attacks liver cells (hepatocytes) and kills almost a million people every year. The HBV is known as a global public health issue [1,2], and it infects around two billion people, with more than 360 million chronic carriers. This serious infection can be easily transferred by any infected bodily fluid contact [3–5], and it can cause acute or chronic disease following transmission. Many mathematical models have been constructed to represent and better comprehend the dynamics of this deadly viral illness [6–9]. All of these models take into account how the HBV virus interacts with both healthy and diseased liver cells. However, HBV infection models with two compartments are rare. Recently, the model for describing the adaptive immune response in an HBV infection model with virus to cell transmission in both liver with CTL immune response and the extrahepatic tissue is studied in [10]. They have used the following system of differential equation:

$$
\begin{cases}
\dfrac{dH_1(t)}{dt} = s_1 - d_1 H_1 - b_1 H_1 V, \\[2mm]
\dfrac{dI_1(t)}{dt} = b_1 H_1 V - a_1 I_1 - p I_1 W, \\[2mm]
\dfrac{dH_2(t)}{dt} = s_2 - d_2 H_2 - b_2 H_2 V, \\[2mm]
\dfrac{dI_2(t)}{dt} = b_2 H_2 V - a_2 I_2, \\[2mm]
\dfrac{dV(t)}{dt} = k_1 I_1 + k_2 I_2 - \sigma V, \\[2mm]
\dfrac{dW(t)}{dt} = q I_1 W - r W.
\end{cases}
$$

where we denote the liver and the second extrahepatic compartment as compartments C_1 and C_2, respectively. In this model, H_1, I_1, H_2, I_2, V and W denote the concentrations of uninfected hepatocytes in C_1, infected hepatocytes in C_1, uninfected hepatocytes in C_2, infected hepatocytes in C_2, free virus and the CTL immune response (in C_1) at time t, respectively. In addition, s_i is the recruitment rate of healthy cells and $\frac{1}{d_i}$ is the average lifespan of uninfected cells in compartment $C_i(i = 1, 2)$. The healthy cells become infected by free virus at a rate $b_1 H_1 V$, infected cells in compartment $C_i(i = 1, 2)$ die at a rate $a_i I_i$, and infected cells in compartment C_1 are cleared by the CTL immune response at a rate $p I_1 W$. Free virus (V) grow in blood at a rate $k_1 I_1 + k_2 I_2$, decay at a rate σV. Finally, CTLs (W) expand in response to viral antigen derived from infected cells at a rate $q I_1 W$ and decay in the absence of antigenic stimulation at a rate rW.

In this paper, we will study the same above problem but using the fractional derivative equations that will be considered is as follows:

$$\begin{cases} D^\alpha H_1(t) = s_1 - d_1 H_1 - b_1 H_1 V, \\ D^\alpha I_1(t) = b_1 H_1 V - a_1 I_1 - p I_1 W, \\ D^\alpha H_2(t) = s_2 - d_2 H_2 - b_2 H_2 V, \\ D^\alpha I_2(t) = b_2 H_2 V - a_2 I_2, \\ D^\alpha V(t) = k_1 I_1 + k_2 I_2 - \sigma V, \\ D^\alpha W(t) = q I_1 W - rW. \end{cases} \quad (1)$$

where α is the order of the fractional derivative and $H_1(0) = H_{10}, I_1(0) - I_{10}, H_2(0) - H_{20}, I_1(0) - I_{20}, V(0) - V_0 W(0) - W_0$ are the initial data, such as our dynamical model with two HBV proliferative compartments: One is the liver, whereas the other is the extrahepatic compartment, which includes serum, peripheral blood mononuclear cells and perihepatic lymph nodes. According to the investigations, the immune response has an influence, or it has no impact on the extrahepatic compartment. It is considered that the CTL response plays a half function in clearing infected hepatocytes. Furthemore, it has no role in the second proliferative compartment of extrahepatic tissue. We notice that the fractional derivative order can be considered as an index of memory in many biological and physical problems [11]. For instance, for evolution problems in biology, we can find this kind of derivative to model HBV [12]. The fractional derivative equations were used study other models such as Kawahar and KdV equations [13–17]. Different papers studied the behavior of many viral infections by using the fractional derivative equations [18–22]. We notice that the Laplace operator has been used to study the stability of a fractional-order delayed predator–prey system [23]. In addition, fractional derivative have shown its efficiency in studying many biological systems [24–26]. Recently, optimal control problems have been studied using fractional derivative equations [27]. These same techniques were applied to study the interaction between tumor cells and the immune system [28]. Therefore, our motivation in this paper is to take into account the memory effect in our biological dynamical system by incorporating the fractional derivative instead of the ordinary one.

The paper is organized as follows. The next section is devoted to the existence, positivity and boundedness of solutions, which is followed in Section 4 by the local stability analysis. In Section 5, we study the global stability of the equilibrium. We construct an appropriate numerical algorithm and give some numerical simulations in Section 6, and the last section concludes the work.

2. Preliminary Results

Is this section, we recall some preliminary definitions of the fractional order integral, Caputo fractional derivative and Mittag–Leffler function [29].

Definition 1. *The fractional integral of order $\alpha > 0$ of a function $\psi : \mathbb{R}_+ \to \mathbb{R}$ is defined by*

$$I^\alpha \psi(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} \psi(s) ds$$

where $\Gamma(.)$ stands for Gamma function.

Definition 2. *The Caputo fractional derivative of order $\alpha > 0$ of a function $\psi : \mathbb{R}_+ \to \mathbb{R}$ is given as follows*

$$D^\alpha \psi(t) = I^{n-a} D^n \psi(t)$$

where $D = \frac{d}{d}t$ and $n - 1 \leq \alpha \leq n, n \in N$. In addition, if $0 < \alpha \leq 1$, we have

$$D^\alpha \psi(t) = \frac{1}{\Gamma(\alpha - 1)} \int_0^t \frac{\psi'(s)}{(t-s)^\alpha} ds$$

Definition 3. *Let $\alpha > 0$. The function*

$$E_a(t) = \sum_{j=0}^{+\infty} \frac{t^j}{\Gamma(aj+1)}$$

is called the Mittag–Leffler function of parameter α.

Let $f : \mathbb{R}^n \to \mathbb{R}^n$ where $n \geq 1$. Consider the fractional order system

$$D^\alpha X(t) = f(X)$$
$$X(0) = X_0 \tag{2}$$

with $0 < \alpha \leq 1$, and $X_0 \in \mathbb{R}^n$. For the global existence of solution of system (2), we have the following lemma.

Lemma 1. *Assume that f satisfies the following conditions*
- *$f(X)$ and $(\partial f / \partial X)(X)$ are continuous on $\mathbb{R}^n$.*
- *$\|f(X)\| \leq c_1 + c_2 \|X\|$ for all $X \in \mathbb{R}^n$, with c_1 and c_2 are two positive constants.*
  Then, the system (2) has a unique solution defind on $\mathbb{R}^+$.

The proof of this lemma follows immediately from [20].

3. Positivity and Boundedness of Solutions

It is commonly known that any solutions reflecting cell densities in issues involving cell population evolution should be non-negative and bounded. As a result, demonstrating the model's positivity and boundedness will be important. First of all, for biological reasons, the initial data $H_{10}, I_{10}, H_{20}, I_{20}, V_0$ and W_0 must be larger than or equal to 0. The main result of this section is given as follows:

Proposition 1. *For any non-negative initial conditions, there exists an unique solution of system (1) defined on $\mathbb{R}^+$. In addition, this solution is non-negative and bounded $t \geq 0$.*

Proof. The model (1) can be described as follows:

$$D^\alpha X(t) = f(X) \tag{3}$$

with

$$X = \begin{pmatrix} H_1 \\ I_1 \\ H_2 \\ I_2 \\ V \\ W \end{pmatrix}$$

and

$$f(X) = \begin{pmatrix} s_1 = d_1 H_1 = b_1 H_1 V \\ b_1 H_1 V = a_1 I_1 = p I_1 W \\ s_2 = d_2 H_2 = b_2 H_2 V \\ b_2 H_2 V = a_2 I_2 \\ k_1 I_1 + k_2 I_2 = \sigma V \\ q_1 W = rW \end{pmatrix}$$

Note that if $\alpha = 1$, (3) will be a system with ODEs. By using the results in [19], we establish the existence of solutions. In the case of FDEs, let

$$A_1 = \begin{pmatrix} s_1 \\ 0 \\ s_2 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$A_2 = \begin{pmatrix} -d_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & -a_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -d_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & -a_2 & 0 & 0 \\ 0 & k_1 & 0 & k_2 & -\sigma & 0 \\ 0 & 0 & 0 & 0 & 0 & -r \end{pmatrix},$$

$$A_3 = \begin{pmatrix} -b_1 & 0 & 0 & 0 & 0 & 0 \\ b_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -b_2 & 0 & 0 & 0 \\ 0 & 0 & b_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$A_4 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -p & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & q & 0 & 0 & 0 & 0 \end{pmatrix}$$

Therefore,

$$f(X) = A_1 + A_2 X + V A_3 X + W A_4 X$$

This implies that

$$\|f(X)\| \le \|A_1\| + (\|A_2\| + \|V\|\|A_3\| + \|W\|\|A_4\|)\|X\|$$

Hence, the proprieties of the previous Lemma are satisfied. Then, system (1) has a unique solution on R^+. Now, we will show that the non-negative solutions $\mathbf{R}_+^6 = \{(H_1, I_1, H_2, I_2, V, W) \in \mathbb{R}^6 : H_1 \ge 0, I_1 \ge 0, H_2 \ge 0, I_2 \ge 0, V \ge 0 \text{ and } W \ge 0\}$ is positively invariant. Indeed, for $(H_1(t), I_1(t), H_2(t), I_2(t), V(t), W(t)) \in \mathbb{R}_+^6$, we have:

$$D^\alpha H_{1\,H_1=0} = s_1 \geq 0; \quad D^\alpha I_{1\,I_1=0} = b_1 H_1 V \geq 0; \quad D^\alpha H_{2\,H_2=0} = s_2 \geq 0;$$
$$D^\alpha I_{2\,I_2=0} = b_2 H_2 V \geq 0; \quad D^\alpha V_{V=0} = k_1 I_1 + k_2 I_2 \geq 0 \text{ and } D^\alpha W_{W=0} = 0 \geq 0$$

Therefore, all solutions initiating in $\mathbb{R}^6_+$ are positive. Next, we will prove that these solutions remain bounded.

$$D^\alpha T_1(t) = s_1 - d_1 H_1 - a_1 I_1 - p I_1 W$$
$$T_i(t) = H_i(t) + I_i(t) \quad \text{and} \quad \delta_1 = \min(d_1, a_1)$$
$$\begin{cases} T_1(t) = T_1(0)e^{-\delta_1 t} + \frac{s_1}{\delta_1}\left(1 - e^{-\delta_1 t}\right) \\ \delta_1 - \min(d_1, a_1); \quad 0 \leq e^{-d_2 t} \leq 1 \quad \text{then} \quad 1 - e^{-d_2 t} \leq 1 \end{cases}$$

$$T_1(t) \leq T_1(0) + \frac{s_1}{\delta_1}$$

Therefore, H_1 and I_1 are bounded.

$$D^\alpha T_2(t) = s_2 - d_2 H_2 - a_2 I_2$$
$$\begin{cases} T_2(t) = T_2(0)e^{-\delta_2 t} + \frac{s_2}{\delta_2}\left(1 - e^{-\delta_2 t}\right) \\ \delta_2 = \min(d_2, a_2); \quad 0 \leq e^{-\delta_2 t} \leq 1 \quad \text{then} \quad 1 - e^{-\delta_2 t} \leq 1 \end{cases}$$

$$T_2(t) \leq T_2(0) + \frac{s_2}{\delta_2}$$

Therefore, H_2 and I_2 are bounded.

$$D^\alpha W(t) = q I_1 W - r W$$

then

$$\begin{aligned} D^\alpha W(t) + rW &= q I_1 W \\ &= \frac{q}{p}\left(-D^\alpha I_1(t) + b_1 H_1 V - a_1 I_1\right) \\ &= \frac{q}{p}\left(-D^\alpha I_1(t) + s_1 - d_1 H_1 - D^\alpha H_1(t) - a_1 I_1\right) \\ &= \frac{q}{p}\left(s_1 - (D^\alpha I_1(t) + a_1 I_1) - (D^\alpha H_1(t) + d_1 H_1)\right) \\ &\leq \left[\frac{q}{p}\left(I_1(0) + H_1(0) - \frac{s_1}{r}\right) + W(0)\right]e^{-rt} \\ &\quad + \frac{p}{q}\left\{\frac{s_1}{r} + \int_0^t [(r - d_1)H_1(\xi) + (r - a_1)I_1(\xi)]e^{r(\xi - t)}d\xi\right\} \\ &\quad - H_1(t) - I_1(t). \\ &\leq W(0) + \frac{p}{q}\left[\max\left(1; 2 - \frac{d_1}{r}\right)H_1(0) + I_1(0) + \max\left(\frac{s_1}{r}; \frac{s_1}{d_1}\right) \\ &\quad + \max\left(0; 1 - \frac{a_1}{r}\right)\|I_1\|_\infty\right] \end{aligned}$$

Therefore, W is bounded. From the fifth equation of (1), we obtain

$$D^\alpha V(t) = k_1 I_1 + k_2 I_2 - \sigma V$$
$$D^\alpha V(t) = V_0 e^{-\sigma t} + (k_1 + k_2)\left\{\int_0^t e^{\sigma(\xi - t)}(I_1(\xi) + I_2(\xi))d\xi\right\}$$
$$\leq V_0 + \frac{(k_1 + k_2)}{\sigma}\|I_1 + I_2\|_\infty\left(1 - e^{\sigma t}\right)$$
$$\leq V_0 + \frac{(k_1 + k_2)}{\sigma}\|I_1 + I_2\|_\infty$$

We conclude that all the solutions are bounded and also, each local solution can be prolonged up to any positive time, which means that the solution of the problem exists globally. □

4. Local Stability of Equilibrium

At any equilibrium system, we have

$$
\begin{cases}
s_1 - d_1 H_1 - b_1 H_1 V = 0 \\
b_1 H_1 V - a_1 I_1 - p I_1 W = 0 \\
s_2 - d_2 H_2 - b_2 H_2 V = 0 \\
b_2 H_2 V - a_2 I_2 = 0 \\
k_1 I_1 + k_2 I_2 - \sigma V = 0 \\
q I_1 W - r W = 0
\end{cases}
\tag{4}
$$

by the first and third equation of this system, we obtain

$$
H_1 = \frac{s_1}{b_1 V + d_1}; \quad H_2 = \frac{s_2}{b_2 V + d_2}
$$

Substituting them into the second and fourth equations of the same system, they yield, respectively,

$$
I_1 = \frac{s_1 b_1 V}{(a_1 + pW)(b_1 V + d_1)}; \quad I_2 = \frac{s_2 b_2 V}{a_2 (b_2 V + d_2)}
$$

When $V \neq 0$ and $W = 0$, substituting I_1 and I_2 of (3) into the fifth equation of (4)

$$
f(V) := \frac{1}{\sigma} \left[\frac{k_1 b_1 s_1}{a_1 (b_1 V + d_1)} + \frac{k_2 b_2 s_2}{a_2 (b_2 V + d_2)} \right] = 1
$$

We can see that this function $f(V)$ is decreasing with respect to V. We have

$$
f \left(\frac{1}{\sigma} \left(\frac{k_1 s_1}{d_1} + \frac{k_2 s_2}{d_2} \right) \right) \leq \frac{1}{1 + \frac{d_1 k_2 s_2}{d_2 k_1 s_1} + \frac{\sigma d_1^2}{k_1 b_1 s_1}} + \frac{1}{1 + \frac{d_2 k_1 s_1}{d_1 k_2 s_2} + \frac{\sigma d_2^2}{k_2 b_2 s_2}} := f_0
$$

By the monotonicity of function $f(V)$, Equation (3) has a unique positive root $V^{(1)}$ only when

$$
f(0) = \frac{1}{\sigma} \left[\frac{k_1 b_1 s_1}{a_1 d_1} + \frac{k_2 b_2 s_2}{a_2 d_2} \right] > 1
$$

Thus, (1) has a boundary equilibrium $E_1 \left(H_1^{(1)}, I_1^{(1)}, H_2^{(1)}, I_2^{(1)}, V^{(1)}, 0 \right)$ when $f(0) > 1$.

When $W \neq 0$, from the last equation of system (4), we have $I_1 = \frac{r}{q} := I_1^{(2)}$. Substituting it and $H_1 = \frac{s_1}{b_1 V + d_1}$ into the second equation of (4) gives

$$
W = \frac{q}{pr(b_1 V + d_1)} \left[b_1 \left(s_1 - \frac{a_1 r}{q} \right) V - \frac{a_1 d_1 r}{q} \right]
$$

Then, a necessary condition on the existence of the positive equilibrium is $s_1 > \frac{a_1 r}{q}$, and for the positive equilibrium $E_2 \left(H_1^{(2)}, I_1^{(2)}, H_2^{(2)}, I_2^{(2)}, V^{(2)}, W^{(2)} \right)$, substituting $I_1 = \frac{r}{q}$ and $I_2 = \frac{s_2 b_2 V}{a_2 (b_2 V + d_2)}$ into the fifth equation of (4) yields

$$
g(V) := \frac{1}{\sigma} \left[\frac{k_1 r}{qV} + \frac{k_2 b_2 s_2}{a_2 (b_2 V + d_2)} \right] = 1
$$

In the case $s_1 > \frac{a_1 r}{q}$, we have

$$g\left(\frac{1}{\sigma}\left(\frac{k_1 s_1}{d_1} + \frac{k_2 s_2}{d_2}\right)\right) \le \frac{1}{1 + \frac{d_1 k_2 s_2}{d_2 k_1 s_1}} + \frac{1}{1 + \frac{d_2 k_1 s_1}{d_1 k_2 s_2} + \frac{\sigma d_2^2}{k_2 b_2 s_2}} < 1$$

Then, according to the monotonicity of function $g(V)$, we have $\lim_{V \to 0^+} g(V) = +\infty$; then, $g(V) = 1$ has a unique root in the interval $\left(\bar{V}, \frac{1}{\sigma}\left(\frac{k_1 s_1}{d_1} + \frac{k_2 s_2}{d_2}\right)\right)$ if and only if $g(\bar{V}) > 1$. For all this, we will determine the steady states of the model (1). The basic infection reproductive number of the system (1) is given by

$$R_0 = \frac{1}{\sigma}\left(\frac{k_1 b_1 s_1}{a_1 d_1} + \frac{k_1 b_2 s_2}{a_2 d_2}\right).$$

From a biological point of view, R_0 denotes the average number of secondary infections generated by one infected cell when all cells are uninfected. Moreover, the same system has the following disease-free equilibrium

$$E_f = \left(\frac{s_1}{d_1}, 0, \frac{s_2}{d_2}, 0, 0, 0\right)$$

In addition, model (1) admits two endemic steady states

$$E_1 = \left(H_1^1, I_1^1, H_2^1, I_2^1, V^1, 0\right)$$

where

$$H_1^1 = \frac{s_1}{b_1 V^1 + d_1},$$

$$I_1^1 = \frac{b_1 s_1 V^1}{a_1(b_1 V^1 + d_1)},$$

$$H_2^1 = \frac{s_2}{b_2 V^1 + d_2},$$

$$I_2^1 = \frac{b_2 s_2 V^1}{a_2(b_2 V^1 + d_2)}.$$

where $V^{(1)}$ is the positive root of (4). This endemic equilibrium exists when $R_0 \ge 1$, and

$$E_2 = \left(H_1^2, I_1^2, H_2^2, I_2^2, V^2, W^2\right)$$

where

$$H_1^2 = \frac{s_1}{b_1 V^2 + d_1},$$

$$I_1^2 = \frac{r}{q},$$

$$H_2^2 = \frac{s_2}{b_2 V^2 + d_2},$$

$$I_2^2 = \frac{b_2 s_2 V^2}{a_2(b_2 V^2 + d_2)}$$

and

$$W^2 = \frac{a_1}{p}(R_1 - 1).$$

Here

$$R_1 = \frac{q I_1^{(1)}}{r}$$

and $V^{(2)}$ is the positive root of (4). This endemic equilibriam exists when $R_1 \ge 1$.

5. Global Stability of the Equilibrium

In this section, we will study the global stability of each equilibrium of system (1) by using some suitable Lyapunov functional and by using LaSalle's invariant principle [4]. For the infection-free equilibrium E_f, we have the following result:

Theorem 1. *If $R_0 \leq 1$, then the infection-free equilibrium $E_0 = \left(\frac{s_1}{d_1}, 0, \frac{s_2}{d_2}, 0, 0, 0 \right)$ is globally asymptotically stable.*

Proof. When $R_0 \leq 1$, we have $\frac{k_1 b_1 s_1}{a_1 d_1 g} < 1$ and $\frac{k_2 b_2 s_2}{a_2 d_2 g} < 1$, that is $\frac{b_1 s_1}{d_1} < \frac{g a_1}{k_1}$ and $\frac{b_2 s_2}{d_2} < \frac{g a_2}{k_2}$. So, $R_0 \leq 1$ is equivalent to the following inequality.

$$0 < \frac{\frac{q b_1 s_1}{p d_1}}{\frac{g a_2}{k_2} - \frac{b_2 s_2}{d_2}} < \frac{\frac{q}{p}\left(\frac{g a_1}{k_1} - \frac{b_1 s_1}{d_1} \right)}{\frac{b_2 s_2}{d_2}}$$

We can choose a positive number m_1 satisfying the inequality

$$\frac{\frac{q b_1 s_1}{p d_1}}{\frac{g a_2}{k_2} - \frac{b_2 s_2}{d_2}} < m_1 < \frac{\frac{q}{p}\left(\frac{g a_1}{k_1} - \frac{b_1 s_1}{d_1} \right)}{\frac{b_2 s_2}{d_2}}$$

then

$$\frac{1}{g}\left(\frac{q b_1 s_1}{p d_1} + m_1 \frac{b_2 s_2}{d_2} \right) < m_1 \frac{a_2}{k_2} \quad \text{and} \quad \frac{1}{g}\left(\frac{q b_1 s_1}{p d_1} + m_1 \frac{b_2 s_2}{d_2} \right) < \frac{q a_1}{p k_1}$$

Furthermore, for the given m_1, we choose a positive number m_2 satisfying the inequality

$$\frac{1}{g}\left(\frac{q b_1 s_1}{p d_1} + m_1 \frac{b_2 s_2}{d_2} \right) < m_2 < \min\left\{ m_1 \frac{a_2}{k_2}, \frac{q a_1}{p k_1} \right\}$$

When m_1 and m_2 are given, we have a Lyapunov function

$$L_f(t) = \frac{q}{p} I_1(t) + m_1 I_2(t) + m_2 V(t) + w(t)$$

the derivative of L_f along solutions of our model is given by

$$\begin{aligned}
D^a L_f(t) &\leq \left(m_2 k_1 - \frac{q}{p} a_1 \right) I_1 + (m_2 k_2 - m_1 a_2) I_2 \\
&\quad + \left(\frac{q}{p} b_1 H_1 + m_1 b_2 H_2 - m_2 g \right) V - rw \\
&\leq -\left(\frac{q}{p} a_1 - m_2 k_1 \right) I_1 \\
&\quad - (m_1 a_2 - m_2 k_2) I_2 - \left(m_2 g - \frac{s}{p} b_1 \frac{s_1}{d_1} - m_1 b_2 \frac{s_2}{d_2} \right) V - rw \\
&\leq 0
\end{aligned}$$

Thus, when $R_0 \leq 1$, then $D^\alpha L_f(t) \leq 0$. Let M_f be the largest invariant set in $\left\{ (H_1, 0, H_2, 0, 0, 0); D^\alpha L_f(t) = 0 \right\}$. We observe that $D^\alpha L_f(t) = 0$ if and only if $H_1 = H_1^{(0)} = \frac{s_1}{d_1}, I_1 = 0, H_2 = H_2^{(0)} = \frac{s_2}{d_2}, I_2 = 0, V = 0$ and $W = 0$. Thus, $M_f = \left\{ E_f \right\} = \{ (H_1, I_1, H_2, I_2, V, W) \}$. It follows from LaSalle's invariance principle [8] that the infection-free equilibrium E_f is globally asymptotically stable whenever $R_f \leq 1$. □

Theorem 2. *If $R_1 < 1 < R_0$, then the infection equilibrium $E_1\left(H_1^{(1)}, I_1^{(1)}, H_2^{(1)}, I_2^{(1)}, V^{(1)}, 0\right)$ is globally asymptotically stable.*

Proof. First, we define a Lyapunov function L_0 as follows:

$$
\begin{aligned}
L_1(t) = {} & \frac{k_1}{a_1}\left(H_1(t) - H_1^1 - H_1^1 \ln \frac{H_1(t)}{H_1^1} + I_1(t) - I_1^1 - I_1^1 \ln \frac{I_1(t)}{I_1^1}\right) \\
& + \frac{k_2}{a_2}\left(H_2(t) - H_2^1 - H_2^1 \ln \frac{H_2(t)}{H_2^1} + I_2(t) - I_2^1 - I_2^1 \ln \frac{I_2(t)}{I_2^1}\right) \\
& + \left(V(t) - V^1 - V^1 \ln \frac{V(t)}{V^1}\right) + \frac{pk_1}{qa_1}Z(t)
\end{aligned}
$$

calculating the derivative of L_f along positive solutions of system (4), it follows that

$$
\begin{aligned}
D^\alpha L_1(t) \leq {} & \frac{k_1}{a_1}\left[\left(1 - \frac{H_1^1}{H_1}\right)(s_1 - b_1 H_1 V - d_1 H_1) + \left(1 - \frac{I_1^1}{I_1}\right)(b_1 H_1 V - a_1 I_1 - p I_1 Z)\right] \\
& + \frac{k_2}{a_2}\left[\left(1 - \frac{H_2^1}{H_2}\right)(s_2 - b_2 H_2 V - d_2 H_2) + \left(1 - \frac{I_2^1}{I_2}\right)(b_2 H_2 V - a_2 I_2)\right] \\
& + \left(1 - \frac{V^1}{V}\right)(k_1 I_1 - k_2 I_2 - \sigma V) + \frac{pk_1}{qa_1}(qI_1 - r)Z
\end{aligned}
$$

$$
\begin{aligned}
D^\alpha L_1(t) \leq {} & \frac{k_1 d_1 H_1^1}{a_1}\left(2 - \frac{H_1^1}{H_1} - \frac{H_1}{H_1^1}\right) + k_1 I_1^1\left(3 - \frac{H_1^1}{H_1} - \frac{H_1 V I_1^1}{H_1^1 V^1 I_1} - \frac{V^1 I_1}{V I_1^1}\right) \\
& + \frac{k_2 d_2 H_2^1}{a_2}\left(2 - \frac{H_2^1}{H_2} - \frac{H_2}{H_2^1}\right) + k_2 I_2^1\left(3 - \frac{H_2^1}{H_2} - \frac{H_2 V I_2^1}{H_2^1 V^1 I_2} - \frac{V^1 I_2}{V I_2^1}\right) \\
& + \frac{pk_1 r}{qa_1}(R_1 - 1)Z
\end{aligned}
$$

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that

$$
2 - \frac{H_1^1}{H_1} - \frac{H_1}{H_1^1} \leq 0
$$

end

$$
3 - \frac{H_1^1}{H_1} - \frac{H_1 V I_1^1}{H_1^1 V^1 I_1} - \frac{V^1 I_1}{V I_1^1} \leq 0
$$

Thus, when $R_0 \leq 1$ then $D^\circ L_f(t) \leq 0$. Let M_1 be the largest invariant set in $\left\{(H_1, I_1, H_2, I_2, V, W); D^\circ L_f(t) = 0\right\}$. We observe that $D^\alpha L_f(t) = 0$ if and only if $H_1 = H_1^1, I_1 = I_1^1, Z = 0$ and $\frac{I_1}{I_1^1} = \frac{I_2}{I_2^1} = \frac{V}{V^1}$. Thus, $M_1 = \{E_1\} = \{(H_1, I_1, H_2, I_2, V, W)\}$. Thus, it follows from LaSalle's invariance principle [8] that the infection-free equilibrium E_1 is globally asymptotically stable whenever $R_0 \leq 1$. $\square$

For the second endemic equilibrium E_2, we have the following result:

Theorem 3. *If $R_0 > 1$ and $R_1 > 1$ the infection equilibrium $E_2\left(H_1^{(2)}, I_1^{(2)}, H_2^{(2)}, I_2^{(2)}, V^{(2)}, W^{(2)}\right)$ of system (1) is globally asymptotically stable.*

Proof. We define first a Lyapunov function L_2 as follows:

$$L_2(t) = \frac{k_1}{a_1 + pW^{(2)}} \left(H_1 - H_1^{(2)} - H_1^{(2)} \ln\left(\frac{H_1}{H_1^{(2)}}\right) + I_1 - I_1^{(2)} - I_1^{(2)} \ln\left(\frac{I_1}{I_1^{(2)}}\right) \right)$$

$$+ \frac{k_2}{a_2} \left(H_2 - H_2^{(2)} - H_2^{(2)} \ln\left(\frac{H_2}{H_2^{(2)}}\right) + I_2 - I_2^{(2)} - I_2^{(2)} \ln\left(\frac{I_2}{I_2^{(2)}}\right) \right)$$

$$+ \frac{k_2}{a_2} \left(V - V^{(2)} - V^{(2)} \ln\left(\frac{V}{V^{(2)}}\right) \right)$$

$$+ \frac{pk_1}{q(a_1 + pW^{(2)})} \left(W - W^{(2)} - W^{(2)} \ln\left(\frac{W}{W^{(2)}}\right) \right)$$

The derivative of L_2 along the positive solutions of the system (1) is

$$D^\alpha L_2(t) \leq \frac{k_1}{a_1 + pW^{(2)}} \left[\left(1 - \frac{H_1^{(2)}}{H_1} \right) (s_1 - d_1 H_1 - b_1 H_1 V) \right.$$

$$\left. + \left(1 - \frac{I_1^{(2)}}{I_1} \right) (b_1 H_1 V - p I_1 W) \right]$$

$$+ \frac{k_2}{a_2} \left[\left(1 - \frac{H_2^{(2)}}{H_2} \right) (s_2 - d_2 H_2 - b_2 H_2 V) + \left(1 - \frac{I_2^{(2)}}{I_2} \right) (b_2 H_2 V - a_2 I_2) \right]$$

$$+ \left(1 - \frac{V^{(2)}}{V} \right) (k_1 I_1 + k_2 I_2 - gV) + \frac{pk_1}{q(a_1 + pW^{(2)})} \left(1 - \frac{W^{(2)}}{W} \right) (qI_1 - r)W$$

Then

$$D^\alpha L_2(t) \leq \frac{k_1 d_1 H_1^{(2)}}{a_1 + pW^{(2)}} \left(2 - \frac{H_1^{(2)}}{H_1} - \frac{H_1}{H_1^{(2)}} \right)$$

$$+ k_1 I_1^{(2)} \left(3 - \frac{H_1^{(2)}}{H_1} - \frac{H_1 V I_1^{(2)}}{H_1^{(2)} V^{(2)} I_1} - \frac{V^{(2)} I_1}{V I_1^{(2)}} \right)$$

$$+ \frac{k_2 d_2 H_2^{(2)}}{a_2} \left(2 - \frac{H_2^{(2)}}{H_2} - \frac{H_2}{H_2^{(2)}} \right)$$

$$+ k_2 I_2^{(2)} \left(3 - \frac{H_2^{(2)}}{H_2} - \frac{H_2 V I_2^{(2)}}{H_2^{(2)} V^{(2)} I_2} - \frac{V^{(2)} I_2}{V I_2^{(2)}} \right)$$

Thus, when $R_0 > 1$ and $R_1 > 1$, it implies $D^\alpha L_2(t) \leq 0$. Let M_2 be the largest invariant set in $\{(H_1, I_1, H_2, I_2, V, W); D^\alpha L_2(t) = 0\}$. We observe that $D^\alpha L_2(t) = 0$ if and only if $H_1 = H_1^{(2)}, I_1 = I_1^{(2)}, H_2 = H_2^{(2)}, I_2 = I_2^{(2)}, V = V^{(2)}$ and $W = W^{(2)}$ for any time t. Therefore, $M_2 = \{E_2\} = \{(H_1, I_1, H_2, I_2, V, W)\}$. Since E_2 exists whenever $R^{CTL} > 1$, then by the Lyapunov–LaSalle invariance principle [4], E_2 is globally asymptotically stable if $R^{CTL} > 1$ and $R_1^{CTL,W} \leq 1$. □

6. Numerical Simulations

In the previous sections, we have studied the theoretical part of our fractional problem (1). In this present section, we will present some numerical simulations to the same problem. We notice that the simulation parameters were inspired from [10].

Figure 1 shows the infection dynamics for the following parameters as in the first numerical result of [10]: $s_1 = 1$, $s_2 = 0.8$, $b_1 = 0.08$, $b_2 = 0.1$, $d_1 = 0.2$, $d_2 = 0.2$, $a_1 = 0.2$, $a_2 = 0.2$, $k_1 = 1$, $k_2 = 1.2$, $p = 0.3$, $r = 0.2$, $\sigma = 5$ and $q = 0.1$. Within these chosen parameters, we have that the basic reproduction number is less than unity $R_0 = 0.88 < 1$, and we

observe the convergence of the curves, which corresponds to the stability of the disease-free equilibrium $E_f = (5, 0, 4, 0, 0, 0)$. This result is completely is in good agreement with [10] and also confirm our theoretical result given in Theorem 1.

Figure 2 shows the infection dynamics for the following parameters: $s_1 = 1$, $s_2 = 0.8$, $b_1 = 0.08$, $b_2 = 0.1$, $d_1 = 0.4$, $d_2 = 0.2$, $a_1 = 0.2$, $a_2 = 0.2$, $k_1 = 1$, $k_2 = 1.2$, $p = 0.3$, $r = 0.5$, $\sigma = 2.3$ and $q = 0.56$. Within these parameters, we can easily compute the reproduction numbers $R_0 = 1.4783 > 1$ and $R_1 = 0.8929 < 1$, which means that the first one is greater than unity while the second is less than one. This predicts the numerical stability of the first endemic equilibrium E_1. Indeed, we observe that the curves converge toward the first endemic equilibrium $E_1 = (2.009, 0.9807, 2.4844, 1.5155, 1.2224, 0)$, which confirms our theoretical finding concerning the stability of E_1.

Finally, Figure 3 shows the infection dynamics for the following parameters: $s_1 = 1$, $s_2 = 0.8$, $b_1 = 0.08$, $b_2 = 0.1$, $d_1 = 0.2$, $d_2 = 0.2$, $a_1 = 0.2$, $a_2 = 0.2$, $k_1 = 1$, $k_2 = 1.2$, $p = 0.3$, $r = 0.2$, $\sigma = 2$ and $q = 0.16$. Within these parameters, we can easily compute the reproduction numbers $R_0 = 2.2 > 1$ and $R_1 = 1.25 > 1$, which means that both of them are greater than unity. This predicts the numerical stability of the second endemic equilibrium E_2. Indeed, we observe that the curves converge toward the first endemic equilibrium $E_2 = (2.9069, 1.3333, 2.1052, 1.8947, 1.800, 0.2221)$, which confirms our theoretical finding concerning the stability E_2 of model (1), which is globally asymptotically stable; this is consistent with Theorem 3.
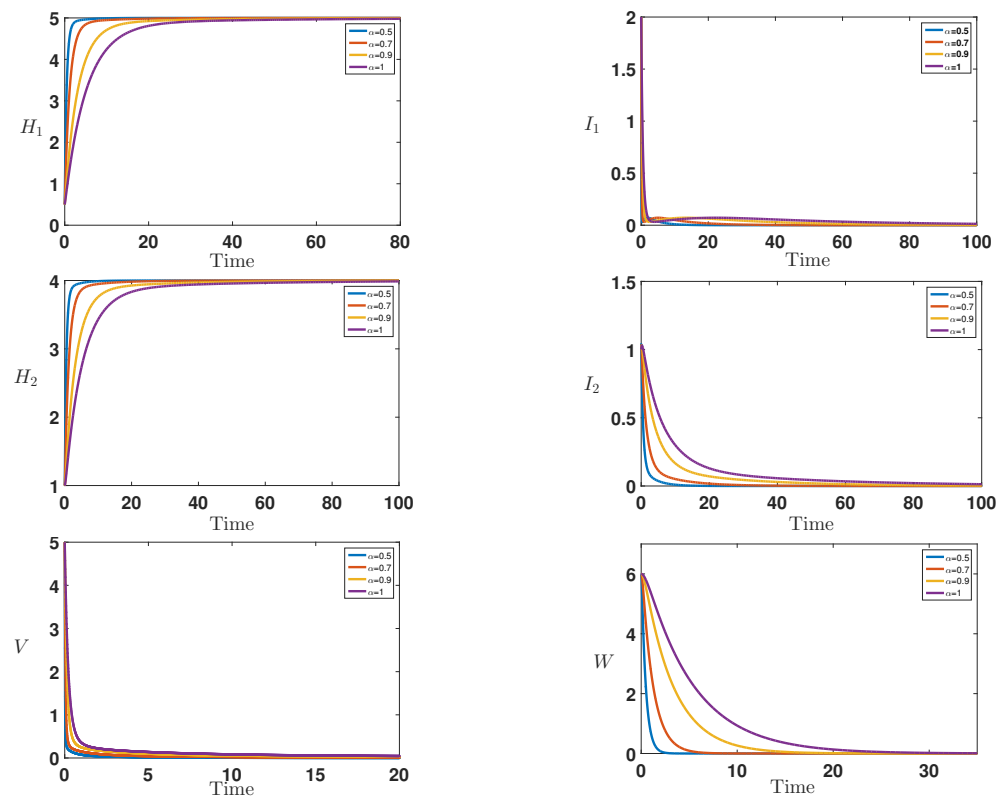

Figure 1. Behavior of the infection during the time for $s_1 = 1$, $s_2 = 0.8$, $b_1 = 0.08$, $b_2 = 0.1$, $d_1 = 0.2$, $d_2 = 0.2$, $a_1 = 0.2$, $a_2 = 0.2$, $k_1 = 1$, $k_2 = 1.2$, $p = 0.3$, $r = 0.2$, $\sigma = 5$ and $q = 0.1$, which correspond to the stability of the disease-free equilibrium $E_f = (5, 0, 4, 0, 0, 0)$ with $R_0 = 0.88 < 1$.
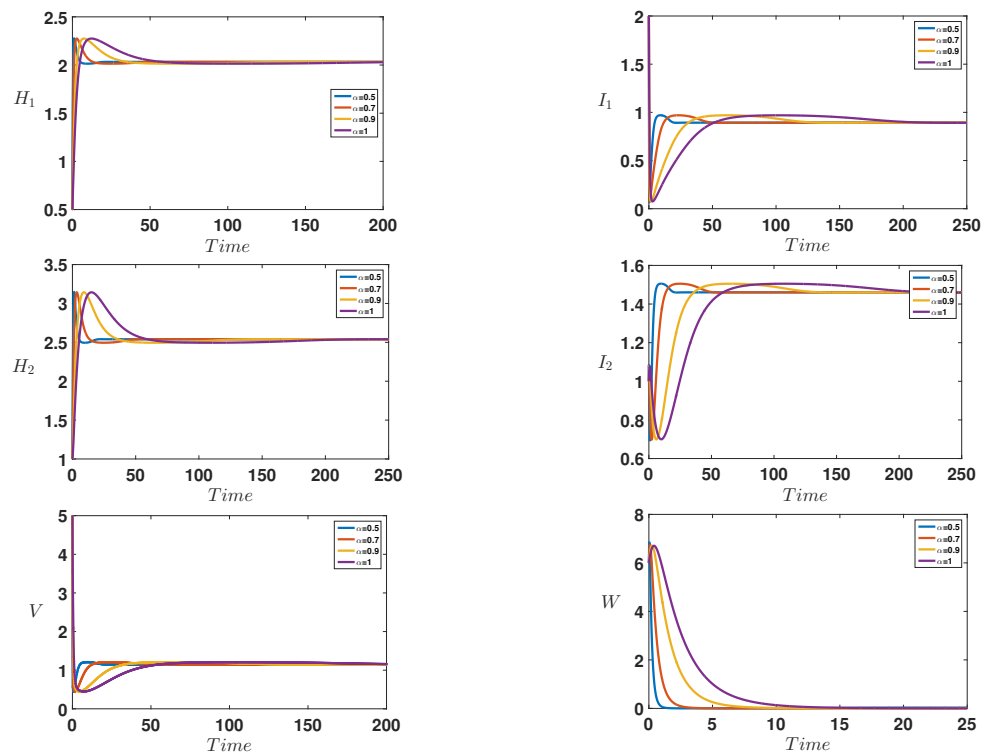
Figure 2. Behavior of the infection during the time for $s_1 = 1$, $s_2 = 0.8$, $b_1 = 0.08$, $b_2 = 0.1$, $d_1 = 0.4$, $d_2 = 0.2$, $a_1 = 0.2$, $a_2 = 0.2$, $k_1 = 1$, $k_2 = 1.2$, $p = 0.3$, $r = 0.5$, $\sigma = 2.3$ and $q = 0.56$, which correspond to the stability of the endemic equilibrium $E_1 = (2.009, 0.9807, 2.4844, 1.5155, 1.2224, 0)$ with $R_0 = 1.4783 > 1$ and $R_1 = 0.8929 < 1$.
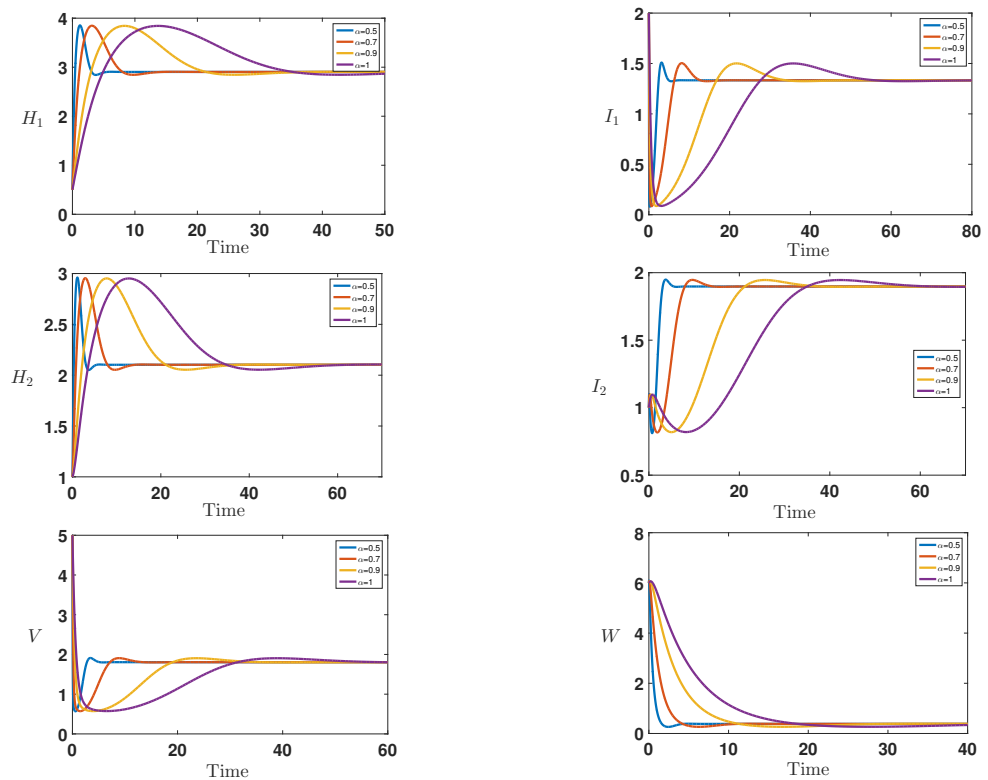

Figure 3. Behavior of the infection during the time for $s_1 = 1$, $s_2 = 0.8$, $b_1 = 0.08$, $b_2 = 0.1$, $d_1 = 0.2$, $d_2 = 0.2$, $a_1 = 0.2$, $a_2 = 0.2$, $k_1 = 1$, $k_2 = 1.2$, $p = 0.3$, $r = 0.2$, $\sigma = 2$ and $q = 0.16$, which correspond to the stability of the endemic equilibrium $E_2 = (2.9069, 1.3333, 2.1052, 1.8947, 1.800, 0.2221)$ $(R_0 = 2.2 > 1$ and $R_1 = 1.25 > 1)$.

7. Conclusions

In this paper, we have studied a mathematical model describing HBV infection in intrahepatic and extrahepatic tissues. In our suggested model, we have taken into consideration the effect of CTL immune response. The positivity and boundedness of solutions for non-negative initial data were proven, which is consistent with the biological background. The local stability of the equilibrium was established. Moreover, the global stability of the disease free equilibrium and the endemic equilibrium was also fulfilled by using some appropriate Lyapanov functional. Numerical tests were performed to support our theoretical findings. In the end of this paper, we have studied the effect of the fractional derivative on the numerical stability of each equilibrium. It has been revealed the fractional order derivative has no influence on the stability but only on the speed of convergence toward the equilibria.

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