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Stability Analysis of Caputo Fractional Order Viral Dynamics of Hepatitis B Cellular Infection

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Abstract: We present a Caputo fractional order mathematical model that describes the cellular infection of the Hepatitis B virus and the immune response of the body with Holling type II functional response. We study the existence of unique positive solutions and the local and global stability of virus-free and endemic equilibria. Finally, we present numerical results using the Adam-type predictor–corrector iterative scheme.

Keywords: Caputo derivative; hepatitis B; Ulam–Hyers stability; predictor–corrector algorithm; global stability; local stability; Routh–Hurwitz

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1. Introduction

Hepatitis B is a known killer infectious disease caused by the Hepatitis B virus (HBV), which attacks the liver cells (Hepatocyte), resulting in changes in the antigen structure of the surface of the liver cells, thus, leading to attack and destruction by a mechanism called 'self-mediated immune damage'.

Although "recovered" patients have lifetime protective immunity, tiny levels of HBV DNA can still be discovered occasionally. These traces of HBV DNA are infectious and stimulate HBV-specific B- and T-cell responses, which control viremia [1]. However, HBV replication is strongly suppressed by the antiviral effects of inflammatory cytokines generated by HBV-specific $CD8+$ T lymphocytes when they detect the antigen in the infected or transgenic liver, as shown in chimpanzee [2] and transgenic mouse [3].

Hepatitis B infection is in two phases; acute and chronic. The acute stage is the earliest stage of the infection whereby the body can recover by its immune system within six (6) months. The acute infection stage might be asymptotic and characterized by viral replication. Loss of appetite, joint and muscle discomfort, low-grade fever, and potential stomach aches are all signs of an acute infection. Recovery from acute HBV infection means that the virus is no longer in the bloodstream, but inactive in the liver. However, if one uses immune-suppressing drugs, the virus in your liver might be reactivated in the future. HBV replicates only within the host cell since it lacks the enzymes necessary for protein and nucleic acid synthesis [4]. Chronic HBV infection occurs when the virus is still detectable six months after the infection, indicating that the virus has not been fully cleared by the immune system and is still present in the patient's blood and liver. The majority of patients with chronic infections are asymptomatic. HBV is transmitted from an infected person to an uninfected person through sexual transmission, child-birth relation, misuse of contaminated needles such as syringes, exchange of infected body fluids such as blood, saliva, menstrual, seminal, and vaginal fluid [5].

It is also well-known that infected people do not always show symptoms in the early stages, although some may experience an acute illness that lasts several weeks, including Jaundice (yellowing of the skin and eye), dark urine, and extreme fatigue, nausea, vomiting, and some abdominal pains. Despite the above symptoms mentioned, symptoms exhibited by patients also depend on the status of the immune system of the patient, the age, and general health of the patient [4].

Due to the severity of hepatitis B infection, it has intrigued many scientists and researchers to investigate the dynamics of HBV. In [6], a spatio-temporal dynamics of a fractional model for HBV infection with cellular immunity was proposed. A time-fractional diffusion model for HBV infection with capsids and Cytotoxic T lymphocytes (CTL) immune response and were able to show that the diffusion and the order of fractional derivatives in the sense of Caputo do not affect the stability of the equilibria, but they can affect the time to arrive at the equilibria. When the order of the fractional derivative increases, for example, the model's solutions converge quickly to the equilibrium points.

In [7], the authors looked at a fractional-order HBV immunological model's global analysis and simulation. Using the Lyapunov function to prove the model's stability, they derived basic reproduction numbers and presented their relationship with the corresponding equilibria. Studying the hepatitis B virus, the authors in [8] incorporated the immune response and took into account both cytolytic and noncytolytic effect pathways. The dynamics of immune response to hepatitis B, which takes into account contributions from innate and adaptive immune responses, as well as cytokines, has also been studied, see, [9].

In this article, we consider an HBV model with a Holling type 2 functional response rate and three (3) compartments, i.e., healthy hepatocytes (H), infected hepatocytes (I), and the body's immune response (R). We study the existence and uniqueness of the solutions and the equilibrium states, i.e., virus-free and endemic equilibrium state. When the virus present in the liver cells exceeds the cytokines, the virus will overcome the cytokines and multiply in the body, resulting in an endemic state where the virus comes to stay in the body. When cytokines outnumber the viruses in the body, the viruses are cleared from the body, and the person is virus-free.

The rest of the paper is organized as follows; Section 2 presents preliminary results for fractional calculus. We present the fractional order model and the analysis in Section 3. In Section 4, we present the local and global stability analysis. The numerical results and simulations are presented in Section 5. Finally, we present the conclusions in Section 6.

2. Mathematical Preliminary on Fractional Calculus

In this section, we present useful results from the theory of fractional calculus; see, for example, the monographs [10,11] for further details.

Definition 1 ([11]). *The fractional order integral of the function $f : [0, +\infty) \to \mathbb{R})$ of order $\alpha \in (0, 1)$ is defined in the sense of Riemann–Liouville as where $[0, T] \subset \mathbb{R}_+$. Then fractional integral of order v for a function g in the sense of Riemann–Liouville is defined as*

$$\mathcal{I}^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) d\tau, \quad t > 0, \tag{1}$$

where $[0, T] \subset \mathbb{R}^+$ and $\Gamma(\alpha) = \int_0^{\infty} t^{\alpha-1} e^{-t}\, dt, \alpha > 0$, is the Euler gamma function.

Definition 2 ([11]). *For a function $f \in C^n([0, +\infty], \mathbb{R})$, the Caputo fractional-order derivative of order α is defined by*

$${}^{c}D^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} = \int_0^t (t-\tau)^{n-\alpha-1} f^{(n)}(\tau) d\tau, \quad t > 0, \tag{2}$$

where $n = \lfloor \alpha \rfloor + 1$ and $\lfloor \alpha \rfloor$ denotes the smallest integer that is less or equal to α.

Finally, a relation between 1 and 2 is given by

Lemma 1. *Let $\alpha \geq 0$ and $n = \lfloor \alpha \rfloor + 1$. Then*

$$\mathcal{I}^{\alpha}({}^{c}D^{\alpha} f(t)) = f(t) - \sum_{k=0}^{n-1} \frac{f^{k}(0)}{k!} t^{k}.$$

In particular, if $0 < \alpha \leq 1$, then

$$\mathcal{I}^{\alpha}({}^{c}D^{\alpha} f(t)) = f(t) - f(0).$$

The generalized mean value theorem for the Caputo fractional order is given by

Lemma 2. *For $\alpha \in (0, 1]$, let $f(t) \in C([a, b])$ and $D^{\alpha} f(t) \in (a, b]$. Then it holds*

$$f(t) = f(a) + \frac{1}{\Gamma(\alpha)} D^{\alpha} f(\eta)(t - a)^{\alpha}, \quad 0 \leq \eta \leq t, \quad t \in (a, b]. \tag{3}$$

3. Fractional Order Model Derivation and Analysis

We consider a liver consisting of Healthy Hepatocyte (H), Infected hepatocytes (I), and immune response-dependent cytotoxic cells (R). We assume a logistic growth of healthy hepatocytes, see, e.g., [12,13]. Healthy Hepatocytes of the liver are known to have half-lives of more than six months; see, [14]. In the presence of the Hepatitis B virus, we assume that the rate at which hepatocytes become infected is proportional to HI. Given β as the contact rate and assuming that infected hepatocytes die at a rate μ_1, the dynamic model for the infected hepatocytes and the immune response can be described as

$$\begin{aligned} \frac{dH}{dt} &= r_1 H\left(1 - \frac{H}{K}\right) - \beta HI, \\ \frac{dI}{dt} &= \beta HI - c_1 RI - \mu_1 I, \\ \frac{dR}{dt} &= \delta HI + \frac{r_2 RI}{\sigma + I} - c_2 RI - \mu_2 R, \end{aligned} \tag{4}$$

with the initial conditions $H(0) = H_0 \geq 0, I(0) = I_0 \geq 0$ and $R(0) = R_0 \geq 0$, where c_1 and c_2 are the rates of deactivation of virons and cytotoxic cells, respectively. Let δ be the rate of production of cytotoxic cells, and μ_2 be the baseline degradation rate. We note that the immune response of the cytotoxic cells to the viral invasion was included via a positive feedback mechanism, with a response term $\frac{r_2 RI}{\sigma + I}$ which is a saturating function of the amount of virus present, the full description of the parameters can be seen in Table 1. Following [15,16], the fractional order model of the mathematical model (4) is given by Caputo derivativeas follows

$$\begin{aligned} {}^{C}D_t^{\alpha} H &= r_1^{\alpha} H\left(1 - \frac{H}{K}\right) - \beta^{\alpha} HI, \\ {}^{C}D_t^{\alpha} I &= \beta^{\alpha} HI - c_1^{\alpha} RI - \mu_1^{\alpha} I, \\ {}^{C}D_t^{\alpha} R &= \delta^{\alpha} HI + \frac{r_2^{\alpha} RI}{\sigma^{\alpha} + I} - c_2^{\alpha} RI - \mu_2^{\alpha} R, \end{aligned} \tag{5}$$

subject to the initial conditions $H(0) = H_0 \geq 0, I(0) = I_0 \geq 0$ and $R(0) = R_0 \geq 0$, where ${}^{C}D^{\alpha}$ denotes Caputo fractional derivative with the order of the derivative $\alpha \in (0, 1]$.

Table 1. The parameters involved in the model equation are described in detail (5).

Parameters	Description
β	Contact rate (rate of infection of the normal cell)
μ_1	Natural death rate of HBV
μ_2	Natural death rate of Cytotoxic cell
δ	Production rate of Cytotoxic cells
σ	Cytotoxic cell simulation half saturation rate
r_1	Growth rate of uninfected hepatocytes
r_2	Rate simulation of Cytotoxic cells by HBV
c_1	Rate of destruction of HBV by Cytotoxic cells
c_2	Rate of deactivation of Cytotoxic cells by HBV
K	Carrying capacity
$\mathcal{R}_0$	Basic reproduction Number
α	Fractional order

3.1. Qualitative Properties

Here, we study the well-posedness of the fractional order model. By means of a Banach contraction mapping, we the existence and uniqueness of the solutions.

Let $X(t) = (H, I, R)^T$ and $\mathcal{K}(t, X(t))^T = (\phi_i)^T, i = 1, 2, 3$, where,

$$\begin{aligned} \phi_1 &= r_1^\alpha H\left(1 - \frac{H}{K}\right) - \beta^\alpha HI, \\ \phi_2 &= \beta^\alpha HI - c_1^\alpha RI - \mu_1^\alpha I, \\ \phi_3 &= \delta^\alpha HI + \frac{r_2^\alpha RI}{\sigma^\alpha + I} - c_2^\alpha RI - \mu_2^\alpha R. \end{aligned} \tag{6}$$

The dynamical system (5) can be written as,

$${}^{C}D_t^\alpha X(t) = \mathcal{K}(t, X(t)), \text{ with } X(0) = X_0 \geq 0 \text{ and } t \in [0, T], \quad 0 < \alpha \leq 1, \tag{7}$$

which is equivalent to (6). The fractional model has integral representation,

$$\begin{aligned} X(t) &= X_0 + \mathcal{L}_0^\alpha \mathcal{K}(t, X(t)), \\ &= X_0 + \frac{1}{\Gamma(\alpha)} \int_0^T (t - \tau)^{\alpha - 1} \mathcal{K}(\tau, X(\tau)) d\tau, \quad \text{where } n - 1 < \alpha < n. \end{aligned} \tag{8}$$

As a result, we show that the fractional model is bounded and positive as long as positive initial conditions are provided. By using the integral representation (8), we present an analysis of the model. We consider a Banach space, $\mathcal{E}$, of all continuous functions from $[0, T]$ to $\mathbb{R}$, i.e., $\mathcal{E} = \mathcal{C}([0, T]; \mathbb{R})$, endowed with the norm,

$$||X||_{\mathcal{E}} = \sup_{t \in [0,T]} \{|X(t)|\} \quad \text{where} \quad |X(t)| = |H(t)| + |I(t)| + |R(t)|,$$

Moreover, $H, I, R \in \mathcal{C}([0, T]; \mathbb{R})$. Let us consider a well-defined operator $\mathcal{P} : \mathcal{E} \to \mathcal{E}$ such that

$$(\mathcal{P}X)(t) = X_0 + \frac{1}{\Gamma(\alpha)} \int_0^T (t - \tau)^{\alpha - 1} \mathcal{K}(\tau, X(\tau)) d\tau. \tag{9}$$

3.2. Positivity and Boundedness of Solution

The model (5) will be biologically meaningful given that the solution of the system with non-negative initial conditions will remain non-negative for any given time $t > 0$. This is true for this model, given that the theorem below is satisfied.

Theorem 1. *Let $X(t) = (H, I, R)^T$ then for $X(0) \geq 0$ the solution $X(t)$ of system is bounded and remains positive for $t \geq 0$.*

Proof. Let us consider the trajectory of solution along H-axis where $I = R = 0$ and $H(0) = H_0 \geq 0$. Given,

$$^{C}D_t^{\alpha} H = r_1^{\alpha} H\left(1 - \frac{H}{K}\right). \tag{10}$$

We know from (8) that Equation (10) can be expressed as,

$$\begin{aligned} H(t) &= H_0 + \frac{1}{\Gamma(\alpha)} \int_0^b (H - \tau)^{\alpha - 1} \mathcal{K}(\tau, X(t)) d\tau \\ &= H_0 + \frac{1}{\Gamma(\alpha)} \int_0^b (H - \tau)^{\alpha - 1} \left[r_1^{\alpha} H\left(1 - \frac{H}{K}\right)\right] d\tau. \end{aligned}$$

By using $\tau = Hy$ and applying the beta-gamma relations, we obtain,

$$H(t) = H_0 + H^{\alpha+1} E_{\alpha_1}(1 - H) \geq 0, \quad \text{where} \quad E_{\alpha_1} = \frac{r_1^{\alpha}}{\alpha\Gamma(\alpha)}. \tag{11}$$

Similar arguments as above yields

$$I(t) = I_0 + I^{\alpha+1} E_{\alpha_2} > 0 \quad \text{and} \quad R(t) = R_0 + R^{\alpha+1} E_{\alpha_3} > 0 \tag{12}$$

where $E_{\alpha_2} = \frac{\mu_1^{\alpha}}{\alpha\Gamma(\alpha)}$ and $E_{\alpha_3} = \frac{\mu_2^{\alpha}}{\alpha\Gamma(\alpha)}$, yielding non-negative invariance on all axes. Considering a positive solution in the $I - R$ plane such that for some t^*, we have $H(t^*) = 0, I(t^*) > 0$ and $R(t^*) > 0$ and $H(t) < H(t^*)$. In the $I - R$ plane, $^{c}D_t^{\alpha} H|_{t=t^*} > 0$. Thus, we obtain $H(t) > H(t^*)$ by the mean value theorem for the Caputo-fractional order derivative Lemma 2 which is a contradiction to our earlier statement. □

For the boundedness of the solution, we show that the model and solution are continuous and exist within a given closed interval or region Ω.

Theorem 2. *The model (5) has solutions bounded within the invariant region given by*

$$\Omega := \left\{(H, I, R) \in \mathbb{R} : 0 \leq N(t) \leq \gamma r_1^{\alpha}, 0 \leq H(t) \leq \gamma r_1^{\alpha}\right\}.$$

Proof. Since $N(t)$ is the total Population, it follows from Theorem 1 that $N(t) = H(t) + I(t) + R(t)$. Using (11) and (12), we obtain, $N(t) \leq N_0 + \frac{1}{\alpha\Gamma(\alpha)}\left[H^{\alpha+1} r_1^{\alpha}\right]$. By taking limits of both sides, we have

$$\lim_{t \to \infty} \sup N(t) \leq N_0 + \gamma r_1^{\alpha}, \quad \text{where} \quad \gamma = \frac{H^{\alpha+1}}{\alpha\Gamma(\alpha)}.$$

□

3.3. Existence and Uniqueness of the Solution

We demonstrate that there is a solution to the model (5), i.e., the model is mathematically and biologically consistent. To prove this, we use the lemma below.

Lemma 3. *Let $\overline{X} = (\overline{H}, \overline{I}, \overline{R})^T$. The function $\mathcal{K} = (\phi_i)^T$ defined above satisfies $||\mathcal{K}(t, X(t)) - \mathcal{K}(t, \overline{X}(t))||_{\mathcal{E}} \leq L_{\mathcal{K}} ||X - \overline{X}||_{\mathcal{E}}$ for some $L_{\mathcal{K}} > 0$.*

Proof. H, I, and R are all dependent on t and from the first component of $\mathcal{K}$ see (6) we observe that,

$$\begin{aligned}\Big|(\phi_1(t,X(t))-\phi_1(t,\overline{X}(t)))\Big| &= \Big|r_1^\alpha H - \frac{r_1^\alpha H^2}{K} - \beta^\alpha HI - r_1^\alpha \overline{H} + \frac{r_1^\alpha \overline{H^2}}{K} + \beta^\alpha \overline{HI}\Big|,\\ &\le r_1^\alpha |H-\overline{H}| + \frac{r_1^\alpha}{K}\lambda|H-\overline{H}| + \beta^\alpha|HI-\overline{HI}|\\ &\le r_1^\alpha |H-\overline{H}| + \frac{r_1^\alpha}{K}\lambda|H-\overline{H}| + \beta^\alpha|H-\overline{H}| + \beta^\alpha|I+\overline{I}|, \quad (13)\end{aligned}$$

where $\lambda(t) = H + \overline{H}$. Grouping constant terms and simplifying (13) we obtain,

$$\begin{aligned}\Big|(\phi_1(t,X(t))-\phi_1(t,\overline{X}(t)))\Big| &= \Big(r_1^\alpha + \frac{r_1^\alpha}{K}\lambda + \beta^\alpha\Big)\Big|H-\overline{H}\Big| + \beta^\alpha|I-\overline{I}|\\ &\le L_1\Big(|H-\overline{H}| + |I-\overline{I}|\Big).\end{aligned}$$

where $L_1 = \max_{t\in[0,T]}\{f_1+g_1\}$, with $f_1 = \Big(r_1^\alpha + \frac{r_1^\alpha}{K}\lambda + \beta^\alpha\Big)$ and $g_1 = \beta^\alpha$. Similarly, we do same for second equation in (6) and we get,

$$\Big|(\phi_2(t,X(t))-\phi_2(t,\overline{X}(t))\Big| \le L_2\Big(|H-\overline{H}+|I-\overline{I}|+|R-\overline{R}|\Big)$$

where $L_2 = \max_{t\in[0,T]}\{P_1+P_1+P_3\}$ with $P_1 = \beta^\alpha, P_2 = \beta^\alpha + C_1^\alpha + \mu_1^\alpha), P_3 = C_1^\alpha$ and finally, we can express,

$$\Big|\phi_3(t,X(t))-\phi_3(t,\overline{X}(t))\Big| \le L_3\Big(|H-\overline{H}|+|I-\overline{I}|+|R-\overline{R}|\Big),$$

where $L_3 = \max_{t\in[0,T]}\{\tau^\alpha + n_1 + n_2\}$, with $n_1 = \frac{r_1^\alpha}{\sigma^\alpha+1} + C_2^\alpha$ and $n_2 = \frac{r_2^\alpha}{\sigma^\alpha+1} + \mu_2^\alpha$. Finally, we obtain,

$$||\mathcal{K}(t,X(t))-\mathcal{K}(t,\overline{X}(t))||_{\mathcal{E}} = \sup_{t\in[0,T]}\sum_{i=1}^{3}\Big|\phi_i(t,X(t))-\phi_i(t,\overline{X}(t))\Big| \le L_{\mathcal{K}}||X-\overline{X}||_{\mathcal{E}}, \quad (14)$$

and $L_{\mathcal{K}} = L_1 + L_2 + L_3$. □

Next, we show that the solution to the model problem exists and is unique using the Banach contraction mapping and follows the technique from [17].

Theorem 3. *Let the result of Lemma 3 hold and let* $\Omega = \frac{T^\alpha}{\Gamma(\alpha+1)}$. *If* $\Omega L_{\mathcal{K}} < 1$, *then there exist a unique solution of model* (5) *on* $[0,T]$.

Proof. By Banach contraction mapping, we will show that $\mathcal{P}$ is both a self-map and a contraction. By definition, $\sup_{t\in[0,T]}\|\mathcal{K}(t,0)\| = \mathcal{Q}$ and let $\kappa > \dfrac{\|X_0\| + \Omega\mathcal{Q}}{1-\Omega L_{\mathcal{K}}}$ and a close convex set $B_K = \{X\in\mathcal{E} : \|X\|_{\mathcal{E}} \le \kappa\}$. In the case of the self-map property, it is sufficient to demonstrate that $\mathcal{P}B_K \subset B_K$, so let $X \in B_K$, then

$$\begin{aligned}\|(\mathcal{P}X)(t)\|_{\mathcal{E}} &= \sup_{t\in[0,T]}\Big\{\Big|X_0 + \frac{1}{\Gamma(\alpha)}\int_0^t (t-\tau)^{\alpha-1}\mathcal{K}(\tau,X(\tau))d\tau\Big|\Big\}\\ &\le |X_0| + \frac{1}{\Gamma(\alpha)}\sup_{t\in[0,T]}\Big\{\int_0^t (t-\tau)^{\alpha-1}\Big(|\mathcal{K}(\tau,X(\tau))-\mathcal{K}(\tau,0)| + |\mathcal{K}(\tau,0)|\Big)d\tau\Big\}\end{aligned}$$

$$
\begin{aligned}
&\leq |X_0| + \frac{1}{\Gamma(\alpha)} \sup_{t\in[0,T]} \Big\{ \int_0^t (t-\tau)^{\alpha-1} d\tau \Big(\|\mathcal{K}(\tau, X(\tau)) - \mathcal{K}(\tau,0)\|_{\mathcal{E}} + \|\mathcal{K}(\tau,0) d\tau\|_{\mathcal{E}} \Big) \Big\} \\
&\leq |X_0| + \frac{1}{\Gamma(\alpha)} \sup_{t\in[0,T]} \Big(\|\mathcal{K}(\tau, X(\tau)) - \mathcal{K}(\tau,0)\|_{\mathcal{E}} + \|\mathcal{K}(\tau,0)\|_{\mathcal{E}} \Big) \sup_{t\in[0,T]} \int_0^t (t-\tau)^{\alpha-1} d\tau \\
&= |X_0| + \frac{L_{\mathcal{K}} \|X\|_{\mathcal{E}} + \mathcal{Q}}{\Gamma(\alpha)} \Big(\frac{T^{\alpha}}{\alpha} \Big) \\
&= |X_0| + \Omega(L_{\mathcal{K}} \kappa + \mathcal{Q}) \leq \kappa,
\end{aligned}
$$

where $\Omega = \frac{T^{\alpha}}{\Gamma(\alpha+1)}$. Thus $\mathcal{P}B_{\kappa} \subset B_{\kappa}$ and $\mathcal{P}$ is a self-map. Next, we show that $\mathcal{P}$ is a contraction.

$$
\begin{aligned}
\|\mathcal{P}X - \mathcal{P}\tilde{X}\|_{\mathcal{E}} &= \sup_{t\in[0,T]} \Big\{ \Big| (\mathcal{P}X)(t) - (\mathcal{P}\tilde{X})(t) \Big| \Big\} \\
&= \frac{1}{\Gamma(\alpha)} \sup_{t\in[0,T]} \Big\{ \int_0^t (t-\tau)^{\alpha-1} \Big| \mathcal{K}(\tau, X(\tau)) - \mathcal{K}(\tau, \tilde{X}(\tau)) \Big| d\tau \Big\} \\
&\leq \frac{L_{\mathcal{K}}}{\Gamma(\alpha)} \sup_{t\in[0,T]} \Big\{ \int_0^t (t-\tau)^{\alpha-1} \Big| X(\tau) - \tilde{X}(\tau) \Big| d\tau \Big\} \\
&\leq \Omega L_{\mathcal{K}} \|X - \tilde{X}\|_{\mathcal{E}}.
\end{aligned}
$$

If $\Omega L_{\mathcal{K}} < 1$, then $\mathcal{P}$ is a contraction mapping, and thus, there exists a unique fixed point on $[0, T]$ via Banach contraction principle. □

The existence of the solution follows from Schauder's fixed point theorem.

Lemma 4. *Let $\beta_1, \beta_2 \in \mathcal{E}$ such that*

$$
|\mathcal{K}(t, X(t))| \leq \beta_1(t) + \beta_2 |X(t)|, \quad \textit{for all} \quad X \in \mathcal{E}, t \in [0,T] \tag{15}
$$

such that $\beta_1^* = \sup_{t\in[0,T]} |\beta_1(t)|, \beta_2^* = \sup_{t\in[0,T]} |\beta_2(t)| < 1$. Then, the operator $\mathcal{P}$ is completely continuous.

Proof. For all $X \in B_{\kappa}$, we obtain

$$
\begin{aligned}
\|(\mathcal{P}X)(t)\|_{\mathcal{E}} &= \sup_{t\in[0,T]} \Big\{ \Big| X_0 + \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} \mathcal{K}(\tau, X(\tau)) d\tau \Big| \Big\} \\
&\leq |X_0| + \frac{1}{\Gamma(\alpha)} \sup_{t\in[0,T]} \Big\{ \int_0^t (t-\tau)^{\alpha-1} \Big| \mathcal{K}(\tau, X(\tau)) d\tau \Big| \Big\} \\
&\leq |X_0| + \sup_{t\in[0,T]} \frac{|\mathcal{K}(t, X(t))|}{\Gamma(\alpha)} \sup_{t\in[0,T]} \int_0^t (t-\tau)^{\alpha-1} \, d\tau \\
&\leq |X_0| + \frac{(\beta_1^* + \beta_2^* \|X(t)\|_{\mathcal{E}})}{\Gamma(\alpha)} \Big(\frac{T^{\alpha}}{\alpha} \Big) \\
&= |X_0| + \Omega(\beta_1^* + \beta_2^* \|X(t)\|_{\mathcal{E}}) < +\infty.
\end{aligned}
$$

Thus, $\mathcal{P}$ is uniformly bounded. Next, we show that $\mathcal{P}$ is equicontinuous. Let $t_1, t_2 \in [0,T]$ such that $t_2 \geq t_1$, and $\sup_{(t,X)\in[0,T]\times B_K} |\mathcal{K}(t, X(t))| = \mathcal{K}^*$, then

$$
\begin{aligned}
\|(\mathcal{P}X)(t_2) - (\mathcal{P}X)(t_1)\|_{\mathcal{E}} &= \sup_{t\in[0,T]} \Big\{ \Big| (\mathcal{P}X)(t_2) - (\mathcal{P}X)(t_1) \Big| \Big\} \\
&= \frac{1}{\Gamma(\alpha)} \sup_{t\in[0,T]} \Big| \int_0^{t_1} [(t_2-\tau)^{\alpha-1} - (t_1-\tau)^{\alpha-1}] \mathcal{K}(\tau, X(\tau)) \, d\tau
\end{aligned}
$$

$$+\int_{t_1}^{t_2}[(t_2-\tau)^{\alpha-1}\mathcal{K}(\tau,X(\tau))\,d\tau\Big|$$
$$\leq \frac{\mathcal{K}^*}{\Gamma(\alpha)}[2(t_2-t_1)^{\alpha}+(t_2-t_1)]\to 0,\quad \text{as}\quad t_2\to t_1.$$

Thus, $\mathcal{P}$ is equicontinuous. It is completely continuous as a result of the Arzelá-Ascoli theorem. □

4. Equilibrium Points and Basic Reproduction Number

The model (5) has a virus-free equilibrium (VFE) obtained by setting the right-hand side of (5) to zero. Using the next-generation matrix method, the new virus terms and the remaining transfer terms are given by

$$\mathcal{F}(x)=\begin{pmatrix}\beta^{\alpha}H\ I\end{pmatrix}\quad\text{and}\quad\mathcal{V}(x)=\begin{pmatrix}c_1^{\alpha}RI+\mu_1^{\alpha}\ I\end{pmatrix}.$$

The effective basic reproduction number is given by

$$\mathcal{R}_0=\rho(FV^{-1})=\beta^{\alpha}K\Big(\frac{1}{\mu_1^{\alpha}}\Big)=\frac{\beta^{\alpha}K}{\mu_1^{\alpha}},\tag{16}$$

where ρ denotes the spectral radius, $F=\beta^{\alpha}K$ and $V^{-1}=1/\mu_1^{\alpha}$. Next, we consider other equilibrium points, $E^1=(H_1,I_1,R_1)$. Here, we consider the case where there are no healthy Hepatocytes, i.e., we equate the right-hand side of (5) to zero, and assume $H_1=0$ in the model (5) yielding

$$H_1=0$$
$$-c_1^{\alpha}R_1I_1-\mu_1^{\alpha}I_1=0\tag{17}$$
$$\frac{r_2^{\alpha}R_1I_1}{\sigma^{\alpha}+I_1}-c_2^{\alpha}R_1I_1-\mu_2^{\alpha}R_1=0\tag{18}$$

From (17), we have $R_1=-\mu_1^{\alpha}/c_1^{\alpha}$. By substituting and simplifying, we have

$$I_1^{1,2}=\frac{r_2^{\alpha}-c_2^{\alpha}\sigma^{\alpha}-\mu_2^{\alpha}\pm\sqrt{(c_2^{\alpha}\sigma^{\alpha}+\mu_2^{\alpha}-r_2^{\alpha})^2-4c_2^{\alpha}\mu_2^{\alpha}\sigma^{\alpha}}}{2c_2^{\alpha}}.$$

The final equilibrium point is given by $E^2=(H_2,I_2,R_2)$. Again, we set the right-hand side of (5) to zero yielding,

$$I_2=\frac{r_1^{\alpha}\Big(1-\frac{H_2}{K}\Big)}{\beta^{\alpha}}.\tag{19}$$

The second equation of (5) yields

$$I_2(\beta^{\alpha}H_2-c_1^{\alpha}R_2-\mu_1^{\alpha})=0.$$

Since I_2 is non-zero, we have

$$R_2=\frac{\beta^{\alpha}H_2-\mu_1^{\alpha}}{c_1^{\alpha}},\quad\text{where}\quad c_1^{\alpha}>0.\tag{20}$$

Finally, the last equation of (5) yields

$$H_2=\frac{c_2^{\alpha}R_2}{\tau^{\alpha}}+\frac{\mu_2^{\alpha}R_2}{\tau^{\alpha}I_2}-\frac{r_2^{\alpha}R_2}{\tau^{\alpha}(\sigma^{\alpha}+I_2)}.\tag{21}$$

4.1. Local Stability Analysis

Here, we present the local stability analysis of the model.

4.1.1. Local Stability of VFE Point

At this stage, we assume there is no viral infection of the Hepatocytes, i.e., the person is virus free. Following [18], we present the local stability of the virus-free equilibrium in the following theorem.

Theorem 4. *The virus-free equilibrium point* $E^0 = (K, 0, 0)$ *of the fractional model is locally asymptotically stable (LAS) if* $\mathcal{R}_0 \leq 1$, *and unstable if* $\mathcal{R}_0 > 1$.

Proof. The local stability analysis of the VFE is determined by using the eigenvalues of the Jacobian of (5) given by

$$J = \begin{pmatrix} -r_1^\alpha - \beta^\alpha I & -\beta^\alpha H & 0 \\ \beta^\alpha I & \beta^\alpha H - c_1^\alpha R - \mu_1^\alpha & -c_1^\alpha I \\ \tau^\alpha I & \tau^\alpha H + \dfrac{r_2^\alpha R \sigma^\alpha}{(\sigma^\alpha + 1)^2} - c_2^\alpha R & \dfrac{r_2^\alpha I}{\sigma^\alpha + I} - c_2^\alpha I - \mu_2^\alpha \end{pmatrix} \tag{22}$$

Evaluating the Jacobian matrix (J) at the VFE point E^0, yields,

$$J(E^0) = \begin{pmatrix} -r_1^\alpha & -\beta^\alpha K & 0 \\ 0 & \beta^\alpha K - \mu_1^\alpha & 0 \\ 0 & \tau^\alpha K & -\mu_2^\alpha \end{pmatrix}.$$

The eigenvalues of the Jacobian matrix determine an equilibrium's local stability where the eigenvalues are $(\lambda_i < 0)$ and $i = 1, 2, 3$.

$$\lambda_1 = -r_1^\alpha < 0, \quad \lambda_2 = \beta^\alpha K - \mu_1^\alpha < 0, \quad \lambda_3 = -\mu_2^\alpha < 0. \tag{23}$$

The virus-free equilibrium is locally stable, given that all the eigenvalues are negative. Considering Equation (23) we have,

$$\beta^\alpha K - \mu_1^\alpha < 0, \quad \frac{\beta^\alpha K}{\mu_1^\alpha} < \frac{\mu_1^\alpha}{\mu_1^\alpha}, \quad \frac{\beta^\alpha K}{\mu_1^\alpha} < 1. \tag{24}$$

Comparing Equations (24) and (16), we can conclude that $\mathcal{R}_0 < 1$ and since the basic reproductive number $(\mathcal{R}_0 < 1)$ and $\lambda_i < 0$ for $i = 1, 2, 3$ implies that E^0 is locally asymptotically stable. □

4.1.2. Local Stability of Virus Endemic Point

In this section, we investigate the stability of the Virus Endemic Equilibrium Point(VEE) to see if a small change around it will cause a drastic change or effect on the model or will cause it to return to its original state. In this model, we consider two-state endemic points and investigate their stability. We prove this by showing that $\mathcal{R}_0 > 1$ by the theorem below.

Theorem 5. *The VEE* $E^1 = (0, I_1, R_1)$ *of the system* (5) *is locally asymptotically stable whenever* $\mathcal{R}_0 \leq 1$ *and unstable whenever* $\mathcal{R}_0 > 1$.

Proof. We proceed by substituting E^1 into (22), to obtain

$$J(E^1) = \begin{pmatrix} r_1^\alpha - \beta^\alpha I_1 & 0 & 0 \\ \beta^\alpha I_1 & -c_1^\alpha R_1 - \mu_1^\alpha & -c_1^\alpha I_1 \\ \tau^\alpha I_1 & \frac{r_2 \sigma^\alpha R_1}{(\sigma^\alpha + I_1)^2} - c_2^\alpha R_1 & \frac{r_2^\alpha I_1}{\sigma^\alpha + I_1} - c_2^\alpha I_1 - \mu_2^\alpha \end{pmatrix}.$$

The characteristic equation of matrix $J(E^1)$ is $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$ where

$$a_1 = \beta^\alpha I_1 + c_1^\alpha R_1 + c_2^\alpha I_1 + \mu_1^\alpha + \mu_2^\alpha + r_1^\alpha - \frac{r_2^\alpha I_1}{\sigma^\alpha + I_1}, \quad a_2 = \Gamma_1 - \Gamma_2, \quad \text{and} \quad a_3 = \Gamma_3 - \Gamma_4,$$

with

$$\Gamma_1 = \beta^\alpha c_1^\alpha I_1 R_1 + \beta^\alpha c_2^\alpha I_1^2 + \beta^\alpha \mu_1^\alpha I_1 + c_2^\alpha \mu_1^\alpha I_1 + \beta^\alpha \mu_2^\alpha I_1 + c_1^\alpha \mu_2 v R_1 + \mu_1^\alpha \mu_2^\alpha + \frac{r_1^\alpha r_2^\alpha I_1}{\sigma^\alpha + I_1} + \frac{c_1^\alpha r_2^\alpha \sigma^\alpha I_1 R_1}{2\sigma^\alpha I_1 + \sigma^{2\alpha} + I_1^2}$$

$$\Gamma_2 = c_1^\alpha r_1^\alpha R_1 + \mu_1^\alpha r_1^\alpha + \mu_2^\alpha r_1^\alpha + c_2^\alpha r_1^\alpha I_1 + \frac{\beta^\alpha r_2^\alpha I_1^2}{\sigma^\alpha + I_1} + \frac{c_1^\alpha r_2^\alpha I_1 R_1}{\sigma^\alpha + I_1} + \frac{\mu_1^\alpha r_2^\alpha I_1}{\sigma^\alpha + I_1}$$

$$\Gamma_3 = \frac{c_1^\alpha r_2^\alpha \sigma^\alpha \beta^\alpha I_1^2 R_1}{2\sigma^\alpha I_1 + \sigma^{2\alpha} + I_1^2} + \frac{c_1^\alpha r_1^\alpha r_2^\alpha I_1 R_1}{\sigma^\alpha + I_1} + \frac{\mu_1^\alpha r_1^\alpha r_2^\alpha I_1}{\sigma^\alpha + I_1} + \beta^\alpha c_2^\alpha \mu_1^\alpha I_1^2 + \beta^\alpha c_1^\alpha \mu_2^\alpha I_1 R_1 + \beta^\alpha \mu_1^\alpha \mu_2^\alpha I_1$$

$$\Gamma_4 = \frac{\beta^\alpha \mu_1^\alpha r_2^\alpha I_1^2}{\sigma^\alpha + I_1} + \frac{\beta^\alpha c_1^\alpha r_2^\alpha I_1^2 R_1}{\sigma^\alpha + I_1} + \frac{c_1^\alpha r_1^\alpha r_2^\alpha \sigma^\alpha I_1 R_1}{\sigma^{2\alpha} + 2\sigma^\alpha I_1 + I_1^2} + \mu_1^\alpha \mu_2^\alpha r_1^\alpha + c_2^\alpha \mu_1^\alpha r_2^\alpha I_1 + c_1^\alpha \mu_2^\alpha r_1^\alpha R_1.$$

If $(\beta^\alpha I_1 + c_1^\alpha R_1 + c_2^\alpha I_1 + \mu_1^\alpha + \mu_2^\alpha + r_1^\alpha) > \frac{r_2^\alpha I_1}{\sigma^\alpha + I_1}$, $\Gamma_1 > \Gamma_2$ and $\Gamma_3 > \Gamma_4$ then a_1, a_2, a_3 and $(a_1 a_2 - a_3)$ are all non-negative. By the Routh–Hurwitz criterion [19], we can conclude that the endemic equilibrium point E^1 is locally asymptotically stable. □

Theorem 6. *If $\mathcal{R}_0 > 1$, then E^2 is unstable and stable when $\mathcal{R}_0 \leq 1$ and a unique endemic equilibrium $E^2 = (H_2, I_2, R_2)$ exist and are locally asymptotically stable in the interior of Ω with $E^2 > 0$.*

Proof. We also evaluate the Jacobian matrix (22) at the endemic state E^2. We have that

$$J(E^2) = \begin{pmatrix} r_1^\alpha - \frac{2r_1^\alpha H_2}{K} - \beta^\alpha I_2 & \beta^\alpha H_2 & 0 \\ \beta^\alpha I_2 & \beta^\alpha H_2 - c_1^\alpha R_2 - \mu_1^\alpha & -c_1^\alpha I_2 \\ \tau^\alpha I_2 & \tau^\alpha H_2 + \frac{r_2^\alpha \sigma^\alpha R_2}{(\sigma^\alpha + I_2)^2} - c_2^\alpha R_2 & \frac{r_2 I_2}{\sigma^\alpha + I_2} - c_2^\alpha I_2 - \mu_2^\alpha \end{pmatrix}.$$

The characteristic equation of matrix $J(E^2)$ is $\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3$ where

$$b_1 = \mathcal{E}_1 - \mathcal{E}_2, \quad b_2 = \mathcal{E}_3 - \mathcal{E}_4, \quad \text{and} \quad b_3 = \mathcal{E}_5 - \mathcal{E}_6$$

with

$$\mathcal{E}_1 = \beta^\alpha I_2 + c_1^\alpha R_2 + c_2^\alpha I_2 + \mu_1^\alpha + \mu_2^\alpha + \frac{2r_1^\alpha H_2}{K}$$

$$\mathcal{E}_2 = \beta^\alpha H_2 + r_1^\alpha + \frac{r_2^\alpha I_2}{\sigma^\alpha + I_2}.$$

$$\mathcal{E}_3 = \beta^\alpha I_2 \left(c_1^\alpha R_2 + c_2^\alpha I_2 + \mu_1^\alpha + \mu_2^\alpha + \frac{r_2^\alpha H_2}{\sigma^\alpha + I_2} \right) + H_2 \left(\tau^\alpha c_1^\alpha I_2 + \beta^\alpha r_1^\alpha + \frac{2c_1^\alpha r_1^\alpha R_2}{K} + \frac{2c_2^\alpha r_1^\alpha I_2}{K} + \frac{2r_1^\alpha \mu_2^\alpha}{K} \right)$$
$$+ c_2^\alpha \mu_1^\alpha I_2 + c_1^\alpha \mu_2^\alpha R_2 + \mu_1^\alpha \mu_2^\alpha + \frac{c_1^\alpha r_2^\alpha \sigma^\alpha I_2 R_2}{\sigma^{2\alpha} + 2\sigma^\alpha I_2 + I_2^2} + \frac{2\mu_1^\alpha r_1^\alpha H_2}{K} + \frac{r_1^\alpha r_2^\alpha I_2}{\sigma^\alpha + I_2}$$

$$\mathcal{E}_4 = \beta^\alpha c_2^\alpha H_2 I_2 + \beta^\alpha \mu_2^\alpha H_2 + c_1^\alpha r_1^\alpha R_2 + c_2^\alpha r_1^\alpha I_2 + \mu_1^\alpha r_1^\alpha + \mu_2^\alpha r_1^\alpha + \frac{2\beta^\alpha r_1^\alpha H_2}{K} + \frac{\beta^\alpha r_2^\alpha I_2^2}{\sigma^\alpha + I_2}$$

$$+\frac{c_1^\alpha r_2^\alpha I_2 R_2}{\sigma^\alpha + I_2} + \frac{\mu_1^\alpha r_2^\alpha I_2}{\sigma^\alpha + I_2} + \frac{2r_1^\alpha r_2^\alpha H_2 I_2}{(\sigma^\alpha + I_2)K}$$

$$\mathcal{E}_5 = \beta^\alpha I_2 \left(\frac{c_1^\alpha r_2^\alpha \sigma^\alpha R_2}{I_2^2 + 2\sigma^\alpha I_2 + \sigma^{2\alpha}} + c_2^\alpha \mu_1^\alpha I_2 + c_1^\alpha \mu_2^\alpha R_2 + c_2^\alpha r_1^\alpha H_2 + \mu_1^\alpha \mu_2^\alpha + \frac{2r_1^\alpha r_2^\alpha H_2^2}{(\sigma^\alpha + I_2)K} \right)$$

$$+\frac{2c_1^\alpha r_1^\alpha r_2^\alpha \sigma^\alpha H_2 I_2 R_2}{(I_2^2 + 2\sigma^\alpha I_2 + \sigma^{2\alpha})K} + \frac{2c_1^\alpha r_1^\alpha \tau^\alpha H_2^2 I_2}{K} + \frac{2c_2^\alpha \mu_1^\alpha r_1^\alpha H_2 I_2}{K} + \beta^\alpha \mu_2^\alpha r_1^\alpha H_2 + \frac{2c_1^\alpha \mu_2^\alpha r_1 H_2 R_2}{K}$$

$$+\frac{c_1^\alpha r_1^\alpha r_2^\alpha I_2 R_2}{\sigma^\alpha + I_2} + \frac{2\mu_1^\alpha \mu_2 r_1^\alpha H_2}{K} + \frac{\mu_1^\alpha r_1^\alpha r_2^\alpha I_2}{\sigma^\alpha + I_2}$$

$$\mathcal{E}_6 = \beta^\alpha I_2 \left(\frac{2c_2^\alpha r_1^\alpha H_2^2}{K} + \frac{c_1^\alpha r_2^\alpha I_2 R_2}{\sigma^\alpha + I_2} + \frac{\mu_1^\alpha r_2^\alpha I_2}{\sigma^\alpha + I_2} + \frac{r_1^\alpha r_2^\alpha H_2}{\sigma^\alpha + I_2} \right) + \frac{c_1^\alpha r_1^\alpha r_2^\alpha \sigma^\alpha R_2 I_2}{I_2^2 + 2\sigma^\alpha I_2 + \sigma^{2\alpha}} + c_1^\alpha r_1^\alpha \mu_2^\alpha R_2 + c_2^\alpha r_1^\alpha \mu_1^\alpha I_2$$

$$+\mu_1^\alpha \mu_2^\alpha r_1^\alpha + \frac{2\beta^\alpha \mu_2^\alpha r_1^\alpha H_2^2}{K} + H_2 I_2 \left(c_1^\alpha r_1^\alpha \tau^\alpha + \frac{2c_1^\alpha r_1^\alpha r_2^\alpha R_2}{(\sigma^\alpha + I_2)K} + \frac{2\mu_1^\alpha r_1^\alpha r_2^\alpha}{(\sigma^\alpha + I_2)K} \right).$$

If $\mathcal{E}_1 > \mathcal{E}_2$, $\mathcal{E}_3 > \mathcal{E}_4$ and $\mathcal{E}_5 > \mathcal{E}_6$ which implies that b_1, b_2, b_3 and $(b_1 b_2 - b_3)$ are all non-negative. Then by Routh–Hurwitz criterion [19], the endemic equilibrium point E^2 is locally asymptotically stable. □

4.2. Global Stability Analysis

To obtain the global stability of the equilibrium points, we use the Ulam–Hyers stability criteria. We show that the fractional model (5) is both stable and generalized stable in the sense of Ulam–Hyers. We say $\overline{X} \in \mathcal{E}$ is a solution of

$$\left| {}^c D_t^\alpha X(t) - \mathcal{K}(t, X(t)) \right| \leq \epsilon, \quad t \in [0, T], \tag{25}$$

if and only if there exists $h \in \mathcal{E}$ satisfying,

1. $|h(t)| \leq \epsilon$,
2. ${}^c D_t^\alpha = \mathcal{K}(t, \overline{X}(t)) + h(t)$, $t \in [0, T]$.

Note that any function satisfying (2) also satisfies the integral inequality given,

$$\left| \overline{X}(t) - \overline{X}(0) - \frac{1}{\Gamma(\alpha)} \int_0^t (t - \tau)^{\alpha - 1} \mathcal{K}(\tau, \overline{X}(\tau)) \right| \leq \Omega\epsilon, \ t \in [0, T]. \tag{26}$$

Definition 3. *The fractional order model see (5) and equivalently (7) is Ulam–Hyers stable if there exist $C_\mathcal{K} > 0$ such that for every $\epsilon > 0$, and for each $\overline{X} \in \mathcal{E}$ satisfying (25), there exist a solution $X \in \mathcal{E}$ of the model see (5) with,*

$$\left\| \overline{X}(t) - X(t) \right\|_\mathcal{E} \leq C_{\mathcal{K}\epsilon}.$$

Definition 4. *The fractional order model (5) and (7) is said to be generalized Ulam–Hyers stability if there exists a continuous function $\phi_\mathcal{K} : \mathbb{R}^+ \to \mathbb{R}^+$ with $\phi_\mathcal{K}(0) = 0$, such that, for each solution $\overline{X} \in \mathcal{E}$ of (25), there exist a solution $X \in \mathcal{E}$ of the model (5) such that ,*

$$\left\| \overline{X}(t) - X(t) \right\|_\mathcal{E} \leq \phi_{\mathcal{K}_\epsilon}, \ t \in [0, T].$$

The stability of the fractional-order model is now presented as follows;

Theorem 7. *Let the hypothesis and result of Lemma 3 hold see (3), $\Omega = \frac{b}{\Gamma(a)}$ and $1 - \Omega L_\mathcal{K} > 1$. Then the fractional order model (5) and (7) is Ulam–Hyers stable and consequently generalized Ulam–Hyers stable.*

Proof. Let X be a unique solution of (7) guaranteed by theorem(3.3) see (3), $\overline{X}$ satisfies (25) and recalling the expression for (8), (26) we have for $\epsilon > 0, t \in [0, T]$ we have that,

$$\begin{aligned}
\|\overline{X}(t) - X(t)\|_{\mathcal{E}} &= \sup_{t\in[0,T]} \left|\overline{X}(t) - X_0 - \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)\mathcal{K}(\tau, X(\tau))d\tau\right| \\
&\leq \sup_{t\in[0,T]} \left|\overline{X}(t) - \overline{X}_0 - \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1}\mathcal{K}(\tau, \overline{X}(\tau))d\tau\right| \\
&+ \sup_{t\in[0,T]} \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1}\left|\mathcal{K}(\tau, \overline{X}(\tau)) - \mathcal{K}(\tau, X(\tau))\right|d\tau \\
&\leq \Omega\epsilon + \Omega L_{\mathcal{K}}\|\overline{X} - X\|_{\mathcal{E}}. \qquad (27)
\end{aligned}$$

From the above, we obtain $\|\overline{X} - X\|_{\mathcal{E}} \leq C_{\mathcal{K}}$, where $C_{\mathcal{K}} = \frac{\Omega\epsilon}{1-\Omega L_{\mathcal{K}}}$. We conclude that the proposed problem (5) is both Ulam–Hyers and generalized Ulam–Hyers stable since $\varphi_K(\epsilon) = C_{\mathcal{K}}\epsilon$ such that $\varphi_K(0) = 0$. □

4.2.1. Global Stability of VFE Point

Using a Lyapunov function, we demonstrate that the virus-free equilibrium point E^0 is globally asymptotically stable.

Theorem 8. *The virus free equilibrium, E^0, is globally asymptotically stable if $\mathcal{R}_0 > 1$.*

Proof. Consider the Lyapunov function of the Goh–Volterra type,

$$\mathcal{L} = H_0\Psi\Big(\frac{H}{H_0}\Big) + I_0\Psi\Big(\frac{I}{I_0}\Big) + R_0\Psi\Big(\frac{R}{R_0}\Big),$$

where $\Psi(x) = x - 1 - \ln x$, $\forall x > 0$. The solution of the system (5) is determined by the derivative of $\mathcal{L}$ as follows

$$\begin{aligned}
{}^{C}D_t^{\alpha}\mathcal{L} &= \Big(1 - \frac{H_0}{H}\Big){}^{C}D_t^{\alpha}H + \Big(1 - \frac{I_0}{I}\Big){}^{C}D_t^{\alpha}I + \Big(1 - \frac{R_0}{R}\Big){}^{C}D_t^{\alpha}R \\
&= \Big(1 - \frac{H_0}{H}\Big)\Big(r_1^{\alpha}H - \frac{r_1^{\alpha}H^2}{K} - \beta^{\alpha}HI\Big) + \Big(1 - \frac{I_0}{I}\Big)\Big(\beta^{\alpha}HI - c_1^{\alpha}RI - \mu_1^{\alpha}I\Big) \\
&+ \Big(1 - \frac{R_0}{R}\Big)\Big(\tau^{\alpha}HI + \frac{r_2^{\alpha}RI}{\sigma^{\alpha} + I} - c_2^{\alpha}RI - \mu_2^{\alpha}R\Big).
\end{aligned}$$

By evaluating the above expression at the E^0, we obtain,

$$\begin{aligned}
{}^{C}D_t^{\alpha}\mathcal{L} &= \Big(1 - \frac{K}{H}\Big)\Big(r_1^{\alpha}H - \frac{r_1^{\alpha}H^2}{K} - \beta^{\alpha}HI\Big) + \beta^{\alpha}HI - c_1^{\alpha}RI - \mu_1^{\alpha}I + \tau^{\alpha}HI + \frac{r_2^{\alpha}RI}{\sigma^{\alpha} + I} - c_2^{\alpha}RI - \mu_2^{\alpha}R \\
&= -r_1^{\alpha}R + r_1^{\alpha}K + \beta^{\alpha}KI - c_1^{\alpha}RI - \mu_1^{\alpha}I + \tau^{\alpha}KI + \frac{r_2^{\alpha}RI}{\sigma^{\alpha} + I} - c_2^{\alpha}RI - \mu_2^{\alpha}R \\
&\leq r_1^{\alpha}K + \beta^{\alpha}KI + \tau^{\alpha}KI - \mu_1^{\alpha}I + \frac{r_2^{\alpha}RI}{\sigma^{\alpha} + I} \\
&= \mu_1^{\alpha}\frac{\beta^{\alpha}KI}{\mu_1^{\alpha}} - \mu_1^{\alpha}I + \varrho = \mu_1^{\alpha}I(\mathcal{R}_0 - 1) + \varrho, \qquad (28)
\end{aligned}$$

where we have assumed that $H = K$ at $H_{\max}$ and $\varrho = r_1^{\alpha}K + \tau^{\alpha}KI + \frac{r_2^{\alpha}RI}{\sigma^{\alpha} + I}$. Therefore, ${}^{C}D_t^{\alpha}\mathcal{L} \leq 0$ if $\mathcal{R}_0 \leq 1$. Furthermore, by the LaSalle's invariance principle, the virus-free equilibrium point (E^0) is globally asymptotically stable. □

4.2.2. Global Stability of Virus EE Point

Finally, we investigate the global stability of the endemic equilibrium points.

Theorem 9. *The virus EE, E^1, is globally asymptotically stable if $\mathcal{R}_0 > 1$.*

Proof. We consider a Lyapunov function,

$$\mathcal{L}_1 = H_1\Psi\Big(\frac{H}{H_1}\Big) + I_1\Psi\Big(\frac{I}{I_1}\Big) + R_1\Psi\Big(\frac{R}{R_1}\Big),$$

where $\Psi(x) = x - 1 - \ln x$, $\forall x > 0$. By differentiating and evaluating at $E^1 = (0, I_1, R_1)$, we obtain

$$\begin{aligned}
{}^{C}D_t^{\alpha}\mathcal{L} &= \Big(1 - \frac{H_1}{H}\Big)\Big(r_1^{\alpha}H_1 - \frac{r_1^{\alpha}H_1^2}{K} - \beta^{\alpha}H_1I_1\Big) + \Big(1 - \frac{I_1}{I}\Big)\Big(\beta^{\alpha}H_1I_1 - c_1^{\alpha}R_1I_1 - \mu_1^{\alpha}I_1\Big)\\
&\quad + \Big(1 - \frac{R_1}{R}\Big)\Big(\tau^{\alpha}H_1I_1 + \frac{r_2^{\alpha}R_1I_1}{\sigma^{\alpha} + I_1} - c_2^{\alpha}R_1I_1 - \mu_2^{\alpha}R_1\Big).\\
&= -c_1^{\alpha}R_1I_1 - \mu_1^{\alpha}I_1 - \frac{c_1^{\alpha}R_1I_1^2}{I} - \frac{\mu_1^{\alpha}I_1^2}{I} + \frac{r_2^{\alpha}R_1I_1}{\sigma^{\alpha} + I_1} - c_2^{\alpha}\,R_1I_1\\
&\quad - \mu_2^{\alpha}R_1 - \frac{r_2^{\alpha}R_1^2I_1}{R(\sigma^{\alpha} + I_1)} - \frac{c_2^{\alpha}R_1^2I_2}{R} - \frac{\mu_2^{\alpha}R_1^2}{R}\\
&\le \mu_1^{\alpha}I_1(1 - \mathcal{R}_0) + \Gamma_1 - \Gamma_2,
\end{aligned}$$

where

$$\Gamma_1 = c_1^{\alpha}RI_1 + \tau^{\alpha}HI + \frac{r_2^{\alpha}RI}{\sigma^{\alpha} + I} + \frac{\tau^{\alpha}HIR_1}{R} + \frac{r_2^{\alpha}IR_1}{\sigma^{\alpha} + I},$$

and

$$\Gamma_2 = c_1^{\alpha}RI + \mu_1^{\alpha}I + c_2^{\alpha}RI + \mu_2^{\alpha}(R - R_1).$$

If $\mathcal{R}_0 > 1$ then ${}^{C}D_t^{\alpha}\mathcal{L}_1 \le 0$ provided $\Gamma_1 = \Gamma_2$. Hence, ${}^{C}D_t^{\alpha}\mathcal{L}_1 \le 0$ is negative semi-definite, and by the LaSalle's invariance principle [20], the endemic equilibrium point, E^1 is globally asymptotically stable. □

We prove the global stability of the second endemic equilibrium point.

Theorem 10. *The virus EE, E^2, is globally asymptotically stable if $\mathcal{R}_0 > 1$.*

Proof. Again, we consider the Goh–Volterra type lyapunov function,

$$\mathcal{L}_2 = H_2\Psi\Big(\frac{H}{H_2}\Big) + I_2\Psi\Big(\frac{I}{I_2}\Big) + R_2\Psi\Big(\frac{R}{R_2}\Big), \tag{29}$$

where $\Psi(x) = x - 1 - \ln x$, $\forall x > 0$. It follows that By differentiating and evaluating at $E^2 = (H_2, I_2, R_2)$, we obtain

$$\begin{aligned}
{}^{C}D_t^{\alpha}\mathcal{L}_2 &= \Big(1 - \frac{H_2}{H}\Big)\Big(r_1^{\alpha}H_2 - \frac{r_1^{\alpha}H_2^2}{K} - \beta^{\alpha}H_2I_2\Big) + \Big(1 - \frac{I_2}{I}\Big)\Big(\beta^{\alpha}H_2I_2 - c_1^{\alpha}R_2I_2 - \mu_1^{\alpha}I_2\Big)\\
&\quad + \Big(1 - \frac{R_2}{R}\Big)\Big(\tau^{\alpha}H_2I_2 + \frac{r_2^{\alpha}R_2I_2}{\sigma^{\alpha} + I_2} - c_2^{\alpha}R_2I_2 - \mu_2^{\alpha}R_2\Big).\\
&= r_1^{\alpha}H_2 - \frac{r_1^{\alpha}H_2^2}{K} - \frac{r_1^{\alpha}H_2^2}{K} - \frac{r_1^{\alpha}H_2^3}{H_2K} - \frac{\beta^{\alpha}H_2^2I_2}{H_2} - c_1^{\alpha}R_2I_2 - \mu_1^{\alpha}I_2\\
&\quad - \frac{\beta^{\alpha}H_2I_2^2}{I_2} - \frac{c_1^{\alpha}R_2I_2^2}{I_2} - \frac{\mu_1^{\alpha}I_2^2}{I_2} + \tau^{\alpha}H_2I_2 + \frac{r_2^{\alpha}R_2I_2}{\sigma^{\alpha} + I_2} - c_2^{\alpha}R_2I_2 - \mu_2^{\alpha}R_2\\
&\quad - \frac{\tau^{\alpha}H_2I_2R_2}{R_2} - \frac{r_2^{\alpha}R_2^2I_2}{R_2(\sigma^{\alpha} + I_2)} - \frac{c_2^{\alpha}R_2^2I_2}{R_2} - \frac{\mu_2^{\alpha}R_2^2}{R_2},
\end{aligned}$$

$$\leq I_2\mu_1^\alpha(1-\mathcal{R}_0)+\Gamma_3-\Gamma_4,$$

where

$$\Gamma_3=\beta^\alpha H_2 I+c_1^\alpha R I_2+c_2^\alpha R_2 I+\mu_2^\alpha R_2+\tau^\alpha K I+\frac{r_2^\alpha R I}{\sigma^\alpha+I}$$

and

$$\Gamma_4=c_1^\alpha R I+\mu_1^\alpha I+c_2^\alpha R I+\mu_2^\alpha R+\frac{\tau^\alpha K R_2 I}{R}+\frac{r_2^\alpha R_2 I}{\sigma^\alpha+I}.$$

If $\mathcal{R}_0>1$ then ${}^C D_t^\alpha \mathcal{L}_2\leq 0$ provided $\Gamma_3=\Gamma_4$. Then by LaSalle's invariance principle [20], the endemic equilibrium point, E^2, is globally asymptotically stable. □

5. Numerical Results and Simulation

In this section, we present the numerical simulation to explain the dynamics of the Caputo fractional order nonlinear HBV mathematical model using the Adams-type predictor–corrector iterative scheme, see for example, [21,22] to solve the fractional-order differential equations. Using an equivalent integral formulation of our fractional model (7), we consider a uniform time discretization of $[0,T]$ given by $t_n=nh$, $n=0,1,2,\ldots,N$ where $h=T/n$ denote the step size. For any given approximation $X_h(t_n)\approx X(t_n)$, the next approximate $X_h(t_{n+1})$ is derived via the Adams-type predictor–corrector iterative scheme as follows;

Predictor:

$$X_h^p(t_{n+1})=\sum_{k=0}^{\lceil\alpha\rceil-1}\frac{t_{n+1}^k}{k!}X_0^k+\frac{1}{\Gamma(\alpha)}\sum_{i=0}^{n}b_{i,n+1}\mathcal{K}(t_i,X_h^c(t_i))$$

Corrector:

$$X_h^c(t_{n+1})=\sum_{k=0}^{\lceil\alpha\rceil-1}\frac{t_{n+1}^k}{k!}X_0^k+\frac{h^\alpha}{\Gamma(\alpha+2)}\mathcal{K}(t_{i+1},X_h^p(t_{i+1}))+\frac{h^\alpha}{\Gamma(\alpha+2)}\sum_{i=0}^{n}a_{i,n+1}\mathcal{K}(t_i,X_h(t_i))$$

with

$$a_{i,n+1}=\begin{cases}n^{\alpha+1}-(n-\alpha)(n+1)^\alpha, & \text{if } i=0\\ (n-i+2)^{\alpha+1}+(n-i)^{\alpha+1}-2(n-i+1)^{\alpha+1}, & \text{if } 1\leq i\leq n\\ 1, & \text{if } i=n+1\end{cases}$$

and

$$b_{i,n+1}=\frac{h^\alpha}{\alpha}\left[(n-i+1)^\alpha-(n-i)^\alpha\right].$$

5.1. Example 1

In this example, we assume parameter values as follows $\beta=4.14704,\mu_1=0.0693$, $\mu_2=0.693,\tau=10,\sigma=1.35,r_1=6.2,r_2=0.02,c_1=0.2,c_2=0.037,K=2\times10^{11}$. We consider the initial conditions $H_0=0.1,I_0=0.1,R_0=0$ with a time span of 0 to 20 days and varying values of the fractional order α are reported in Figures 1–3. Finally in Figures 4 and 5, we present the dynamics of the model for $\alpha=0.7$ and $\alpha=0.9$. Here, we obtain a basic reporduction number $\mathcal{R}_0>1$. This example demonstrates the case where the healthy hepatocytes are growing slower than the infected hepatocytes, which activates the growth of more immune response cytotoxic cells, as can be seen in Figures 3 and 4.

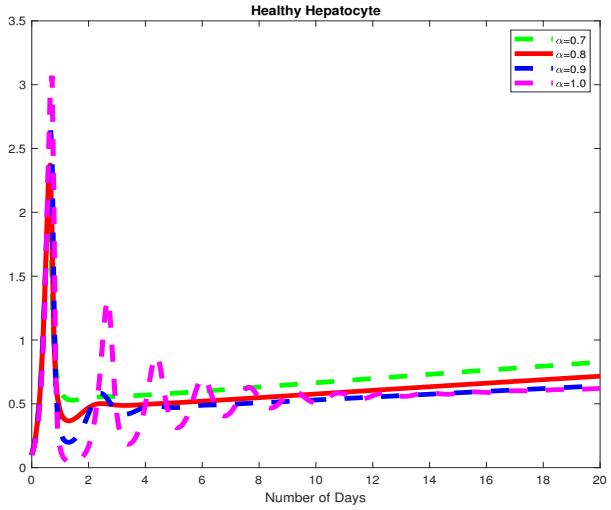

Figure 1. The dynamics of the healthy hepatocytes, H, for varying fractional order α.

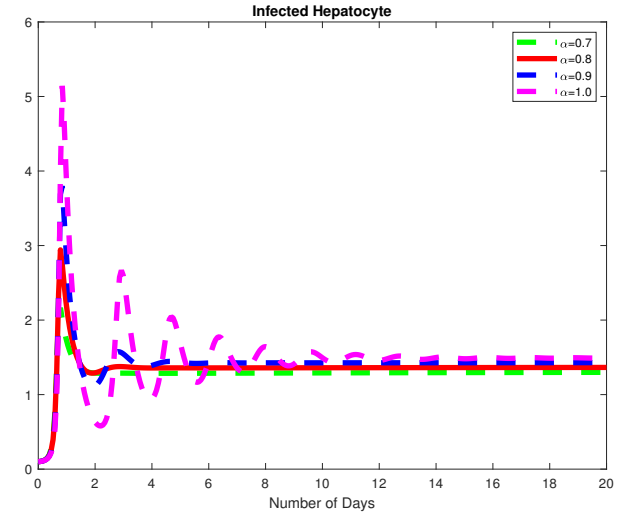

Figure 2. The dynamics of the Infected hepatocytes, I, for varying fractional order α.

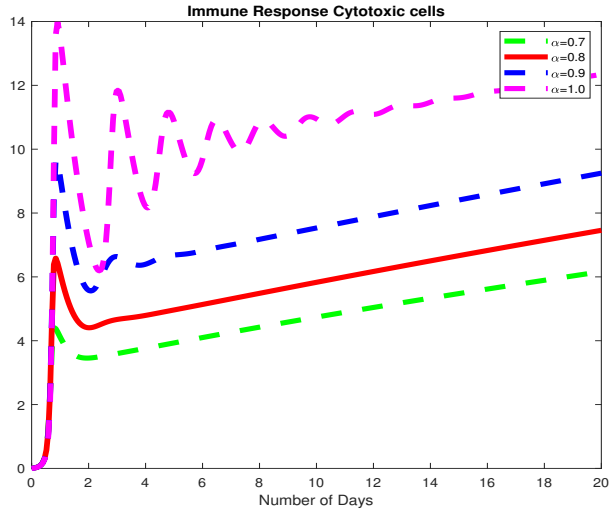

Figure 3. The dynamics of the immune response cytotoxic cells, R, for varying fractional order α.

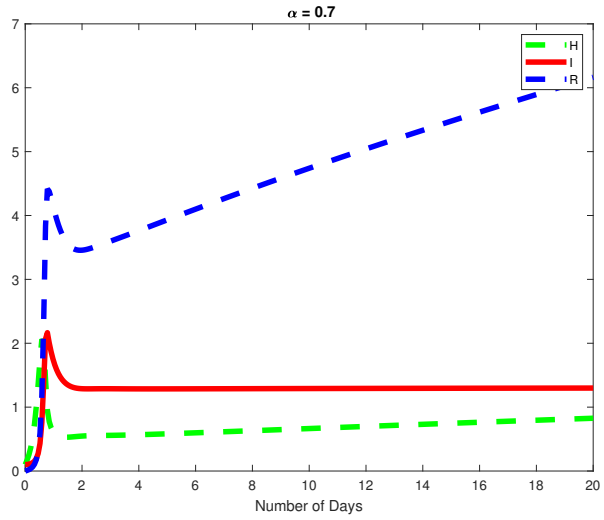

Figure 4. For the same fractional order, we plot the dynamics of the Healthy and Infected Hepatocyte as well as the Immune response cytotoxic cells for $\alpha = 0.7$.

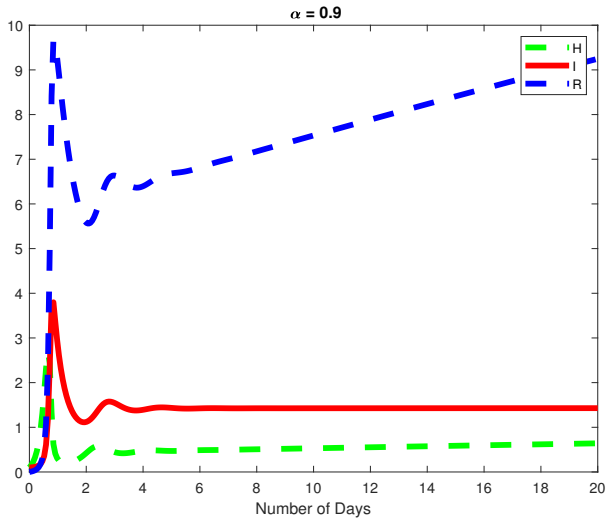

Figure 5. For the same fractional order, we plot the dynamics of the Healthy and Infected Hepatocyte as well as the Immune response cytotoxic cells for $\alpha = 0.9$.

5.2. Example 2

In this example, we consider the parameters values $r_1 = 0.2, K = 1, \beta = 0.3$, $c_1 = 0.02, \mu_1 = 0.01, \tau = 0.0001, \sigma = 0.001, r_2 = 0.01, c_2 = 1, \mu_2 = 0.02$. Here, we demonstrate the case where $\mathcal{R}_0 \leq 1$, which means that the virus will die out after a number of days, see Figures 6–8. Again we see in Figures 9 and 10, the dynamics of the model for varying parameters $\alpha = 0.7$ and $\alpha = 0.9$. This example demonstrates the case where the healthy hepatocytes are growing faster than the infected hepatocytes. This activates a minimal growth of immune response cytotoxic cells, as can be seen in Figures 9 and 10.

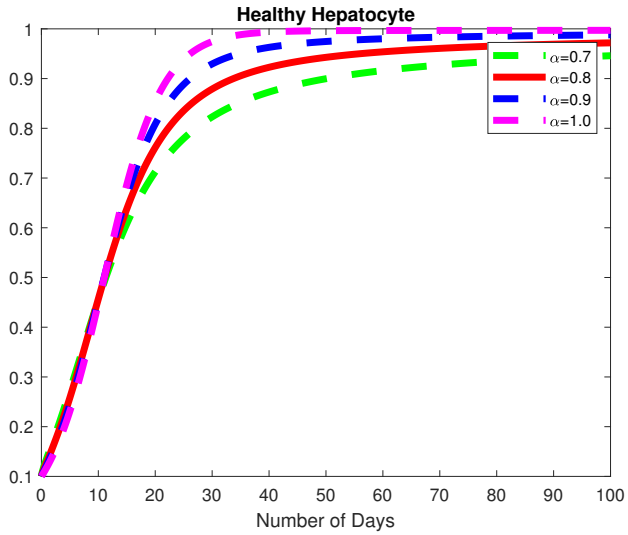

Figure 6. The dynamics of the healthy hepatocytes, H, for varying fractional order α.

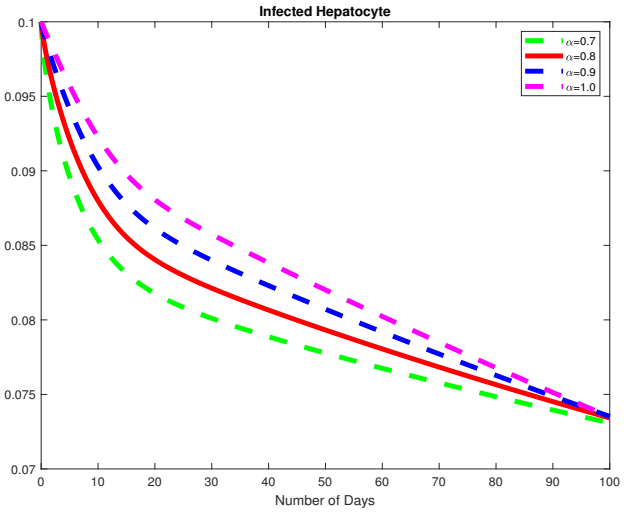

Figure 7. The dynamics of the infected hepatocytes, I, for varying fractional order α.

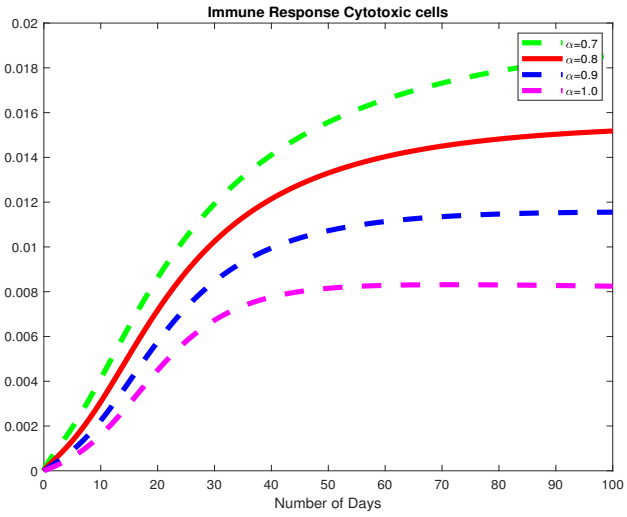

Figure 8. The dynamics of the immune response cytotoxic cells, R, for varying fractional order α.

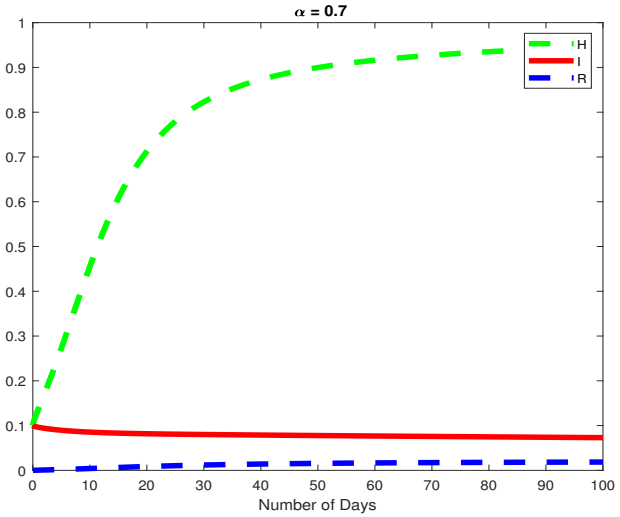

Figure 9. The dynamics of the Healthy (H) and Infected (I) Hepatocyte and the Immune resonse cytotoxic cells (R) for $\alpha = 0.7$.

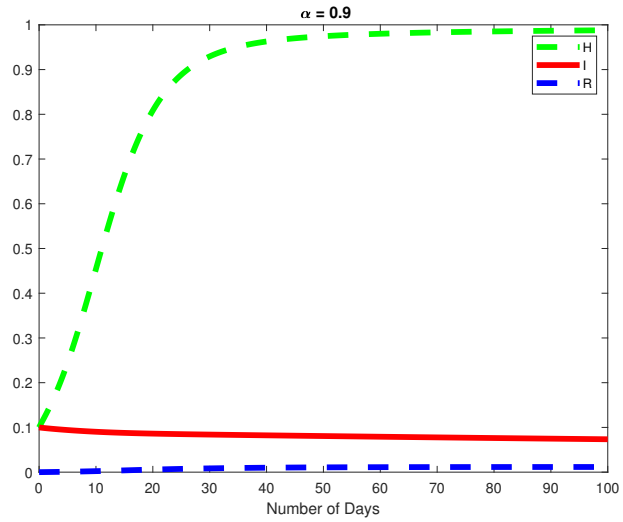

Figure 10. The dynamics of the Healthy (H) and Infected (I) Hepatocyte and the Immune response cytotoxic cells (R) for $\alpha = 0.9$.

5.3. Example 3

Next, we study the parameters β and μ_1 to understand the dynamics of the model with respect to the basic reproduction number, $\mathcal{R}_0$. Using the parameter values from Example 2 at a fractional order of $\alpha = 0.7$, we choose varying values for β. Here, we note that the basic viral reproduction number $\mathcal{R}_0 < 1$, for $\beta = \{0.0008, 0.008\}$. Thus, if the infection rate of the normal cells is less than the natural death rate of the HB virus; then the HB virus will finally die out as depicted in Figures 11–13. We also notice that, for $\beta < \mu_1$, the Healthy Hepatocytes grow whiles the for $\beta > \mu_1$, the Healthy Hepatocytes diminishes.

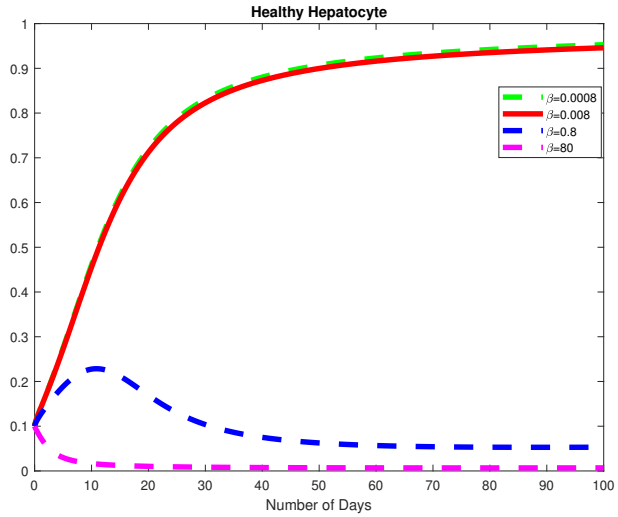

Figure 11. The dynamics of the Healthy Hepatocytes (H) for varying values of β.

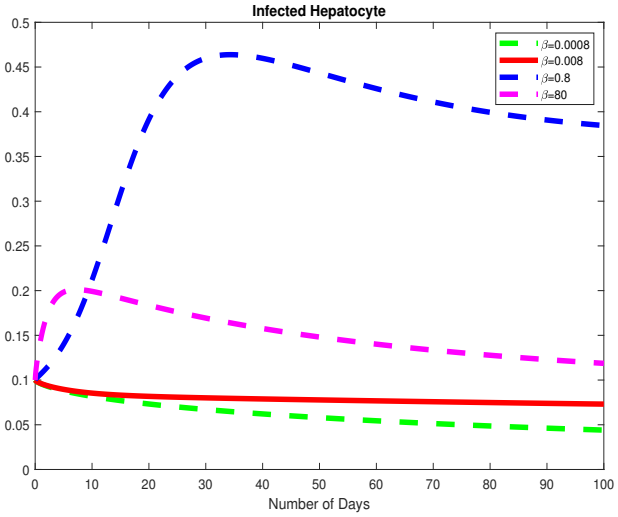

Figure 12. The dynamics of the Infected Hepatocytes (I) for varying values of β.

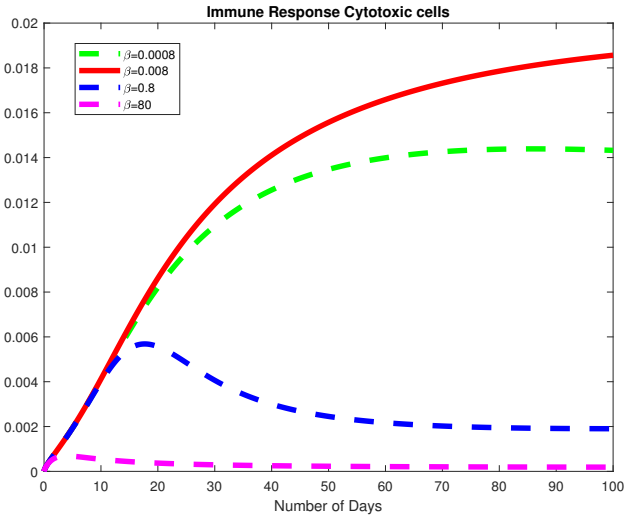

Figure 13. The dynamics of the Immune Response Cytotoxic cells (R) for varying values of β.

5.4. Example 4

In this example, we consider all the parameter values in Example 2 except for μ_1 for a fixed fractional order $\alpha = 0.7$. We used varying values of $\mu_1 = \{0.0001, 0.001, 0.1, 10\}$. We obtained the basic viral reproduction number $\mathcal{R}_0 < 1$ for all the values except at $\mu_1 = 0.0001$, which means that the virus will be removed whenever the natural death rate of the virus is less than the rate of infection of healthy hepatocytes, see Figures 14–16. In Figure 17, we notice that when the Healthy Hepatocytes are high, the infected Hepatocytes are low and lead to a low amount of the immune response cytotoxic cells.

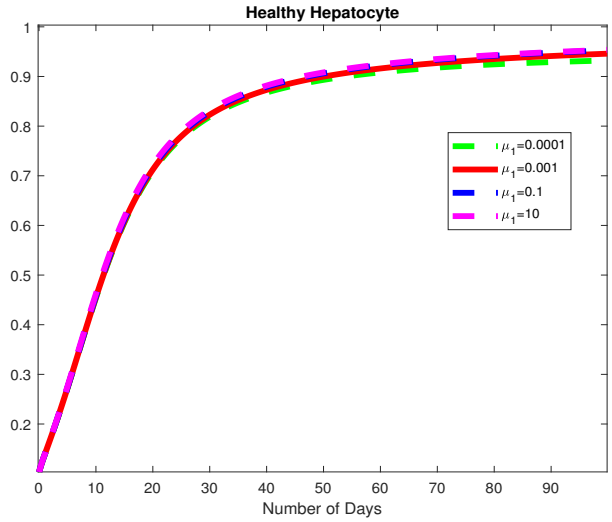

Figure 14. The dynamics of the Healthy Hepatocytes (H) for varying values of μ_1.

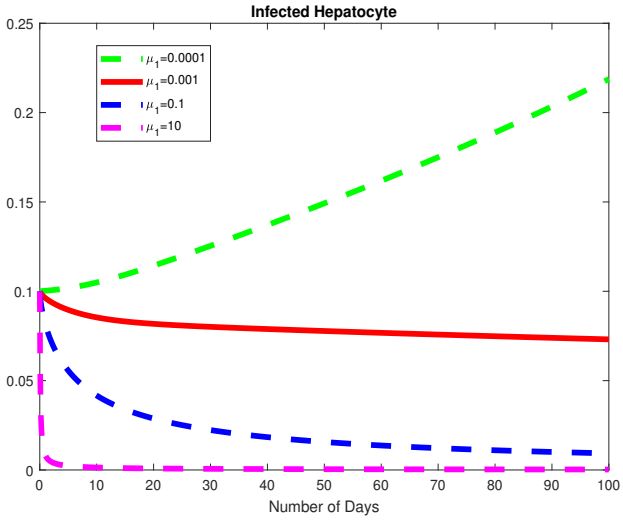

Figure 15. The dynamics of the Infected Hepatocytes (I) for varying values of μ_1.

Analyzing the impact of K in the model, we realize that, in both endemic and disease-free states, a significant increase in the value of K does not change the state of stability, for instance, keeping all parameters constant in the case of endemic with $\mu_1 = 0.01$, when $K = 10, \mathcal{R}_0 = 6 > 1$,and when $K = 1000, \mathcal{R}_0 = 600 > 1$. we also analyzed β, which affects the rate at which Healthy hepatocytes become infected; thus, an increase in β always causes the infected hepatocytes to increase, indicating a positive relationship between β and I. An increase in β in an endemic condition indicates that the virus will eventually affect all the healthy hepatocytes, and once there are no healthy hepatocytes left to rely on, the virus will eventually go extinct see (10). Taking $\alpha = 1$, when $\mu_1 = 0.01$ and $\beta = 0.3$, $\mathcal{R}_0 = 30$. similarly when $\beta = 0.1$, $\mathcal{R}_0 = 10$. The maximum value β can take in the endemic case is

1.2 and a minimum value of 0.1. In the case of disease free when $\mu_1 = 0.5$, β takes values $0 < \beta < 0.5$. Thus, when $\beta = 0.3$, $\mathcal{R}_0 = 0.6 < 1$ and when $\beta = 0.4$, $\mathcal{R}_0 = 0.8 < 1$.

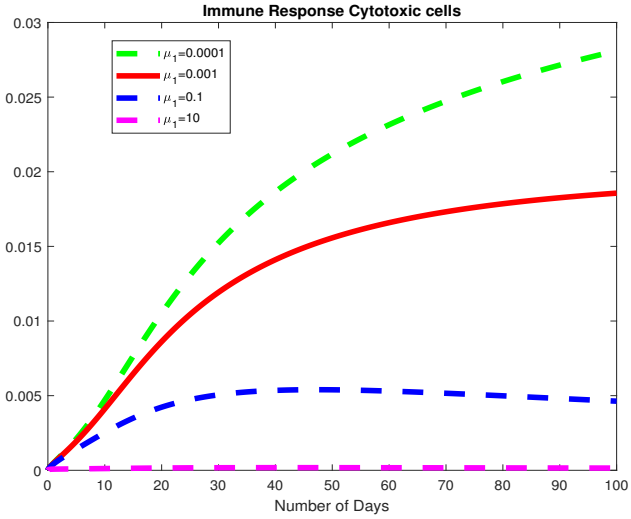

Figure 16. The dynamics of the Immune response cytotoxic cells (R) for varying values of μ_1.

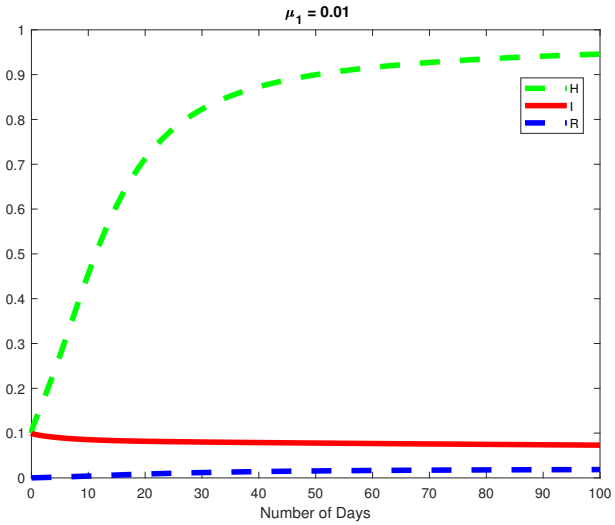

Figure 17. The dynamics of the model for $\mu_1 = 0.01$ at a fractional order of $\alpha = 0.7$.

6. Conclusions

We presented the theoretical and numerical simulations for Caputo fractional order model for Hepatitis B cellular viral infection. We presented the existence and uniqueness as well as the boundedness of the model. We showed that the virus-free equilibrium (VFE) is locally asymptotically stable when $\mathcal{R}_0 \leq 1$ else is unstable, i.e., replicating and becomes persistent in the liver. By means of Routh–Hurwitz, we established local stability. Using Ulam–Hyers stability, we showed that the fractional model is globally asymptotically stable. Subsequently, we presented the global stability results for the virus-free and endemic equilibrium points. Finally, using a predictor–corrector iterative scheme, several numerical simulations were presented for different fractional orders of the derivative, which corresponds to the analytical results predicted.

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