The Optimal Control Strategy of Virus Transmission Based on Caputo-Fabrizio Order

Liangli Yang[1], Yongmei Su[1]*, Xue Yang[1] and Zhen Wang[2]

[1]*School of Mathematics and Physics, University of Science and Technology Beijing, Beijing, China,* [2]*Center for Optical Imagery Analysis and Learning (OPTIMAL), Northwestern Polytechnical University, Xi'an, China*

Hepatitis B virus (HBV) is a serious threat to human health as it can cause the chronic hepatitis B, and eventually liver cancer. It also has become one of the major threats to public health in the world. In this paper, considering the rationality of using standard incidence in Caputo-Fabrizio fractional order HBV infection model, we propose a model with standard incidence. The analysis of local stability about the equilibrium and the simulation of global stability are given. We also use the real data to estimate the parameters of this model. The simulation results can fit the data well. Moreover, we propose an optimal control model and give the optimal therapy strategy, which show that optimal therapy can reduce the cost and side effects while ensuring the therapeutic effect.

Keywords: caputo-fabrizio, optimal control, parameter estimation, HBV model, stability

1 INTRODUCTION

Hepatitis B virus (HBV) is a partially double-stranded DNA virus and can cause liver diseases such as hepatitis, cirrhosis and liver cancer, and eventually death. When the virus invades the human body, it enters the liver cells by binding to the receptor. Then, HBV-DNA is transported to the nucleus of liver cells and converted into cccDNA under the action of host enzymes. Since cccDNA is not easily degraded, chronic hepatitis B is difficult to be cured [1, 2]. Despite the highly effective recombinant vaccine has been available from 1981 [3], and more and more population are actively vaccinated, the number of the HBV infected is still increasing. More than two billion people have been infected worldwide, and 350 million people are suffering from chronic hepatitis B [4]. HBV has become a major threat to global public health.

Mathematical models can be used to simulate and predict the process of biodynamics. Researchers analyzed the dynamics of the model from different aspects. An immune model was given by Su et al. [5] and the existence, uniqueness and global stability of the model were also analyzed. Anwarud [6] proposed a HBV model with the effect of vaccine and treatment and gave the optimal control strategy. Li et al. [7] analyzed the network vulnerability based on Markov criticality and applied it in lots of biosystem networks. Kalyan [8] considered the intracellular delay in the production of the infected hepatocytes and incorporated a time lag in his model. The spatial diffusion was also used by Khalid [9]. However, most of the papers are limited in the classical integer order.

Fractional calculus is an arbitrary order generalization of classical integral calculus which has the characters of memory, history and nonlocality. There are many definitions of fractional calculus. Among them, Caputo order is one of the widely used types. Kai Diethel [10] summarized the application of Caputo in various field and the numerical methods of fractional order. Devendra [11] derived analysis and numerical solutions of nonlinear fractional problems in nanofluid dynamics, nanoscale heat conduction and carbon nanotube current. Ivan [12] gave a fractional order Ebola

epidemic model to study its outbreak. Min Ma [13] considered the diffusion issue in fractional order models and gave the numerical method. Hatıra [14] proposed HIV model with Caputo and constant proportional Caputo operators. Fatmawati [15] gave the Caputo order model of HIV transmission with awareness effect. To reduce the transmission of HIV, Caputo order model for the transmission of HIV epidemic with optimal control was proposed by Parvaiz [16]. The theory of Caputo fractional order in dynamic system has also been derived. The local stability was similar to that in integer order and derived by E. Ahmed [17]. The global stability of fractional order was also given by Boukhouima [18]. And other theorems [19] of the Caputo order systems have been derived and widely used in papers. However, the singular kernel of the Caputo fractional derivative causes a lot of difficult problems both in integral calculation and discretization.

To avoid the shortage of the singular kernel, some researchers have proposed new definitions of fractional order. These definitions include the Caputo-Fabrizio derivative defined by an exponential decay law [20] and Atangana–Baleanu derivative defined by a Mittag–Leffler law [21]. Although Caputo-Fabrizio order does not conform to the traditional fractional calculus [22], it is also used in lots of biodynamic system. Esmehan [23] gave a cancer-immune system and discussed the model by adding IL-12 cytokine and anti-PD-L1 inhibitor. Elvin [24] proposed and analyzed a Caputo–Fabrizio fractional model for the HIV/AIDS epidemic which includes an antiretroviral treatment compartment. Human liver model involving Caputo–Fabrizio derivative was also proposed by Dumitru [25]. Hakimeh [26] proposed a Caputo–Fabrizio model for hearing loss due to Mumps virus with optimal control. The basic theorems of this order have also been proved, including the existence and uniqueness of the solution and the local stability of the equilibrium point [27].

Many papers study HBV with mathematic models. The earliest study can be traced back to the three-state model proposed by Novak et al. [28] and the analysis of the model and basic reproduction number were given. With the development of HBV, researchers have found that the bilinear incidence can not describe the real infection within body well. So Min et al. [29] modified βxv to $\frac{\beta xv}{x+y}$ which can be seen as the standard incidence. Similarly, Y. J. et al. [30] gave a model by using the standard incidence rate and the logistic function. They also gave the optimal therapy in its corresponding control model. The factional order is also used in HBV models. Salman proposed a within-host fractional order HBV model with Caputo order [31]. Compared with models above, this paper considered not only Caputo fractional order, but also the cure of infected hepatocytes. At the same time, Caputo-Fabrizio order can be also used in HBV models. Saeed Ahmad [32] gave a Caputo-Fabrizio order model describing the dynamics of hepatitis B infectious disease and used the Banach fixed point theory approach. Fei Gao [33] proposed the Caputo-Fabrizio with delay, analyzed and simulated the stability of its equilibrium points. However, the infection incidence is bilinear and the real data of HBV infection is not used in his model.

So far, almost no paper considered the Caputo-Fabrizio order model with standard incidence which is more reasonable. And Caputo-Fabrizio order also has the character of memory and can effectively avoid the singularity of Caputo order. Besides, there are seldom papers considered parameter estimation based on the real data and optimal control in Caputo Fabrizio order HBV infection models. Based on the above discussion, we first propose a Caputo-Fabrizio fractional order model with standard incidence. Then, we use the clinical data to estimate the parameters of our model. Finally, we propose an optimal control model based on the treatment for chronic hepatitis B and give the optimal therapy strategy. Using the actual data to estimate the parameters of the HBV model can make our model have medical significance. And the optimal treatment strategy can reduce the cost and side effects while ensuring the therapeutic effect.
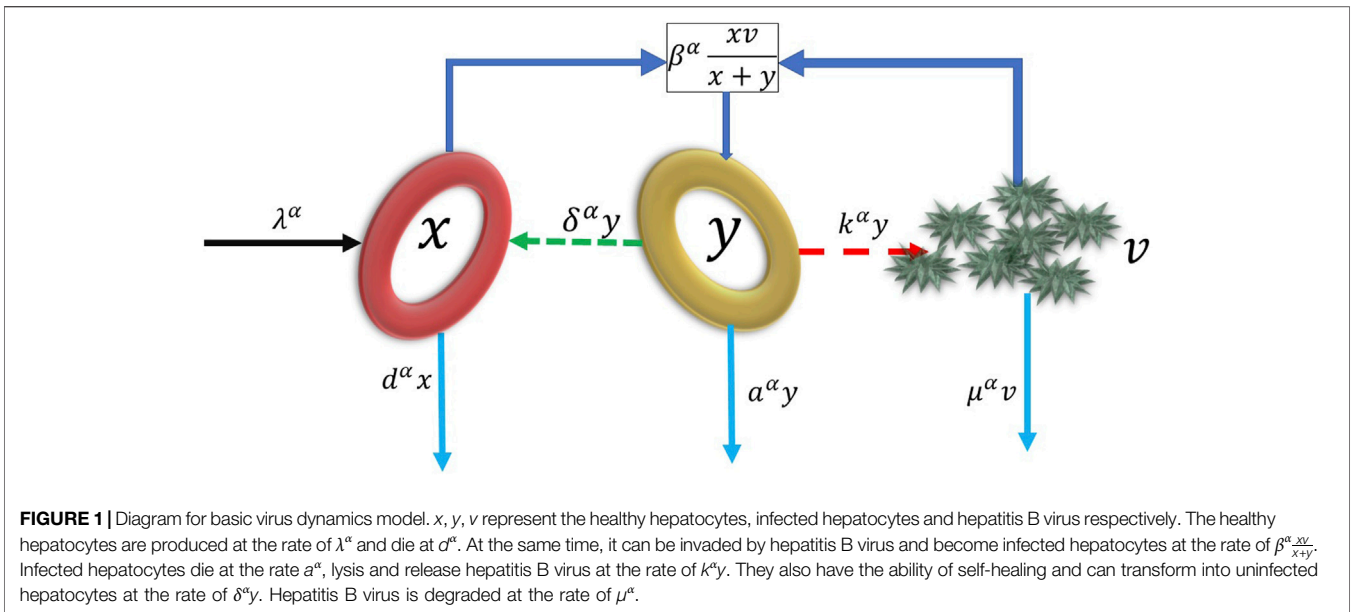
2 MODEL FORMULATION

In general, the process of hepatitis B infection [34] mainly includes susceptible hepatocytes, infected hepatocytes, and hepatitis B virus. Uninfected hepatocytes are produced at a certain rate. HBV particles can invade hepatocytes through interaction with the receptors on the liver surface. They reproduce new viruses by various functions and release them into the bloodstream with the lysis of infected cells. The hepatitis B virus genes can naturally be lost which lead to a certain proportion of the infected cells transforming into uninfected hepatocytes. At the same time, liver cells and viruses will gradually die out. The simplified process is shown in **Figure 1**. And based on this process, we first give the Caputo-Fabrizio model based on the standard incidence as follows:

$$
\begin{cases}
{}_{0}^{CF}D_t^\alpha x = \lambda^\alpha - d^\alpha x - \beta^\alpha \dfrac{xv}{x+y} + \delta^\alpha y \\[2mm]
{}_{0}^{CF}D_t^\alpha y = \beta^\alpha \dfrac{xv}{x+y} - a^\alpha y - \delta^\alpha y \\[2mm]
{}_{0}^{CF}D_t^\alpha v = k^\alpha y - \mu^\alpha v
\end{cases} \tag{1}
$$

Here $x(t)$, $y(t)$, $v(t)$ are the healthy hepatocytes, infected hepatocytes and hepatitis B virus respectively. α is the fractional order. Uninfected cells produce at a constant rate of λ^α. Healthy and infected hepatocyte die at the rate of $d^\alpha x$ and $a^\alpha y$ respectively. The infected rate is $\beta^\alpha \frac{xv}{x+y}$. Infected hepatocytes can be cured by noncytolytic processes at the rate of δ per cell. Free virus is produced from infected cells at the rate of $k^\alpha y$ and attenuated at the rate of $\mu^\alpha v$. The initial values are given as $x(t_0) = x_0, y(t_0) = y_0, v(t_0) = v_0$.

Assume that $\lambda = \lambda^\alpha$, $d = d^\alpha$, $\beta = \beta^\alpha$, $\delta = \delta^\alpha$, $a = a^\alpha$, $k = k^\alpha$, $\mu = \mu^\alpha$, model 1) will be transformed to model (2). And the meaning of parameters in our framework is given in **Table 1**.

FIGURE 1 | Diagram for basic virus dynamics model. x, y, v represent the healthy hepatocytes, infected hepatocytes and hepatitis B virus respectively. The healthy hepatocytes are produced at the rate of λ^α and die at d^α. At the same time, it can be invaded by hepatitis B virus and become infected hepatocytes at the rate of $\beta^\alpha \frac{xv}{x+y}$. Infected hepatocytes die at the rate a^α, lysis and release hepatitis B virus at the rate of $k^\alpha y$. They also have the ability of self-healing and can transform into uninfected hepatocytes at the rate of $\delta^\alpha y$. Hepatitis B virus is degraded at the rate of μ^α.

TABLE 1 | The meaning of parameters in our framework.

Parameters	Meaning
λ	Production rate of healthy hepatocytes
d	death rate of healthy hepatocytes
β	infection rate of healthy hepatocytes
a	death rate of infected hepatocytes
k	The number of viruses by the lysis of infected cells
μ	death rate of virus
δ	Self healing rate of infected cells

$$\begin{cases} {}^{CF}_{0}D^\alpha_t x = \lambda - dx - \beta\dfrac{xv}{x+y} + \delta y \\[2mm] {}^{CF}_{0}D^\alpha_t y = \beta\dfrac{xv}{x+y} - ay - \delta y \\[2mm] {}^{CF}_{0}D^\alpha_t v = ky - \mu v \end{cases} \quad (2)$$

Since our model is a fractional order model, CF represents the Caputo-Fabrizio order, and here we will give some basic definition of Caputo-Fabrizio fractional calculus in Definition 1 and 2.

Let $H^1(a, b) = \{f | f \in L^2(a, b)\}$ and $f' \in L^2(a, b)$, where $L^2(a, b)$ is the space of square integrable functions on the interval (a, b).

Definition 1 ([21]) *The definition of Caputo-Fabrizio order differential was later modified by Losada and Nieto as*

$$ {}^{CF}_{a}D^\alpha_t f(t) = \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \int_a^t f'(x) \exp\left[-\alpha\frac{t-x}{1-\alpha}\right] dx. \quad (3) $$

Definition 2. ([21]) *Let $\alpha \in [0, 1]$, then fractional integral of α for function $f(x)$ can be expressed as*

$$ {}^{CF}_{a}I^\alpha_t f(t) = \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} f(t) + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_a^t f(x) dx. \quad (4) $$

Remark 1. In Definition 1, the definition of **Eq. 4** is the mean of $f(t)$ and $\int_a^t f(x) dx$. Therefore $\frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} + \frac{2\alpha}{(2-\alpha)M(\alpha)} = 1$, which implies $M(\alpha) = \frac{2}{2-\alpha}$, $\alpha \in [0, 1]$.

The rest of this paper is organized as follows. **Section 3** gives the analysis and simulation of the local stability of equilibrium points. The parameter estimation are given in **Section 4**, and the last two sections give the theorems and simulation of optimal control model and our conclusion respectively.

3 STABILITY ANALYSIS

In biology models, the stable analysis of the system can help us to understand the process of the biology phenomenon. The following two basic lemmas [35] can be used for stability analysis. Lemma 1 give the characteristic equation form of Caputo-Fabrizio order linear system. Lemma two give the criterion of local stability.

Lemma 1. *Let $F(t) \in R^n$ and $M \in R^{n \times n}$, then the characteristic equation related to the linear system ${}^{CF}_{t_0}D^\alpha_t F(t) = MF(t)$ supplemented with the order $\alpha \in (0, 1)$ is given by $\det[sI_{n \times n} - (1-\alpha)M - \alpha M] = 0$.*

Lemma 2. *Suppose that the matrix $sI_{n \times n} - (1-\alpha)M - \alpha M$ is invertible. Then, if and only if all roots of the characteristic equation have negative real parts, the fractional linear Caputo-Fabrizio system is asymptotically stable at the free equilibrium point.*

There are two equilibria in model (2): The disease-free equilibrium $E_0 = (\frac{\lambda}{d}, 0, 0)$ and the endemic-free equilibrium $E_1 = (\frac{\lambda}{R_0 a - a + d}, \frac{(R_0-1)\lambda}{R_0 a - a + d}, \frac{k}{\mu}\frac{(R_0-1)\lambda}{R_0 a - a + d})$. And the basic reproduction number [36] R_0 of system 2) is $\frac{\beta k}{\mu(a+\delta)}$. Here we will give the analysis of the two equilibria.

Theorem 1. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$. If $R_0 > 1$, it is unstable.* PROOF. The Jacobian matrix at E_0 is given:

TABLE 2 | The initial values of the simulation of E_0 and E_1. Here x_0, y_0, v_0 are the initial values of the healthy, infected hepatocyte and HBV.

Variables	x_0	y_0	v_0	α
X_{01}	100	10	10	0.3
X_{02}	1,000	100	100	0.5
X_{03}	10,000	1,000	1,000	0.7
X_{04}	100,000	10,000	10,000	0.9

TABLE 3 | The parameters using in the simulation of disease-free equilibrium E_0. The meaning of the parameters are in **Table. 1**. Here the basic reproduction number $R_0 = 0.0075 < 1$.

Parameters	λ	d	β	a	k	μ	δ
Values	1	0.002	0.003	0.002	0.0001	0.02	5×10^{-8}

$$J_1 = \begin{bmatrix} -d & \delta & -\beta \\ 0 & -a-\delta & \beta \\ o & k & -\mu \end{bmatrix} \quad (5)$$

From Lemma 1, the characteristic equation of system (2) is $s(I - (1-\alpha)J_1) - \alpha J_1 = 0$. We can denote three roots as

$$s_1 = \frac{\alpha}{-1+\alpha}$$

$$s_2 = \frac{2\alpha(1-\alpha)\mu(a+\delta)(R_0-1) - c_1 + \sqrt{c_1^2 + 4\mu(a+\delta)(R_0-1)}}{2(1+(1-\alpha)(a+\delta+\mu)+(1-R_0)(a+\delta)(1-\alpha)^2)}$$

$$s_3 = \frac{2\alpha(1-\alpha)\mu(a+\delta)(R_0-1) - c_1 - \sqrt{c_1^2 + 4\mu(a+\delta)(R_0-1)}}{2(1+(1-\alpha)(a+\delta+\mu)+(1-R_0)(a+\delta)(1-\alpha)^2)}$$

(6)

Here $c_1 = (a + \delta + \mu)\alpha$.

It is obvious to see that $s_1 < 0$ as $0 < \alpha < 1$. If $R_0 < 1$, $s_2 < 0$, $s_3 < 0$. Otherwise $s_2 > 0$ and $s_3 > 0$. From Lemma 2, it can be proved that when $R_0 < 1$, the disease free equilibrium E_0 is locally asymptotically stable. When $R_0 > 1$, E_0 is unstable.

The local stability of disease-free equilibrium indicates that HBV infection will not persist. Basic reproduction number R_0 is an important index to measure whether the disease will die out. When $R_0 < 1$, the disease will die out, and when $R_0 > 1$, we will have the endemic equilibrium E_1. We give the analysis of the its stability in Theorem 2.

Theorem 2. *If $R_0 > 1$, the endemic equilibrium E_1 is asymptotically stable.*

Proof. The Jacobian matrix at E_1 is given as

$$J_2 = \begin{bmatrix} -d - \beta\frac{v_1 y_1}{(x_1+y_1)^2} & \delta + \beta\frac{x_1 v_1}{(x_1+y_1)^2} & -\beta\frac{x_1}{x_1+y_1} \\ \beta\frac{v_1 y_1}{(x_1+y_1)^2} & -\beta\frac{x_1 v_1}{(x_1+y_1)^2} - a - \delta & \beta\frac{x_1}{x_1+y_1} \\ o & k & -\mu \end{bmatrix} \quad (7)$$

From Lemma 1, the characteristic equation of system (2) is $(I - (1-\alpha)J_2) - \alpha J_2 = 0$ which can be rewritten as $a_1 s^3 + a_2 s^2 + a_3 s^1 + a_4 = 0$.

Let $l_1 = \beta\frac{v_1 y_1}{(x_1+y_1)^2}$, $l_2 = \beta\frac{x_1 v_1}{(x_1+y_1)^2}$, $l_3 = \beta\frac{x_1}{x_1+y_1}$, we will get that

$$\begin{aligned} a_4 &= \mu\alpha^3(al_1 + dl_2) \\ a_3 &= \alpha^2(ad + d\delta + al_1 + dl_2 + d\mu + l_1\mu + l_2\mu) + \alpha^2(1-\alpha)(3al_1\mu + 3dl_2\mu) \\ a_2 &= \alpha(a + d + \delta + l_1 + l_2 + \mu) + (1-\alpha)^2\alpha(3al_1\mu + 3dl_2\mu) \\ &\quad + 2(1-\alpha)(ad + d\delta + al_1 + dl_2 + d\mu + l_1\mu + l_2\mu) \\ a_1 &= 1 + (1-\alpha)(a + d + \delta + l_1 + l_2 + \mu) + (1-\alpha)^3(3al_1\mu + 3dl_2\mu) \\ &\quad + (1-\alpha)^2(d(a + \mu + \delta) + al_1 + dl_2 + l_1\mu + l_2\mu) \end{aligned}$$

(8)

As $0 < \alpha < 1$, thus $a_1, a_2, a_3, a_4 > 0$.

Set $d_1 = \frac{a_2}{a_1}, d_2 = \frac{a_3}{a_1}, d_3 = \frac{a_4}{a_1}, q = ad + d\delta + al_1 + dl_2 + d\mu + l_1\mu + l_2\mu$, then

$$\begin{aligned} a_2 a_3 - a_1 a_4 &= q(a + d + \delta + l_1 + l_2) + \mu(ad + d\delta + d\mu + l_1\mu + l_2\mu) \\ &\quad + (1-\alpha)^2(\alpha^2 2q(3al_1\mu + 4dl_2\mu) + \alpha^3 2q(al_1 + dl_2) \\ &\quad + (1-\alpha)^3\alpha^3\mu^2(al_1 + dl_2)(8al_1 + 11dl_2) \end{aligned}$$

(9)

As $0 < \alpha < 1$, $a_2 a_3 - a_1 a_4 > 0$ and $d_1 d_2 - d_3 = \frac{a_2 a_3 - a_1 a_4}{a_1^2} > 0$. Thus we can prove the stability of E_1.

The local asymptotic stability of the endemic equilibrium indicates the possible physical state of the patients without drug intervention. When $R_0 > 1$, the disease will always exist.

4 SIMULATION AND PARAMETER ESTIMATION

First we use the predictor-corrector Adams-Bashforth-Moulton (ABM) technique of the Caputo-Fabrizio equation to carry out the simulation. we will give the simulation results of equilibria E_0 and E_1. And the initial values are given in **Table. 2**.

For the disease-free equilibrium E_0, we select the parameters in **Table. 3** which is satisfied the condition in Theorem 1. The simulation results are shown in **Figure 2**. As we have proved the local stability of the equilibrium in **Section 3** and **Figure 2** can also validates this proof. Here x can approach to 500 which is $\frac{\lambda}{d}$, y and v are 0. However, due to the lack of theory, it is difficult to prove the global stability. As we choose the initial values which is quite different from each other, the simulation results always tend to the same value. Therefore, we can think E_0 might be globally asymptotically stable. Similarly, we use the parameters in **Table 4** to the simulate the endemic equilibrium E_1, the simulation results is shown in **Figure 3** which shows the simulation results is consistent with Theorem 2.

Then, we use the real data in **Table 5** [37] to estimate the parameters of our model. The estimation range of parameters are $[1 \times 10^5, 1 \times 10^7]$, $(0, 100)$ for λ and k and $(0, 1)$ for others which are in line with the actual human physiological structure. Our estimated results are shown in **Table 6** which make $R_0 < 1$ and simulation is shown in **Figure 4**. The fractional order is estimated as 0, 7,519, this shows that fractional order is applicable in the model. k is estimated as 0.0574 and μ is 0.799, this shows the drugs have been used and have obvious effect. The estimated results of a and d are 0.01 and 0.0038, which is similar to the data that is used in papers [30]. From **Figure 4**, we can see that our model can fit the data well. The hepatitis B virus can reduced rapidly in the first few weeks. And then it tends to a more gentle
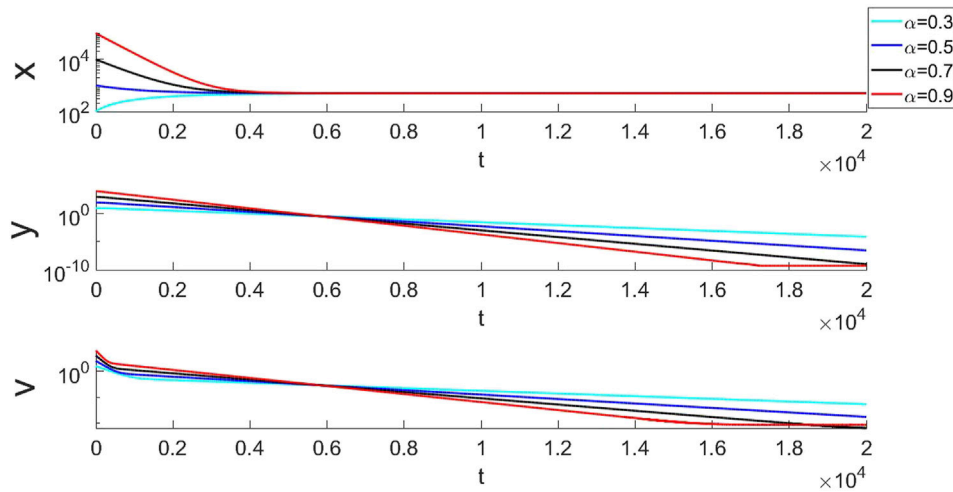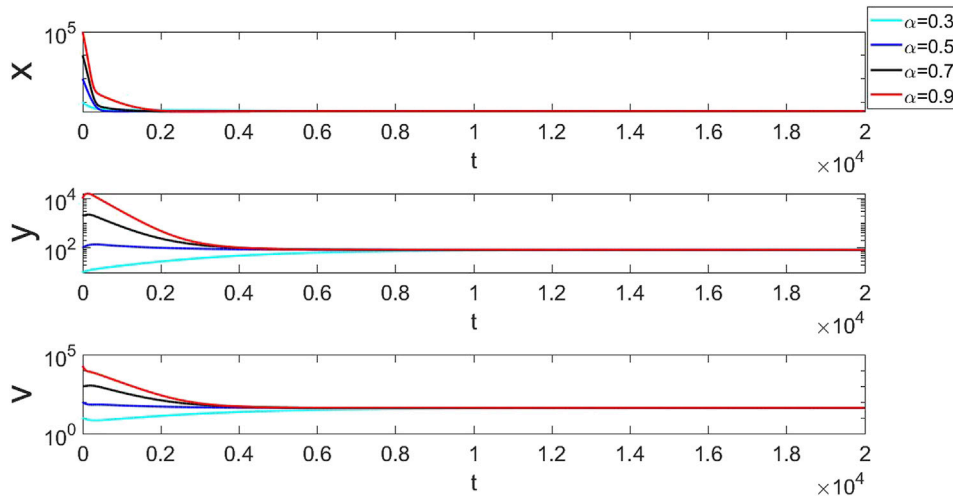
FIGURE 2 | The simulation results of E_0 with four different set of initial values. Under different fractional orders and initial values, x can always approach to 500 with different initial values. y and v approaches to 0.

TABLE 4 | The parameters using in the simulation of endemic equilibrium E_1. The basic reproducion number $R_0 = 2 > 1$.

Parameters	λ	d	β	a	k	μ	δ
Values	1	0.002	0.003	0.002	0.01	0.02	0.05

downward trend. However, the infected hepatocytes reduce exponentially, but decreasing rate is slower than that of hepatitis B virus. Due to the reduce of infected hepatocytes and hepatitis B virus, healthy hepatocytes are less likely infected, therefore they are in a state of first increasing and then regional stability. This phenomenon is consistent with Theorem 1.
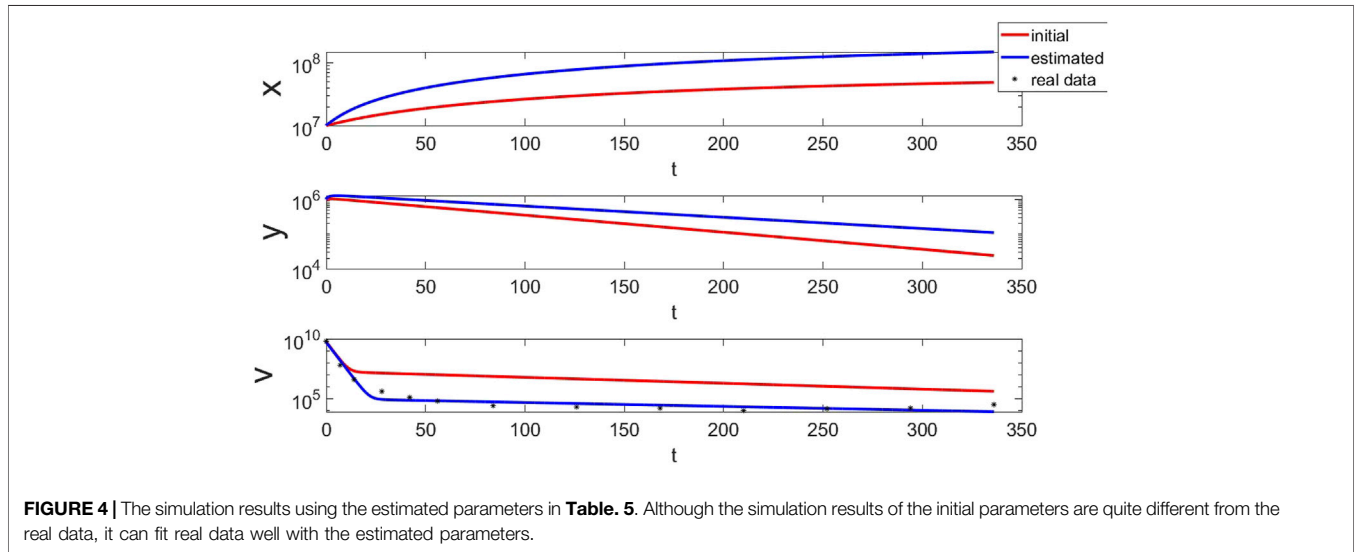

FIGURE 3 | The simulation results of the endemic equilibrium E_1. In this simulation, x can always approach to 41.667. y, v are 81.3 and 41.667 respectively. This is consistent with our calculation of the value of the equilibrium point.

TABLE 5 | The number of hepatitis B virus and the corresponding measurement time during the treatment of hepatitis B patients. The number of HBV here is shown in log format.

Days	0	7	21	28	42	56	84	126	168	252	210	294	336
HBV DNA (log)	9.8	7.8	6.6	5.6	5.1	4.8	4.4	4.3	4.2	4.0	4.2	4.2	4.5

TABLE 6 | The estimated parameters by the least square method with using the read data of HBV virus and date. The parameters estimated here are in the normal range.

Parameters	α	λ	d	β	a	k	μ	δ
Values	0.7519	8.952×10^5	0.0038	5.116×10^{-5}	0.01	0.0574	0.799	10^{-10}

FIGURE 4 | The simulation results using the estimated parameters in **Table. 5**. Although the simulation results of the initial parameters are quite different from the real data, it can fit real data well with the estimated parameters.
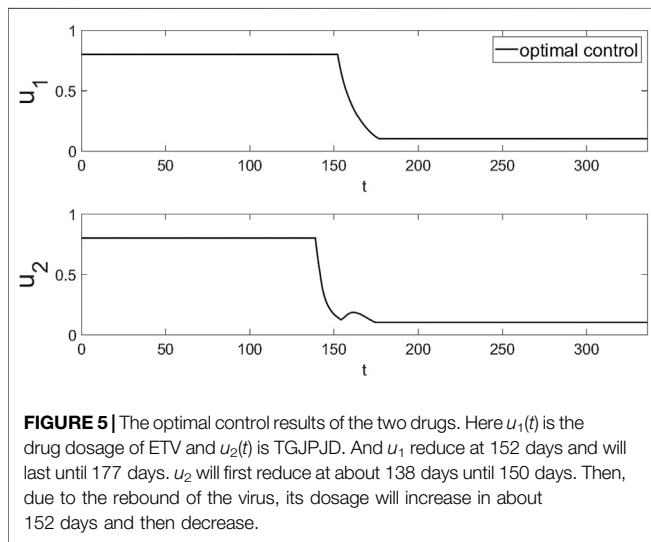
FIGURE 5 | The optimal control results of the two drugs. Here $u_1(t)$ is the drug dosage of ETV and $u_2(t)$ is TGJPJD. And u_1 reduce at 152 days and will last until 177 days. u_2 will first reduce at about 138 days until 150 days. Then, due to the rebound of the virus, its dosage will increase in about 152 days and then decrease.

5 OPTIMAL CONTROL PROBLEM

In paper [38], a combined treatment of HBV infection was designed with Entecavir (ETV) and Chinese herbal Tiaogan Jianpi Jiedu granules (TGJPJD). ETV can be used to reduce the replication of hepatitis B virus [39]. TGJPJD can kill hepatitis B virus by activating immunity. And based on the combined therapy of HBV, we propose our control model.

$$\begin{cases} {}^{CF}_0 D_t^\alpha x = \lambda - dx - \beta \frac{xv}{x+y} + \delta y \\ {}^{CF}_0 D_t^\alpha y = \beta \frac{xv}{x+y} - ay - \delta y \\ {}^{CF}_0 D_t^\alpha v = (1-u_1(t))ky - (1+u_2(t))\mu v \end{cases} \quad (10)$$

The parameters have the same meaning as given in **Table. 1** $u_1(t)$ $(0 < u_1(t) < 1)$ and $u_2(t)$ $(0 < u_2(t) < 1)$ are the control variables and represent the drug effect of ETV and TGJPJD respectively. In order to achieve the therapeutic effect with lower the cost and side effects, we give the following objective function. Here a_2, a_3, b_2, b_3, c_1, c_2 represent the corresponding weight of each variable.

$$J(u) = \frac{1}{2}\left(a_2 y^2 + a_3 v^2\right) + \frac{1}{2}\int_0^{t_f}(b_2 y^2 + b_3 v^2 + c_1 u_1^2 + c_2 u_2^2)dt. \quad (11)$$

The Hamilton function of $J(u)$ can be written as

$$H = p_1\left(\lambda - dx - \frac{\beta xv}{x+y} + \delta y\right) + p_2\left(\frac{\beta xv}{x+y} - ay - \delta y\right) + p_3\left((1-u_1)ky - (1+u_2)\mu v\right) + (b_2 y^2 + b_3 v^2 + c_1 u_1^2 + c_2 u_2^2) \quad (12)$$

Optimization process has many applications in dynamic systems [40–42]. In our paper, the optimal control problem is a process in which we find the best $u(t)$ to minimize the performance index functional $J(t)$. By using
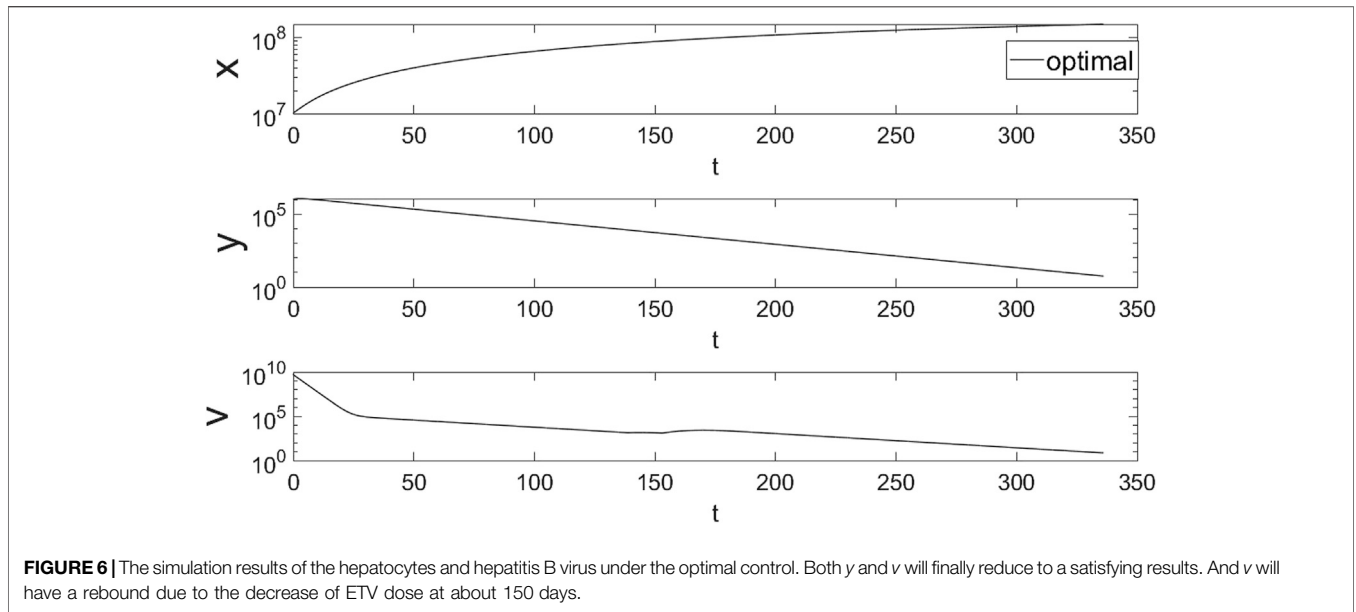
FIGURE 6 | The simulation results of the hepatocytes and hepatitis B virus under the optimal control. Both y and v will finally reduce to a satisfying results. And v will have a rebound due to the decrease of ETV dose at about 150 days.

Pontryagin's minimum principlex [43], we can transform the original problem into a constrained functional and find its theoretical optimization. And the optimal control therapy our model based the above theorem which can make $J(u)$ minimum are given as follows:

$$\begin{cases} u_1 = \min\left[\max\left(\dfrac{kyp_3}{c_1}, 0\right), 1\right] \\ u_2 = \min\left[\max\left(\dfrac{\mu p_3 v}{c_2}, 0\right)\right], 1\right] \end{cases} \quad (13)$$

Using the parameters as we estimated in **Section 5**, we give the simulation results in **Figure 5** and **Figure 6**. From the simulation in **Figure 5** and **Figure 6**, we can see that the dosage of the two drugs should be kept at the maximum at the initial stage, but the dosage of TGJPJD can be gradually reduced at about 138 days and will last 12 days. The dosage of ETV could be reduced at about 150 days, but the reduction of ETV would result in the rebound of virus, it is necessary to further strengthen the dosage of TGJPJD. So the dose of TGJPJD will increase at about 150 days and then reduce. Finally, it will be the lowest dose at about 174 days. With the enhancement of the immunity by TGJPJD, the two drugs can be maintained at a lower level to achieve better therapeutic effect.

In **Figure 6**, the healthy hepatocytes will always keep increasing and then begin to stabilize. And the infected cells will reduce due to the drugs and the reduce of virus. hepatitis B virus will first reduce at about 150 days. And then due to the decrease of the ETV, the number of viruses showed a rebound trend. However, by adjusting the dosage of TGJPJD granule, the final number of virus can be reduced to less than 500, reaching the standard of cure.

TABLE 7 | The comparasion of objective function J with different drug dosage. The maximum dosage is ($u_1 = u_2 = 0.9$) and the minimum dosage is ($u_1 = u_2 = 0.1$).

	Maximum	Optimal	Minimum
objective function	1.7155×10^{15}	1.7037×10^{15}	2.9415×10^{15}

In order to show the advantages of optimal control of therapeutic strategies, we also compare the objective function values of optimal as we give above with the maximizing drug dosage ($u_1 = u_2 = 0.9$) and minimizing drug dosage ($u_1 = u_2 = 0.1$), and show them in **Table. 7**. The results show that with the optimal therapy, the cost can be minimized, and the corresponding treatment effect can also be satisfying.

6 CONCLUSION

In this paper, a Caputo-Fabrizio fractional HBV model with standard incidence were proposed. The local stability of the equilibria were analyzed and global stability were simulated. At the same time, parameters were estimated based on the real data. With the estimated parameters, our model can simulate the data well. Finally, based on clinic combination therapy of HBV with ETV and TGJPJD, we proposed an optimal control model and gave the optimal therapy, which showed therapeutic effect can be achieved with lower drug dosage and side effects. However, cellular immunity and humoral immunity are not carefully considered in our model. In the optimal control model, the metabolism of drugs in the liver is not analyzed, and HBV replication in cells is not reflected. For our future work, we will apply the

latest therapeutic regimens for chronic hepatitis B in our model and analyze it according to the corresponding clinical data. The metabolism of drugs should also be considered. Besides, we will consider the effect of cellular immunity and humoral immunity which is essential.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors conceived the study and performed the analyses. LY wrote the code. LY and YS wrote the article. All authors reviewed and revised the article.

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