A FRACTIONAL ORDER HBV MODEL WITH HOSPITALIZATION

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Abstract. Hepatitis B is a viral infection that can cause both acute and chronic disease and mainly attacks the liver. The present paper describes the dynamics of HBV with hospitalization. Due to the fatal nature of this disease, it is necessary to formulate a new mathematical model in order to reduce the burden of HBV. Therefore, we formulate a new HBV model with fractional order derivative. The fractional order model is formulated in Caputo sense. Two equilibria for the model exist: the disease-free and the endemic equilibriums. It is shown, that the disease-free equilibrium is both locally and globally asymptotically stable if $R_0 < 1$ for any $\alpha \in (0, 1)$. The sensitivity analysis of the model parameters are calculated and their results are depicted. The numerical results for the stability of the endemic equilibrium are presented. The complex dynamics of the disease can be best described by using the fractional derivative and this is illustrated through many graphical results.

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1. Introduction. Infection of HBV is a global health problem that cause both acute and chronic diseases and can lead to cirrhosis and primary hepatocellular carcinoma [6]. It mainly affects the liver. An estimate of world health organization (WHO) shows that about 240 million of the people worldwide have a chronic liver infection and more than 0.78 million people died in 2015 due to the infection of hepatitis B. [7]. Hepatitis B is also known as blood-borne virus transmitted from person to person through infectious blood, or contaminated water or food, sexual contacts, transfusion of bloods and reuse of unsafe syringe or needle, [7]. This type of transmission is known as horizontal transmission. It can also be transmitted from infected mother to a newborn baby known as vertical transmission.

Mathematical models of deterministic type play vital role to explore the spread and control of infectious diseases. In last few decades, several mathematical models of deterministic type have been developed to better understand the transmission dynamics and control of HBV but these models have been restricted to classical integer-order or delay differential equations. For example in [29], the authors proposed a mathematical model of HBV to study the dynamics and control of HBV transmission in China. Thornley et al. proposed transmission model of HBV to control it in the population of New Zealand using different control strategies [27]. Pang et al. [18], discussed HBV compartmental model to illustrate the importance of vaccination and other controlling parameters for HBV infection. Zou et al. [30], considered an infectious disease model to analyze the dynamics and prevalence of hepatitis B in Mainland China. A transmission model of HBV with the impact of immigrants and media coverage was proposed by Khan et al. [14, 15]. More mathematical models of the integer-order for the dynamics of HBV, can be found in [24, 9].

Overview of fractional calculus. In fractional calculus (FC) mathematical models are developed with α-order fractional derivatives and integrals, where α most commonly belongs to the intervals [0, 1] or [1, 2], [20, 23]. In the last few decades applications of FC have taken off and can be found in various branches of science for example engineering, biology and epidemiology, [2, 10, 17, 25, 26]. Using the epidemic modeling with fractional derivatives have more advantages comparing to the integer case. The reason is that the fractional order differential equations (FODEs) involve memory which occurs in most biological models. In some situations, the FODEs models are more consistent and helpful in the real phenomena than the integer-order models due to the fact that fractional derivatives and integrals enable the description of the memory and hereditary properties inherent in various processes [20, 23]. The integer-order derivative can not shows the dynamics among two points which may not be the same. To overcome such problems by local differentiation motivate researchers like Riemann and Liouville to introduce the concept of differentiation with non-local or fractional orders operator [23]. Caputo and Fabrizio [8] introduced a new derivative with fractional order based on the exponential kernel. In 2016, Atangana and Baleanu suggested another version of fractional order derivative which used the generalized Mittag-Leffler function as non-local and non-singular kernel [3], and is implemented successfully in modeling of various real phenomenons [4, 5]. In existing literature there are various mathematical models with fractional order such as, in [12], a fractional order model for dengue outbreak in Cape Verde islands. Sing et al. [26], formulated a fractional model on giving up smoking. Pinto and Carvalho [19] introduced a fractional order model for the co-infection of HIV and TB in 2017. Sakulrang et al. [21], shows that the order
of fractional derivative is an important factor in epidemics. They use different approaches by using fractional calculus for real data fitting. Recently a fractional order HBV model with infected cell is proposed in [22].

In the present paper, we introduce a fractional order HBV model with Hospitalization. We will use the new Caputo derivative [8] to explore the dynamics of HBV. First, some basic concepts about the fractional calculus will be provided. For the stability analysis, we will use the order of the fractional derivative \( \alpha \in [0, 1] \) in the Caputo sense. Therefore, we first give the definitions of new fractional order integral and derivative [2]. For the fractional order differentiation, we will use the Caputo definition due to its convenience for initial conditions of the differential equations.

2. Preliminaries on the Caputo fractional calculus. We begin by introducing the Caputo fractional derivative and state related theorems.

Definition 2.1. The fractional integral of order \( \alpha > 0 \) for a function \( g : R^+ \rightarrow R \) is defined by

\[
I^\alpha_t (g(t)) = \frac{1}{\Gamma(\alpha)} \int_0^t (t - \chi)^{\alpha-1} g(\chi) d\chi.
\]

Here and elsewhere \( \Gamma \) denotes the Gamma function.

Definition 2.2. The Caputo fractional order derivative for function \( g \in C^n \) of order \( \alpha \) is given below

\[
C^\alpha D_t^n (g(t)) = I^{n-\alpha} D^n g(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{g^n(\chi)}{(t-\chi)^{\alpha-n+1}} d\chi,
\]

which is well defined for absolutely continuous functions and \( n - 1 < \alpha < n \in N \). Note that the value of the Caputo fractional derivative of the function \( g \) at point \( t \) involves all the values of \( g^n(\chi) \), for \( \chi \in [0, t] \). Clearly \( C^\alpha D_t^n (g(t)) \) tends to \( g'(t) \) as \( \alpha \rightarrow 1 \).

Definition 2.3. [16] The constant \( z^* \) is an equilibrium point of the Caputo fractional dynamic system given below

\[
C^\alpha D_t^n z(t) = f(t, z(t)), \quad \alpha \in (0, 1), \tag{1}
\]

if and only if, \( f(t, z^*) = 0 \).

Now we state theorem for an extension of the Lyapunov method for Caputo fractional order nonlinear systems [11].

Theorem 2.4. (Uniform asymptotic stability theorem see [11]) If \( z^* \) be an equilibrium point for the non autonomous fractional order system given in (1) and \( \Phi \in R^n \) be a domain containing \( z^* \) and let \( G : [0, \infty) \times \Phi \rightarrow R \), be a continuously differentiable function such that

\[
V_1(z) \leq G(t, z(t)) \leq V_2(z), \tag{2}
\]

and

\[
C^\alpha D_t^n G(t, z(t)) \leq -V_3(z), \tag{3}
\]

for all \( \alpha \in (0, 1) \) and all \( z \in \Phi \). Where \( V_1(z) \), \( V_2(z) \) and \( V_3(z) \) are continuous positive definite functions on \( \Phi \), then the equilibrium point of system (1) is uniformly asymptotically stable.
3. Fractional order HBV model formulation. In this section we present the proposed fractional order mathematical model of HBV infection. To develop the model, total human population is divided into six epidemiological sub-compartments denoted by susceptible $S(t)$, exposed $E(t)$, acute $A(t)$, carriers $C(t)$, hospitalized $H(t)$ and recovered individuals $R(t)$.

The transmission dynamics of fractional order HBV is given by the following system of non-linear differential equations with Caputo fractional derivative:

$$
\begin{align*}
C D^\alpha_t S &= b(1 - \psi C(t)) - dS(t) - \beta S(t)(A(t) + \mu C(t)), \\
C D^\alpha_t E &= \beta S(t)(A(t) + \mu C(t)) + b\psi C(t) - (d + \delta)E(t), \\
C D^\alpha_t A &= \delta E(t) - (h_1 + d + d_A + \gamma)A(t), \\
C D^\alpha_t C &= \gamma A(t) - (d + d_C + h_2)C(t), \\
C D^\alpha_t H &= h_1 A(t) + h_2 C(t) - (d + \xi)H(t), \\
C D^\alpha_t R &= \xi H(t) - dR(t).
\end{align*}
$$

Where $N(t) = S(t) + E(t) + A(t) + C(t) + H(t) + R(t)$. Recruitment rate is $b$ and the natural death rate in all classes is $d$. The infection contact rate is denoted by parameter $\beta$, the proportion of prenatally infected individuals is denoted by $\psi$, while the carriers infectiousness related to acute infection is given by $\mu$. The progression rate from class $E$ to $A$ is $\delta$ and acute individuals becomes carrier at the $\gamma$. The acute and carrier individuals are hospitalized at the rates $h_1$ and $h_2$ respectively. The hospitalized individuals are recovered after proper treatment at the rate $\xi$. The disease mortality rates in the acute class $A$ and carrier class $C$ are $d_A$ and $d_C$ respectively. The detail description of the model parameters are given in Table 1. Since the last equation of (4) is independent on the rest, so we ignore it and consider the first five equations of the model.

| parameters | description of parameter | Values |
|------------|--------------------------|--------|
| $b$        | Birth rate               | 0.4    |
| $d$        | Natural death rate       | 0.01   |
| $h_1$      | The acute individuals to be hospitalized | 0.01 |
| $h_2$      | Flow rate from carrier class to the hospitalized class | 0.01 |
| $\beta$    | The transmission coefficient | 0.0002 |
| $\delta$   | Rate of flow from exposed to carrier | 0.01 |
| $d_A$      | mortality rate due to acute infection | 0.001 |
| $d_C$      | carrier individuals death rate | 0.002 |
| $\gamma$   | the rate by which acute individuals move to carries class | 0.01 |
| $\xi$      | The rate of recovery     | 0.02   |
| $\psi$     | Un-immunized children born to carrier mothers | 0.2 |
| $\mu$      | Carriers infectiousness related to acute infection | 0.2 |
4. Analysis of the model.

4.1. Positivity and boundedness of the solutions. The HBV model (4) will be meaningful epidemiologically, if the solutions of the system (4) with non-negative initial data will remain non-negative for all time \( t > 0 \).

**Lemma 4.1.** For all \( t > 1 \) and the initial data \( P(0) \geq 0 \), where \( P(t) = (S(t), E(t), A(t), C(t), H(t), R(t)) \), the solution of model (4) are non-negative for all \( t > 0 \), if they exist. Furthermore,

\[
\lim_{t \to \infty} \sup N(t) \leq \frac{b}{d}.
\]

**Proof.** Let \( \lambda_1(t) = 1 - \psi C(t) \) and \( \lambda_2(t) = \beta(A(t) + \mu C(t)) \) then from the first equation of system (4) we have

\[
C^D_t \alpha S = b\lambda_1(t) - (\lambda_2(t) + d)S.
\]

The above equation can be rewritten as:

\[
C^D_t \left[ S(t)\exp\left( dt + \int_0^t \lambda_2(s)ds \right) \right] = b\lambda_1(t)\exp\left[ dt + \int_0^t \lambda_2(s)ds \right].
\]

Hence:

\[
S(t_1)\exp\left( dt + \int_0^{t_1} \lambda_2(s)ds \right) - S(0) = \int_0^{t_1} b\lambda_1 \exp\left( dw + \int_0^w \lambda_2(s)ds \right) dw.
\]

Thus the solution of (6) is given below:

\[
S(t_1) = S(0)\exp\left( - (dt_1 + \int_0^{t_1} \lambda_2(s)ds) \right) + \exp\left( - (dt_1 + \int_0^{t_1} \lambda_2(s)ds) \right) \times \int_0^{t_1} b\lambda_1 \exp\left( dw + \int_0^w \lambda_2(s)ds \right) dw > 0.
\]

Similarly, it can be shown that \( P > 0 \) for all time \( t > 0 \). Further, adding components of the model (4) gives

\[
C^D_t \alpha N = b - dN(t) - d_AA - d_CC \leq b - dN(t),
\]

then

\[
b - (d + d_A + d_C)N \leq C^D_t \alpha N \leq b - dN(t),
\]

which gives

\[
\frac{d}{d + d_A + d_C} \leq \lim_{t \to \infty} \inf N(t) \leq \lim_{t \to \infty} \sup N(t) \leq \frac{b}{d},
\]

hence we prove that

\[
\lim_{t \to \infty} \sup N(t) \leq \frac{b}{d}.
\]

The fractional order HBV model (4) will be studied in a biologically-feasible region as given below:

\[
\Omega = \{(S, E, A, C, H) \subset \mathbb{R}_+^5 : S + E + A + C + H \leq \frac{b}{d}\}.
\]
5. Existence of equilibria of the model. The disease free equilibrium (DFE), $K_0$, of the model (4) is calculated as follows:

$$K_0 = (S^0, 0, 0, 0, 0) = \left( \frac{b}{d}, 0, 0, 0, 0 \right),$$

The basic reproduction number $R_0$ of the model is obtained by using the next generation technique [13] and is given by

$$R_0 = \frac{db\psi \delta \gamma + \beta b\delta (d + d_C + h_2 + \mu \gamma)}{d(d + \delta)(h_1 + d + d_A + \gamma)(d + soln/d) + h_2).$$

A unique endemic equilibrium $E_1$ of the proposed model (4) exists if $R_0 > 1$ and is given below:

$$\begin{align*}
S^* &= \frac{S^0}{b(R_0 - 1)}, \\
E^* &= \frac{E_0}{b(R_0 - 1)}, \\
A^* &= \frac{A_0}{b(R_0 - 1)}, \\
C^* &= \frac{C_0}{b(R_0 - 1)}, \\
H^* &= \frac{H_0}{b(R_0 - 1)}.
\end{align*}$$

Hence we state the following lemma.

**Lemma 5.1.** A unique positive endemic equilibrium exists when $R_0$ exceeds 1.

5.1. Stability analysis of DFE. The Jacobian of (4) at DFE, $J_{K_0}$, is given below:

$$J_{K_0} = \begin{pmatrix}
-d & 0 & -bS^0 & -(b\psi + \beta \mu S^0) & 0 \\
0 & -(d + \delta) & \beta S^0 & (\beta \mu S^0 + b\psi) & 0 \\
0 & \delta & - (h_1 + d + d_A + \gamma) & 0 & 0 \\
0 & 0 & \gamma & -(d + d_C + h_2) & 0 \\
0 & 0 & h_1 & h_2 & -(d + \xi)
\end{pmatrix}.$$  

We state the following theorem for locally asymptotically stable (LAS) of DFE case.

**Theorem 5.2.** The DFE of the system (4) about an equilibrium point $K_0 = (\frac{b}{d}, 0, 0, 0, 0)$, is LAS if and only if $R_0 < 1$, otherwise unstable.

**Proof.** To show the LAS of the system (4) at DFE $K_0$, it is enough to show that all eigenvalues, $\lambda_i$, $i = 1, 2, 3, 4, 5$ of $J_{K_0}$ satisfy the following condition [1]:

$$|\arg \lambda_i| > \frac{\alpha \pi}{2}. \quad (7)$$

The characteristic equation associated to $J_{K_0}$ is,

$$\begin{align*}
(\lambda + d)(\lambda + (d + \xi)) & \left( \lambda^3 + C_1 \lambda^2 + C_2 \lambda + C_3 \right) = 0, \quad (8)
\end{align*}$$

where

$$\begin{align*}
C_1 &= (d + \delta) + (h_1 + d + d_A + \gamma) + (d + d_C + h_2), \\
C_2 &= (h_1 + d + d_A + \gamma)(d + d_C + h_2)
\end{align*}$$
where the time fractional order derivative of \( \beta \) the parameters. Table 2 shows that the parameters increases with the parameter, while negative (-) sign shows the decrease in \( R \). Using system (4) we get obtain \( R^2 \). The positive (+) sign in Table 2 shows that the basic reproduction number parameters and their sensitivity indexes have been obtained and tabulated in Table 6.

Sensitivity analysis of \( R \). Table 1 shows that the basic reproduction number, while the rest of the parameters have negative effect which means that increase of theses parameters will decrease

\[
C_3 = (d + \delta)(h_1 + d + d_A + \gamma)(d + dc + h_2)(1 - R_0). \tag{9}
\]

The real parts of the first two eigenvalues \(-d\) and \(-(d + \xi)\) are negative and clearly if \( R_0 < 1 \), then \( C_i > 0 \), for \( i = 1, 2, 3 \), and \( C_1 C_2 > C_3 \). Thus using the Routh-Hurwitz criteria for fractional order models [1], all the eigenvalues have negative real parts and satisfy the condition (7), provided that the discriminant of the cubic polynomial in (8) is positive. Hence the DFE denoted by \( K_0 \) is LAS.

5.2. Global stability analysis of DFE.

**Theorem 5.3.** For \( \alpha \in (0, 1) \) and \( R_0 < 1 \) the DFE, \( K_0 \), of the system (4), is stable globally asymptotically on \( \Omega \) and unstable for \( R_0 > 1 \).

**Proof.** To establish the global stability of the DFE, we construct the following Lyapunov function:

\[
L(t) = A_1 E(t) + A_2 A(t) + A_3 C(t),
\]

where \( A_i \), for \( i = 1, 2, 3 \), are some positive constants to be chosen later. Calculating the time fractional order derivative of \( L(t) \) along the solutions of system (4), we obtain

\[
C D^\alpha_t L(t) = A_1 C D^\alpha_t E + A_2 C D^\alpha_t A + A_3 C D^\alpha_t C.
\]

Using system (4) we get

\[
C D^\alpha_t L(t)
\]

\[
= A_1 \left[ \beta S(A + \mu C) + b \psi C - (d + \delta)E \right] +
\]

\[
A_2 \left[ \delta E - (h_1 + d + d_A + \gamma)A \right] + A_3 \left[ \gamma A - (d + dc + h_2)C \right]
\]

\[
= \left[ A_1 \beta S^\alpha + \gamma A_3 - (d + h_1 + d_A + \gamma)A_2 \right] A +
\]

\[
A_2 \delta - (d + \delta)A_1 \right] E + \left[ (\mu \beta S^\alpha + b \psi)A_1 - (d + dc + h_2)A_3 \right] C \tag{10}
\]

Now choosing \( A_1 = 1 \), \( A_2 = \frac{d + \delta}{\delta} \), \( A_3 = \frac{\psi + \mu \beta S^\alpha}{d + dc + h_2} \) and simplifying we obtained:

\[
C D^\alpha_t L(t) \leq \frac{(d + \delta)(d + h_1 + d_A + \gamma)}{\delta} \left[ R_0 - 1 \right] A. \tag{11}
\]

Clearly if \( R_0 < 1 \) then \( C D^\alpha_t L(t) \) is negative. Therefore, by Theorem (2.4) we conclude that the DFE, \( K_0 \) is uniformly asymptotically stable in \( \Omega \).

6. Sensitivity analysis of \( R_0 \). In this section, we present the sensitivity analysis of \( R_0 \) to analyze the model robustness to the model parameters. The relevant parameters and their sensitivity indexes have been obtained and tabulated in Table 2. The positive (+) sign in Table 2 shows that the basic reproduction number \( R_0 \) increases with the parameter, while negative (-) sign shows the decrease in \( R_0 \) for the parameters. Table 2 shows that the parameters \( \beta, \delta, \gamma, \mu \) and \( \psi \) have positive effect on \( R_0 \) which describes that the increase (decrease) of these parameters will increase (decrease) the basic reproduction number, while the rest of the parameters have negative effect which means that increase of theses parameters will decrease
| Parameter | Sensitivity index |
|-----------|-------------------|
| $\beta$   | +0.7165           |
| $\delta$  | +0.5000           |
| $\gamma$  | +0.3680           |
| $h_1$     | -0.0455           |
| $h_2$     | -0.3739           |
| $\mu$     | +0.0161           |
| $\psi$    | +0.8064           |
| $d_A$     | -0.0454           |
| $d_C$     | -0.0748           |

Table 2. Sensitivity indices of $R_0$ with respect to the model parameters.

Figure 1. The effect of $\delta$ and $h_1$ on $R_0$.

the value of $R_0$. Figures 1, 3, 5 and 7 show the graphical results of the sensitive parameters to the basic reproduction number $R_0$, while Figures 2, 4, 6 and 8 are the associated contour plots of the parameters versus $R_0$.

7. Numerical results. In this section, we find the numerical simulations of the fractional order HBV model with hospitalization. To illustrate the numerical results, we use the parameters values given in Table 1. The numerical values in the simulations are given in Table 1 for which the basic reproduction number $R_0 = 1.0248 > 1$. The corresponding graphical results in Figures (9-14) shows the behavior of the susceptible, exposed, acute, carrier, hospitalized and recovered for the fractional values of $\alpha = 1, 0.95, 0.90, 0.85$. The fractional values of $\alpha$ have a significant effect on the graphical results of the state variables. Figure 15 shows the total number of infected individuals for different value of the parameter $\alpha$. The graphical results for $h_1$ and $h_2$ with $\alpha$ have been shown in Figure 16 and 17.
8. **Conclusion.** We analyzed the dynamics of Caputo fractional order HBV model with hospitalization. The basic results are derived and discussed. The local and global stability of the fractional model are obtained. The basic reproduction number for the fractional order model is presented and its sensitivity to the model parameters are tabulated. The various parameters sensitive to the basic reproduction number are plotted with their contour graphics. Further, we used the set of values...
given in Table 1, for which the basic reproduction number $R_0 > 1$ and presented the graphical results of the model by taking different values of $\alpha$. The fractional values of $\alpha$ give more accurate and biologically feasible results. Therefore, the use of fractional order model for the dynamics of HBV with hospitalization could be useful to obtain reasonable information about the disease dynamics and its eradication.
Figure 6. Contour plot of $\mu$ and $h_2$.

Figure 7. The effect of $\mu$ and $h_1$ on $R_0$. 
Figure 8. Contour plot of $\mu$ and $h_1$.

Figure 9. The plot shows the susceptible individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$. 
Figure 10. The plot shows the exposed individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$.

Figure 11. The plot shows the acute individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$. 
Figure 12. The plot shows the carrier individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$.

Figure 13. The plot shows the hospitalized individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$. 
Figure 14. The plot shows the recovered individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$.

Figure 15. The plot shows the total number of infected individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$. 
Figure 16. The plot shows the total number of infected individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$ and $h_1$.

Figure 17. The plot shows the total number of infected individuals when $R_0 = 1.0248 > 1$ for different values of $\alpha$ and $h_2$. 
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