

# Analysis of a fractional reaction-diffusion HBV model with cure of infected cells

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## Abstract

In this paper, we propose a fractional reaction-diffusion model in order to better understand the mechanisms and dynamics of hepatitis B virus (HBV) infection in human body. The infection transmission is modeled by Hattaf-Yousfi functional response and the fractional derivative is in the sense of Caputo. The global stability of the model equilibria is analyzed by means of Lyapunov functionals. Finally, numerical simulations are presented to support our analytical results.

**Keywords:** HBV infection, diffusion, fractional partial differential equations, global asymptotic stability.

## 1 Introduction

In the recent years, fractional calculus has attracted the attention of many researchers. Hattaf [1] proposed a new fractional derivative with non-singular kernel which generalizes many forms existing in the literature such as the Caputo-Fabrizio and Atangana-Baleanu fractional derivatives. Further, there are some new methods used to solve numerically fractional models considered to explain deeper investigations of real world problems [2–6].

On the other hand, hepatitis B is a dangerous infectious disease caused by the hepatitis B virus (HBV). It affects the lives of 257 million people and responsible for the deaths of 56000 people every year according to World Health Organization (WHO) estimates [7]. Therefore, several mathematical models have been proposed and developed to describe the dynamics of HBV

dynamics. For instance, Manna and Chakrabarty [8] proposed and analyzed the dynamics of HBV infection by taking into account the spacial mobility of both HBV DNA-containing capsids and viruses. Their work was an extension of that presented in [9]. Guo et al. [10] studied a nonlinear system of partial differential equations (PDEs) for HBV infection with three time delays, general incidence rate and spatial diffusion only in the viruses. Hattaf and Yousfi [11] developed a mathematical HBV infection model with two modes of transmission, and allows the movement of HBV DNA-containing capsids and viruses, and three distributed delays. Since fractional order models possess property of memory, Bachraoui et al. [12] proposed a mathematical model governed by fractional differential equations (FDEs) to more explore the dynamic characteristics of the HBV infection. They have improved and generalized the ordinary differential equation (ODE) models [9, 13] and also the FDE models [14–16] by using the Hattaf’s incidence rate [17] that includes the common types such as the bilinear incidence rate, the saturated incidence rate and the Beddington-DeAngelis functional response [18, 19].

In this study, we present an extension of our model presented in [12] by considering the mobility of capsids and viruses. So, we propose the following mathematical model formulated by fractional partial differential equations (FPDEs) to better describe the dynamics of HBV infection under the effects of diffusion and memory:

$$\begin{cases} \partial_t^\alpha U &= \sigma - \delta U(x, t) - F(U(x, t), V(x, t))V(x, t) + \epsilon I(x, t), \\ \partial_t^\alpha I &= F(U(x, t), V(x, t))V(x, t) - (\rho + \epsilon)I(x, t), \\ \partial_t^\alpha C &= d_C \Delta C + \kappa I(x, t) - (\rho + \eta)C(x, t), \\ \partial_t^\alpha V &= d_V \Delta V + \eta C(x, t) - \nu V(x, t). \end{cases} \quad (1)$$

The state variables  $U(x, t)$ ,  $I(x, t)$ ,  $C(x, t)$  and  $V(x, t)$  are respectively the concentrations of uninfected liver cells, infected liver cells, HBV DNA-containing capsids and virions at location  $x$  and time  $t$ . Uninfected liver cells are produced at constant rate  $\sigma$ , die at rate  $\delta U$  and become infected by virus at rate  $F(U, V)V$ . The parameters  $\epsilon$ ,  $\rho$ ,  $\kappa$ ,  $\eta$  and  $\nu$  are respectively the cure rate of infected liver cells, the death rate of infected liver cells and capsids, the production rate of capsids from infected liver cells, the rate at which the capsids are converted to virions, and the viral clearance rate. The positive constants

$d_C$  and  $d_V$  are the diffusion coefficients of capsids and virus.  $\Delta = \sum_{i=1}^n \frac{\partial^2}{\partial x_i^2}$  is

the Laplacian operator. The incidence function of (1) is described by Hattaf-Yousfi functional response [17] of the form  $F(U, V) = \frac{bU}{\alpha_0 + \alpha_1 U + \alpha_2 V + \alpha_3 UV}$ , where the nonnegative constants  $\alpha_i$ ,  $i = 0, 1, 2, 3$ , measure the saturation, inhibitory or psychological effects, and the positive constant  $b$  is the infection rate. This functional response covers several specific cases available in the literature such as the bilinear and saturation incidences, the Beddington-DeAnglis and Crowley-Martin functional responses, and the specific functional response introduced by Hattaf et al. [20]. Finally,  $\partial_t^\alpha$  is the Caputo fractional derivative of order  $\alpha \in (0, 1]$ . The choice of this type of fractional derivative is motivated by the fact that the fractional derivative of a constant is equal to zero, and  $\alpha$  was chosen in the interval  $(0, 1]$  to have the same initial conditions as those of the PDE systems. Further, a recent study in [21] has shown that the fractional order model gives better predictions than that of the integer model about the plasma virus load of the patients.

Throughout this paper, we consider system (1) with initial conditions

$$\begin{aligned} U(x, 0) &= U_0(x) \geq 0, \quad I(x, 0) = I_0(x) \geq 0, \\ V(x, 0) &= V_0(x) \geq 0, \quad C(x, 0) = C_0(x) \geq 0, \quad \forall x \in \bar{\Omega}, \end{aligned} \quad (2)$$

and zero-flux boundary conditions

$$\frac{\partial C}{\partial \vec{n}} = \frac{\partial V}{\partial \vec{n}} = 0, \quad \text{on } \partial\Omega \times (0, +\infty),$$

where  $\Omega$  is a bounded domain in  $\mathbb{R}^n$  with smooth boundary  $\partial\Omega$ , and  $\frac{\partial}{\partial \vec{n}}$  denotes the outward normal derivative on  $\partial\Omega$ . From the biological point of view, these boundary conditions indicate that the capsids and free virus particles do not move across the boundary  $\partial\Omega$ .

The rest of the paper is organized as follows. The following section is devoted to the calculations of the basic reproduction number and steady states of model (1). The global dynamics of the FPDE model is analyzed in Section 3. To support the analytical results, we present some numerical simulations in Section 4. Finally, we end the paper with biological and mathematical conclusions in Section 5.

## 2 Equilibria of the FPDE model

It is easy to verify that the only infection-free steady state of the FPDE model (1) is  $P_0(U^0, 0, 0, 0)$ , where  $U^0 = \frac{\sigma}{\delta}$ . Then the basic reproduction

number of (1) given by

$$\mathcal{R}_0 = \frac{\kappa\eta F(U^0, 0)}{\nu(\eta + \rho)(\epsilon + \rho)}. \quad (3)$$

The other steady states verify the following system:

$$\sigma - \delta U - F(U, V)V + \epsilon I = 0, \quad (4)$$

$$F(U, V)V - (\epsilon + \rho)I = 0, \quad (5)$$

$$\kappa I - (\eta + \rho)C = 0, \quad (6)$$

$$\eta C - \nu V = 0. \quad (7)$$

From (4)-(7), we get  $I = \frac{\sigma - \delta U}{\rho}$ ,  $C = \frac{\kappa(\sigma - \delta U)}{\rho(\eta + \rho)}$ ,  $V = \frac{\eta\kappa(\sigma - \delta U)}{\nu\rho(\eta + \rho)}$  and

$$F\left(U, \frac{\eta\kappa(\sigma - \delta U)}{\nu\rho(\eta + \rho)}\right) = \frac{\nu(\eta + \rho)(\rho + \epsilon)}{\kappa\eta}. \quad (8)$$

$I = \frac{\sigma - \delta U}{\rho} \geq 0$  implies that  $U \leq \frac{\sigma}{\delta}$ . So, we consider the function  $G$  defined on interval  $[0, \frac{\sigma}{\delta}]$  by

$$G(U) = F\left(U, \frac{\eta\kappa(\sigma - \delta U)}{\nu\rho(\eta + \rho)}\right) - \frac{\nu(\eta + \rho)(\rho + \epsilon)}{\kappa\eta}. \quad (9)$$

We have  $G(0) = -\frac{\nu(\eta + \rho)(\rho + \epsilon)}{\kappa\eta} < 0$ ,  $G\left(\frac{\sigma}{\delta}\right) = \frac{\nu(\eta + \rho)(\rho + \epsilon)}{\kappa\eta} (\mathcal{R}_0 - 1)$  and

$$G'(U) = \frac{\partial F}{\partial U} - \frac{\kappa\eta\delta}{\nu\rho(\eta + \rho)} \frac{\partial F}{\partial V} > 0. \quad (10)$$

If  $\mathcal{R}_0 > 1$ , we deduce that system (1) admits a unique infection equilibrium  $P_1(U_1, I_1, C_1, V_1)$  with  $U_1 \in \left(0, \frac{\sigma}{\delta}\right)$ ,  $I_1 = \frac{\sigma - \delta U_1}{\rho}$ ,  $C_1 = \frac{\kappa(\sigma - \delta U_1)}{\rho(\eta + \rho)}$  and  $V_1 = \frac{\eta\kappa(\sigma - \delta U_1)}{\nu\rho(\eta + \rho)}$ .

We summarize the above discussions in the following result.

**Theorem 2.1.**

- (i) When  $\mathcal{R}_0 \leq 1$ , the FPDE model (1) has one infection-free steady state  $P_0(U^0, 0, 0, 0)$ , where  $U^0 = \frac{\sigma}{\delta}$ .
- (ii) When  $\mathcal{R}_0 > 1$ , the FPDE model (1) has uniquely one chronic infection steady state  $P_1(U_1, I_1, C_1, V_1)$ , where  $U_1 \in \left(0, \frac{\sigma}{\delta}\right)$ ,  $I_1 = \frac{\sigma - \delta U_1}{\rho}$ ,  $C_1 = \frac{\kappa(\sigma - \delta U_1)}{\rho(\eta + \rho)}$  and  $V_1 = \frac{\eta\kappa(\sigma - \delta U_1)}{\nu\rho(\eta + \rho)}$ .

### 3 Global dynamics

This section analyzes the global dynamics of the FPDE model (1).

**Theorem 3.1.** *The infection-free steady state  $P_0$  is globally asymptotically stable if  $\mathcal{R}_0 \leq 1$ .*

**Proof.** Let

$$L_0(t) = \int_{\Omega} \left[ \frac{\alpha_0}{\alpha_0 + \alpha_1 U^0} U^0 \Phi \left( \frac{U}{U^0} \right) + \frac{\alpha_0 \epsilon (U(x, t) - U^0 + I(x, t))^2}{2(\rho + \delta)(\alpha_0 + \alpha_1 U^0) U^0} \right. \\ \left. + I(x, t) + \frac{\epsilon + \rho}{\kappa} C(x, t) + \frac{(\epsilon + \rho)(\eta + \rho)}{\kappa \eta} V(x, t) \right] dx,$$

where  $\Phi(x) = x - 1 - \ln(x)$  for  $x > 0$ . According to [22], we obtain

$$D^\alpha L_0(t) \leq \int_{\Omega} \left[ \frac{\alpha_0}{\alpha_0 + \alpha_1 U^0} \left( 1 - \frac{U^0}{U} \right) \partial_t^\alpha U + \partial_t^\alpha I + \frac{\alpha_0 \epsilon (U - U^0 + I)(\partial_t^\alpha U + \partial_t^\alpha I)}{(\rho + \delta)(\alpha_0 + \alpha_1 U^0) U^0} \right. \\ \left. + \frac{\epsilon + \rho}{\kappa} \partial_t^\alpha C + \frac{(\epsilon + \rho)(\eta + \rho)}{\kappa \eta} \partial_t^\alpha V \right] dx.$$

By  $\sigma = \delta U^0$ , we have

$$D^\alpha L_0(t) \leq \int_{\Omega} \left[ - \left( \frac{1}{U} + \frac{\epsilon}{(\rho + \delta) U^0} \right) \frac{\alpha_0 \delta (U - U^0)^2}{\alpha_0 + \alpha_1 U^0} - \frac{\alpha_0 \epsilon \rho I^2}{(\rho + \delta)(\alpha_0 + \alpha_1 U^0) U^0} \right. \\ \left. - \frac{\alpha_0 \epsilon I (U - U^0)^2}{(\alpha_0 + \alpha_1 U^0) U^0 U} + \frac{\nu(\epsilon + \rho)(\eta + \rho)}{\kappa \eta} \left( \mathcal{R}_0 \frac{F(U, V)}{F(U^0, 0)} - 1 \right) V \right] dx, \\ \leq - \int_{\Omega} \left[ \left( \frac{1}{U} + \frac{\epsilon}{(\rho + \delta) U^0} \right) \frac{\alpha_0 \delta (U - U^0)^2}{\alpha_0 + \alpha_1 U^0} + \frac{\alpha_0 \epsilon \rho I^2}{(\rho + \delta)(\alpha_0 + \alpha_1 U^0) U^0} \right. \\ \left. + \frac{\alpha_0 \epsilon I (U - U^0)^2}{(\alpha_0 + \alpha_1 U^0) U^0 U} - \frac{\nu(\epsilon + \rho)(\eta + \rho)}{\kappa \eta} (\mathcal{R}_0 - 1) V \right] dx.$$

Then  $D^\alpha L_0(t) \leq 0$  when  $\mathcal{R}_0 \leq 1$ . Additionally,  $\{P_0\}$  is the largest invariant set in  $\{(U, I, C, V) \mid D^\alpha L_0(t) = 0\}$ . By LaSalle's invariance principle [23],  $P_0$  is globally asymptotically stable if  $\mathcal{R}_0 \leq 1$ . ■

**Theorem 3.2.** *The chronic infection steady state  $P_1$  is globally asymptotically stable when  $\mathcal{R}_0 > 1$  and*

$$\mathcal{R}_0 \leq 1 + \frac{[\delta \rho \nu (\eta + \rho) + \alpha_2 \delta \sigma \kappa \eta] (\epsilon + \rho) + \alpha_3 \epsilon \eta \kappa \sigma^2}{\epsilon \nu \rho (\epsilon + \rho) (\alpha_0 \delta + \alpha_1 \sigma)}. \quad (11)$$

**Proof.** Let

$$\begin{aligned}
L_1(t) = & \int_{\Omega} \left[ \frac{\alpha_0 + \alpha_2 V_1}{\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1} U_1 \Phi \left( \frac{U}{U_1} \right) \right. \\
& + \frac{\epsilon (\alpha_0 + \alpha_2 V_1) (U(x, t) - U_1 + I(x, t) - I_1)^2}{2(\rho + \delta) (\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1) U_1} \\
& \left. + I_1 \Phi \left( \frac{I}{I_1} \right) + \frac{\epsilon + \rho}{\kappa} C_1 \Phi \left( \frac{C}{C_1} \right) + \frac{(\epsilon + \rho) (\eta + \rho)}{\kappa \eta} V_1 \Phi \left( \frac{V}{V_1} \right) \right] dx.
\end{aligned}$$

Then

$$\begin{aligned}
D^\alpha L_1(t) \leq & \int_{\Omega} \left[ \frac{\alpha_0 + \alpha_2 V_1}{\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1} \left( 1 - \frac{U_1}{U} \right) \partial_t^\alpha U \right. \\
& + \frac{\epsilon (\alpha_0 + \alpha_2 V_1) (U - U_1 + I - I_1) (\partial_t^\alpha U + \partial_t^\alpha I)}{(\rho + \delta) (\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1) U_1} + \left( 1 - \frac{I_1}{I} \right) \partial_t^\alpha I \\
& \left. + \frac{\epsilon + \rho}{\kappa} \left( 1 - \frac{C_1}{C} \right) \partial_t^\alpha C + \frac{(\epsilon + \rho) (\eta + \rho)}{\kappa \eta} \left( 1 - \frac{V_1}{V} \right) \partial_t^\alpha V \right] dx.
\end{aligned}$$

Since  $\sigma = \delta U_1 + \rho I_1$ ,  $F(U_1, V_1) V_1 = (\epsilon + \rho) I_1$ ,  $\kappa I_1 = (\eta + \rho) C_1$  and  $1 - \frac{F(U_1, V_1)}{F(U, V_1)} = \frac{\alpha_0 + \alpha_2 V_1}{\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1} \left( 1 - \frac{U_1}{U} \right)$ , we have

$$\begin{aligned}
D^\alpha L_1(t) \leq & \int_{\Omega} \left[ \frac{-\delta (\alpha_0 + \alpha_2 V_1) (U - U_1)^2}{(\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1) U} + \frac{\epsilon (\alpha_0 + \alpha_2 V_1) (U - U_1) (I - I_1)}{(\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1) U} \right. \\
& + F(U, V_1) V_1 \left( 1 - \frac{F(U_1, V_1)}{F(U, V_1)} + \frac{F(U, V) V_1}{F(U, V_1) V_1} \right) + F(U_1, V_1) V_1 \left( 1 - \frac{I C_1}{I_1 C} \right) \\
& + F(U_1, V_1) V_1 \left( 1 - \frac{F(U, V) V I_1}{F(U_1, V_1) I V_1} \right) + F(U_1, V_1) V_1 \left( 1 - \frac{V}{V_1} - \frac{C V_1}{C_1 V} \right) \\
& \left. - \frac{\epsilon (\alpha_0 + \alpha_2 V_1) [\delta (U - U_1)^2 + \rho (I - I_1)^2 + (\delta + \rho) (U - U_1) (I - I_1)]}{(\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1) (\delta + \rho) U_1} \right] dx \\
& - \frac{\epsilon + \rho}{\kappa} d_C C_1 \int_{\Omega} \frac{\|\nabla C\|^2}{C^2} dx - \frac{(\epsilon + \rho) (\eta + \rho)}{\kappa \eta} d_V V_1 \int_{\Omega} \frac{\|\nabla V\|^2}{V^2} dx.
\end{aligned}$$

Hence,

$$\begin{aligned}
D^\alpha L_1(t) \leq & - \int_{\Omega} \left[ \frac{(\alpha_0 + \alpha_2 V_1) (U - U_1)^2}{(\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1) U U_1} \left( (\delta U_1 - \epsilon I_1) + \frac{\delta \epsilon U}{\rho + \delta} + \epsilon I \right) \right. \\
& + \frac{\epsilon \rho (\alpha_0 + \alpha_2 V_1) (I - I_1)^2}{(\alpha_0 + \alpha_1 U_1 + \alpha_2 V_1 + \alpha_3 U_1 V_1) (\rho + \delta) U_1} \\
& - F(U_1, V_1) V_1 \left( 5 - \frac{F(U_1, V_1)}{F(U, V_1)} - \frac{C_1 I}{C I_1} - \frac{F(U, V)}{F(U_1, V_1)} \frac{V I_1}{V_1 I} - \frac{C V_1}{C_1 V} - \frac{F(U, V_1)}{F(U, V)} \right) \\
& \left. + \frac{F(U_1, V_1) V_1 (\alpha_0 + \alpha_1 U) (\alpha_2 + \alpha_3 U) (V - V_1)^2}{(\alpha_0 + \alpha_1 U + \alpha_2 V_1 + \alpha_3 U V_1) (\alpha_0 + \alpha_1 U + \alpha_2 V + \alpha_3 U V) V_1} \right] dx \\
& - \frac{\epsilon + \rho}{\kappa} d_C C_1 \int_{\Omega} \frac{\|\nabla C\|^2}{C^2} dx - \frac{(\epsilon + \rho) (\eta + \rho)}{\kappa \eta} d_V V_1 \int_{\Omega} \frac{\|\nabla V\|^2}{V^2} dx.
\end{aligned}$$

Since  $5 - \frac{F(U_1, V_1)}{F(U, V_1)} - \frac{C_1 I}{C I_1} - \frac{F(U, V)}{F(U_1, V_1)} \frac{V I_1}{V_1 I} - \frac{C V_1}{C_1 V} - \frac{F(U, V_1)}{F(U, V)} \leq 0$ , we have  $D^\alpha L_1(t) \leq 0$  if  $\mathcal{R}_0 > 1$  and  $\epsilon I_1 \leq \delta U_1$ . The last condition is equivalent to

$$\mathcal{R}_0 \leq 1 + \frac{[\delta \rho \nu (\eta + \rho) + \alpha_2 \delta \sigma \kappa \eta] (\epsilon + \rho) + \alpha_3 \epsilon \eta \kappa \sigma^2}{\epsilon \nu \rho (\epsilon + \rho) (\alpha_0 \delta + \alpha_1 \sigma)}.$$

Also,  $\{P_1\}$  is the largest invariant set in  $\{(U, I, C, V) \mid D^\alpha L_1(t) = 0\}$ . According to LaSalle's invariance principle, we deduce that  $P_1$  is globally asymptotically stable. This completes the proof. ■

## 4 Numerical simulations

In this section, we present some numerical illustrations to support the obtained analytical results.

Let  $\Delta t$  be the time step size,  $\Omega = [x_{\min}, x_{\max}]$  and  $\Delta x = (x_{\max} - x_{\min}) / N$  be the space step size with  $N$  is a positive integer. The grid points for the space are  $x_i = x_{\min} + i \Delta x$  for  $i \in \{0, \dots, N\}$ , and for time are  $t_m = m \Delta t$  for  $m \in \mathbb{N}$ . From Grünwald-Letnikov method [24], the Caputo fractional derivative is approximated as follows

$${}^C \partial_t^\alpha l(x_i, t_m) \approx \frac{1}{\Delta t^\alpha} \sum_{j=0}^m \beta_j^\alpha l(x_i, t_{m-j}) - \tilde{l}_m, \quad (12)$$

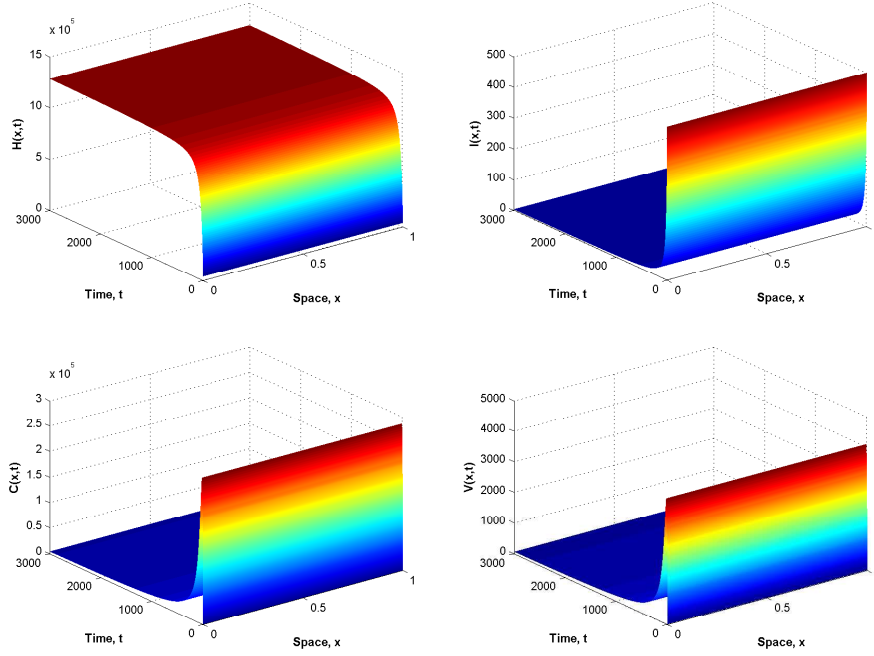


Figure 1: Stability of the infection-free steady state  $P_0$ .

where  $\tilde{l}_m = \frac{l(x_i,0)t_m^{-\alpha}}{\Gamma(1-\alpha)}$  and  $\beta_j^\alpha$  are the fractional binomial coefficients  $\binom{\alpha}{j}$  with the recursion formula

$$\beta_j^\alpha = \left(1 - \frac{1+\alpha}{j}\right) \beta_{j-1}^\alpha, \quad \beta_0^\alpha = 1.$$

Let  $(U_i^m, I_i^m, C_i^m, V_i^m)$  be the approximations of the solution  $(U, I, C, V)$  of (1) at the discretized point  $(x_i, t_m)$ . Then by applying (12), we get

$$\begin{aligned} \frac{1}{\Delta t^\alpha} \left( U_i^{m+1} + \sum_{j=1}^{m+1} \beta_j^\alpha U_i^{m+1-j} \right) - \tilde{U}_i^{m+1} &= \sigma - \delta U_i^m - F(U_i^m, V_i^m) V_i^m + \epsilon I_i^m, \\ \frac{1}{\Delta t^\alpha} \left( I_i^{m+1} + \sum_{j=1}^{m+1} \beta_j^\alpha I_i^{m+1-j} \right) - \tilde{I}_i^{m+1} &= F(U_i^m, V_i^m) V_i^m - (\epsilon + \rho) I_i^m, \\ \frac{1}{\Delta t^\alpha} \left( C_i^{m+1} + \sum_{j=1}^{m+1} \beta_j^\alpha C_i^{m+1-j} \right) - \tilde{C}_i^{m+1} &= d_C \frac{C_{i+1}^m - 2C_i^m + C_{i-1}^m}{\Delta x^2} + \kappa I_i^m - (\eta + \rho) C_i^m, \end{aligned}$$

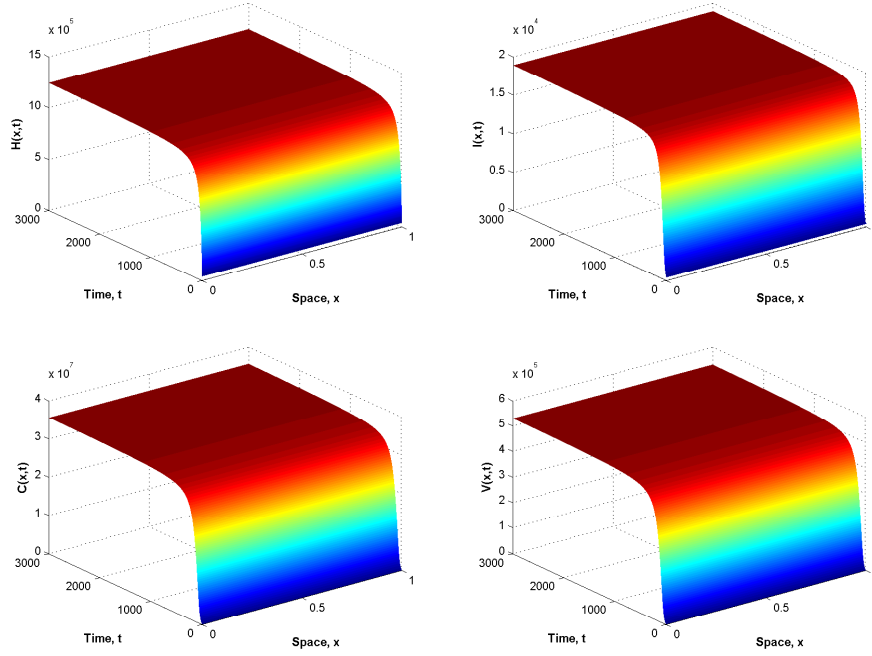


Figure 2: Stability of the chronic infection steady state  $P_1$ .

$$\frac{1}{\Delta t^\alpha} \left( V_i^{m+1} + \sum_{j=1}^{m+1} \beta_j^\alpha V_i^{m+1-j} \right) - \tilde{V}_i^{m+1} = d_V \frac{V_{i+1}^m - 2V_i^m + V_{i-1}^m}{\Delta x^2} + \eta C_i^m - \nu V_i^m.$$

Hence,

$$U_i^{m+1} = - \sum_{j=1}^{m+1} \beta_j^\alpha U_i^{m+1-j} + \Delta t^\alpha \left[ \tilde{U}_i^{m+1} + \sigma - \delta H_i^m - F(U_i^m, V_i^m) V_i^m + \epsilon I_i^m \right],$$

$$I_i^{m+1} = - \sum_{j=1}^{m+1} \beta_j^\alpha I_i^{m+1-j} + \Delta t^\alpha \left[ \tilde{I}_i^{m+1} + F(U_i^m, V_i^m) V_i^m - (\epsilon + \rho) I_i^m \right],$$

$$C_i^{m+1} = - \sum_{j=1}^{m+1} \beta_j^\alpha C_i^{m+1-j} + \Delta t^\alpha \left[ \tilde{C}_i^{m+1} + d_C \frac{C_{i+1}^m - 2C_i^m + C_{i-1}^m}{\Delta x^2} + \kappa I_i^m - (\eta + \rho) C_i^m \right],$$

$$V_i^{m+1} = - \sum_{j=1}^{m+1} \beta_j^\alpha V_i^{m+1-j} + \Delta t^\alpha \left[ \tilde{V}_i^{m+1} + d_V \frac{V_{i+1}^m - 2V_i^m + V_{i-1}^m}{\Delta x^2} + \eta C_i^m - \nu V_i^m \right].$$

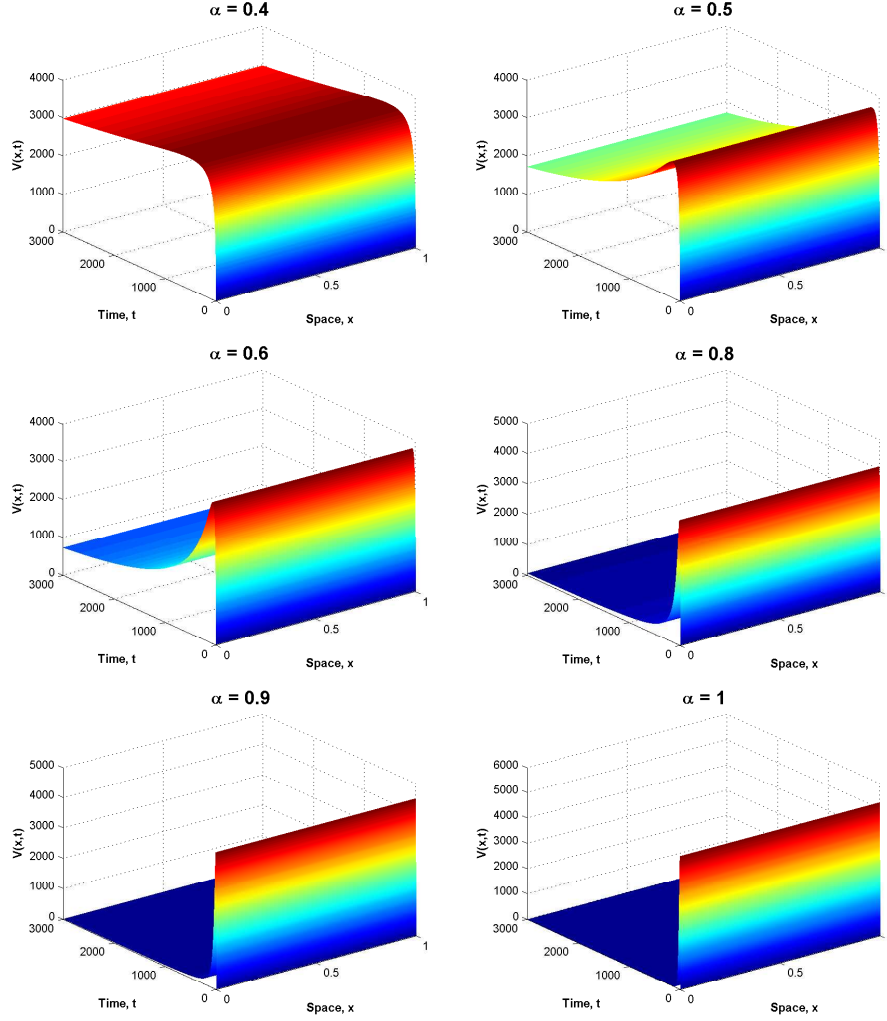


Figure 3: The state variable  $V(x, t)$  with different values of  $\alpha$ .

For numerical simulations, we choose  $\Omega = [0, 1]$ ,  $d_C = 0.1$ ,  $d_V = 0.1$ ,  $\sigma = 50400$ ,  $b = 3.6 \times 10^{-6}$ ,  $\delta = 0.039$ ,  $\rho = 0.0693$ ,  $\kappa = 150$ ,  $\eta = 0.01$ ,  $\epsilon = 0.01$ ,  $\alpha = 0.8$ ,  $\alpha_0 = 0.1$ ,  $\alpha_1 = 0.1$ ,  $\alpha_2 = 0.01$  and  $\alpha_3 = 0.000001$ . By simple calculation, we find  $\mathcal{R}_0 = 0.0128 < 1$ . According to Theorem 3.1, the infection-free steady state  $P_0(1.2923 \times 10^6, 0, 0, 0)$  is globally asymptotically stable which means that the virus will disappear and the patient will be completely cured. Figure 1 confirms this result.

To numerically illustrate the global stability of the second steady state of model (1), we take  $b = 0.0018$  without changing the values of the other parameters. In this case,  $\mathcal{R}_0 = 6.4083 > 1$ . From Theorem 2.1, FPDE model (1) has the unique chronic infection steady state  $P_1(1.244 \times 10^6, 1.891 \times 10^4, 3.562 \times 10^7, 5.314 \times 10^5)$ . Additionally, we have

$$1 + \frac{[\delta\rho\nu(\eta + \rho) + \alpha_2\delta\sigma\kappa\eta](\epsilon + \rho) + \alpha_3\epsilon\eta\kappa\sigma^2}{\epsilon\nu\rho(\epsilon + \rho)(\alpha_0\delta + \alpha_1\sigma)} = 218.9236,$$

which implies that (11) holds. By Theorem 3.2,  $P_1$  is globally asymptotically stable. Figure 2 validates this result.

## 5 Conclusions

In this article, we have presented a fractional reaction-diffusion HBV model that takes into account the HBV DNA-containing capsids and the cure of infected liver cells. The spatial diffusion is considered in capsids and virions, and the incidence of infection is described by Hattaf-Yousfi functional response that includes various forms existing in the literature. We have shown that the global dynamics of the FPDEs model is fully determined by a threshold parameter called the basic reproduction number and labeled by  $\mathcal{R}_0$ . More concretely, the infection-free steady state  $P_0$  is globally asymptotically stable if  $\mathcal{R}_0 \leq 1$ , which biologically means that the HBV is cleared. However, the chronic infection steady state  $P_1$  is globally asymptotically stable when  $\mathcal{R}_0 > 1$  and the condition (11) holds. In this case, the HBV persists in the liver and the infection becomes chronic.

According to the above analytic results and the numerical simulations, we deduce that the diffusion and the order of fractional derivative in sense of Caputo have no effects on the stability of both steady states, but they can affect the time for arriving to these steady states. For example, the trajectories quickly converge towards the equilibria of the model for higher values of the fractional derivative order (see, Figures 3). On the other hand, the models and results presented in [8, 9, 12–16] are improved and extended.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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