Hepatitis C virus fractional-order model: mathematical analysis

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Abstract
Mathematical analysis of epidemics is crucial for the prediction of diseases over time and helps to guide decision makers in terms of public health policy. It is in this context that the purpose of this paper is to study a fractional-order differential mathematical model of HCV infection dynamics, incorporating two fundamental modes of transmission of the infection: virus-to-cell and cell-to-cell along with a cure rate of infected cells. The model includes four compartments, namely, the susceptible hepatocytes, the infected ones, the viral load and the humoral immune response, which is activated in the host to attack the virus. Each compartment involves a long memory effect that is modeled by a Caputo fractional derivative. Our paper starts with the investigation of some basic analytical results. First, we introduce some preliminaries about the needed fractional calculus tools. Next, we establish the well-posedness of our mathematical model in terms of proving the existence, positivity and boundedness of solutions. We present the different problem steady states depending on some reproduction numbers. After that, the paper moves to the stage of proving the global stability of the three steady states. To evaluate the theoretical study of the global stability, we apply a numerical method based on the fundamental theorem of fractional calculus as well as a three-step Lagrange polynomial interpolation method. The numerical simulations show that the free-endemic equilibrium is stable if the basic reproduction number is less than unity. In addition, the numerical tests demonstrate the stability of the other endemic equilibria under some optimal conditions. It is observed that the numerical simulations and the founding theoretical results are coherents.

Keywords HCV infection · Cure rate · Global stability · Fractional-order model · Numerical simulation

Introduction
It is known that the hepatitis C virus (HCV) is a serious disease facing the public health nowadays. HCV is a blood-borne virus which attacks the hepatocytes and leads to an inflammation of the liver. In fact, the virus can begin with a simple illness and then transform to chronic illness such as cancer and liver cirrhosis. The HCV can be transmitted either through drug injections, unsafe blood transfusion or unsafe sexual practices and so on. According to the World Health Organization (WHO), about 58 million people suffer from chronic HCV infection in the world; 3.2 million of them are adolescents and children. Each year about 1.5 million new infection cases occur. Since there is no vaccine available so far to prevent HCV (WHO 2021), every year an estimated of 290 thousand people die mostly from primary liver cancer, namely, the hepatocellular carcinoma.

To minimize the costly public health effects and the loss of lives, mathematical modeling has become very important in understanding the viral dynamics of an epidemic, which helps to highlight how diseases progress to show its likely outcome and to predict its future growth patterns, which can help to inform the public health authorities to take the necessary measures (Nowak and Bangham 1996; Dunia and Bonnecaze 2013; Goyal et al. 2019; Wang et al. 2020).

For the case of HCV infection, Neumann et al. (1998) first simplest HCV viral mathematical model has played a vital role in understanding HCV dynamics and in the design and evaluation of antiviral therapies.
It is known that HCV can disseminate in the body between hepatocytes either by means of virus-to-cell infection or by means of direct cell-to-cell virus transfer. This dissemination of HCV infection results in focal areas of infection, where cell-to-cell contact is responsible for the infection (Brimacombe et al. 2011). Many researches provided a mathematical model of HCV viral dynamics by incorporating both modes of transmission of the infection (Mojaver and Kheiri 2016; Dhar et al. 2021). For these mentioned papers, it is obvious that when the model considers only cell-free transmission of the virus, an underestimation in the value of the basic reproduction number occurs, in comparison to the model, where cell-to-cell transmission is included.

All the afore-mentioned papers present their HCV models using the ordinary differential equations (ODE). Recently, several researchers have extended the modeling of the HCV viral dynamics by fractional order derivative system (FOD) (Khodabakhshi et al. 2017; Ahmed and El-Saka 2010; Yang et al. 2021; Saad et al. 2020a, b; Carvalho and Pinto 2018). The latter contains equations with derivatives of non-integer order called fractional derivative, which appears for the first time in a question in a letter from Gottfried Wilhelm Leibniz to Guillaume de l'Hôpital; the question was if the nth derivative exists with $n = 1/2$ (Ross 1977). There are several types of fractional derivatives, among which we mention Riemann–Liouville, Caputo and Atangana-Baleanu (Podlubny 1999; Atangana and Baleanu 2016). One of the major advantages of the fractional order models is describing the memory effect. For this reason, several fields other than biology use this fractional calculation to well modelize the real problems, such as image processing, mechanics problems and finance issues (Zhang et al. 2022; Chen et al. 2022; Wang et al. 2022).

For the case of biology, it is proved that the main biological features of immune response and the membranes of cells involve memory (Huo et al. 2015). Hence, differential equations with a Caputo fractional order derivative have been employed to model the infection dynamics of several infectious diseases, such as Tuberculosis, Dengue fever, HBV and Covid-19 (Khan et al. 2022; Boulaaras et al. 2022; Karaman 2022; Chatterjee and Ahmad 2021). By comparing the acquired results via fractional calculus and via classical calculus to the clinical data, it was easy to see that fractional calculus is an effective tool for modeling epidemic disease (Barros et al. 2021; Alla Hamou et al. 2021; Qureshi 2020). These convincingly studies conclude that fractional order differential operators are more effective than traditional integer-order ones to model the nonlinear epidemic systems, because they produce more realistic results. Hence, fractional order differential equations are more efficient and constitute a strong mathematical tools for biological systems investigation.
Our inspiration for this study derives from all the biological properties mentioned before as well as the important role of fractional order differential equations in modeling the HCV viral dynamics. Recently, an HCV mathematical model is described using the classical integer order derivative (Pan and Chakrabarty 2018). This tackled model includes four compartments describing the interaction between susceptible hepatocytes and infected ones, the viral load and the humoral immune response. In fact, their HCV mathematical model describes the HCV viral infection by two modes of the virus transmission; virus-to-cell and cell-to-cell under the presence of the non-cytolytic cure of infected cells within the same model. Their mathematical model takes the following form:

\[
\begin{align*}
\frac{dT}{dt} & = \lambda - \beta_1 TV - \beta_2 TI - d_1 T + \rho I, \\
\frac{dI}{dt} & = \beta_1 TV + \beta_2 TI - d_2 I - \rho I, \\
\frac{dV}{dt} & = kI - qVW - d_3 V, \\
\frac{dW}{dt} & = gVW - d_4 W.
\end{align*}
\]  

(1)

We note that \( T \) and \( I \) stand for the susceptible and the infected hepatocytes, respectively. While \( V \) is the viral load and \( W \) represents the humoral immune response. From the liver, uninfected hepatocytes are made with a rate \( \lambda \) and dies naturally with a rate \( d_1T \) and becomes infected by virions and infected cells with a rate \( \beta_1TV \) and \( \beta_2TI \), respectively. The infected hepatocytes decay naturally with a rate \( d_2I \) and becomes cured with a rate \( \rho I \). Encouraged by infected cells, the free virions are produced with a rate \( kI \) and become extinct naturally with a rate \( d_3V \). Following the entry of the free viruses, the activation of B cells is turned on with a rate \( gVW \), which extinct at a rate \( d_4W \). Virions gets neutralized by the effect of B cells with a rate \( qVW \).

The memory effects on the viral dynamics of the HCV infection are ignored in the above-mentioned ODE system (1). We aim to explore the influence of memory effects on the dynamic behavior of the model (1). To this end, we replace the classical derivative in (1) with Caputo fractional derivative. We obtain, the following system:

\[
\begin{align*}
D^\alpha T & = \lambda - \beta_1 TV - \beta_2 TI - d_1 T + \rho I, \\
D^\alpha I & = \beta_1 TV + \beta_2 TI - d_2 I - \rho I, \\
D^\alpha V & = kI - qVW - d_3 V, \\
D^\alpha W & = gVW - d_4 W.
\end{align*}
\]

(2)

Here, \( D^\alpha \) signify the Caputo fractional derivative of order \( \alpha \). The initial conditions; \( T(0) = T_0, I(0) = I_0, V(0) = V_0 \) and \( W(0) = W_0 \) are all positives. We consider that all the parameters have positive values. Our HCV model is schematically represented in Fig. 1. To the best of our knowledge, this is the first HCV Caputo fractional-order model which incorporates both modes of transmission of the virus, the virus-to-cell and cell-to-cell, under the presence of the humoral immune response and the cure rate of infected cells.

The paper’s organization is as follows; the next section gives some preliminary important results. Then, it moves to the determination of some basic analytical results with the perspective to proving the positivity and boundedness of solutions and finding the three steady states of the model (2). For all the equilibria, we demonstrate the global stability in “Global stability of the equilibria”. Numerical simulations are shown in “Numerical simulations and discussion”, and that is for performing the global stability analysis of the steady states. The last section is a conclusion of the this work.
Preliminaries

In this section, we introduce some definitions about the Mittag–Leffler function, the fractional integral and the Caputo fractional derivative.

Definition 1 (Podlubny 1999) For a given function \( \Phi : \mathbb{R}_+ \to \mathbb{R} \), we define the fractional integral of order \( \alpha \) of \( \Phi \) as

\[
I^\alpha \Phi(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} \Phi(s) ds,
\]

with \( \Gamma \) represented the Gamma function.

Definition 2 (Podlubny 1999) For a given function \( \Phi : \mathbb{R}_+ \to \mathbb{R} \), we define the Caputo fractional derivative of order \( \alpha \) of \( \Phi \) as

\[
D^\alpha \Phi(t) = I^{n-\alpha}D^n \Phi(t),
\]

with \( D^\alpha \Phi \) is the usual \( n \)th derivative of the function \( \Phi \) and \( n - 1 \leq \alpha < n, n \in \mathbb{N} \). In particular for \( 0 < \alpha \leq 1 \), the definition returns to the following form:

\[
D^\alpha \Phi(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{\Phi'(s)}{(t-s)^\alpha} ds.
\]

Definition 3 (Podlubny 1999) We define the function \( E_\alpha \), called the Mittag–Leffler function by the following form:

\[
E_\alpha(t) = \sum_{j=0}^{\infty} \frac{t^j}{\Gamma(\alpha j + 1)},
\]

with, \( \alpha > 0 \).

To get the next section, we announce the following lemma, but first of all we present the general fractional system defined by

\[
D^\alpha Y(t) = F(Y),
\]

\[
Y(0) = Y_0.
\]

For \( F : \mathbb{R}^m \to \mathbb{R}^m \) where \( m \geq 1 \), with \( 0 < \alpha \leq 1 \) and \( y_0 \in \mathbb{R}^m \).

Lemma 1 (Lin 2007) we suppose that \( F \) verify the two conditions

(i) \( F(Y) \) and \( (\partial F/\partial Y)(Y) \) are continuous on \( \mathbb{R}^m \).

(ii) \( \|F(Y)\| \leq u_1 + u_2 \|Y\| \) for all \( Y \in \mathbb{R}^m \), with \( u_1 \) and \( u_2 \) are positive constants.

So, the system admits a unique solution defined on \([0, \infty)\).

The proof of this lemma is found in this reference (Lin 2007).

Basic analytical results

In this section, we will show some basic analytical results.

Positivity and boundedness of solutions

The result of the positivity and boundedness of the solutions of system (2) is given as follows

Theorem 1 If \( T_0, I_0, V_0, W_0 \) are all positive, then a unique and global solution exists and defined on \([0, \infty)\). Furthermore, this solution is positive and bounded on \([0, \infty)\).

Proof We can describe the model (2) by the following equation:

\[
D^\alpha X(t) = F(X),
\]

with

\[
X = \begin{pmatrix} T \\ I \\ V \\ W \end{pmatrix},
\]

and

\[
F(X) = \begin{pmatrix} \lambda - \beta_1 TV - \beta_2 TI - d_1 T + \rho I \\ \beta_1 TV + \beta_2 TI - d_2 I - \rho I \\ kI - qVW - d_3 V \\ gVW - d_4 W \end{pmatrix}.
\]

Moreover, \( F \) can be re-written as follows:

\[
F(X) = A_1 + A_2 X + A_3 TX + A_4 VX.
\]

where

\[
A_1 = \begin{pmatrix} \lambda \\ 0 \\ 0 \\ 0 \end{pmatrix},
\]

\[
A_2 = \begin{pmatrix} -d_1 & \rho & 0 & 0 \\ 0 & -d_2 - \rho & 0 & 0 \\ 0 & k & -d_3 & 0 \\ 0 & 0 & 0 & -d_4 \end{pmatrix},
\]

\[
A_3 = \begin{pmatrix} 0 & -\beta_2 & -\beta_1 & 0 \\ 0 & \beta_2 & \beta_1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},
\]

and
$A_4 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -q & 0 \\ 0 & 0 & 0 & g \end{pmatrix}$. \hspace{1cm} (14)

If we apply a norm to Eq. (11) we obtain

$$\|F(X)\| \leq \|A_1\| + \left(\|A_2\| + \|A_3\|\|T\| + \|A_4\|\|V\|\right)\|X\|. \hspace{1cm} (15)$$

Since the conditions of the Lemma (1) are verified, the system (2) admits a unique solution defined on $[0, \infty)$, we have

$$D^\alpha T|_{t=0} = \lambda + \rho I \geq 0,$$

$$D^\alpha I|_{t=0} = \beta_1 TV \geq 0,$$

$$D^\alpha V|_{t=0} = kI \geq 0,$$

$$D^\alpha W|_{t=0} = 0 \geq 0. \hspace{1cm} (16)$$

Consequently, all the solutions with positive initial data in $R^+_4$ are positives. We introduce the function

$$F(t) = C_1 T(t) + C_2 I(t) + C_3 V(t) + C_4 W(t), \hspace{1cm} (17)$$

where $C_1, C_2, C_3$ and $C_4$ are positive constants that need to be discovered. Taking the fractional derivative of order $\alpha$ of $F(t)$ along the solution of (2), we have

$$D^\alpha F(t) = C_1 \left(\lambda - \beta_1 TV - \beta_2 TI - d_1 T + \rho I\right) + C_2 \left(\beta_1 TV + \beta_2 TI - d_1 I - \rho I\right) + C_3 \left(kI - d_3 V - qVW\right) + C_4 \left(gVW - d_4 W\right) = \lambda C_1 + (\beta_1 C_2 - \beta_1 C_1) TV + (\beta_2 C_2 - \beta_2 C_1) TI - \rho C_2 I + C_3(1 - k)I - d_3 C_4 I + (1 - C_3) V - d_4 C_4 W. \hspace{1cm} (18)$$

Now choosing, $C_1 = C_2 = 1$, and $C_3 = \frac{\varepsilon}{g} C_4$. After some evident simplification, we have

$$7D^\alpha F(t) = \lambda - d_1 T - \left(d_2 - \frac{gkC_4}{q}\right) I - \frac{gd_3 C_4}{q} V - C_4 d_4 W. \hspace{1cm} (19)$$

Choosing $C_4 = \frac{\varepsilon g d_3}{2gk}$, gives

$$D^\alpha F(t) = \frac{\lambda - d_1 T - d_2 I - \frac{gd_3 d_2}{2gk} V - \frac{gd_3 d_4}{2gk} W}{7} \leq \frac{\lambda - \gamma F(t)}{7}. \hspace{1cm} (20)$$

where $\gamma = \min \left\{ d_1, \frac{d_2}{2}, \frac{gd_3 d_2}{2gk}, \frac{gd_3 d_4}{2gk} \right\}$. It follows that

$$F(t) \leq F(0) E_\alpha(-\gamma t^\alpha) + \frac{\lambda}{\gamma} (1 - E_\alpha(-\gamma t^\alpha)). \hspace{1cm} (21)$$

Since $0 < \nu_a(-\gamma t^\alpha) \leq 1$ and $1 - \nu_a(-\gamma t^\alpha) \leq 1$, we get

$$F(t) \leq F(0) + \frac{\lambda}{\gamma}. \hspace{1cm} (22)$$

Which implies that the solutions are bounded. \hspace{1cm} $\square$

**Steady states**

Now, we determine the steady states. First, let define the basic reproduction number of the system (2) which is given by

$$R_0 = \frac{\lambda(\beta_1 k + \beta_2 d_3)}{d_1 d_3 (d_2 + \rho)}. \hspace{1cm} (23)$$

Note that biologically the basic reproduction rate is the average number of new infected cells due to one infected cell put in an environment full of susceptible cells. The system (2) admits three steady states, called The disease free equilibrium (DFE), $E_f = (T_f, 0, 0, 0)$, where $T_f = \frac{\lambda}{d_1}$. The first endemic steady state is $E_1 = (T_1, I_1, V_1, 0)$, where

$$T_1 = \frac{d_3 (d_2 + \rho)}{\beta_1 k + \beta_2 d_3},$$

$$I_1 = \frac{d_1 T_1}{d_3} (R_0 - 1),$$

$$V_1 = \frac{k}{d_3} I_1.$$ 

Clearly, $E_1$ exists if $R_0 > 1$. The second endemic steady state is, $E_2 = (T_2, I_2, V_2, W_2)$, where

$$T_2 = \frac{(d_2 + \rho) I_2}{\beta_1 V_2 + \beta_2 I_2},$$

$$I_2 = \frac{-a_2 + \sqrt{a_2^2 + 4a_1 a_3}}{2a_1},$$

$$V_2 = \frac{d_1}{g},$$

$$W_2 = \frac{d_3}{q} (R_1 - 1),$$

with $a_1 = \beta_2 g d_2$, $a_2 = \beta_1 d_2 d_4 + gd_1 (d_2 + \rho) - \lambda g d_2$, $a_3 = \lambda \beta_1 d_1$, $a_4 = \lambda \beta_1 d_1$. Here, $R_1 = \frac{\varepsilon g d_3 I_2}{g d_1 (d_2 + \rho) + d_1 d_3 (\beta_1 k + \beta_2 d_3)}$ defines the viral reproduction number in the chronic stage of infection with the effect of the humoral immune response. Obviously, $E_2$ exists if $R_1 > 1$. Here, we need to define a parameter called the humoral immune reproduction number, $R_W = \frac{\varepsilon g d_3 (\beta_1 k + \beta_2 d_3)}{g d_1 (d_2 + \rho) + d_1 d_3 (\beta_1 k + \beta_2 d_3)}$, which will be used in the
rest of this paper. Biologically, $R_w$ is the average number of new infected cells in the presence of the humoral immune response. We will need the following lemma in the sequel of this paper.

**Lemma 2**

(i) $R_1 > 1 \iff R_w > 1,$

(ii) $R_1 = 1 \iff R_w = 1,$

(iii) $R_1 < 1 \iff R_w < 1.$

**Proof**

Certainly, $R_1 > 1 \iff I_2 > \frac{d_2d_4}{gk} \iff \frac{\alpha_2+\sqrt{\alpha_2^2+4\alpha_1\alpha_3}}{2\alpha_1} > \frac{d_2d_4}{gk}$

In other words

$$R_1 > 1 \iff \left(\frac{\alpha_2+\sqrt{\alpha_2^2+4\alpha_1\alpha_3}}{2\alpha_1}\right)^2 > 0.$$ 

The inequality can be simplified to

$$R_1 > 1 \iff \frac{4\beta_1^2d_3d_4}{k^2} \left[gkd_1d_3(d_2 + \rho) + d_2d_3(\beta_1k + \beta_2d_3)\right] (R_w - 1) > 0.$$ 

Thus, $R_1 > 1 \iff R_w > 1.$ For (ii) and (iii), they can be proved by a similar argument.

**Global stability of the equilibria**

For the investigation of the global stability we will create appropriate Lyapunov functions to apply the LaSalle’s invariance principle (Huo et al. 2015). First, we define the function $h$, such that $h(x) = x - 1 - \ln(x), x > 0$, with $h(x) \geq 0, \forall x > 0$ and $h(x) = 0 \iff x = 1$.

**Theorem 2** If $\mathcal{R}_0 \leq 1$, then the disease free equilibrium $E_f$ is globally asymptotically stable.

**Proof** We introduce the Lyapunov function $L_f$ in the following way

$$L_f(t) = T_fh\left(\frac{T(t)}{T_f}\right) + I(t) + \frac{\beta_1T_f}{d_1}V(t) + \frac{\beta_1qT_f}{gd_3}W(t) + \frac{\rho}{2(d_1 + d_2)T_f}\left[(T(t) - T_f) + I(t)\right]^2.$$ 

Considering system’s positive solutions, the derivative of $L_f$ is identified by

$$D^aL_f(t) \leq \left(1 - \frac{T_f}{T(t)}\right)D^aT(t) + D^aI(t) + \frac{\beta_1T_f}{d_1}D^aV(t) + \frac{\beta_1qT_f}{gd_3}D^aW(t) + \frac{\rho}{(d_1 + d_2)T_f}\left[(T(t) - T_f) + I(t)\right](D^aT(t) + D^aI(t)).$$

Using the relation $\lambda = d_1T_f$, we get

$$D^aL_f \leq \left(1 - \frac{T_f}{T}\right)(-\beta_1TV - \beta_2TI - d_1(T - T_f) + \rho I) + \frac{\beta_1T_f}{d_1}(kl - qVW - d_1V) + \frac{\beta_1qT_f}{gd_3}(qVW - d_1W) - \frac{\rho}{(d_1 + d_2)T_f}\left[(T - T_f) + I\right](d_1(T - T_f) + d_2I).$$

We observe that

$$\rho\left(1 - \frac{T_f}{T}\right)I = -\rho\left(\frac{T_f}{T} - 2\right) + \frac{\rho}{T_f}(T - T_f)I.$$ 

Thus

$$D^aL_f \leq -\left(d_1T_f + \rho I + \frac{\rho d_1T_f}{d_1 + d_2}\right)\left(\frac{T_f}{T} + T_f - 2\right) - \frac{\rho d_2I^2}{(d_1 + d_2)T_f} - \frac{\beta_1d_4qT_fW}{gd_3} + (d_2 + \rho)I(\mathcal{R}_0 - 1).$$

Applying the result of that the arithmetic mean is bigger than or equal to the geometric mean, we get

$$\frac{T_f}{T} + T_f - 2 \geq 0.$$ 

Hence, when $\mathcal{R}_0 \leq 1$ then $D^aL_f \leq 0$. Let $M_1$ be the largest invariant set in $\{(T, I, V, W) | D^aL_f = 0\}$. We remark that $D^aL_f = 0$ if and only if $T = T_f, I = 0, V = 0$ and $W = 0$. Hence, $M_1 = \{E_f\} = \{(\frac{\rho}{\alpha_1}, 0, 0, 0)\}$. Then, the invariance principal of LaSalle implies that $E_f$ is globally asymptotically stable when $\mathcal{R}_0 \leq 1.$

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Theorem 3 If $R_1 \leq 1 < R_0 \leq 1 + \frac{d_2}{\rho}$, then the first endemic steady state $E_1$ is globally asymptotically stable.

Proof We introduce the Lyapunov function $L_1$ in the following way:

\[
L_1(t) = T_1 h \left( \frac{T(t)}{T_1} \right) + I_1 h \left( \frac{I(t)}{I_1} \right) + \frac{\beta_1 T_1 V_1^2}{k l_1} h \left( \frac{V(t)}{V_1} \right) + \frac{\beta q T_1 V_1}{g k l_1} W(t) + \frac{\rho}{2(d_1 + d_2) T_1} \left( (T(t) - T_1) + (I(t) - I_1) \right)^2.
\]  

(32)

Considering system’s positive solutions, the derivative of $L_1$ is identified by

\[
D^s L_1 \leq \left( 1 - \frac{T_1}{T} \right) D^s T + (1 - \frac{I_1}{I}) D^s I + \frac{\beta_1 T_1 V_1}{k l_1} \left( 1 - \frac{V_1}{V} \right) D^s V + \frac{\beta q T_1 V_1}{g k l_1} D^s W + \frac{\rho}{(d_1 + d_2) T_1} \left( (T(t) - T_1) + (I(t) - I_1) \right) (D^s T + D^s I).
\]

At the equilibrium $E_1$, we have

\[
\lambda - \beta_1 T_1 V_1 - \beta_2 T_1 I_1 - d_1 T_1 + \rho I_1 = 0,
\]

\[
\beta_1 T_1 V_1 + \beta_2 T_1 I_1 - d_1 T_1 + \rho I_1 = 0,
\]

\[
kl_1 - qV_1 W_1 - d_1 V_1 = 0,
\]

\[
gV_1 W_1 - d_1 W_1 = 0.
\]

Using the relation (34), we obtain

\[
D^s L_1 \leq \left( 1 - \frac{T_1}{T} \right) \left[ \beta_1 T_1 V_1 + \beta_2 T_1 I_1 - \beta_1 T_1 V_1 - \beta_2 T_1 I_1 - d_1 T_1 + \rho I_1 \right] \left( \frac{T(t)}{T_1} + \frac{T_1}{T} - 2 \right)
\]

\[
+ \frac{\beta_1 T_1 V_1}{k l_1} \left( 1 - \frac{V_1}{V} \right) \left( k l - \frac{k l V}{V_1} - qVW \right)
\]

\[
+ \frac{\beta q T_1 V_1}{g k l_1} (gVW - d_1 W)
\]

\[
- \frac{\rho}{(d_1 + d_2) T_1} \left( (T(t) - T_1) + (I(t) - I_1) \right) \left[ d_1 (T(t) - T_1) + d_2 (I(t) - I_1) \right].
\]

(35)

We remark that

\[
\rho \left( 1 - \frac{T_1}{T} \right) (I - I_1) = - \rho (I - I_1) \left( \frac{T}{T_1} + \frac{T_1}{T} - 2 \right) + \frac{\rho}{T_1} (T - T_1) (I - I_1).
\]

(36)

Thus

\[
D^s L_1 \leq - \frac{\rho d_2}{(d_1 + d_2) T_1} (I - I_1)^2 - \beta_1 T_1 V_1 \left[ \frac{T_1}{T} + \frac{IV_1}{I_1 V} + \frac{T_1 V}{T_1 IV_1} - 3 \right] - \beta_2 T_1 I_1 \left[ \frac{T}{T_1} + \frac{T_1}{T} - 2 \right] + \frac{\lambda \beta q T_1 W}{d_1 d_2 R_W} (R_W - 1).
\]

(37)

Applying the result of that the arithmetic mean is bigger than or equal to the geometric mean, we get

\[
\frac{T}{T_1} + \frac{T_1}{T} - 2 \geq 0 \text{ and } \frac{T_1}{T} + \frac{IV_1}{I_1 V} + \frac{T_1 V}{T_1 IV_1} - 3 \geq 0.
\]

(38)

We also remark that

\[
d_1 T_1 - \rho I_1 = \frac{\lambda}{d_2 R_0} (d_2 + \rho - \rho R_0).
\]

(39)

Therefore, when $R_W \leq 1$ and $R_0 \leq 1 + \frac{d_2}{\rho}$, then $D^s L_1 \leq 0$.

That is to say $D^s L_1 \leq 0$ when $R_1 \leq 1$ and $R_0 \leq 1 + \frac{d_2}{\rho}$ (using Lemma 2). Let $M_2$ be the largest invariant set in $\{(T, I, V, W) \mid D^s L_1 = 0\}$. Obviously, $D^s L_1 = 0$ if and only if $T = T_1$, $I = I_1$, $V = V_1$, and $W = W_1$. Thus, $M_2 = \{E_1\} = \{(T_1, I_1, V_1, W_1)\}$. Then, the invariance principal of LaSalle implies that $E_1$ is globally asymptotically stable when $R_1 \leq 1$ and $R_0 \leq 1 + \frac{d_2}{\rho}$. \( \square \)

Theorem 4 If $R_1 > 1$ and $d_1 T_1 - \rho I_2 \geq 0$, the second endemic steady state $E_2$ is globally asymptotically stable.
Proof. We introduce the Lyapunov function $L_2$ in the following way:

\[ L_2(t) = T_2 b\left(\frac{t}{T_2}\right) + I_2 b\left(\frac{I_2}{I_2}\right) + \frac{\beta_1 T_2 V_2}{\delta T_2} b\left(\frac{V_2}{V_2}\right) + \frac{\beta_1 q T_2 V_2 W_2}{g k \delta T_2} b\left(\frac{W_2}{W_2}\right) + \rho \frac{T_2}{2 (d_1 + d_2) T_2} \left[ (T(t) - T_2) + (I(t) - I_2) \right] . \]  

Considering system’s positive solutions, the derivative of $L_2$ is identified by

\[ D^\alpha L_2 \leq \left( 1 - \frac{T_2}{T} \right) D^\alpha T + \left( 1 - \frac{I_2}{I} \right) D^\alpha I + \frac{\beta_1 T_2 V_2}{k \delta T_2} \left( 1 - \frac{V_2}{V} \right) D^\alpha V + \frac{\beta_1 q T_2 V_2 W_2}{g k \delta T_2} \left( 1 - \frac{W_2}{W} \right) D^\alpha W + \rho \frac{T}{(d_1 + d_2) T_2} \left[ (T(t) - T_2) + (I(t) - I_2) \right] \left( D^\alpha T + D^\alpha I \right) . \]

At the equilibrium $E_2$, we have

\[ \lambda - \beta_1 T_2 V_2 - \beta_2 T_2 I_2 - d_1 T_2 + \alpha I_2 = 0, \]
\[ \beta_1 T_2 V_2 + \beta_2 T_2 I_2 - d_2 I_2 + \alpha I_2 = 0, \]
\[ k \delta T_2 - q V_2 W_2 - d_1 V_2 = 0, \]
\[ g V_2 W_2 - d_2 W_2 = 0. \]

Using the relation (42), we get

\[ D^\alpha L_2 \leq \left( 1 - \frac{T_2}{T} \right) \left[ \beta_1 T_2 V_2 + \beta_2 T_2 I_2 - \frac{\beta_1 T_2 V_2 I_2}{I_2} - \beta_2 T_2 I_2 \right] + \rho \frac{I_2}{(d_1 + d_2) T_2} \left[ (T(t) - T_2) + (I(t) - I_2) \right] \left[ d_1 (T - T_2) + d_2 (I - I_2) \right] . \]

Therefore

\[
D^\alpha L_2 \leq - \left[ d_1 T_2 - \rho I_2 + \rho I + \frac{\rho d_1 T}{d_1 + d_2} \right] \left( T - T_2 \right)^2
- \frac{\rho d_2}{(d_1 + d_2) T_2} \left( I - I_2 \right)^2
- \beta_1 T_2 V_2 \left[ \frac{T_2}{T} + \frac{I_2}{I_2} + \frac{T I}{T_2} - 3 \right]
- \beta_2 T_2 I_2 \left[ \frac{T}{T_2} + \frac{T_2}{T} - 2 \right].
\]

Thus, when $R_1 > 1$ and $d_1 T_2 - \rho I_2 \geq 0$ then $D^\alpha L_2 \leq 0$. Let $M_3$ be the largest invariant set in $\{(T, I, V, W) \mid D^\alpha L_2 = 0\}$. Clearly, $D^\alpha L_2 = 0$ if and only if $T = T_2$, $I = I_2$, $V = V_2$, and $W = W_2$. Hence $M_3 = \{E_2\} = \{(T_2, I_2, V_2, W_2)\}$. Then, the invariance principle of LaSalle implies that $E_2$ is globally asymptotically stable when $R_1 > 1$ and $d_1 T_2 - \rho I_2 \geq 0$. \hfill \qed

Numerical simulations and discussion

This section is devoted to validate the acquired theoretical results. First, we will introduce the numerical method to solve the aforementioned fractional model (2). Next, we will discuss different numerical simulations dealing of the equilibria stability.

Numerical method

It is easy to see that the fractional system (2) can be converted into

\[ \rho \left( 1 - \frac{T_2}{T} \right) \left( T - T_2 \right) = -\rho \left( \frac{T}{T_2} + \frac{T_2}{T} - 2 \right) \]
\[ + \frac{\rho}{T_2} (T - T_2) (I - I_2) . \]
where the functional $X$ is given in (9) and the functional $F$ is defined in (10). We consider the following uniform grid:

$$h = \frac{T}{N}, \quad T_m = mh, \quad t_0 = 0 \text{ and } T_m = T.$$  

(47)

For a given $t = t_{m+1}$, $m = 0, 1, 2, \ldots, N$, it follows

$$X(t_{m+1}) = X_0 + \frac{1}{I(a)} \int_0^t F(s, X(s))(t_{m+1} - s)^{a-1} \, ds$$

$$= X_0 + \frac{1}{I(a)} \sum_{k=0}^N \int_{t_k}^{t_{k+1}} F(s, X(s))(t_{m+1} - s)^{a-1} \, ds.$$  

(48)

To approximate the function $F(s, X(s))$, we take into account the Lagrange interpolation, the latter consists in dividing the interval $[t_k, t_{k+1}]$ in many subintervals and then, in each subinterval we use a lower order Lagrange interpolation. Authors in (Atangana and Owolabi 2018) used two subintervals to approximate the function. In this paper, we suggest to use three subintervals instead of two, for this, we consider the following Lagrange interpolant polynomial:

$$P_k(s) = \frac{(s - t_{k/2})(s - t_k)}{(t_{k-1} - t_{k/2})(t_{k-1} - t_k)} F(t_{k-1}, X(t_{k-1}))$$

$$\quad + \frac{(s - t_k)(s - t_{k/2})}{(t_k - t_{k/2})(t_k - t_{k/2})} F(t_{k/2}, X(t_{k/2}))$$

$$\quad + \frac{(s - t_{k/2})(s - t_{k-1})}{(t_{k-1} - t_{k/2})(t_{k-1} - t_{k-1})} F(t_{k-1}, X(t_{k-1}))$$

$$= \frac{2F(t_{k-1}, X(t_{k-1}))}{h^2} (s - t_{k/2})(s - t_k)$$

$$- \frac{4F(t_{1/2}, X(t_{1/2}))}{h^2} (s - t_{k-1})(s - t_k)$$

$$+ \frac{2F(t_k, X(t_k))}{h^2} (s - t_{k-1})(s - t_{k/2})$$

$$\approx \frac{2F(t_{k-1}, X_{k-1})}{h^2} (s - t_{k/2})(s - t_k)$$

$$- \frac{4F(t_{k/2}, X_{k/2})}{h^2} (s - t_{k-1})(s - t_k)$$

$$+ \frac{2F(t_k, X_k)}{h^2} (s - t_{k-1})(s - t_{k/2}),$$

(49)

where $t_{k/2} = (t_{k-1} + t_k)/2$. Substituting in Eq. (48), we get

$$X_{m+1} = X_0 + \frac{1}{I(a)} \sum_{k=0}^N \frac{2F(t_k, X_k)}{h^2} A_{a,k,1}$$

$$- \frac{1}{I(a)} \sum_{k=0}^N \frac{4F(t_{k+1}, X_{k+1})}{h^2} B_{a,k,2}$$

$$+ \frac{1}{I(a)} \sum_{k=0}^N \frac{2F(t_k, X_k)}{h^2} C_{a,k,3},$$

(50)

where

$$A_{a,k,1} = \int_{t_k}^{t_{k+1}} (s - t_{k/2})(s - t_k)(t_{m+1} - s)^{a-1} \, ds,$$

$$B_{a,k,2} = \int_{t_k}^{t_{k+1}} (s - t_{k-1})(s - t_k)(t_{m+1} - s)^{a-1} \, ds,$$

$$C_{a,k,3} = \int_{t_k}^{t_{k+1}} (s - t_{k-1})(s - t_{k/2})(t_{m+1} - s)^{a-1} \, ds.$$  

(51)

A simple integration leads to

$$A_{a,k,1} = \frac{h^{a+2}}{a(a+1)(a+2)}$$

$$\times \left[ (m + 1 - k)^{a+1} \left( \frac{3}{2}(a+2) + 2(m + 1 - k) \right) - (m - k)^{a+1} \left( \frac{3}{2}(a+1)(a+2) + 2(m - k)^2 \right) \right],$$

$$B_{a,k,2} = \frac{h^{a+2}}{a(a+1)(a+2)}$$

$$\times \left[ (m + 1 - k)^{a+1} (2m - 2k + a + 3) - (m - k)^{a+1} (2(a+1)(a+2) + 3(m - k) - (a+2) + 2(m - k)^2) \right],$$

$$C_{a,k,3} = \frac{h^{a+2}}{a(a+1)(a+2)}$$

$$\times \left[ (m + 1 - k)^{a+1} \left( \frac{3}{2}(a+2) + 2(m - k + 1) \right) - (m - k)^{a+1} (3a + 1) \right],$$

$$\times \left( a + 2 + \frac{7}{2}(a - 2)(m - k + 2)(m - k)^2 \right).$$

(52)

Substituting Eq. (52) in Eq. (50), we obtain

$$X_{m+1} = X_0 + \frac{m h^a F(t_k, X_k)}{I(a+3)} D_{m,k,a}$$

$$- \sum_{k=0}^m \frac{m h^a F(t_{k+1}, X_{k+1})}{I(a+3)} E_{m,k,a}$$

$$+ \sum_{k=0}^m m h^a F(t_k, X_k) F_{m,k,a},$$

(53)

where
\[ D_{m,k} = (m + 1 - k)^{\alpha + 1} \left( \frac{1}{2} (\alpha + 2) + 2(m + 1 - k) \right) \]
\[ - (m - k)^\alpha \left( \frac{3}{2} (\alpha + 1)(\alpha + 2) + \frac{5}{2}(m - k)(\alpha + 2) + 2(m - k)^2 \right) \]
\[ E_{m,k} = (m + 1 - k)^{\alpha + 1} (2m - 2k + \alpha + 3) \]
\[ - (m - k)^\alpha \left( 2(\alpha + 1)(\alpha + 2) + 3(m - k)(\alpha + 2) + 2(m - k)^2 \right) \]
\[ F_{m,k} = (m + 1 - k)^{\alpha + 1} \left( \frac{3}{2} (\alpha + 2) + 2(m - k + 1) \right) \]
\[ - (m - k)^\alpha \left( 3(\alpha + 1)(\alpha + 2) + \frac{7}{2}(\alpha + 2)(m - k) + 2(m - k)^2 \right). \]

(54)

**Numerical simulations**

By applying the numerical method shown in the previous subsection, with the parameters listed in Table 1, we will perform different numerical simulations to show numerically the stability of each equilibrium.

**Disease-free equilibrium stability**

This part of numerical simulations is devoted to show numerically the stability of the disease-free equilibrium. Indeed, we will choose some adequate parameters that verify the condition of the basic reproduction number is less than unity. For this reason, we will take into consideration the parameters as shown in the second column of Table 1. For different values of \( \alpha \), Fig. 2 indicates that the curves which describe the density of susceptible, infected cells, the virions and the B cells converge, respectively, towards the coordinates of the DFE; \( E_f = (100, 0, 0, 0) \). In this case, we find that the value of the basic reproduction number is \( \mathcal{R}_0 = 0.5775 < 1 \), i.e., the conditions of the Theorem 2 are verified, which ensures that the theoretical and numerical results are coherent. From this first numerical result, we observe that the uninfected cells are increasing progressively to reach their maximal value, which is \( \lambda / d_1 = 100 \). However, the other problem variables are vanishing towards zero. This finding result indicates that the infection will eventually be cleared if there is an insufficient generation of virions and infected cells, which are needed for the persistence of infection. We observe that the fractional order derivative value has no effect on the stability of the DFE but only on the convergence speed toward the steady state.

**Table 1** The list of parameter values for the numerical simulations

| Parameters | Fig. 2 | Fig. 3 | Fig. 4 | Sources |
|------------|-------|-------|--------|---------|
| \( \lambda \) | 1 | 1 | 10 | Pan and Chakrabarty (2018) |
| \( \beta_1 \) | 0.01 | 0.01 | 0.01 | Pan and Chakrabarty (2018) |
| \( \beta_2 \) | 0.001 | 0.01 | 0.01 | Pan and Chakrabarty (2018) |
| \( d_1 \) | 0.01 | 0.01 | 0.01 | Pan and Chakrabarty (2018) |
| \( d_2 \) | 1 | 0.5 | 1 | Pan and Chakrabarty (2018); Reyes-Silveyra and Mikler (2016) |
| \( d_3 \) | 6 | 6 | 6 | Pan and Chakrabarty (2018) |
| \( d_4 \) | 0.3 | 0.3 | 0.3 | Pan and Chakrabarty (2018) |
| \( \rho \) | 0.01 | 0.01 | 0.01 | Pan and Chakrabarty (2018) |
| \( k \) | 2.9 | 2.9 | 2.9 | Pan and Chakrabarty (2018) |
| \( q \) | 0.006 | 0.006 | 0.006 | Pan and Chakrabarty (2018) |
| \( g \) | 0.1 | 0.1 | 0.1 | Pan and Chakrabarty (2018) |

**The first endemic steady state stability**

This second part of numerical simulations is dedicated to show numerically the stability of the first endemic equilibrium. Indeed, we will choose some adequate parameters that verify the condition of the basic reproduction number is greater than unity and the viral reproduction number is less than unity. For this reason, we will take into consideration the parameters as shown in the third column of Table 1. During a period of several days, the viral dynamics of the HCV infection is depicted in Fig. 3. The latter indicates that there is a convergence towards the first endemic steady state \( E_1 = (34.3820, 1.3124, 0.6343, 0) \). In other words, since the conditions of the Theorem 3 are verified;
\[ R_1 = 0.2641 < 1 < R_0 = 2.9085 < 1 + \frac{d}{\rho} = 51, \]
we can say that the numerical simulation confirms the theoretical result. From this figure, we observe that all the problem variables are oscillating in time. A damped oscillation are observed during the progress of the infection. The B cells are vanishing toward zero after successive oscillations. Oppositely, the uninfected cells, the infected cells and the virus load converge towards a strictly positive level. In addition, we observe that the B cells are not activated in the humoral immune response, since there no sufficient quantity of HCV virions. Despite the fractional order derivative value takes four different values, all the curves of each variable converge toward the same steady state which prove that fractional derivative order has no effect on the stability of \( E_1 \). More precisely, the decrease in the value of \( \alpha \) leads to a fast convergence of the solutions towards \( E_1 \).

The second endemic steady state stability

The purpose of this third part is to numerically demonstrate the stability of the second infected equilibrium. For this reason, we need to consider parameters that verify the finding theoretical conditions mentioned in Theorem 4, which is the case for parameters listed above in the third column in Table 1. Figure 4 describes the behavior of HCV infection in the host; the trajectories \( T, I, V \) and \( W \) converge towards the coordinates of \( E_2 = (76.2402, 9.2376, 3.0000, 488.2796) \), respectively. In this case, we have the following conditions \( R_1 = 1.4883 > 1 \) and \( d_i T_2 - \rho I_2 = 0.6700 \leq 0, \) this confirms that the second endemic steady state is globally asymptotically stable, which is announced before in Theorem 4. We observe that the curves of all the four problem variables the uninfected cells, the infected ones, the viral load and the B cells oscillate before approaching towards their respective coordinates of the second endemic equilibrium \( E_2 \). Besides, we remark that in the case of the equilibrium \( E_2 \), the environment provide sufficient level of HCV virions, and consequently the B cells are activated to destroy them. This numerical result is presented for four different values of the fractional-order, namely, \( \alpha = 0.5, \alpha = 0.7, \alpha = 0.9 \) and \( \alpha = 1 \). We notice that for all this different values of \( \alpha \), the stability of \( E_2 \) is acquired. Hence, the stability of this steady state is not influenced by the value of the fractional-order \( \alpha \). More precisely, we remark that the decrease in the value of \( \alpha \), leads to a fast convergence of the solution towards \( E_2 \).

Conclusions

The present paper studied an HCV fractional-order model with the Caputo fractional derivative. The model incorporates four fractional derivative equations representing the interaction between the susceptible hepatocytes, the infected ones, the HCV free virions and the humoral immune response. In fact, we have attempted to formulate an HCV fractional-order model, which incorporates both modes of transmission of the infection, the virus-to-cell and cell-to-cell and takes into consideration the effect of the cure rate of infected cells and the effect of the humoral immunity. The results of the paper have started with proving

![Fig. 3 Infection dynamics showing the stability of the first endemic equilibrium \( E_1 \) for different values of \( \alpha \)](image1)

![Fig. 4 Infection dynamics showing the stability of the second endemic equilibrium \( E_2 \) for different values of \( \alpha \)](image2)
some basic analytical results, like positivity and boundedness of solutions and finding the equilibria. It moves then to finding some important thresholds, which are the basic reproduction number $R_0$, the viral reproduction number in the chronic stage of the HCV infection $R_1$ and the humoral immune reproduction number $R_p$. It is clear that the formula of the basic reproduction number of our model reveals that if we neglect either cell-to-cell transmission or virus-to-cell transfer, then the value of the basic reproduction number might not be significant. The global stability of the equilibria are proved by applying the Lyapunov approach and La-Salle’s fractional invariance principle. To achieve numerical simulations, a numerical method is established using a three-step Lagrange polynomial interpolation method. The numerical simulations are given for two purposes; first, the three-step Lagrange polynomial interpolation method. The numerical simulations indicate that the effect of the fractional order on the HCV viral dynamical behavior. The numerical simulations indicate that the theoretical results and the numerical ones are in good agreement and that the changing in the value of $\alpha$ has no effect on the stability of all equilibrium points. Effectively, we have observed that the fractional order derivative value has no effect on the stability of the steady states but only on the convergence speed toward the related equilibrium. More precisely, as long as the value of $\alpha$ is small, as long as the convergence is fast. Moreover, smaller values of the fractional derivative order of the system leads to a faster convergence of its solution towards the equilibrium points.

Data availability The manuscript has no associated data.

Declarations

Conflict of interest The authors declare no conflict of interest.

References

Ahmed E, El-Saka HA (2010) On fractional order models for Hepatitis C. Nonlinear Biomed Phys 4(1):1. https://doi.org/10.1186/1753-4631-4-1
Alberts B, Johnson A, Lewis J (2002) Molecular biology of the cell. 4th edn. Garland, New York
Alla Hamou A, Azroul E, Lamrani Alaoui A (2021) Fractional model and numerical algorithms for predicting COVID-19 with isolation and quarantine strategies. Int J Appl Comput Math 7(4):142. https://doi.org/10.1007/s40819-021-01866-3
Atangana A, Baleanu D (2016) New fractional derivatives with nonlocal and non-singular kernel: theory and application to heat transfer model. arXiv preprint arXiv:1602.03408
Atangana A, Owolabi KM (2018) New numerical approach for fractional differential equations. Math Model Nat Phenom 13(1):3
Barros LCD, Lopes MM, Pedro FS, Esmi E, Santos JPCD, Sánchez DE (2021) The memory effect on fractional calculus: an application in the spread of COVID-19. Comput Appl Math 40(3):72. https://doi.org/10.1007/s40314-021-01456-z
Boulaaras S, Jan R, Khan A, Ahsan M (2022) Dynamical analysis of the transmission of dengue fever via Caputo-Fabrizio fractional derivative. Chaos Solit Fract X 8:100072
Brimacome CL, Grove J, Meredith LW, Hu K, Syder AJ, Flores MV, Timpe JM, Krieger SE, Baumert TF, Tellinghuisen TL, Wong-Staal F, Balfe P, McKeating JA (2011) Neutralizing antibody-resistant hepatitis C virus cell-to-cell transmission. J Virol 85(1):596–605. https://doi.org/10.1128/JVI.01592-10
Carvalho AR, Pinto CM, Baleanu D (2018) HIV/HCv coinfection model: a fractional-order perspective for the effect of the HIV viral load. Adv Differ Equ 1:2. https://doi.org/10.1186/s13662-017-1456-z
Chatterjee AN, Ahmad B (2021) A fractional-order differential equation model of COVID-19 infection of epithelial cells. Chaos Solit Fract 147:110952 https://doi.org/10.1016/j.chaos.2021.110952
Chen W, Sun H, Li X et al (2022) Fractional derivative modeling in mechanics and engineering. Springer, New York
Dahari H, Major M, Zhang X, Mihalik K, Rice CM, Perelson AS, Feinstone SM, Neumann AU (2005) Mathematical modeling of primary hepatitis C infection: noncytolytic clearance and early blockage of virion production. Gastroenterology 128(4):1056–1066. https://doi.org/10.1053/j.gastro.2005.01.049
Dhar M, Samaddar S, Bhattacharya P (2021) Modeling the cell-to-cell transmission dynamics of viral infection under the exposure of non-cytolytic cure. J Appl Math Comput 65(1):885–911. https://doi.org/10.1007/s12190-020-01420-w
Dubey B, Dubey P, Dubey US (2016) Modeling the intracellular pathogen-immune interaction with cure rate. Commun Nonlinear Sci Numer Simul 38:72–90. https://doi.org/10.1016/j.cnsns.2016.02.007
Dunia R, Bonnecaze R (2013) Mathematical modeling of viral infection dynamics in spherical organs. J Math Biol 67(6):1425–1455. https://doi.org/10.1007/s00285-012-0593-y
Gharahasanlou TK, Roomi V, Hemmatzadeh Z (2022) Global stability analysis of viral infection model with logistic growth rate, general incidence function and cellular immunity. Math Comput Simul 194:64–79. https://doi.org/10.1016/j.matcom.2021.11.015
Goyal A, Liao LE, Perelson AS (2019) Within-host mathematical models of hepatitis B virus infection: past, present, and future. Curr Opin Syst Biol 18:27–35. https://doi.org/10.1016/j.coisb.2019.10.003
Huo J, Zhao H, Zhu L (2015) The effect of vaccines on backward bifurcation in a fractional order HIV model. Nonlinear Anal Real World Appl 26(Complete):289–305. https://doi.org/10.1016/j.nonrwa.2015.05.014
Karaman B (2022) The global stability investigation of the mathematical design of a fractional-order HBV infection. J Appl Math Comput. https://doi.org/10.1007/s12190-022-01721-2
Khan H, Alam K, Gulzar H, Etemad S, Rezapour S (2022) A case study of fractional-fractional tuberculosis model in China: existence and stability theories along with numerical simulations. Math Comput Simul 198:455–473
Khodabakhshi N, Vaempour SM, Baleanu D (2017) On dynamics of fractional-order model of HCV infection. J Math Anal 8(1):16–27
Lin W (2007) Global existence theory and chaos control of fractional differential equations. J Math Anal Appl 332(1):709–726. https://doi.org/10.1016/j.jmaa.2006.10.040
Mojaver A, Kheiri H (2016) Dynamical analysis of a class of hepatitis C virus infection models with application of optimal control. Int
