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Analysis of fractional-order models for hepatitis B

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Abstract This paper presents two models for hepatitis B, both given by fractional differential equations. The first model is formulated without parameters that indicate drug therapy, while the second one considers the drug therapy. The basic reproduction number and the stability analysis are considered for both models. Moreover, some numerical simulations by nonstandard finite difference schemes are presented. The numerical results show that the solutions converges to an equilibrium point as predicted in the stability analysis.

Keywords Fractional modeling · Hepatitis B · Fractional calculus · Fractional stability

Mathematics Subject Classification Primary 06B10; Secondary 06D05

1 Introduction

The hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major global health problem that affects approximately one hundred million people (Ferreira 2000). It can cause chronic infection and puts people at high risk of death from cirrhosis and liver cancer. For example, in Brazil at least 15% of population

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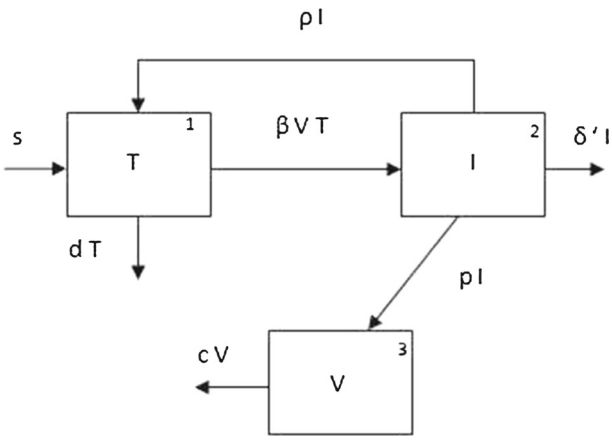

Fig. 1 Diagrammatic representation of the mathematical model for hepatitis B without therapy

have been infected with the virus and about 1% with the chronic liver disease (Forde et al. 2016; Lewin et al. 2001). The transmission can occur through sexual relationships and blood transmission. The main symptoms are fever, fatigue, loss of appetite, nausea, vomiting among others (Degertekin and Lok Anna 2009; Ferreira 2000).

Mathematical models have been used to analyze viral infection dynamics of HIV and hepatitis B and C over time. Especially for hepatitis B, there are a lot of mathematical models which describe the dynamics of this disease (Ciupe 2007; Forde et al. 2016; Zhou and Sun 2014). These models, usually, are given by a ordinary differential equation (ODE) system usually considering three state variables at the time t: target cells, $T(t)$, infected cells, $I(t)$, and free virus, $V(t)$. Most of these models do not consider parameters that include drug therapy in its formulation (Ciupe 2007; Degertekin and Lok Anna 2009; Forde et al. 2016). Figure 1 shows the schematic representation of this disease.

Therefore, the dynamics of the model are governed by the following classical system of ODE equations:

$$\begin{cases} T'(t) = \bar{s} - \bar{d}T - \bar{\beta}VT + \bar{\rho}I \\ I'(t) = \bar{\beta}VT - \bar{\delta}'I - \bar{\rho}I \\ V'(t) = \bar{p}I - \bar{c}V \end{cases} \tag{1}$$

where $\bar{d}$ is the death rate of target cells, $\bar{\delta}'$ is death rate of infected cells, $\bar{\rho}$ rate of cure, i.e., noncytolytic loss of infected cells, $\bar{\delta} = \bar{\delta}' + \bar{\rho}$ net loss rate of infected cells, $\bar{c}$ free virus clearance rate, $\bar{p}$ is the rate of production of virus per infected cell, $\bar{\beta}$ rate of infection of new target cells and $\bar{s}$ rate of production of new target cells. The units of all the parameters are time^{-1}. Initial values for $T(t)$, $I(t)$, $V(t)$ have to be considered, $T(0)$, $I(0)$, $V(0)$, respectively.

Several studies (Lewin et al. 2001; Nowak et al. 1996) have modified model (1) to include antiviral drug therapy. Treatment with some drug inhibits the formation of new virion. This means that under drug therapy the production rate of new virion, $\bar{p}$, is decreased. Since the drug efficacy is $\bar{\epsilon}$, then under therapy the production virion rate is $(1 - \bar{\epsilon})\bar{p}$. When the drug is 100% ($\bar{\epsilon} = 1$) efficient, it leads to the complete suppression of new virion production. To incorporate the possibility of therapy affecting infection, a parameter that accounts for the

efficacy of the drug in blocking new infection is introduced, $\bar{c}$, so that the infection rate in the presence of drug is $(1-\bar{c})\bar{\beta}$ (Ferreira 2000; Lewin et al. 2001).

On the other hand, the non-integer order calculus, i.e., the branch of calculus that deals with derivatives and integrals of non-integer order, traditionally known as fractional calculus (FC) (Camargo and de Oliveira 2015; Debnath 2003; Ortigueira and Machado 2015; Podlubny 1999), has played a fundamental role in the modeling of several problems. Since fractional derivatives are not local operators, they proved to be accurate to describe processes with memory, i.e., calculating time-fractional derivative at point time requires the previous time (Camargo and de Oliveira 2015), as is the case of many biological systems (Arafa et al. 2016). Besides, fractional differential equation is a possible tool to reduce the errors arising from the neglected parameters in the usual modeling of real-life phenomena (Diethelm 2004; Matignon 1996; Kuroda et al. 2017; Okyene and Oduro 2016; Podlubny 1999; Varalta et al. 2014).

For example, in medicine, it has been shown that the electrical conductance of the membranes of cells of biological organism have fractional order. As a result, they can be classified into groups of non-integer order models (Varalta et al. 2014). Fractional derivatives embody essential features of cell rheological behavior and have enjoyed greatest success in the field of rheology (Arafa et al. 2016). Besides that, models in HIV made it clear that fractional models are more approximate than their integer order form (Arafa et al. 2016; Diethelm et al. 2005).

This paper proposes and solves a fractional version of the usual models for hepatitis B and is organized as follows. In Sect. 2, some definitions of fractional calculus in the sense of Riemann–Liouville, Caputo and Grunwald–Letnikov are presented. In Sect. 4, the fractional models are presented in terms of fractional differential equations (FDE) and the stability is analyzed. In Sect. 5, some numerical simulations are shown. Finally, Sect. 6 brings the concluding remakes.

2 Preliminary concepts

In this section, some basic definitions, special functions and properties of the FC are presented.

Definition 2.1 Let $f:\mathbb{R}\to\mathbb{R}$ be a differential function and $\alpha\in\mathbb{C}$ such that $Re(\alpha)>0$. The Riemann–Liouville operator of order α of $f(t)$, $t\in\mathbb{R}$, denoted by $I^{\alpha}f(t)$, is defined as[1]

$$I^{\alpha}f(t)=\phi_{\alpha}(t)*f(t)=\int_0^t\frac{(t-\tau)^{\alpha-1}}{\Gamma(\alpha)}f(\tau)\,\mathrm{d}\tau, \tag{2}$$

where the symbol $*$ denotes the Laplace convolution and $\phi_{\alpha}(t)$ is the Gel'fand–Shilov function, defined for $\alpha\notin\mathbb{Z}_-$, as $\phi_{\alpha}(t)=\begin{cases}\dfrac{t^{\alpha-1}}{\Gamma(\alpha)}, & \text{if } t\geq 0\\ 0, & \text{if } t<0\end{cases}$ and $\Gamma(\alpha)$ is the Gamma function.

For convenience, we defined $I^0f(t)=f(t)$.

Definition 2.2 Let $f:\mathbb{R}\to\mathbb{R}$ be an differential function, $\alpha\in\mathbb{C}$ with $Re(\alpha)>0$ and m the natural number, such that, $m-1<Re(\alpha)\leq m$. The Caputo fractional derivative of order α

[1] Note that, from Definition 2, that $I^{\alpha}t^{\beta}=t^{\beta+\alpha}\Gamma(\beta+1)/\Gamma(\beta+\alpha+1)$, i.e., the polynomial case is a recovered if $\alpha,\beta\in\mathbb{N}$.

is defined as

$$D^{\alpha} f(t) = I^{m-\alpha} D^{m} f(t) = \phi_{m-\alpha} * D^{m} f(t). \tag{3}$$

Since $I^{0} f(t) = f(t)$, if $\alpha \in \mathbb{N}$ then the usual derivative is recovered. Also from Definition 2.2, $D^{\alpha} t^{\beta} = \frac{t^{\beta-\alpha}\Gamma(\beta+1)}{\Gamma(\beta-\alpha+1)}$, i.e., the classical result is obtained if $\alpha = m$ and $\beta = n$, with $n, m \in \mathbb{N}$, including the case where β is zero, i.e., the derivative of the constant function is zero.[2]

2.1 Laplace transform

Let $\alpha \in \mathbb{C}$ and m be like in Definition 2.2, then from Eq. (3) and Laplace convolution theorem, the Laplace transform of Caputo Fractional derivative of order α is obtained as follows:

$$\begin{aligned} \mathfrak{L}[D^{\alpha} f(t)] &= \mathfrak{L}[\phi_{m-\alpha} * D^{m}] \\ &= \mathfrak{L}[\Phi_{m-\alpha}(t)]\, \mathfrak{L}[D^{m}] \\ &= s^{\alpha-m}\, \mathfrak{L}[D^{m} f(t)]. \end{aligned}$$

As a result,

$$\mathfrak{L}[D^{\alpha} f(t)] = s^{\alpha} F(s) - \sum_{k=0}^{n-1} f^{(k)}(0) s^{\alpha-k-1}. \tag{4}$$

2.2 Mittag–Leffler functions

Here we present the Mittag–Leffler functions.

Definition 2.3 The classical Mittag–Leffler function (MLF) and its generalization with two parameters are complex functions, defined for all $z \in \mathbb{C}$, depending on a complex parameters and defined, respectively, as

$$E_{\alpha}(z) = \sum_{n=0}^{\infty} \frac{z^{n}}{\Gamma(n\alpha+1)}, \quad E_{\alpha,\beta}(z) = \sum_{n=0}^{\infty} \frac{z^{n}}{\Gamma(\alpha n+\beta)}, \quad Re(\alpha),\ Re(\beta) > 0. \tag{5}$$

It comes from Eq. (5) that $E_1(z) = e^{z}$ and $E_{\alpha,1}(z) = E_{\alpha}(z)$. Besides that, the classical MLF function recovers the most important aspect of the exponential function, i.e., taking the Caputo fractional derivative we obtain

$$\frac{\mathrm{d}^{\alpha}}{\mathrm{d}t^{\alpha}} E_{\alpha}(t^{\alpha}) = E_{\alpha}(t^{\alpha}).$$

This is the reason why some authors refer to MLF functions as the fractional generalization of the exponential function (Camargo and de Oliveira 2015).

The Laplace transform to MLF function with two parameters is given by

$$\mathfrak{L}\left[t^{\beta-1} E_{\alpha,\beta}(a\, t^{\alpha})\right] = \frac{s^{\alpha-\beta}}{s^{\alpha}-a} \quad \text{and} \quad \mathfrak{L}^{-1}\left[\frac{s^{\alpha-\beta}}{s^{\alpha}-a}\right] = t^{\beta-1} E_{\alpha,\beta}(a\, t^{\alpha}). \tag{6}$$

where $|a/s^{\alpha}| < 1$. For recovering the Laplace transform of the classical MLF function, consider $\beta = 1$ in the previous equations (Camargo and de Oliveira 2015).

[2] This fact is one of the main differences between the fractional derivatives of Camargo and de Oliveira (2015).

3 Grunwald–Letnikov operator

Next operator is very useful to obtain numerical solutions of fractional differential equations.

Definition 3.1 The Grunwald–Letnikov operator (GL) is given by

$$D^{\alpha}_{GL} f(t) = \lim_{h \to 0} h^{-\alpha} \sum_{j=0}^{[k]} w_j^{(\alpha)} f(t - jh) \quad t \in [0, t_f], \tag{7}$$

where $0 < \alpha < 1$, $[k]$ is the integer part $k = \frac{t-a}{h_k}$, a and t are the real limits of operator D^{α}, which denote the fractional derivative, $h_k > 0$ is the step-size, t_f is the final time and $w_j^{(\alpha)}$ are the weights the coefficients in the power series expansion of $(1 - \xi)^{\alpha}$, i.e.,

$$(1 - \xi)^{\alpha} = \sum_{j=0}^{\infty} w_j^{(\alpha)} \xi^j, \quad w_j^{\alpha} = \frac{\Gamma(j - \alpha)}{\Gamma(-\alpha)\Gamma(j + 1)}$$

and, from a practical point of view, they can be evaluated recursively by means of the following recurrence:

$$w_0^{(\alpha)} = 1\,, \quad w_j^{(\alpha)} = \left(1 - \frac{1 + \alpha}{j}\right) w_{j-1}^{(\alpha)}\,, \quad j = 1, 2, \ldots \tag{8}$$

$$w_0^{(\alpha-1)} = 1\,, \quad w_j^{(\alpha-1)} = \left(1 - \frac{\alpha}{j}\right) w_{j-1}^{(\alpha-1)}\,, \quad j = 1, 2, \ldots. \tag{9}$$

Lemma 3.2 *Let* $0 < \alpha < 1$ *and* $w_n^{(\alpha)}$, $w_n^{(\alpha-1)}$ *be the weights of GL operator. Then for any* $n = 1, 2, \ldots - 1 < w_n^{(\alpha)} < 0$ *and* $0 < w_n^{(\alpha-1)} < 1$.

4 Fractional modeling of hepatitis B

Now we will present two fractional models for hepatitis B, the first model is presented without the drug therapy, while the second one has parameters that simulate the drug effect in the dynamics of the disease. Both models are based on model (1) presented by Lewin et al. (2001).

The main motivation of considering a fractional-order hepatitis B model in this paper is that FC has a relation with memory system. Such cells learn from their experience of fighting any threat. So when we use models with ordinary differential equations, these memory effects are neglected (Forde et al. 2016; Kuroda et al. 2017; Salman and Yousef 2017; Varalta et al. 2014).

4.1 Model of hepatitis B virus (HBV) without drug therapy

To consider the fractional version of the system (1), it is relevant to analyze the dimensions, so the fractional system does not produce inconsistencies. Indeed, there are several equivalent ways to take this in count; for example, in Dokoumetzidis et al. (2010), the authors transform a system of ODEs into a system of integral equation and by choosing an appropriated kernel (in terms of the Gel'fand–Shilov function) introduce the Riemann–Liouville fractional integrals (Podlubny 1999), finally, taking the usual derivative a system of FDEs, with appropriated dimensions and Riemann–Liouville derivatives is obtained.

Since in our applications $\frac{\mathrm{d}}{\mathrm{d}t}$ has the unit of day^{-1}, $\frac{\mathrm{d}^\alpha}{\mathrm{d}t^\alpha}$ has the unit of day$^{-\alpha}$, taking $0 < \alpha \leq 1$ and τ a parameter that possesses the dimension of day, then the unit of $\left[\frac{1}{\tau^{1-\alpha}} \frac{\mathrm{d}^\alpha}{\mathrm{d}t^\alpha}\right]$ is day^{-1} (Podlubny 2002). As a result, the fractional version of Eq. (1) can be introduced in the following way (Gómez et al. 2012):

$$\begin{cases} \frac{1}{\tau^{1-\alpha}} D^\alpha T(t) = \bar{s} - \bar{d}T - \bar{\beta}VT + \bar{\rho}I \\ \frac{1}{\tau^{1-\alpha}} D^\alpha I(t) = \bar{\beta}VT - \bar{\delta}'I - \bar{\rho}I \\ \frac{1}{\tau^{1-\alpha}} D^\alpha V(t) = \bar{p}I - \bar{c}V. \end{cases} \tag{10}$$

Naturally, if $a = \tau^{1-\alpha}\,\bar{a}$, for every constant a, we may rewrite the system as

$$\begin{cases} D^\alpha T(t) = s - dT - \beta VT + \rho I \\ D^\alpha I(t) = \beta VT - \delta' I - \rho I \\ D^\alpha V(t) = pI - cV. \end{cases} \tag{11}$$

where D^α is Caputo derivative of order α, $0 < \alpha \leq 1$. The meaning of the parameters are similar to system (1) presented in Sect. 1. Note that now the units of the each parameter in system (11) are time$^{-\alpha}$ and each one of them depends on τ (Dokoumetzidis et al. 2010).

To prove that the solution of system (11) is non-negative, we introduce the following Lemmas.

Lemma 4.1 *Generalized mean value theorem* (Odibat and Shawagfeh 2007). *Suppose that* $f(x) \in \mathbb{C}[a, b]$ *and* $D^\alpha f(x) \in \mathbb{C}(a, b]$, *for* $0 < \alpha \leq 1$, *then*

$$f(x) = f(a) + \frac{1}{\Gamma(\alpha)}(D^\alpha f)(\xi)(x - a)^\alpha$$

where $a \leq \xi \leq x$, *for all* $x \in (a, b]$.

Lemma 4.2 *Assume that* $f(x) \in \mathbb{C}[a, b]$ *and* $D^\alpha f(x) \in \mathbb{C}(a, b]$ *for* $0 < \alpha \leq 1$. *If* $D^\alpha f(x) \geq 0$, *for all* $x \in (a, b)$, *then* $f(x)$ *is nondecreasing for each* $x \in [a, b]$. *If* $D^\alpha f(x) \leq 0$, *for all* $x \in (a, b)$, *so* $f(x)$ *in non-increasing for each* $x \in [a, b]$.

Theorem 4.3 *There is a unique solution to system* (11) *and the solution will remain in* $\mathbb{R}^3_+$.

The proof of existence and unity can be seen in Odibat and Shawagfeh (2007). In the following, we will show that the domain $\mathbb{R}^3_+$ is a positively invariant set.

Proposition 4.4 *The region* $\Omega = \{(T(t), I(t), V(t)) : 0 \leq T(t) + I(t) \leq 1\,, 0 \leq V(t) \leq 1\}$ *is a positively invariant set for system* (11).

Proof Suppose $T(0) + I(0) \leq 1$ and $V(0) \leq 1$. Then, in the system (11), we get

$$\begin{aligned} D^\alpha(T(t) + I(t)) &= s - dT(t) - \delta' I(t) \\ &\leq s + dT(t) + dI(t). \end{aligned}$$

From the Laplace transform properties

$$\mathfrak{L}[T(t) + I(t)] \leq \frac{\lambda^{-1}s}{\lambda^\alpha - d} + \frac{\lambda^{\alpha-1}}{\lambda^\alpha - d}[T(0) + I(0)],$$

where λ is the Laplace transform parameter and $Re(\lambda) > 0$. We can rewrite last inequality as

$$\mathfrak{L}[T(t) + I(t)] \leq \frac{\lambda^{\alpha-(1+\alpha)}s}{\lambda^{\alpha} - d} + \frac{\lambda^{\alpha-1}}{\lambda^{\alpha} - d}[T(0) + I(0)]. \tag{12}$$

Applying $\mathfrak{L}^{-1}$ we have

$$\begin{aligned}\mathfrak{L}^{-1}[\mathfrak{L}[T(t) + I(t)]] &\leq \mathfrak{L}^{-1}\left[\frac{s\lambda^{\alpha-(1+\alpha)}}{\lambda^{\alpha} - d}\right] + \mathfrak{L}^{-1}\left[\frac{\lambda^{\alpha-1}}{\lambda^{\alpha} - d}\right][T(0) + I(0)] \\ &\leq t^{(1+\alpha)-1}E_{\alpha,1+\alpha}(dt^{\alpha})s + E_{\alpha,1}(dt^{\alpha}).\end{aligned}$$

Using the identity to ML function, $E_{\alpha,\beta}(z) = zE_{\alpha,\alpha+\beta}(z) + \dfrac{1}{\Gamma(\beta)}$, Machado (2003)

$$T(t) + I(t) \leq [t^{2\alpha}sd + 1]E_{\alpha,1}(dt^{\alpha}) + 1$$

From convergence of ML function (Machado 2003), we conclude $0 \leq T(t) + I(t) \leq 1$. Using the same sort of calculation, we can show that $0 \leq V(t) \leq 1$.

4.2 Equilibria and asymptotical stability

Now the existence and stability of the equilibrium points of system (11) is presented. To prove the locally asymptotical stability of equilibria of system (11), the following Theorem is useful.

Theorem 4.5 (Ahmed et al. 2007) *The equilibrium* (x^*, y^*) *of the following fractional-order differential system*

$$\begin{cases} D^{\alpha}x(t) = f_1(x(t), y(t)) \\ D^{\alpha}y(t) = f_2(x(t), y(t)) \\ x(0) = x_0, \quad y(0) = y_0. \end{cases} \tag{13}$$

is locally asymptotically stable if all the eigenvalues of the Jacobian matrix, J*, evaluated at the equilibrium satisfy the following condition* $|\arg(\lambda_i)| > \dfrac{\alpha\pi}{2}$.

Theorem 4.6 *System* (11) *has the disease-free equilibrium point*

$$\overline{P}_0 = (\overline{T}_0, \overline{I}_0, \overline{V}_0) = \left(\frac{s}{d}, 0, 0\right), \tag{14}$$

for all the values of the parameters in this system, whereas only if $R_0 > 1$*, there is (unique) endemic equilibrium point as*

$$\begin{aligned}\overline{P}_1 &= (\overline{T}_1, \overline{I}_1, \overline{V}_1), \\ \overline{T}_1 &= \frac{-c(\delta' + \rho)}{p\beta}, \\ \overline{I}_1 &= \frac{\beta ps - cd(\delta' - \rho)}{\beta p\delta'}, \\ \overline{V}_1 &= \frac{sp}{\delta' c} - \frac{d(\delta' - \rho)}{\beta\delta.}.\end{aligned} \tag{15}$$

4.2.1 The basic reproduction number R_0

Definition 4.7 The basic reproduction number, denoted by R_0, is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual.

Remark 4.8 For simple infectious processes, this parameter determines a threshold, that is, if $R_0 > 1$ an initial infection generates a secondary infection, i.e., a proliferation of the disease is spectated. On the other hand, if $R_0 < 1$ an initial infection creates less than one secondary infection, it causes the extinction of the disease (Diekmann et al. 2009; Dietz 1983).

Remark 4.9 The basic reproduction number, R_0, for hepatitis B is the number of new infected cells that will appear from a single infected cell.

Motivated by Driessche and Watmough (2002) we calculate this parameter to system (11). Consider the follow system, which describes two populations, $I(t)$ and $V(t)$. The first one represents the production of new infections and the second one gets the change in the state of infected individuals.

$$\begin{cases} D^\alpha I(t) = \beta V(t)T(t) - \delta' I(t) - \rho I(t) \\ D^\alpha V(t) = pI(t) - cV(t) \end{cases} \tag{16}$$

Computing the Jacobian matrix of system (16) evaluated at the disease-free point (14), we get F and V matrices.

$$F = \begin{vmatrix} 0 & \beta\frac{s}{d} \\ p & 0 \end{vmatrix}, \quad V = \begin{vmatrix} -\delta' - \rho & 0 \\ 0 & -c \end{vmatrix}. \tag{17}$$

Then, $K = -V^{-1}F = \begin{vmatrix} 0 & \beta\dfrac{s}{d(\delta'+\rho)} \\ \dfrac{p}{c} & 0 \end{vmatrix}$. The eigenvalues of K are

$$\lambda_1 = +\sqrt{\frac{p\beta s}{c(\delta'+\rho)d}}, \quad \lambda_2 = -\sqrt{\frac{p\beta s}{c(\delta'+\rho)d}}.$$

Therefore,[3]

$$R_0 = \frac{p\beta s}{c(\delta'+\rho)d}. \tag{18}$$

Theorem 4.10 *The disease-free equilibrium $\overline{P}_0$ is locally asymptotically stable if $R_0 < 1$.*

Proof Computing the Jacobian matrix of system (11) evaluated at the disease-free point, $\overline{P}_0$, one gets

$$J(\overline{P}_0) = \begin{vmatrix} -d & \rho & -\frac{\beta s}{d} \\ 0 & \delta' - \rho & \frac{s\beta}{d} \\ 0 & p & -c \end{vmatrix}. \tag{19}$$

[3] As made in Driessche and Watmough (2002) the basic reproduction number will be the biggest eigenvalue of K. For convenience, we omit the square root.

and consequently, the eigenvalues of $J(\overline{P}_0)$ are

$$\lambda_1 = -d,\ \lambda_2 = \frac{-(\delta+c)-\sqrt{\Delta}}{2},\ \lambda_3 = \frac{-(\delta+c)+\sqrt{\Delta}}{2}$$

where

$$\begin{aligned}\Delta &= (\delta+c)^2 + 4\beta\frac{s}{d}p - 4c\delta.\\ &= \delta^2 + 2\delta c + c^2 + 4\beta\frac{s}{d}p - 4c\delta\\ &= (\delta-c)^2 + 4\beta\frac{s}{d}p\end{aligned}$$

Then $\Delta > 0$. If $R_0 < 1$ we observe $\beta\frac{s}{d}p < c\delta$. Then

$$\begin{aligned}\Delta &< (\delta+c)^2 + 4c\delta - 4c\delta\\ \Delta &< (\delta+c)^2.\end{aligned}$$

It is easy to see that λ_1 and λ_2 are negative numbers. On the other hand,

$$\lambda_3 = \frac{-(\delta+c)+\sqrt{\Delta}}{2} < \frac{-(\delta+c)+\sqrt{(\delta+c)^2}}{2} = 0.$$

Therefore, $\lambda_3 < 0$. Then, we have that all eigenvalues of the Jacobian matrix at $J(\overline{P}_0)$ are negative, i.e., $|\arg(\lambda_i)| = \pi,\ \ i = 1, 2, 3$, and from Theorem 4.5, we have the disease-free equilibrium point as locally asymptotically stable.

Now the local stability of the endemic equilibrium point $\overline{P}_1$ is shown. First the definition of an additive compound matrix (ACM) is presented (Tumwiine 2007).

Definition 4.11 Let A be any $n \times m$ matrix of real and complex numbers, and let $a_{i_1,\ldots,j_k}$ be the minor of A determined by the rows $(i_1, \ldots, i_k)$ and the columns $(j_1, \ldots, j_2)$, $1 \le i_1 < i_2 < \cdots < i_k < n$, $1 \le j_1 < j_2 < \cdots < j_k < m$. The kth multiplicative compound matrix, A^k, of A is the $\binom{n}{k} \times \binom{n}{k}$ matrix whose entries, written in a lexicographic order, are $a_{i_1,\ldots,j_k}$. When A is a $n \times m$ matrix with columns, $a_1, a_2, \ldots, a_k$, then A^k is the exterior product $a_1 \wedge a_2 \wedge \cdots \wedge a_k$.

Definition 4.12 If $A = a_{ij}$ is a $n \times n$ matrix, its kth additive compound $A^{[k]}$ of the A is the $\binom{n}{k} \times \binom{n}{k}$ matrix given by $A^{[k]} = |D(I + hA)^{(k)}| = 0$, where D is a differentiation with respect to h. For any integer $i = 1, \ldots, \binom{n}{k}$, let $(i) = (i_1, \ldots, i_k)$ be the ith member in the lexicographic ordering of all $k-tuples$ of integers such that $1 \le i_1 < i_2 < \cdots < i_k \le i_n$. Then,

$$b_{ij} = \begin{cases} a_{i_1 i_1} + \cdots + a_{i_k i_k}, & \text{if } (i) = (j)\\ (-1)^{r+s} a_{i_s i_r}, & \text{if } i_s \text{ does not occur in } (j) \text{ and } j_s \text{ does not occur in } (i)\\ 0, & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries.}\end{cases}$$

Remark 4.13 For $n = 3$, the matrices $A^{[k]}$ are

$$A^{[1]} = A,\ A^{[2]} = \begin{bmatrix} a_{11}+a_{22} & a_{23} & -a_{13}\\ a_{32} & a_{11}+a_{33} & a_{12}\\ -a_{31} & a_{21} & a_{22}+a_{33}\end{bmatrix},\ A^{[3]} = a_{11}+a_{22}+a_{33}.$$

Lemma 4.14 *Let M be a real matrix 3×3. If $\mathrm{tr}(M) < 0$, $\det(M) < 0$ and $\det(M^{[2]}) < 0$, then all eigenvalues of M have negative real part.*

This Lemma is stated and proved in McCallemail and David (2009).

Theorem 4.15 *The endemic equilibrium point, $\overline{P}_1$, is locally asymptotically stable if $R_0 > 1$.*

Proof The Jacobian matrix of system (11) in the endemic equilibrium point, $\overline{P}_1$, is given by

$$J(\overline{P}_1) = \begin{vmatrix} -\frac{\beta ps - cd\rho}{c\delta} & \rho & -\frac{c(\delta+\rho)}{p} \\ \frac{\beta ps - cd\delta - cd\rho}{\delta c} & \delta - \rho & \frac{c(\delta+\rho)}{d} \\ 0 & p & -c \end{vmatrix}. \tag{20}$$

Since $R_0 > 1$ it is easy to see that $tr(J(\overline{P}_1)) = \dfrac{-\beta ps + cd\rho}{(\delta - \rho)c} - \rho - c < 0$.

Then,

$$\begin{aligned} \det(J(\overline{P}_1)) &= \frac{-(\delta - \rho)}{\delta - \rho}[(\beta ps - cd\delta) + \beta ps + cd\delta] \\ &= \frac{1}{\delta - \rho}[-\delta(\beta ps - cd\delta) + \rho(\beta ps - cd\delta)] \\ &= -(\beta ps - cd\rho). \end{aligned}$$

Therefore, as all are constant positive parameters and from the hypothesis $R_0 > 1 \rightarrow \beta ps > cd\delta$, it follows that $\det(J(\overline{P}_1)) < 0$.

Let $J^{[2]}(\overline{P}_1)$ be the additive compound matrix.

$$J^{[2]}(\overline{P}_1) = \begin{vmatrix} -V\beta - d - \delta & -T\beta & T\beta \\ p & -V\beta - d - c & \rho \\ 0 & \beta V & -\rho - c. \end{vmatrix}.$$

Then,

$$\begin{aligned} \det(J^{[2]}(\overline{P}_1)) &= (-V\beta - d - \rho)(-V\beta - d - c)(\delta - c) + T\beta p\beta V \\ &\quad - [\beta V\rho(-V\beta - d - \rho) - T\beta p(-\delta - c)] \\ &= -[\delta(V\beta + d + \delta)(V\beta + d + c) + c(V\beta + d + \delta)(V\beta + d + c) \\ &\quad - \beta Vp(V\beta + d + \delta) + \delta(T\beta p) + c(T\beta p)] < 0. \end{aligned}$$

Therefore, $\det(J^{[2]}(\overline{P}_1)) < 0$ and from Lemma 4.14, the equilibrium point $\overline{P}_1$ is locally asymptotically stable. □

4.3 Model of hepatitis B virus (HBV) drug therapy

Now, to understand the various action modes of antiviral therapy in the solution of system (11) we introduce some parameters that model the efficacy of drug in blocking new infections by HBV. The drug efficacy, $\bar{\epsilon}$, then under therapy the production virion rate is $(1-\bar{\epsilon})\bar{p}$. When the drug is 100% ($\bar{\epsilon} = 1$) efficient, it leads the complete suppression of new virion production. To incorporate the possibility of therapy affecting infection, a parameter that accounts for the efficacy of the drug in blocking new infection is introduced, $\bar{c}$, so that the infection rate in the presence of drug is $(1 - \bar{c})\bar{\beta}$ (Ferreira 2000; Lewin et al. 2001). As explained in Sect. 4.1

the fractional model for hepatitis B with drug therapy can be written as

$$\begin{cases} D^{\alpha}T(t) = s - dT(t) - (1-\eta)\beta V(t)T(t) + \rho I(t) \\ D^{\alpha}I(t) = (1-\eta)\beta V(t)T(t) - \delta' I(t) - \rho I(t) \\ D^{\alpha}V(t) = (1-\epsilon)pI(t) - cV(t), \end{cases} \tag{21}$$

where D^{α} is the Caputo fractional derivative of order α, $0 < \alpha \leq 1$, and each parameter depends on τ as in Eq. (21).

Theorem 4.16 *System* (21) *has the disease-free equilibrium point*

$$P_0 = (T_0, I_0, V_0) = \left(\frac{s}{d}, 0, 0\right), \tag{22}$$

for all the parameter values in this system, whereas only if $R_0 > 1$, *there is (unique) endemic equilibrium point as*

$$P_1 = (T_1, I_1, V_1), \tag{23}$$

where

$$\begin{aligned} T_1 &= \frac{-c(\delta' + \rho)}{p(1-\eta)\beta(1-\epsilon)}, \\ I_1 &= \frac{(1-\eta)\beta(1-\epsilon)ps - cd(\delta' - \rho)}{(1-\eta)\beta(1-\epsilon)p\delta'}, \\ V_1 &= \frac{s(1-\epsilon)p}{\delta' c} - \frac{d(\delta' - \rho)}{(1-\eta)\beta\delta'}. \end{aligned}$$

The basic reproduction number, R_0, to system (21) is

$$R_0 = \frac{p\beta s(1-\eta)(1-\epsilon)}{cd(\delta' + \rho)}. \tag{24}$$

Theorem 4.17 *The disease-free equilibrium* P_0 *is locally asymptotically stable if* $R_0 < 1$.

Theorem 4.18 *The endemic equilibrium point,* P_1, *is locally asymptotically stable if* $R_0 > 1$.

The stability analysis of model (21) is similar to model (11), and so we omit its proof.

5 Numerical simulations

In this section, different possible scenarios, depending on the order of the fractional derivative, α, are presented to analyze the hepatitis B model dynamics. To solve a nonlinear differential system set with fractional order, a method based on the nonstandard finite difference schemes (NSFD) approach (Cardoso et al. 2017; Mickens and Smith 1990; Ongun et al. 2013) is used.

Given a mesh-grid $t_N = t_0 + hN$, N is the number of points of the discretization, from GL operator (7), a fractional derivative can be proximate according to the NSFD schemes as follows:

$$D^{\alpha}f(t) \cong \frac{1}{\phi(h,\lambda)} \sum_{j=0}^{N} w_j^{(\alpha)} (f(t - jh)), \tag{25}$$

Table 1 Biological parameters

Parameters	Description	Value (day^{-1})
$\bar{s}$	Rate of production target cells	10
$\bar{d}$	Death rate of target cells	0.5
$\bar{\beta}$	Infection of new target cells	0.00122
$\bar{\rho}$	Rate of cure	0.1
$\bar{\delta}'$	Rate of infected cells	0.3
$\bar{p}$	Production of virus	0.8
$\bar{c}$	Free virus clearance	0.7
$\bar{c}$	Efficacy blocking new infection	0.01
$\bar{\epsilon}$	Drug efficacy	0.41

where the dominator function $\phi(h, \lambda)$ is a function of h, and must satisfy the consistency condition,

$$\phi(h, \lambda) = h + O(h^p)\ ,\ p > \alpha, h \to 0,$$

where $O(h^p)$ is the truncate error. λ is a vector parameter.

The nonlinear term on the right-hand side of the system (11) is replaced by:

$$T(t) \to T(t_{i-1}),\ V(t)T(t) \to V(t_{i-1})T(t_{i-1}),\ V(t) \to V(t_{i-1}),\ I(t) \to I(t_{i-1}),$$

$i = 1, \ldots, N$.

Applying the truncated GL discretization (25) in the system (11) we obtain:

$$\begin{cases} T_i = w_i^{(\alpha-1)} T_0 - \sum_{j=1}^{n} w^{\alpha}(T_{n-j}) + \phi(h, \lambda)[s - dT_{i-1} - \beta V_{i-1} T_{i-1} + \rho I_{i-1}] \\ I_i = w_i^{(\alpha-1)} I_0 - \sum_{j=1}^{n} w^{\alpha}(I_{n-j}) + \phi(h, \lambda)[\beta V_{i-1} T_{i-1} \delta' I_{i-1} - \rho I_{i-1}] \\ V_i = w_i^{(\alpha-1)} V_0 - \sum_{j=1}^{n} w^{\alpha}(V_{n-j}) + \phi(h, \lambda)[pI_{i-1} - cV_{i-1}]. \end{cases}$$

Here, we adopted the denominator function $\phi(h, \mu + 1) = \dfrac{1 - e^{-h^{\alpha}(\mu+1)}}{\mu + 1}$ (Mickens and Smith 1990; Ongun et al. 2013).

For all simulations performed, the numerical parameters are: $h = \frac{\mathrm{T}}{N} = 0.01$, for a total time of simulation T given; $\mu = 3$ (Lewin et al. 2001) to the denominator function ϕ.

The biological parameters are described from Table 1 (Ferreira 2000; Forde et al. 2016). Note that the biological parameters are denoted with a bar and the corresponding parameters, without bar, are functions of τ, according to the relation mentioned before, i.e, $a = \tau^{1-\alpha}\ \bar{a}$. In reference Gómez et al. (2012) the value of τ is estimated according to the value of the constant terms presented in the corresponding ODE. In our numerical simulation several values of τ were considered and the behavior of the system was essentially the same. We were able to note that the bigger the τ, the slower is the convergence to the equilibrium point. Now we present the numerical results taking $\tau = 0.02$.

5.1 Numerical tests

5.1.1 Test 1

In Figs. 2 and 3, we can see the numerical solution of model (11). Figure 2 shows the dynamics of hepatitis B, with initial condition of $T(0) = 1.4 \times 10^1$, $I(0) = 0.13 \times 10^2$, $T(0) = 0.1 \times 10^2$, reproduction number $R_0 = 0.64$ and several values of the fractional order, α. As can be seen, following the course of the disease, the system evolves to the free equilibrium point with population number of $(20, 0, 0)$, as determined by Eq. (14). The convergence to the equilibrium point, when $R_0 < 1$, is predicted by Theorem 4.10.

Figure 3 shows the dynamics of hepatitis B, when the reproduction number is $R_0 > 1$. As can be seen, following the course of the disease, the system evolves to the endemic equilibrium point with population number of $(0.04; 96.8; 0.8)$, as determined by Eq. 15. In this case, we can note that the disease is proliferating. The convergence to the endemic equilibrium point, when $R_0 > 1$, is predicted by Theorem 4.15.

The comparison between different values of the fractional order is shown in both Figs. 2 and 3 with the same control parameter shown in Table 1. We can see in Fig. 2 that smallest values to α imply slower convergence to the equilibrium point. On the other hand, in Fig. 3 note that smallest values to α imply a faster convergence to the equilibrium solution.

5.1.2 Test 2

To compare the effects of the efficiency parameters of the fractional Hepatitis model with drug therapy (21), we performed the numerical simulation considering different values for η and ϵ during the simulation. In this simulation, for $t \leq 45$, we have $R_0 > 1$ and drug therapy with a small efficiency in the treatment against the hepatitis B ($\eta = \epsilon = 0.01$), For $t > 45$ days, the efficiency in the treatment is considered higher ($\eta = \epsilon = 0.9$). Figure 4 presents the numerical solution obtained.

We can note that before the day 45, $R_0 > 1$ makes the solution to converge to endemic point P_1, according to Eq. (23). When a drug therapy intervention was simulated, i.e., $\eta = \epsilon = 0.9$, the R_0 becomes less than 1 and the solution converges to free equilibrium point. The convergence to the endemic equilibrium point, when $R_0 > 1$, and to free equilibrium point is predicted by Theorems 4.17 and 4.18, respectively. This behavior was expected because the starting drug is introduced, it is expected that the number of infected cells, $I(t)$, and virus, $V(t)$, decreases along the time t. Moreover, the target cells, $T(t)$, tend to increase during the time t. When $\alpha < 1$ the numerical solution of fractional-order hepatitis model with the drug therapy has similar behavior that is presented in Fig. 4.

The numerical methods of Euler and fourth-order Runge–Kutta (R–K) were also implemented and a variety of numerical simulations was performed to compare with the fractional numerical scheme results obtained here in the absence of an exact solution and data. In all these simulations, the classical behavior of the solutions was observed. It means that when fractional-order α tends to 1, the fractional numerical solution curves tend to the integer numerical solution (Euler and R–K). Considering this, one of important contributions of this paper, where the focus is to describe a new model based on fractional derivative, is that the fractional model can be an alternative, showing accuracy and improvements in the results and having the potential to be used in computational dynamics problems, in particular, in the investigation of hepatitis B disease.

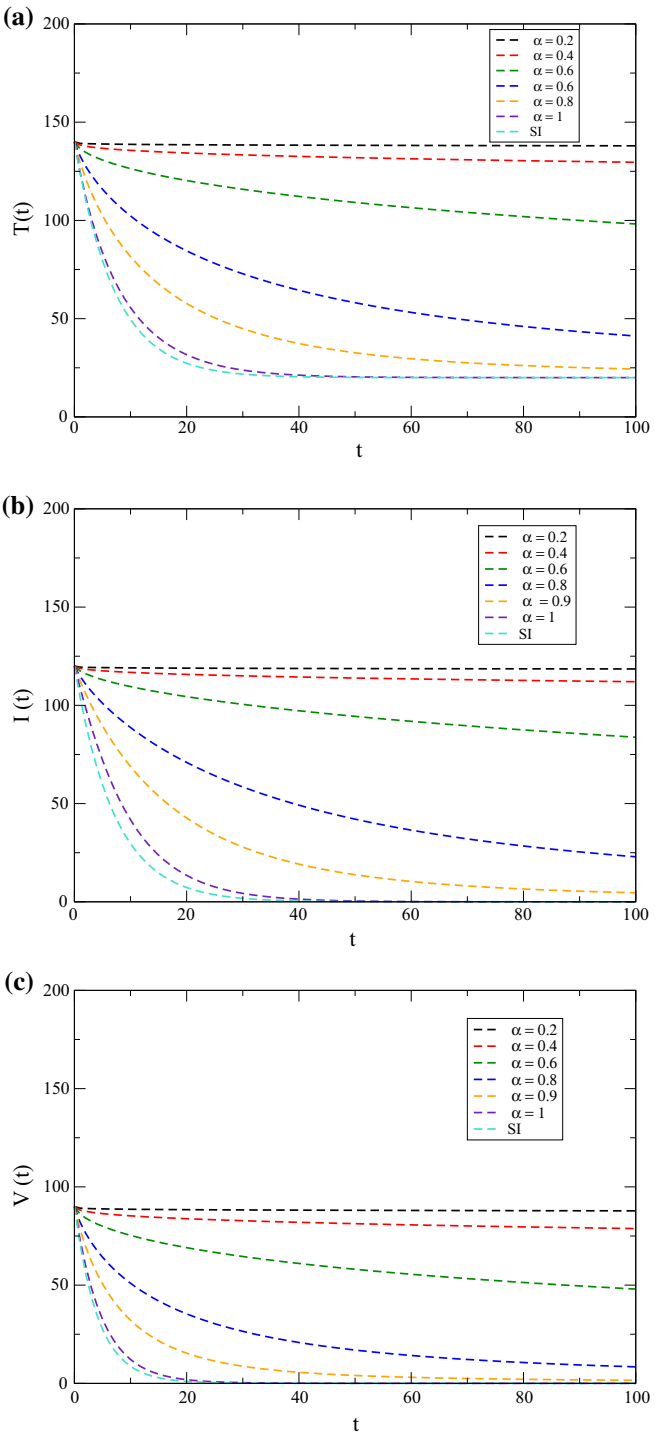

Fig. 2 Numerical solutions of fractional-order hepatitis model without the drug therapy with $\alpha = 0.2, 0.4, 0.6, 0.8, 0.9, 1.0$ and integer solution (SI). **a** T, **b** I and **c** V along the time t (days), $R_0 < 1$

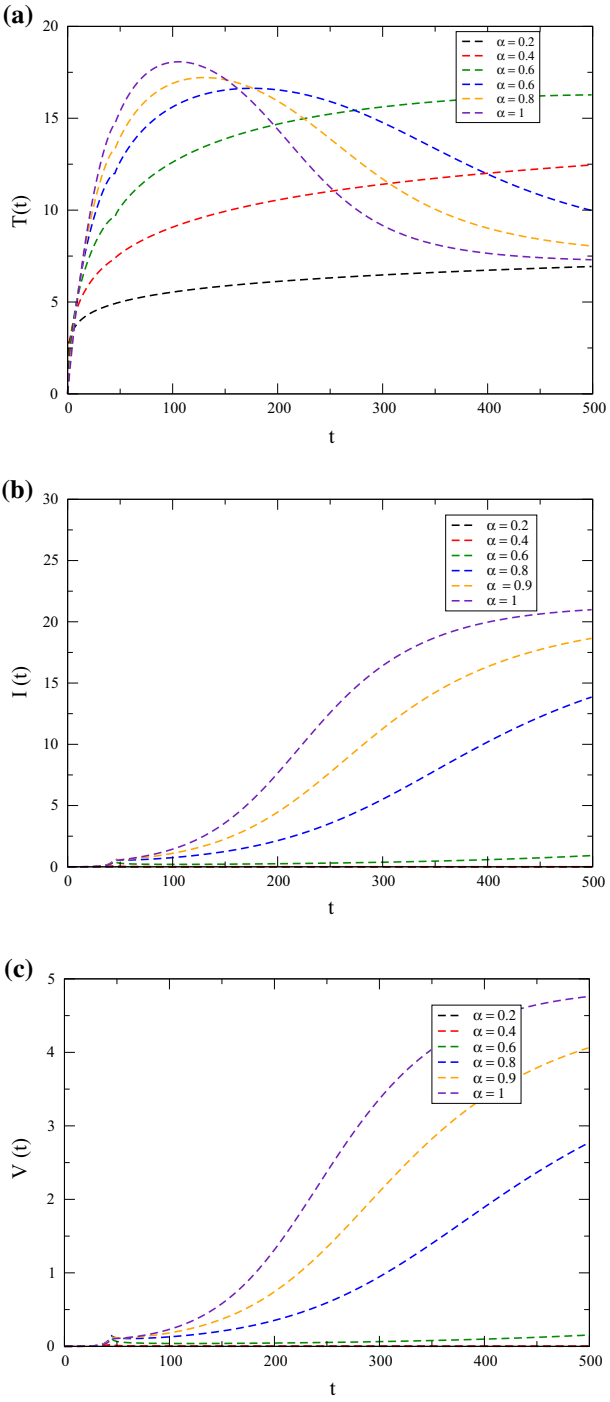

Fig. 3 Numerical solutions of fractional-order hepatitis model without the drug therapy with $\alpha = 0.2, 0.4, 0.6, 0.8, 0.9, 1.0$, $R_0 > 1$

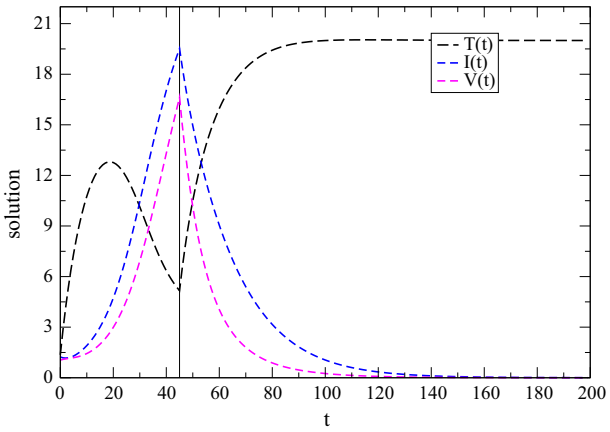

Fig. 4 Numerical solutions of fractional-order hepatitis model with the drug therapy. Comparison of the efficiency in different time intervals for t: $\eta = \epsilon = 0.01$ (small) and $R_0 > 1$, for $t \leq 45$ days; $\eta = \epsilon = 0.9$ (high), for $t > 45$ days. T = 200 days; $\alpha = 1$

6 Conclusions

The fractional modeling has been widely used to generalize and make more precise the usual modeling. The most common reason found for this type of generalization is that "when modeling a particular phenomenon is common to make some simplifications, usually those simplifications, if considered in the model, lead to a decrease in the rate of variation of the phenomenon. Thus, instead of considering several factors in the equation, their influence in the order of the derivative can be embedded" (Kuroda et al. 2017).

This article presents two examples of fractional modeling for the hepatitis B and using several theoretical results the stability is analyzed according to the value of R_0. Besides that, numerical solutions were obtained for different values of the order of the derivative and those numerical results confirmed the analytic prediction.

Finally, the natural continuations of this work can be done introducing different derivative orders to each dependent variable of the systems.

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