Int. J. Adv. Appl. Math. and Mech. 2(2) (2014) 1 - 6 (ISSN: 2347-2529)

Journal homepage: www.ijaamm.com

International Journal of Advances in Applied Mathematics and Mechanics

Stability analysis of a fractional-order HBV infection model

Research Article

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Received 05 November 2014; accepted (in revised version) 23 December 2014

Abstract: In this paper, we introduce a fractional-order HBV infection model. We show the existence of non-negative solutions of the model, and also give a detailed stability analysis of the disease-free and endemic equilibria. Numerical simulations are presented to illustrate the results.

MSC: 92B05 • 26A33

Keywords: Fractional order • HBV infection model • Stability • Predictor-corrector method

1. Introduction

Infection with hepatitis B virus (HBV) is a major health problem, which can lead to cirrhosis and primary hepatocellular carcinoma (HCC) [1, 2]. According to World Health Organization, an estimated 2 billion people worldwide have been infected with the virus and about 350 million carrying HBV, with HBV being responsible for approximately 600,000 deaths each year [3]. Hepatitis B causes about 1 million people, die from chronic active hepatitis, cirrhosis or primary liver cancer annually [3].

Mathematical modeling of HBV infection has provided a lot of understandings of the dynamic of infection. The basic virus infection model introduced by Nowak [4] is widely used in the studies of virus infection dynamics. In [5], Su et. al. presented a HBV infection model in the following:

$$\begin{cases} \frac{dx}{dt} = s - dx - \frac{\beta x v}{x+y} + \rho y, \\ \frac{dy}{dt} = \frac{\beta x v}{x+y} - ay - \rho y, \\ \frac{dv}{dt} = ky - \mu v - \frac{\beta x v}{x+y}, \end{cases} \tag{1}$$

where x, y and v are number of uninfected (susceptible) cells, infected cells, and free virus respectively. Uninfected cells are assumed to be produced at a constant rate s. Uninfected cells are assumed to be die at the rate of dx, and become infected at the rate $\frac{\beta x v}{x+y}$, where β is a rate constant describing the infection process and are assumed to die at the rate ay. Infected hepatocytes are cured by noncytolytic processes at a constant rate ρ per cell. Free virus are assumed to be produced from infected cells at the rate of ky and are removed at the rate of μv. Furthermore, the lossof viral particles rate at a rate $\frac{\beta x v}{x+y}$ when the free-virus particle once enters the target cell.

Fractional calculus is an area of mathematics that addresses generalization of the mathematical operations of differentiation and integration to arbitrary (non-integer) order. In recent years, fractional calculus has been extensively applied in many fields [6–10]. In order to introduced fractional order to the HBV infection model, we firstly present the definition of fractional-order integration and fractional-order differentiation [11]. For fractional-order differentiation, we will use Caputo's definition, due to its convenience for initial conditions of the differential equations.

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Definition 1.1.
The fractional integral of order $\alpha > 0$ of a function $f : \mathbb{R}^+ \to \mathbb{R}$ is given by

$$\mathscr{I}^\alpha = \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t) dt$$

provided the right side is pointwise defined on $\mathbb{R}^+$. Here and elsewhere in this paper, Γ denotes the Gamma function.

Definition 1.2.
The Caputo fractional derivative of order $\alpha \in (n-1, n)$ of a continuous function f : is given by

$$D^\alpha f(x) = \mathscr{I}^{n-\alpha} D^n f(x), \quad D = \frac{d}{dt}.$$

In particular, when $0 < \alpha < 1$, we have

$$D^\alpha f(x) = \frac{1}{\Gamma(1-\alpha)} \int_0^x \frac{f'(t)}{(x-t)^\alpha} dt.$$

Now we introduce fractional order into system (1). The new system is described by the following set of FODE:

$$\begin{cases} D^\alpha x = s - dx - \dfrac{\beta x v}{x+y} + \rho y, \\ D^\alpha y = \dfrac{\beta x v}{x+y} - ay - \rho y, \\ D^\alpha v = ky - \mu v - \dfrac{\beta x v}{x+y}. \end{cases} \tag{2}$$

The meaning of the parameters are similar to system (1). The initial conditions for system (2) are

$$x(0) = x^0 \ge 0, \; y(0) = y^0 \ge 0, \; v(0) = v^0 \ge 0. \tag{3}$$

We denote

$$\mathbb{R}^3_+ = \{(x, y, v) \in \mathbb{R}^3, x \ge 0, y \ge 0, v \ge 0\}.$$

This paper is organized as follows. In Section 2, the established fractional-order model is proved to possess unique non-negative solutions. A detailed analysis on local stability of equilibrium is carried out in Section 3. Simulations and results are given in Section 4.

2. Non-negative solutions

In order to prove that the solutions of system (2) are non-negative, we need the following lemmas.

Lemma 2.1 (Generalized Mean Value Theorem [12]).
Suppose that $f(x) \in \mathbb{C}[a, b]$ and $D^\alpha_a f(x) \in \mathbb{C}(a, b]$, for $0 < \alpha \le 1$, then we have

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

with $a \le \xi \le x$, $\forall x \in (a, b]$.

Lemma 2.2.
Suppose that $f(x) \in \mathbb{C}[a, b]$ and $D^\alpha_a f(x) \in \mathbb{C}(a, b]$, for $0 < \alpha \le 1$. If $D^\alpha_a f(x) \ge 0$, $\forall x \in (a, b)$, then $f(x)$ is nondecreasing for each $x \in [a, b]$. If $D^\alpha_a f(x) \le 0$, $\forall x \in (a, b)$, then $f(x)$ is non increasing for each $x \in [a, b]$.

Theorem 2.1.
There is a unique solution $X(t) = (x, y, v)^\top$ to system (2) with initial condition (3) on $t \ge 0$ and the solution will remain in $\mathbb{R}^3_+$.

Proof. The existence and uniqueness of the solution of (2)-(3) in $(0, +\infty)$ can be obtained from Theorem 3.1 and Remark 3.2 in [13]. In the following, we will show that the domain $\mathbb{R}^3_+$ is positively invariant. Since

$$D^\alpha x|_{x=0} = s + \rho y \ge 0,$$
$$D^\alpha y|_{y=0} = \beta v \ge 0,$$
$$D^\alpha v|_{v=0} = ky \ge 0,$$

on each hyperplane bounding the non-negative orthant, the vector field points into $\mathbb{R}^3_+$ by using Lemma 2.2. □

3. Equilibria and their asymptotical stability

To prove the locally asymptotical stability of equilibria of system (2), the following lemma is useful.

Lemma 3.1 (Ahmed [7]).
The equilibrium (x, y) of the following frictional-order differential system

$$\begin{cases} D^{\alpha}x(t)=f_1(x,y), D^{\alpha}y(t)=f_2(x,y), \alpha\in(0,1], \\ x(0)=x_0, y(0)=y_0 \end{cases}$$

is locally asymptotically stable if all the eigenvalues of the Jacobian matrix

$$J=\begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{pmatrix}$$

evaluated at the equilibrium (x, y) satisfy the following condition:

$$|\arg(\lambda)|>\frac{\alpha\pi}{2}.$$

The basic reproductive ratio of system (2) is $\mathscr{R}_0=\frac{\beta(k-a-\rho)}{(a+\rho)\mu}$. To evaluate the equilibria, we let

$$D^{\alpha}x=0, D^{\alpha}y=0, D^{\alpha}v=0.$$

It is easily to know that if $\mathscr{R}_0<1$, then the disease-free equilibrium $P_0(x_0,0,0)$ is the unique steady state, where $x_0=s/d$; if $\mathscr{R}_0\geq 1$, then in addition to the disease-free equilibrium, there is only one endemic equilibrium $P^*(x^*,y^*,v^*)$, where $x^*=\frac{s}{a(\mathscr{R}_0-1)+d}$, $y^*=\frac{s(\mathscr{R}_0-1)}{a(\mathscr{R}_0-1)+d}$, $v^*=\frac{s(k-a-\rho)(\mathscr{R}_0-1)}{a\mu(\mathscr{R}_0-1)+d\mu}$. When $\mathscr{R}_0=1$, P^* will becomes P_0. In the following, we will discuss the local stability of the disease-free equilibrium and endemic equilibrium.

Theorem 3.1.
The disease-free equilibrium P_0 is locally asymptotically stable if $\mathscr{R}_0<1$ and is unstable if $\mathscr{R}_0>1$.

Proof. The Jacobian matrix $J(P_0)$ for system (2) evaluated at the disease-free equilibrium P_0 is given by

$$J(P_0)=\begin{pmatrix} -d & p & -\beta \\ 0 & -(a+\rho) & \beta \\ 0 & k & -(\mu+\beta) \end{pmatrix}.$$

Hence, the characteristic equation about P_0 is given by

$$(\lambda+\mu)(\lambda^2+A_1\lambda+A_2)=0, \tag{4}$$

where $A_1=a+\mu+\beta+\rho$ and $A_2=\mu\rho+\mu a+a\rho+\rho\beta-k\beta$.
Obviously, $\mathscr{R}_0<1\Leftrightarrow A_2>0$ and $\mathscr{R}_0>1\Leftrightarrow A_2<0$. All the eigenvalues are $\lambda_1=-\mu<0$, $\lambda_{2,3}=\frac{1}{2}[-A_1\pm\sqrt{A_1^2-4A_2}]$.
If $\mathscr{R}_0<1$, then the three roots of the characteristic equation (4) will have negative real parts. Thus, if $\mathscr{R}_0<1$, the disease-free equilibrium P_0 is asymptotically stable.
If $\mathscr{R}_0>1$, at least one eigenvalue will be positive real root. Thus, if $\mathscr{R}_0>1$, the disease-free equilibrium P_0 is unstable.
In the following, we consider the local stability of the endemic equilibrium P^*. The Jacobian matrix $J(P^*)$ evaluated at the endemic equilibrium P^* is given as:

$$J(P^*)=\begin{pmatrix} -\frac{\beta y^*v^*}{(x^*+y^*)^2}-d & \frac{\beta x^*v^*}{(x^*+y^*)^2}+\rho & -\frac{\beta x^*}{x^*+y^*} \\ \frac{\beta y^*v^*}{(x^*+y^*)^2} & -\frac{\beta x^*v^*}{(x^*+y^*)^2}-(a+\rho) & \frac{\beta x^*}{x^*+y^*} \\ \frac{\beta y^*v^*}{(x^*+y^*)^2} & k+\frac{\beta x^*v^*}{(x^*+y^*)^2} & \frac{\beta x^*}{x^*+y^*}-\mu \end{pmatrix}.$$

The characteristic equation of $J(P^*)$ is

$$f(\lambda)=\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0, \tag{5}$$

where

$$a_1=(a+\rho)\mathscr{R}_0+\mu+d+\beta/\mathscr{R}_0,$$
$$a_2=d[a+\rho+\mu+(a+\rho)(\mathscr{R}_0-1)/\mathscr{R}_0+\beta/\mathscr{R}_0]+(a+\rho)\mu(\mathscr{R}_0-1)+a(a+\rho)(\mathscr{R}_0-1)^2/\mathscr{R}_0,$$
$$a_3=\mu a(a+\rho)(\mathscr{R}_0-1)^2/\mathscr{R}_0+d\mu(a+\rho)(\mathscr{R}_0-1)/\mathscr{R}_0.$$

Hence, $a_2>0$ and $a_3>0$ when $\mathscr{R}_0>1$. And we can easily obtain $a_1>0$. Furthermore, $a_1a_2-a_3=\mu[a+\rho+\mu+\beta/\mathscr{R}_0+a\mu(\mathscr{R}_0-1)]+[(a+\rho)\mathscr{R}_0+d+\beta/\mathscr{R}_0][(a+\rho)d(\mathscr{R}_0-1)/\mathscr{R}_0+a(a+\rho)(\mathscr{R}_0-1)^2/\mathscr{R}_0^2+a+\rho+\mu+\beta/\mathscr{R}_0+a\mu(\mathscr{R}_0-1)]>0.$ □

Proposition 3.1.
The endemic equilibrium P^* is locally asymptotically stable if all of the eigenvalues λ of $J(P^*)$ satisfy $\arg(\lambda) > \frac{\alpha\pi}{2}$.

Denote

$$
\begin{aligned}
D(f) = -&\begin{vmatrix} 1 & a_1 & a_2 & a_3 & 0 \\ 0 & 1 & a_1 & a_2 & a_3 \\ 3 & 2a_1 & a_2 & 0 & 0 \\ 0 & 3 & 2a_1 & a_2 & 0 \\ 0 & 0 & 3 & 2a_1 & a_2 \end{vmatrix} \\
&= 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2.
\end{aligned}
$$

Using the results of [6], we have the following proposition.

Proposition 3.2.
Suppose $\mathscr{R}_0 > 1$.
(1) If $D(f) > 0$, then the endemic equilibrium P^* is locally asymptotically stable.
(2) If $D(f) < 0$ and $\frac{1}{2} < \alpha < \frac{2}{3}$, then the endemic equilibrium P^* is locally asymptotically stable.

4. Numerical methods and simulations

According to the Adams predictor-corrector scheme shown in [14, 15], the numerical solution of the initial value problem for system (2) will be yielded as below.
Set $h = \frac{T}{N}$, $t_n = nh$, $n = 0, 1, 2, \cdots, N \in \mathbb{Z}^+$, the system (2) can be discretized as follows:

$$
\begin{cases}
x_{n+1} = x^0 + \frac{h^\alpha}{\Gamma(\alpha+2)}(s - dx^p_{n+1} - \frac{\beta x^p_{n+1} v^p_{n+1}}{x^p_{n+1} + y^p_{n+1}} + \rho y^p_{n+1}), \\
y_{n+1} = y^0 + \frac{h^\alpha}{\Gamma(\alpha+2)}(\frac{\beta x^p_{n+1} v^p_{n+1}}{x^p_{n+1} + y^p_{n+1}} - a y^p_{n+1} - \rho y^p_{n+1}), \\
v_{n+1} = v^0 + \frac{h^\alpha}{\Gamma(\alpha+2)}(k y^p_{n+1} - \mu v^p_{n+1} - \frac{\beta x^p_{n+1} v^p_{n+1}}{x^p_{n+1} + y^p_{n+1}}),
\end{cases} \tag{6}
$$

where

$$
\begin{aligned}
x^p_{n+1} &= x^0 + \frac{h^\alpha}{\Gamma(\alpha)} \sum_{j=0}^{n} \beta_{j,n+1}(s - dx_j - \frac{\beta x_j v_j}{x_j + y_j} + \rho y_j), \\
y^p_{n+1} &= y^0 + \frac{h^\alpha}{\Gamma(\alpha)} \sum_{j=0}^{n} \beta_{j,n+1}[\frac{\beta x_j v_j}{x_j + y_j} - a y_j - \rho y_j], \\
v^p_{n+1} &= v^0 + \frac{h^\alpha}{\Gamma(\alpha)} \sum_{j=0}^{n} \beta_{j,n+1}[k y_j - \mu v_j - \frac{\beta x_j v_j}{x_j + y_j}], \\
x^q_{n+1} &= \sum_{j=0}^{n} \gamma_{j,n+1}(s - dx_j - \frac{\beta x_j v_j}{x_j + y_j} + \rho y_j), \\
y^q_{n+1} &= \sum_{j=0}^{n} \gamma_{j,n+1}[\frac{\beta x_j v_j}{x_j + y_j} - a y_j - \rho y_j], \\
v^q_{n+1} &= \sum_{j=0}^{n} \gamma_{j,n+1}[k y_j - \mu v_j - \frac{\beta x_j v_j}{x_j + y_j}]
\end{aligned}
$$

and

$$
\beta_{j,n+1} = \frac{h^\alpha}{\alpha}((n - j - 1)^\alpha - (n - j)^\alpha),
$$

$$
\gamma_{j,n+1} = \begin{cases}
n^{\alpha+1} - (n - \alpha)(n+1)^\alpha, & j = 0, \\
(n - j + 2)^{\alpha+1} + (n - j)^{\alpha+1} - 2(n - j + 1)^{\alpha+1}, & 0 \le j \le n, \\
1, & j = n + 1.
\end{cases}
$$

For the numerical simulations for system (2), using the above-mentioned method is appropriate. For the parameters $s = 5$, $d = 0.01$, $\beta = 0.02$, $\rho = 0.01$, $a = 0.4$, $k = 1000$, $\mu = 8$, we obtain $\mathscr{R}_0 = 15.23765244$. Furthermore, $a_1 = 14.26071885$, $a_2 = 48.96920158$, $a_3 = 14.26071885$, $a_1a_2 - a_3 = 680.8514660 > 0$ and $D(f) = 144085.7355 > 0$. System (2) exists a positive equilibrium $E^*(0.8764148221, 12.47808963, 1559.121702)$ and it is locally asymptotically stable. The approximate solutions are displayed in Fig. 1 for the step size 0.005 and $\alpha = 0.85, 0.9, 0.95, 1$. The initial conditions are $x(0) = 0.3$, $y(0) = 20$, $v(0) = 1300$. When $\alpha = 1$, system (2) is the classical integer-order system (1). In Figure 1(a), the variation of $x(t)$ versus time t is shown for different values of $\alpha = 0.85, 0.9, 0.95, 1$ by fixing other parameters. It is revealed that increase in α increases with the proportion of susceptible while behavior is reverse after certain value of time. Figure 1(b), (c) depicts $y(t)$, $v(t)$ versus time t with various values of α ($\alpha = 0.85, 0.9, 0.95, 1$, respectively).

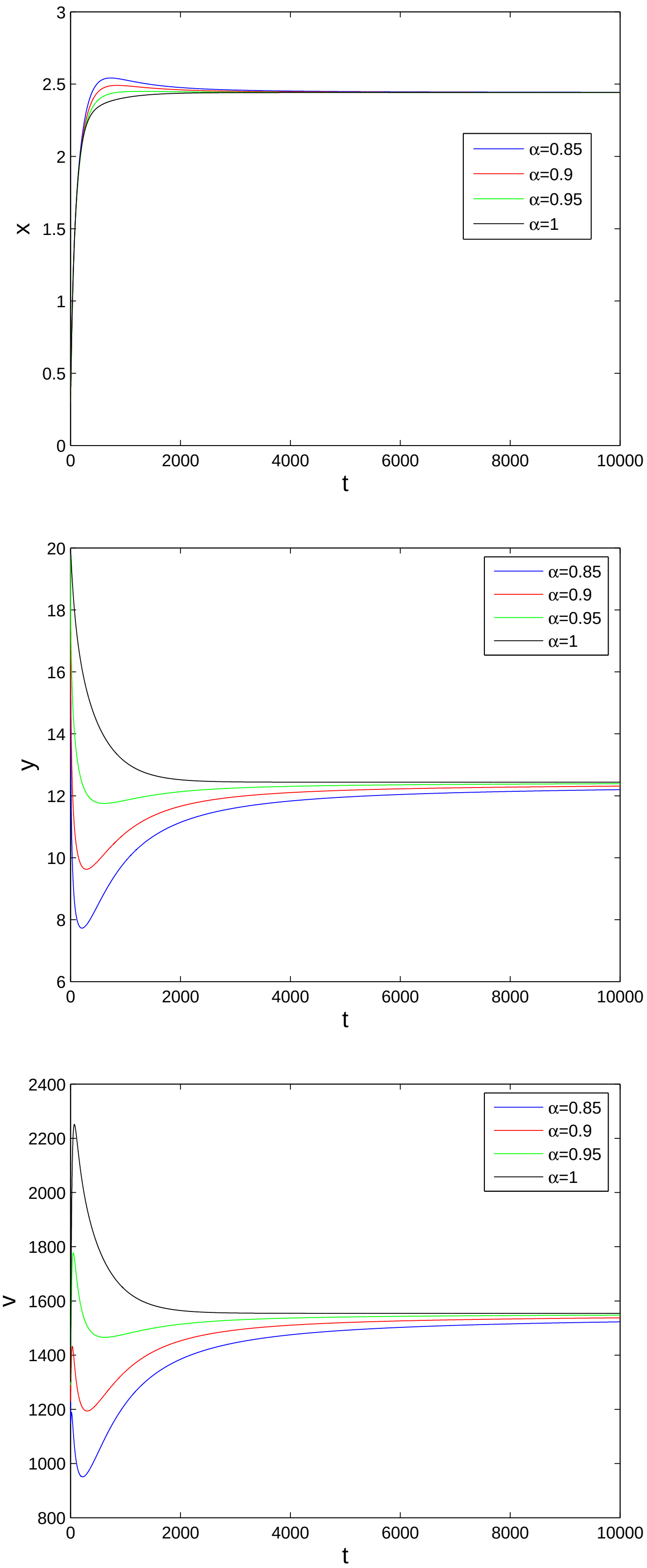

Fig. 1. Time evolution of population of $x(t)$, $y(t)$, $v(t)$ when $s = 5$, $d = 0.01$, $\beta = 0.02$, $\rho = 0.01$, $a = 0.4$, $k = 1000$, $\mu = 8$ for $\alpha = 0.85, 0.9, 0.95, 1$.

Acknowledgements

This work is supported by the Basic and Frontier Technology Research Program of Henan Province (Nos.: 132300410025 and 132300410364), the Key Project for the Education Department of Henan Province (No.: 13A110771) and Student Science Research Program of Xinyang Normal University (No.: 2013-DXS-086).

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