ON DYNAMICS OF FRACTIONAL-ORDER MODEL OF HCV INFECTION

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Abstract. In this paper, we investigate the dynamical behavior of the fractional-order model within Caputo derivative of HCV infection. Stability analysis of the equilibrium points is according to the basic reproduction number $R_0$. The numerical simulations are also presented to illustrate the results.

1. Introduction

We recall that the hepatitis is one of the most prevalent viral diseases and due to different genetic structure of its viruses, it can be categorises to various types; such as: A, B, C, D.

We know that the hepatitis C virus (HCV) can lead to chronic liver disease and in some cases cirrhosis.

At first, it can detect as a common cold, but chronic hepatitis C, unlike a common cold, can be life-threatening due to liver failure and difficulty in patient treatment [24].

Nearly, one million cases of hepatitis C have been reported in the world. Most of the time the sufferers don’t show any symptoms, but in some cases they have common viral infection signs, such as: fatigue, abdominal pain, muscle pain, nausea and anorexia.

Although it is difficult to treat hepatitis C, but in many cases it may be successful. Interferon alpha can make some improvement in liver function, which includes 3 injections per week for 6 to 12 months. Beside that, contemporaneous use of Ribavirin as an antiviral oral medication and Interferon is effective for hepatitis C treatment [26].

It has been proven that mathematical models are fruitful tools in understanding the dynamics of HCV infection (see for example Refs. [19] [11] [8] [9] [7] [6] and the related references).

Recently, the fractional differential calculus has attracted a lot of attention by many researchers of different fields, such as: physics, chemistry, biology, economics,
control theory and biophysics, etc. [14, 17, 22, 13]. Moreover, describing the behavior of the most biological systems which have memory or aftereffect by fractional-order differential equations (FODEs) seems suitable than ordinary differential equations.

Neumann et al. [19] presented the simple model of viral dynamics of HCV by three population, T as uninfected hepatocytes, I as infected hepatocytes and V as free HCV virions, which describes the response to interferon treatment.

\[
\frac{dT}{dt} = s - dT - (1 - \eta)\beta VT, \\
\frac{dI}{dt} = (1 - \eta)\beta VT - \delta I, \\
\frac{dV}{dt} = (1 - \epsilon_p)pI - cV,
\]

Here uninfected hepatocytes are assumed to produce at a constant rate \(s\), die at rate \(d\) per cell and are infected at constant rate \(\beta\). Also, the infected hepatocytes are lost by a rate \(\delta\) per cell. We recall that the viral particles (virions) are produced at rate \(p\) per infected hepatocytes and cleared at rate \(c\) per virion. Here \(\epsilon_p, \eta\) denote the efficacy of treatment in blocking virion production and reducing new infections, respectively.

The main aim of our work is to investigate the dynamics of fractional-order model of HCV infection, which is introduced by Ahmed and El-Saka [3]. The following FODEs of order \(0 < \alpha \leq 1\) are used to analyze the system, namely

\[
D^\alpha T = s - dT - (1 - \eta)\beta VT, \\
D^\alpha I = (1 - \eta)\beta VT - \delta I(1 - I/c_2), \\
D^\alpha V = (1 - \epsilon_p)pI - cV,
\]

with \(T(0) = 2.3908 \times 10^6, I(0) = 2.06897 \times 10^6, V(0) = 10^6\).

In [3], the authors concluded that the added immune response term represents some basic properties of the immune system and that it should be included to study longer term behavior of the disease.

Rida et al. [23] investigated the accuracy of the Generalized Euler method (GEM) for solving the fractional-order model of HCV infection numerically.

In this paper, we first briefly mention some facts and results about fractional calculus, also we show that the fractional model has a unique, non-negative solution, and in spire of [10] we consider the stability of the infected steady state in section 3 and we conclude this paper by considering some numerical examples to demonstrate the usability of the obtained results in section 4.

2. Non-negative solutions

At the beginning of this section, we present some preliminaries of fractional calculus. For more details see [17, 22, 14].

A real function \(f\) is said to be of class \(C\), if \(f\) is piecewise continuous on \((0, \infty)\) and integrable on any finite subinterval of \((0, \infty)\).
Definition 2.1. The Riemann-Liouville fractional integral of order $\alpha > 0$ of the function $f(t)$ of class $C$ is defined as

$$I^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} f(s) \, ds, \quad \alpha > 0, \quad t > 0,$$

$$I^0 f(t) = f(t).$$

Definition 2.2. Let $m - 1 < \alpha \leq m$, $m \in \mathbb{N}$ be a positive real number, $f^{(m)}(t)$ exist and be a function of class $C$. Then Caputo fractional derivative of $f$ is defined as

$$D^\alpha f(t) = I^{m-\alpha} \left( \frac{d^m}{dt^m} f(t) \right).$$

Lemma 2.3. (Generalized Mean Value Theorem). Suppose that $f \in C[a, b]$ and $D^\alpha f \in C(a, b)$ for $0 < \alpha \leq 1$, then we have

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

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

Corollary 2.4. Suppose for $0 < \alpha \leq 1$, $f \in C[a, b], D^\alpha f \in C(a, b]$. If $\forall x \in (a, b), D^\alpha f(x) \geq 0$, then $f(x)$ is nondecreasing for each $x \in [a, b]$. If $\forall x \in (a, b), D^\alpha f(x) \leq 0$, then $f(x)$ is nonincreasing for each $x \in [a, b]$.

Theorem 2.5. Equation (1.2) has a unique solution $x(t) = (T, I, V)$ on $t \geq 0$ and the solution will remain in $\mathbb{R}^3_+$.

Proof. The proof is similar to the Theorem 1 of [10].

3. Equilibrium points and stability

System (1.2) has the following equilibrium points:

(a) $E_0 = (\frac{s}{d}, 0, 0)$.

(b) $E^* = (T^*, I^*, V^*)$, where

$$T^* = \frac{s}{d + (1-\eta)\beta V^*},$$

$$V^* = \left(\frac{1-\epsilon_p}{c}\right) p I^*,$$

and $I^*$ is a positive root of the quadratic equation:

$$\left(\frac{\delta}{c_2}(1-\eta)(1-\epsilon_p)p\beta\right)I^2 + \left(\frac{cd\delta}{c_2} - \delta(1-\eta)(1-\epsilon_p)p\beta\right)I + (1-\eta)(1-\epsilon_p)p\beta - cd\delta = 0,$$

which is obtained by

$$D^\alpha T = D^\alpha I = D^\alpha V = 0.$$

Here the basic reproduction number $R_0$ is defined as

$$R_0 = \frac{(1-\epsilon_p)(1-\eta)p\beta}{cd\delta}.$$

Theorem 3.1. The disease free equilibrium point $E_0$ is locally asymptotically stable, if $R_0 < 1$ and is unstable if $R_0 > 1$. 

□
Proof. The Jacobian matrix of the system (1.2) at the disease free equilibrium point \( E_0 \) is;

\[
J(E_0) = \begin{pmatrix}
-d & 0 & -\frac{(1-\eta)s\beta}{d(1-\eta)s\beta} \\
0 & -\delta & \frac{(1-\eta)s\beta}{d} \\
0 & (1-\epsilon_p)p & -c \\
\end{pmatrix}.
\]

The characteristic equation can be written as;

\[
(-d - \lambda)(\lambda^2 + (\delta + c)\lambda + K) = \lambda^3 + A\lambda^2 + B\lambda + C = 0,
\]

where

\[
K = \delta c - \frac{(1-\epsilon_p)(1-\eta)ps\beta}{d}, \quad A = \delta + c + d, \quad B = d(\delta + c) + K, \quad C = dK.
\]

Here \( A > 0 \) is clear. Since \( R_0 < 1 \) we have \( C, B > 0 \). Now, we show that \( AB - C > 0 \),

\[
AB - C = (\delta + c + d)(d\delta + dc + K) - dK
= \delta^2d + 2\delta dc + dc^2 + d^2\delta + d^2c
+ \delta(\delta c - \frac{(1-\epsilon_p)(1-\eta)ps\beta}{d}) + c(\delta c - \frac{(1-\epsilon_p)(1-\eta)ps\beta}{d}) > 0.
\]

Hence by the Routh-Herwitz theorem the disease free equilibrium point is locally stable for \( R_0 < 1 \).

When \( R_0 > 1 \) we have \( C < 0 \). Therefore the disease free equilibrium point is unstable. \( \square \)

In case \( R_0 > 1 \) to see the stability of the positive infected steady state \( E^* \), we find the Jacobian matrix at this point;

\[
J(E^*) = \begin{pmatrix}
-d - (1-\eta)\beta V^* & 0 & -\frac{(1-\eta)\beta T^*}{(1-\eta)\beta V^*} \\
(1-\eta)\beta V^* & -\delta + \frac{2\delta I^*}{c_2} & \frac{2\delta(1-\eta)\beta V^* T^*}{c_2} \\
0 & (1-\epsilon_p)p & -c \\
\end{pmatrix}.
\]

Then the characteristic equation of the matrix \( J(E^*) \) is;

\[
\lambda^3 + E\lambda^2 + F\lambda + G = 0,
\]

where

\[
E = \delta + d + (1-\eta)\beta V^* - \frac{2\delta}{c_2} I^*,
\]

\[
F = d\delta + c\delta + cd - \frac{2d\delta}{c_2} I^* + (1-\eta)\beta\delta V^* - \frac{2\delta(1-\eta)\beta V^* T^*}{c_2}
+ c(1-\eta)\beta V^* - \frac{2c\delta}{c_2} I^* + p\beta(1-\epsilon_p)(1-\eta)T^*,
\]

\[
G = cd\delta - \frac{2cd\delta}{c_2} I^* - dp\beta(1-\epsilon_p)(1-\eta)T^* + c(1-\eta)\beta\delta V^* - \frac{2c\delta(1-\eta)\beta V^* I^*}{c_2}.
\]

Denote

\[
D(P) = -det \begin{pmatrix}
1 & E & F & G & 0 \\
0 & 1 & E & F & G \\
0 & 0 & 3 & 2E & F \\
0 & 0 & 0 & 3 & 2E \\
\end{pmatrix} = 18EGF + (EF)^2 - 4GE^3 - 4F^3 - 27G^2.
\]

From [2], we have
Proposition 3.2. 
(i) If $D(P) > 0, E > 0, G > 0, EF > G$, then the infected steady state $E^*$ is asymptotically stable (Routh-Hurwitz conditions).
(ii) If $D(P) < 0, E \geq 0, F \geq 0, G > 0$, $0.5 < \alpha < 2/3$, then the infected steady state $E^*$ is asymptotically stable.
(iii) If $D(P) < 0, E > 0, F > 0, EF = G$, $0.5 < \alpha < 1$, then the infected steady state $E^*$ is asymptotically stable.
(iv) If $D(P) < 0, E < 0, F < 0, \alpha > 2/3$, then the infected steady state $E^*$ is unstable.

4. Numerical Simulation

In this section, we proposed some numerical examples for system (1.2) in order to illustrate the asymptotic stability of the infected steady state $E^*$ by proposition 3.2.

Example 4.1. We consider parameter values $s = 5 \times 10^4$, $d = 0.0026$, $\beta = 20.25 \times 10^{-6}$, $\delta = 0.35$, $c = 5 \times 10^6$, $p = 9$, $\epsilon_p = 0.99$, $\eta = 0.01$, we have $E = 3.9536$, $F = 1.2748$, $G = 0.08638$, $EF - G = 4.9838 > 0$, $D(P) = 3.3975 > 0$. Thus by proposition 3.2 (i), the infected steady state $E^*$ is asymptotically stable. Numerical simulations show solution paths approach to the steady state. (Figs. 1).

Example 4.2. In this case, we consider the set of parameters $s = 5 \times 10^4$, $d = 0.002$, $\beta = 2.25 \times 10^{-7}$, $\delta = 0.26$, $c = 9 \times 10^7$, $p = 10$, $\epsilon_p = 0.99$, $\eta = 0.8$, we have $E = 0.367$, $F = 0.054$, $G = 0.00051$, $EF - G = 0.02007 > 0$, $D(P) = -0.00023 > 0$. Thus, by proposition 3.2 (ii), the infected steady state $E^*$ is asymptotically stable. (Figs. 2-3).

Example 4.3. We choose a set of parameters $s = 2.6 \times 10^4$, $d = 0.026$, $\beta = 10.25 \times 10^{-7}$, $\delta = 0.01$, $c = 9 \times 10^7$, $p = 10$, $\epsilon_p = 0.99$, $\eta = 0.1$, we have $E = 2.5806$, $F = 0.2722$, $G = 0.002390$, $EF - G = 0.7004 > 0$, $D(P) = 0.2838 > 0$. Thus by proposition 3.2 (i), the infected steady state $E^*$ is asymptotically stable. (Figs. 4-5).

5. Conclusion

We carried out the analysis on stability of the equilibrium points of the investigate fractional-order model of HCV infection according to the basic reproduction number $R_0$. We observed that when $R_0 < 1$, the disease free equilibrium point becomes locally stable. For the case when $R_0 > 1$, we consider the conditions that the infected steady state is asymptotically stable.

In three examples, we have satisfied the condition of proposition 3.2 and the solution paths of the system (1.2) converge to the steady state.

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Figure 1. Numerical solution of fractional model (1.2) corresponding to $\alpha = 0.51, 0.6, 0.7, 0.8, 0.9$. 
Figure 2. Numerical solution of the investigated fractional model (1.2) for $\alpha = 0.51, 0.55, 0.59, 0.6$. 
Figure 3. Stability of the equilibria $E^*$, for $\alpha = 0.55$. 
Figure 4. Numerical solution of the analyzed fractional model \( (1.2) \) for \( \alpha = 0.51, 0.6, 0.7, 0.8, 0.9 \).
Figure 5. Stability of the equilibria $E^*$, for $\alpha = 0.95$. 