Stability Analysis for a Fractional HIV Infection Model with Immune Response

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Abstract. In this paper, we give a fractional-order differential equation model of HIV infection by introducing Caputo derivative and immune response. We prove that the model established in this paper has a unique nonnegative solution. With characteristic equation and Hurwitz criterion, the local stability of the infection-free equilibrium, the immune-absence equilibrium and the immune-presence equilibrium are analyzed.

1. Introduction
In the past decades, mathematical models have been established for describing the changes in HIV, HBV, HCV and other viral loads in the infected persons, which provide a great help to explore the diagnosis and medical treatments of infectious diseases. Although previous works are restricted to integer order differential equations [1-4]. Since fractional differential equations have the ability to provide an exact description of different nonlinear phenomena, they have received much attention and become popular. The advantage of fractional-order models lies in the fact that they have memory and allow greater degree of freedom in the model. Now the qualitative properties and numerical solutions of fractional order virus infection models have been studied by more and more scholars [5-6]. The immune response following viral infection is universal and necessary in controlling or even eliminating the disease [2]. In view of these references, we take a fractional-order differential equation model of HIV infection with immune response into consideration in this paper as follows:

\[
\begin{align*}
\frac{dx}{dt} &= \lambda - dx - \beta xy, \\
\frac{dy}{dt} &= \beta xy - ay - pyz, \\
\frac{dz}{dt} &= cyz - bz,
\end{align*}
\]

Here \(0 < \alpha \leq 1\); \(x(t)\) is the concentration of uninfected cells at time \(t\); \(y(t)\) is the concentration of infected cells that produce virus at time \(t\); \(z(t)\) is the concentration of antigen-specific CTLs at time \(t\). The initial conditions are

\[
\begin{align*}
x(0) &= x_0, \quad y(0) = y_0, \quad z(0) = z_0.
\end{align*}
\]
\( t \), \( \lambda \) is the growth rate of new healthy cells. \( a \) and \( d \) are the death rate of infected cells and uninfected cells, respectively. \( \beta \) is the rate constant characterizing infection of the cells. \( \beta \) is the death rate of \( p \) is the death rate of infected cells due to the immune system. The immune response is supposed to decay exponentially at a rate \( b \) and get stronger at a rate \( c \). All parameters in the model are positive.

2. Fractional Calculus
In this paper, we will use the following definition and lemmas about fraction calculus.

**Definition 1.** The Caputo (C) fractional derivative of order \( \alpha > 0 \), \( n-1 < \alpha < n \), \( n \in \mathbb{N} \), is defined as

\[
D^\alpha f(t) = I^{n-\alpha} D^n f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t (t-s)^{n-\alpha-1} f^{(n)}(s) ds, \tag{2.1}
\]

where the function \( f(t) \) has absolutely continuous derivatives up to order \( (n-1) \). In particular, when \( 0 < \alpha < 1 \), one has [7]

\[
D^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-s)^{-\alpha} f'(s) ds. \tag{2.2}
\]

**Lemma 2.** Consider the commensurate fractional-order system as follows:

\[
\begin{cases}
D^\alpha x = f(x), \\
x(0) = x_0,
\end{cases}
\tag{2.3}
\]

with \( 0 < \alpha \leq 1 \) and \( x \in \mathbb{R}^n \). The equilibrium points of system (2.3) are calculated by solving the following equation: \( f(x) = 0 \). These points are locally asymptotically stable if all eigenvalues \( r_i \) of Jacobian matrix \( J = \partial f / \partial x \) evaluated at the equilibrium points satisfy [7]:

\[
|\arg(r_i)| > \frac{\theta \pi}{2}. \tag{2.4}
\]

**Lemma 3.** For the polynomial equation,

\[
P(\lambda) = \lambda^n + h_1 \lambda^{n-1} + h_2 \lambda^{n-2} + \cdots + h_n = 0, \tag{2.5}
\]

the conditions which make all the roots of (2.5) satisfy (2.4) are displayed as follows:

(i) for \( n = 1 \), the condition is \( h_1 > 0 \);

(ii) for \( n = 2 \), the conditions are either Routh-Hurwitz conditions or

\[
h_1 < 0, \ 4h_2 > (h_1)^2, \ \left| \tan^{-1}\left( \frac{\sqrt{4h_2-(h_1)^2}}{h_1} \right) \right| > \frac{\alpha \pi}{2}. \tag{2.6}
\]

(iii) for \( n = 3 \),

(a) if the discriminant of \( P(\lambda) \), \( D(P) \) is positive, then Routh-Hurwitz conditions are the necessary and sufficient conditions; that is, \( h_1 > 0, h_2 > 0, \) and \( h_1 h_2 > h_3 \) if \( D(P) > 0 \);

(b) if \( D(P) < 0, h_1 \geq 0, h_2 \geq 0, \) and \( h_1 > 0 \), then (2.4) for (2.5) holds when \( \alpha < 2/3 \);

(c) if \( D(P) < 0, h_1 < 0, \) and \( h_2 < 0 \), then (2.4) for (2.5) holds when \( \alpha > 2/3 \);

(d) if \( D(P) < 0, h_1 > 0, h_2 > 0, \) and \( h_1 h_2 = h_3 \), then (2.4) for (2.5) holds for all \( \alpha \in [0,1) \) [8].

3. Nonnegative Solutions
Let \( R^+_n = \{ W \in \mathbb{R}^n : W \geq 0 \} \) and \( W(t) = (x(t), y(t), z(t))^T \).

**Lemma 4.** Let \( f(x) \in C[a, b] \) and \( D^\alpha f(x) \in C[a, b] \) for \( 0 < \alpha \leq 1 \). Then one has
\[ f(x) = f(a) + \frac{1}{\Gamma(\alpha)} D^\alpha f(x)(x-a)^\alpha, \]  
(3.1)

with \( 0 \leq \xi \leq x, \forall x \in (a,b), \) where \( \Gamma(x) = \int_0^\infty t^{x-1}e^{-t}dt \) [9].

**Remark 5.** Suppose that \( f(x) \in C[a,b] \) and \( D^\alpha f(x) \in C[a,b], \) for \( 0 < \alpha \leq 1 \). It is clear from Lemma 5 that if \( D^\alpha f(x) \geq 0, \forall x \in (a,b), \) then \( f(x) \) is non-decreasing for each \( x \in [a,b] \). If \( D^\alpha f(x) \leq 0, \forall x \in (a,b), \) then \( f(x) \) is non-increasing for each \( x \in [a,b] \).

**Theorem 6.** There is a unique solution for the initial value problem (1.1) with (1.2) and the solution remains in \( R^+ \) [10].

4. **Equilibrium States**

Let \( x^*(t) = 0, \ y^*(t) = 0 \) and \( z^*(t) = 0, \) then obtain the equations as follows:

\[
\begin{align*}
\lambda - dx - \beta xy &= 0, \\
\beta xy - ay - pz &= 0, \\
cy - bz &= 0.
\end{align*}
\]
(4.1)

By solving the equations (4.1), we can obtain the three types of nonnegative equilibrium of model (1.1).

Model (1.1) always has an infection-free equilibrium \( E_0 \), where \( E_0 = (x_0, 0, 0) = (\lambda/d, 0, 0) \).

We denote: \( R_0 = \frac{\lambda \beta}{ad} \), \( R_1 = R_0 - \frac{b \beta}{cd} \). \( R_0 \) is defined as the basic reproductive number of the model (1.1) and \( R_1 \) is defined as the immune reproduction number of the model (1.1).

When \( R_0 < 1 \), Model (1.1) has an immune-absence equilibrium \( E_i \) besides \( E_0 \), where \( E_i = (x_i, y_i, z_i) = \left( \frac{a}{\beta}, \frac{d(R_0 - 1)}{\beta}, 0 \right) \).

When \( R_1 < 1 \), Model (1.1) has an interior immune-presence equilibrium \( E^* \) besides \( E_0 \) and \( E_i \), where \( E^* = (x^*, y^*, z^*) = \left( \frac{\lambda c}{dc + \beta b}, \frac{b}{p(dc + \beta b)}, \frac{\beta \lambda c - ade - a \beta b}{p(dc + \beta b)} \right) \).

5. **Local Stability**

With characteristic equation and Hurwitz criterion, we analyze the local asymptotic stability of the model (1.1).

**Theorem 7.** Consider model (1.1).

1. If \( R_0 < 1 \), the infection-free equilibrium \( E_0 \) is locally asymptotically stable.
2. If \( R_0 > 1 \), the infection-free equilibrium \( E_0 \) is unstable.
3. If \( R_1 = 1 \), it is a critical case.

Proof. The characteristic equation for \( E_0 \) is simplified as follows:

\[ (r + d)(r + b)(r + a - \beta x_0) = 0. \]  
(5.1)

The equation (5.1) has the roots \( r_1 = -d < 0 \) which means \( \arg r_1 = \pi > \alpha(\pi / 2) \), \( r_2 = -b < 0 \) which means \( \arg r_2 = \pi > \alpha(\pi / 2) \), and \( r_3 = \beta x_0 = \alpha(R_0 - 1) \). Because the imaginary part of characteristic root \( r_1 \) is zero, \( R_0 < 1 \) which means \( \arg r_1 = \pi > \alpha(\pi / 2) \) is necessary and sufficient to ensure the local asymptotic stability of the infection-free equilibrium \( E_0 \). If \( R_0 > 1 \),
\[ |\arg r_1| = 0 < \alpha (\pi / 2) \]; hence the infection-free equilibrium \( E_0 \) is unstable. If \( R_0 = 1, r_1 = 0 \), it is a critical case.

**Theorem 8.** Consider model (1.1).

1. If \( R_1 < 1 \), the immune-absence equilibrium \( E_1 \) is locally asymptotically stable.
2. If \( R_1 > 1 \), the immune-absence equilibrium \( E_1 \) is unstable.
3. If \( R_1 = 1 \), it is a critical case.

Proof. The characteristic equation for \( E_1 \) is simplified as follows:

\[
(b + r - cy_1)\left[r^2 + (d + \beta y_1) r + \beta^2 x_1 y_1 \right] = 0. \tag{5.2}
\]

The root of the characteristic equation (5.2) \( \eta = cy_1 - b \) is negative and \( |\arg r_1| = \pi > \alpha (\pi / 2) \)
when \( R_1 < 1 \), positive and \( |\arg r_1| = 0 < \alpha (\pi / 2) \) when \( R_1 > 1 \), and zero when \( R_1 = 1 \), which is a critical case.

Now, we consider the equation

\[
r^2 + (d + \beta y_1) r + \beta^2 x_1 y_1 = 0. \tag{5.3}
\]

Because \( d + \beta y_1 > 0 \) and \( \beta^2 x_1 y_1 > 0 \), the equation (5.3) has two negative real roots, which are denoted by \( r_2 \) and \( r_3 \). It is easy to see \( |\arg r_1| = \pi > \alpha (\pi / 2) \) and \( |\arg r_1| = \pi > \alpha (\pi / 2) \). Hence, when \( R_1 < 1 \), the immune-absence equilibrium \( E_1 \) is locally asymptotically stable; when \( R_1 > 1 \), the immune-absence equilibrium \( E_1 \) is unstable; when \( R_1 = 1 \), it is a critical case.

The characteristic equation for \( E^* \) is simplified as follows:

\[
P(r) = r^3 + a_1 r^2 + a_2 r + a_3 = 0. \tag{5.4}
\]

where \( a_1 = d + \beta y^* > 0, a_2 = cy^* y^* + \beta^2 x^* y^* > 0, a_3 = cy^* y^* (d + \beta y^*) > 0, a_1 a_2 - a_3 > 0 \).

We obtain the discriminant of (5.4)

\[
D(p) = \begin{vmatrix}
-1 & -a_1 & -a_2 & -a_3 & 0 \\
0 & -1 & -a_1 & -a_2 & -a_3 \\
0 & -3 & -2a_1 & -a_2 & 0 \\
0 & 0 & -3 & -2a_1 & -a_2 \\
0 & 0 & 0 & -3 & -2a_1 & -a_2 \\
\end{vmatrix} = 18a_1 a_2 a_3 + (a_1 a_2)^2 - 4a_1 a_3 - 4a_2 a_3 - 27a_3^2.
\]

Using the result (iii) of Lemma 3 and Lemma 2, we obtain the following theorem.

**Theorem 9.** Consider model (1.1). In the condition of \( R_1 > 1 \),

1. if the discriminant of \( P(r) \), \( D(P) \) is positive, namely, \( D(P) > 0 \), then the immune-present equilibrium \( E^* \) is locally asymptotically stable for \( 0 < \alpha \leq 1 \);
2. if \( D(P) < 0 \), then the immune-present equilibrium \( E^* \) is locally asymptotically stable for \( 0 < \alpha < 2 / 3 \).

6. Conclusion
Mathematical model as an important infectious disease theory research method, in explaining disease outbreaks, describing the process of the spread of the epidemic, revealing the mechanism of viral infection and so on, have played a significant role. Because of the non-locality, memory and other properties of fractional order model, fractional differential equations are more practical in biological systems. In this paper, we give a fractional-order differential equation model of HIV infection by introducing Caputo derivative and immune response. We prove that the model which is built in this article has a unique nonnegative solution. With characteristic equation and Hurwitz criterion, we analyze the local asymptotic stability of the model (1.1). We discover that the stability of the infection-
free equilibrium and the immune-absence equilibrium of model (1.1) are the same as that of integer-order HIV infection model. When \( R_0 < 1 \), the infection-free equilibrium \( E_0 \) is locally asymptotically stable; however, when \( R_0 > 1 \), the infection-free equilibrium \( E_0 \) is unstable and when \( R_i < 1 \), the immune-absence equilibrium \( E_i \) is locally asymptotically stable; however, when \( R_i > 1 \), the immune-absence equilibrium \( E_i \) is unstable. When \( R_i > 1 \) and \( D(P) > 0 \), the immune-presence equilibrium \( E^* \) is locally asymptotically stable for \( 0 < \alpha \leq 1 \), while when \( D(P) < 0 \), the immune-presence equilibrium \( E^* \) is locally asymptotically stable only for \( 0 < \alpha < 2/3 \), which are different from integer-order HIV infection model.

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