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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:

$$\begin{cases} x^{\alpha}(t) = \lambda - dx - \beta xy, \\ y^{\alpha}(t) = \beta xy - ay - pyz, \\ z^{\alpha}(t) = cyz - bz, \end{cases} \tag{1.1}$$

$$x(0) = x_0 , y(0) = y_0 , z(0) = z_0 . \tag{1.2}$$

Here $0 < \alpha \le 1$; $x(t)$ 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. λ is the growth rate of new healthy cells. a and d are the death rate of infected cells and uninfected cells, respectively . β is the rate constant characterizing infection of the cells. 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 bz and get stronger at a rate cyz. 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 $\alpha > 0$, $n-1 < \alpha < n, n \in N$, is defined as

$$D^{\alpha} f(t) = I^{n-\alpha} D^{n} f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f^{(n)}(s)}{(t-s)^{\alpha+1-n}} \mathrm{d}s, \tag{2.1}$$

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

$$D^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(s)}{(t-s)^{\alpha}} \mathrm{d}s . \tag{2.2}$$

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 $0 < \alpha \le 1$ and $x \in R^n$. 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]:

$$\left|\arg(r_i)\right| > \frac{\theta\pi}{2} . \tag{2.4}$$

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, $h_1 > 0, h_3 > 0$, and $h_1 h_2 > h_3$ if $D(P) > 0$;

(b) if $D(P) < 0, h_1 \ge 0, h_2 \ge 0$, and $h_3 > 0$, 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 $R_+^3 = \{W \in R^3 : W \ge 0\}$ 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 $0 < \alpha \le 1$. Then one has

$$f(x)=f(a)+\frac{1}{\Gamma(\alpha)}D^{\alpha}f(\xi)(x-a)^{\alpha}, \tag{3.1}$$

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

Remark 5. Suppose that $f(x)\in C[a,b]$ and $D^{\alpha}f(x)\in C[a,b]$, for $0<\alpha\le 1$. It is clear from Lemma 5 that if $D^{\alpha}f(x)\ge 0$, $\forall x\in(a,b)$, then $f(x)$ is non-decreasing for each $x\in[a,b]$. If $D^{\alpha}f(x)\le 0$, $\forall x\in(a,b)$, 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_+^3 [10].

4. Equilibrium States

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

$$\begin{cases}\lambda-dx-\beta xy=0,\\ \beta xy-ay-pyz=0,\\ cyz-bz=0.\end{cases} \tag{4.1}$$

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_1 besides E_0, where $E_1=(x_1,y_1,z_1)=\left(\frac{a}{\beta},\frac{d(R_0-1)}{\beta},0\right)$.

When $R_1<1$, Model (1.1) has an interior immune-presence equilibrium E^* besides E_0 and E_1, where $E^*=\left(x^*,y^*,z^*\right)=\left(\frac{\lambda c}{dc+\beta b},\frac{b}{c},\frac{\beta\lambda c-adc-a\beta b}{p(dc+\beta b)}\right)$.

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 $R_0=1$, it is a critical case.

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

$$(r+d)(r+b)(r+a-\beta x_0)=0. \tag{5.1}$$

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 $r_3=\beta x_0-a=a(R_0-1)$. Because the imaginary part of characteristic root r_3 is zero, $R_0<1$ which means $|\arg r_3|=\pi>\alpha(\pi/2)$ is necessary and sufficient to ensure the local asymptotic stability of the infection-free equilibrium E_0. If $R_0>1$,

$|\arg r_3| = 0 < \alpha(\pi/2)$; hence the infection-free equilibrium E_0 is unstable. If $R_0 = 1$, $r_3 = 0$, 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) $r_1 = cy_1 - b$ 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 $|\arg r_2| = \pi > \alpha(\pi/2)$ and $|\arg r_3| = \pi > \alpha(\pi/2)$. Hence, when $R_1 < 1$, the immune-absence equilibrium E_1 is locally asymptotical 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 $a_1 = d + \beta y^* > 0$, $a_2 = cpy^* z^* + \beta^2 x^* y^* > 0$, $a_3 = cpy^* z^* (d + \beta y^*) > 0$, $a_1 a_2 - a_3 > 0$.

We obtain the discriminant of (5.4)

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

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 $0 < \alpha \le 1$;

(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 builded 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 $R_1 < 1$, the immune-absence equilibrium E_1 is locally asymptotically stable; however, when $R_1 > 1$, the immune-absence equilibrium E_1 is unstable. When $R_1 > 1$ 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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