Stability Analysis and Simulation of a Fractional-order HBV Infection Model Based on Saturation Incidence

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Abstract. Fractional order model has the memory, while the characteristic of the immune response contains the memory. In this paper, we set up a fractional-order HBV immune model based on saturation incidence for the first time. We derive the basic reproductive number \( R_0 \), the cytotoxic T lymphocytes immune response reproductive number \( R_1 \). There are three equilibrium points of our model, the local stability of each equilibrium point was given with corresponding hypothesis about \( R_0 \) or \( R_1 \). Finally we also give some numerical simulation, the simulation shows the individual difference in clinical may be reflected by fractional-order model.

Introduction

In recent years, fractional calculus has become a hotspot and undergone a huge development in many fields. By now, fractional differential equations are widely used in the fields of optics, fluid mechanics, signal processing and other natural sciences [1-3]. Many mathematicians and researchers in the application field are trying to model the differential equations of fractional order in biology, because the researchers found that the biological cell membranes have electron conductivity, which can be classified as a fractional order model [4-5]. In addition, some biological models established by fractional differential equations have proved to be more advantageous than integers [5]. In particular, The biggest difference between the fractional order model and the integer order model is that the fractional order model has the memory, while the characteristic of the immune response contains the memory [1, 5].

So when we discuss virus immune model, fractional mathematical models have become important tools. Paper [5] also proposed a fractional order HIV infection model, Paper [6] proposed a fractional order HIV infection model, considering the logistic growth of the healthy CTL cells, paper [3] had further proposed the following HIV model:

\[
\begin{align*}
\frac{dx}{dt} &= \lambda x - \mu x + \rho x\left(1 - \frac{x+y}{x_{max}}\right) - \beta xv \\
\frac{dy}{dt} &= \beta xv - \delta y \\
\frac{dv}{dt} &= \delta y - \gamma v \quad (1)
\end{align*}
\]

It should be pointed that, when describe the infection between uninfected cells and virus, paper [1,5,6] all use the bilinear incidences \( \beta xv \), so we will consider the model include the immune cell, while the cytotoxic T lymphocytes (CTL) immune response after viral infection is universal and necessary to eliminate or control the disease, as follows:

\[
\begin{align*}
\frac{dx}{dt} &= \lambda dx - \beta xv/(x+v) + \delta y \\
\frac{dy}{dt} &= \beta xv/(x+v) - ay - pyz - \delta y \\
\frac{dv}{dt} &= ky - \mu v \\
\frac{dz}{dt} &= cyz - bz \\
\end{align*}
\]

with \( 0<\alpha<1 \), where the meaning of \( x, y \) and \( v \) are the same as model Eq.1, \( z \) represents the number of CTL. The immune response is assumed to get stronger at a rate \( cyz \), the immune response decays
exponentially at a rate $bz$, which is proportional to their current concentration, the parameter $p$ expresses the efficacy of nonlytic component.

This paper is organized as follows. In section 2 and sections 3, we mainly discussed the existence and uniqueness of positive solutions and the stability of the equilibrium point respectively, we give the global stability of $E_0$ when $\delta=0$. This paper ended with a conclusion in section 4.

The Existence and Uniqueness of Positive Solutions

For the proof of the existence and uniqueness about the positive solution, we firstly prove that there exist a positively invariant region for system Eq.2.

Let

$$N(x)=x(t)+y(t)+\frac{a}{k}v(t)+\frac{p}{c}z(t),$$  \hspace{1cm} (3)

We have

$$N(x)=\lambda - dx - ay - \frac{aw}{k}v - \frac{pb}{c}z \leq \lambda - h(x + y + \frac{a}{k}v + \frac{p}{c}z),$$  \hspace{1cm} (4)

which $h = \min\{d,a,\mu,b\}$, $N(x) \leq \left(\frac{h}{h} + N(0)\right)E_0\left(-ht^\alpha\right) + \frac{h}{h}$, $D = \left\{x+y+\frac{a}{k}v+\frac{p}{c}z \leq \frac{h}{h},x,y,v,z \geq 0\right\}$, it is easy to see that $D$ is a positively invariant region for model Eq.2.

Theorem2.1. The system Eq.2 has an unique solution $X(t) = (x(t),y(t),v(t),z(t))^T$, and the solution will remain nonnegative for all $t \geq 0$.

Proof. Firstly we prove the existence uniqueness of solution. We denoting

$$\eta = \left(\begin{array}{c}
\lambda \\
0 \\
0 \\
0
\end{array}\right), \hspace{1cm} X(t) = \left(\begin{array}{c}
x(t) \\
y(t) \\
v(t) \\
z(t)
\end{array}\right), \hspace{1cm} A_1 = \left(\begin{array}{cccc}
-d & 0 & 0 & 0 \\
0 & -a & 0 & 0 \\
0 & 0 & -\mu & 0 \\
0 & 0 & 0 & -b
\end{array}\right), \hspace{1cm} A_2 = \left(\begin{array}{cccc}
-\beta & 0 & 0 & 0 \\
\beta & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{array}\right), \hspace{1cm} (5)

Obviously $f(t,X)$ satisfies conditions (1)-(3) of the Unique Solution Lemma [7], we only prove system Eq.2 satisfies the last condition (4). Let

$$\eta = \left(\begin{array}{c}
\lambda \\
0 \\
0 \\
0
\end{array}\right), \hspace{1cm} X(t) = \left(\begin{array}{c}
x(t) \\
y(t) \\
v(t) \\
z(t)
\end{array}\right), \hspace{1cm} A_1 = \left(\begin{array}{cccc}
-d & 0 & 0 & 0 \\
0 & -a & 0 & 0 \\
0 & 0 & -\mu & 0 \\
0 & 0 & 0 & -b
\end{array}\right), \hspace{1cm} A_2 = \left(\begin{array}{cccc}
-\beta & 0 & 0 & 0 \\
\beta & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{array}\right), \hspace{1cm} (6)

$$

\begin{align*}
\|f(t,X)\| &= \|A_1X(t) + \frac{v(t)}{x(t) + v(t)}A_2X(t) + \eta\| \\
&\leq \|A_1X(t)\| + \|A_2X(t)\| + m\|A_3X(t)\| + m\|A_4X(t)\| + \|A_5X(t)\| + \|\eta\|
\end{align*}

\begin{align*}
\|f(t,X)\| &\leq \omega + \lambda\|X\|,
\end{align*}

Where $m = \lambda/h, \omega = \|\eta\|, \lambda = \|A_1\| + \|A_2\| + m\|A_3\| + m\|A_4\| + \|A_5\|$. By [7], system Eq.2 has a unique solution. Next we prove the solution is nonnegative for all $t \geq 0$. For model Eq.2, we know

$$x^\alpha(t)|_{t=0} = \lambda - 0y^\alpha(t)|_{t=0} = \lambda, \hspace{1cm} v^\alpha(t)|_{t=0} = k, \hspace{1cm} z^\alpha(t)|_{t=0} = 0 .$$  \hspace{1cm} (9)

By [4], the solution will remain in $R^+_\alpha$. 
Stable Analysis

In this section, we will discuss the stability of the model Eq.2. This system always has an infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$, where $x_0 = \lambda / d$. The basic reproduction number is $R_0 = \beta k / \mu (a + \delta)$, when $R_0 > 1$, the system Eq.2 will have immune-absence equilibrium $E_1 = (x_1, y_1, v_1, 0)$, where

$$ x_1 = \frac{\lambda k}{kd + (a + \mu)(R_0 - 1)}, \quad y_1 = \frac{\mu (R_0 - 1)}{kd + (a + \delta)(R_0 - 1)}, \quad v_1 = \frac{\lambda k}{kd + (a + \delta)(R_0 - 1)}.$$

We can see $R_0 > 1, x_1 > 0, y_1 > 0$ and $v_1 > 0$ and $z_1 = 0$, which means the infected cells and virus coexist but the immune response is not activated yet, that is $cy_1 < b$. Further, we will give the immune response reproductive number $R_1 = cy_1 / b$, when $R_1 > 1$, that is $cy_1 > b$, which means immune response is activated. So when $R_1 > 1$, there is another immune-response equilibrium $E_2 = (x_2, y_2, v_2, z_2)$, where

$$ x_2 = \frac{A + \sqrt{A^2 + 4d(\lambda + \delta) v_2}}{2d}, \quad y_2 = \frac{b}{c}, \quad v_2 = \frac{kb}{\mu c}, \quad z_2 = \frac{\lambda - ay_2 - dx_2}{\beta y_2}. \tag{10} $$

Which $A = \lambda + \delta y_2 + (\beta + d)v_2$.

Now, we introduce the main theorem.

Theorem 3.1 for the model Eq.2.

1. If $R_0 < 1$, the equilibrium $E_0$ is locally asymptotically stable.
2. If $R_0 > 1$, the equilibrium $E_0$ is unstable.

Proof. The characteristic equation for the infection-free equilibrium $E_0$ is given as follows:

$$(\lambda + d)(\lambda + b)(\lambda^2 + (a + \delta + \mu)\lambda + \mu(a + \delta) - \beta k) = 0. \tag{11}$$

We can see that the characteristic roots $\lambda_1 = -d < 0$, $\lambda_2 = -b < 0$, which satisfied $|\arg \lambda_{1,2}| = \pi > \alpha \pi / 2$.

For another two characteristic roots, we will consider the equation $\lambda^2 + (a + \delta + \mu)\lambda + \mu(a + \delta) - \beta k = 0$.

Let $B = a + \delta + \mu > 0$, $C = \mu(a + \delta) - \beta k$. Obviously $R_0 < 1$ can ensure $C > 0$, so we have $\lambda_{3,4} < 0$, which satisfied $|\arg \lambda_{3,4}| = \pi > \alpha \pi / 2$. So if $R_0 < 1$, the equilibrium $E_0$ is locally asymptotically stable, if $R_0 > 1$, $E_0$ is unstable.

Theorem 3.2. For system Eq.2, when $R_0 > 1$,

1. When $R_1 < 1$, if $D(P) > 0$, $E_1$ is locally asymptotically stable for $0 < a < 1$; if $D(P) < 0$, then the equilibrium $E_1$ is locally asymptotically stable for $0 < a < 2/3$.

2. When $R_1 > 1$, the equilibrium $E_1$ is unstable.

Proof. The characteristic equation for the $E_1$ is given as follows:

$$(\lambda - cy_1 + b)(\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3) = 0. \tag{12}$$

Where

$$ a_1 = \mu + d + \beta v_1^2 / (x_1 + v_1)^2 > 0, \tag{13} $$

$$ a_2 = \mu (d + \beta v_1^2 / (x_1 + v_1)^2) + d(a + \delta) + \beta av_1^2 / (x_1 + v_1)^2 + \mu(a + \delta)(1 - \frac{1}{R_0}) > 0, \tag{14} $$

$$ a_3 = d \mu(a + \delta)(1 - \frac{1}{R_0}) + \frac{\beta av_1^2}{(x_1 + v_1)^2} > 0. \tag{15} $$

We can see the $\lambda_1 = cy_1 - b$, when $R_1 < 1$, $\lambda_1$ is negative and $|\arg \lambda_1| = \pi > \alpha \pi / 2$ hold.

$$ a_1 a_2 - a_3 = \left( a + \delta + d + \frac{\beta v_1^2}{(x_1 + v_1)^2} \right) \left( \mu(d + \frac{\beta v_1^2}{(x_1 + v_1)^2}) + d(a + \delta) + \frac{\beta v_1^2}{(x_1 + v_1)^2} + \mu(a + \delta)(1 - \frac{1}{R_0}) \right) + \frac{\beta k x_1^2}{(x_1 + v_1)^2} $$

$$ + \mu^2 \left( d + \frac{\beta v_1^2}{(x_1 + v_1)^2} \right) > 0, \tag{16} $$
Hence according to [8], we know when \( R_1 < 1 \), if \( D(P) > 0 \), \( E_1 \) is locally asymptotically stable for \( \theta < \alpha < 1 \); if \( D(P) < 0 \), then the equilibrium \( E_1 \) is locally asymptotically stable for \( \theta < \alpha < 2/3 \). When \( R_1 > 1 \), the equilibrium \( E_1 \) is unstable.

For the immune-response equilibrium \( E_2=(x_2,y_2,v_2,z_2) \). We assume that the characteristic equation for the \( E_2 \) is given as follows: \( P(\lambda)=\lambda^4+a_1\lambda^3+a_2\lambda^2+a_3\lambda+a_4=0 \). By [2], when \( n=4 \), the characteristic equation has negative real roots only if \( a_n > 0, n=0,1,3 \) and \( a_3a_2a_1 > a_1^2 + a_3^2a_0 \).

In the following part, we will give the global stability of \( E_0 \) when \( \delta=0 \).

**Theorem 3.3** For system Eq.2,

1. If \( R_0 < 1 \), the equilibrium \( E_0 \) is global asymptotically stable.
2. If \( R_0 > 1 \), the equilibrium \( E_0 \) is unstable.

**Proof.**

Let \( V(x)=y(t)+\frac{p}{e}z(t)+\frac{a}{k}v(t) \). We have

\[
D^\alpha V = D^\alpha y(t) + \frac{p}{e} D^\alpha z(t) + \frac{a}{k} D^\alpha v(t) \\
= \beta xv/(x+v) - ay - pyz + \frac{p}{e} (cyz - bz) + \frac{a}{k} (ky - uv) \\
= (x/(x+v))*\beta v - pbz/c - \frac{\mu a}{k} v \\
\leq \beta v - \mu av/k = (R_0 - 1)v/k. 
\]

Since \( R_0 < 1 \), we have \( D^\alpha V \leq 0 \). Let \( M = \{(x,y,v,z) \in D, D^\alpha V = 0 \} \), obviously \( M \subset \{(x,y,v,z) \in D, v=0 \} \). Let \( E \) is the largest positively invariant subset of \( M \), by the third equation of system Eq.2, we can know \( v=0 \). So in \( E \), the first and last equation will be as follows:

\[
\begin{cases}
  x^\alpha = \lambda d x \\
  z^\alpha = -bz
\end{cases}
\]

Its solution is

\[
\begin{cases}
  x(t) = \left( -\lambda/d + x(0) \right) E_0(-dt^\alpha) + \lambda/d \\
  z(t) = z(0) E_0(-bt^\alpha)
\end{cases}
\]

We have \( \lim_{t \to \infty} x(t) = \frac{\lambda}{d} \), \( \lim_{t \to \infty} z(t) = 0 \). Thus, by the Lvapunov-Lasalle Theorem [7], all solutions in the set \( D \) approach the infection-free equilibrium \( E_0 \). Noting that \( E_0 \) is locally asymptotically stable, so \( E_0 \) is global asymptotically stable.

**Discussion and Conclusion**

In this paper, we discussed a fractional order HBV model with saturation incidence. For the model Eq.2, We obtain the basic reproductive numbers \( R_0 \) and the cytotoxic T lymphocytes immune response reproductive number \( R_1 \). When \( R_0 < 1 \), we have proved that \( E_0 \) is global asymptotically stable with different order \( \alpha \). When \( R_0 > 1, R_1 < 1 \), \( E_1 \) is locally asymptotically stable different order \( \alpha \). When \( R_1 > 1 \), we also give the local stable condition of \( E_2 \). The simulation shows that the dynamic routes have different change rate with different order \( \alpha \) at former stage even with the same initial condition. So can think that the individual difference in clinical may be reflected by fractional-order model.
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