Global Dynamics of a Fractional Order HIV Model with Both Virus-to-Cell and Cell-to-Cell Transmissions and Therapy Effect

Hui Miao, Xamxinur Abdurahman*, Zhidong Teng and Chengjun Kang

***Abstract*—A fractional order HIV model with both virus-to-cell and cell-to-cell transmissions and therapy effect is investigated. The conditions for the existence of the equilibria are determined. Local stability analysis of the HIV model is studied by using the fractional Routh-Hurwitz stability conditions. We have generalized the integer LaSalle's invariant theorem into fractional system and given some sufficient conditions for the disease-free equilibrium and endemic equilibrium being globally asymptotical stability. We applied an efficient numerical method based on converting the fractional derivative to integer derivative to solve the HIV model. Some numerical examples are provided to illustrate our results. The fractional derivatives are described in the Caputo sense.**

***Index Terms*—Fractional order; HIV dynamics; Local and global stability; Lyapunov functional.**

I. Introduction

HUMAN immunodeficiency virus (HIV) which targets the $CD4^+$ T-cells is now a major epidemic worldwide. It causes the destruction and decline of $CD4^+$ T-cells which results in decreasing the body's ability to fight infection. The progression of this disease can be influenced by factors such as genetic differences among individuals, co-infection with other microbes, age and the level of virulence of an individual strain of virus.

Mathematical models have been developed to describe the within-host dynamics of various viral infections, mostly focusing on virus-to-cell spread in the bloodstream, such as HIV [1-5,13,27], hepatitis C virus (HCV) [6,7,10], human T-cell lymphotropic virus I (HTLV-1) [8,9], etc. The classical viral infection model is composed of the interactions among susceptible target cells, infected target cells and free virus.

However, in most virus infections, some recent studies reveal that direct cell-to-cell transmission also is vital to the spread of the virus. HIV is thought to be active in areas such as the lymph nodes and the brain where cell-to-cell spread would be a much more important mode of infection than virus-to-cell spread [11]. Gummuluru et al. [12] demonstrates that cell-to-cell spread of HIV is the predominant route of viral spread since viral replication in a system with rapid cell turnover kinetics depends on cell-to-cell transfer of virus. Based on these observations, researchers have constructed within-host viral infection models for the dynamics of cell-to-cell transmission of HIV [2]. Understanding the viral dynamics is very significant in terms of applications.

This process of HIV pathogenesis can be slowed down or reversed to a certain extent by Highly Active Antiretroviral Treatment (HAART). Primarily HAART inhibits the process of virus particle formation. This keeps the viral load down and in turn increases the quantity of $CD4^+$ T-cells. The advent of anti-retroviral drugs has been considered as important breakthrough in HIV treatment. Anti-viral drug treatment for HIV infections causes rapid reduction in plasma virus load. HAART is generally a combination of reverse transcriptase inhibitor (RTI) drugs and protease inhibitor (PI) drugs. RTI drugs are designed to prevent the conversion of HIV RNA to DNA in early stages of HIV replication. Thus RTI drugs block conversion of uninfected cells to infected cells. PI drugs are designed to intervene in the last stage of the virus replication cycle to prevent HIV from being properly assembled, and thus cause the newly produced virus to be noninfectious. Once treatment is initiated three distinct viral decay phases are seen in patients [24]. Considering an antiretroviral therapy in the presence of both virus-to-cell and cell-to-cell transmissions seems to be an interesting and worthy project.

In recent decades, with the rapid development of computer technology, fractional calculus has been extensively applied in many fields. Many researchers have tried to model real processes using the fractional calculus. Ahmed et al. [16] developed the fractional-order predator-prey model and the fractional-order rabies model. In biology, it has been shown that modeling some biological model by fractional ordinary differential equation (FODE) has more advantages than classical integer order modeling. Particular emphasis is that a major difference between fractional order models and integer order models is that fractional order models possess memory, while the main features of immune response involve memory. Hence, we propose a fractional order HIV infection model with both virus-to-cell and cell-to-cell transmissions and therapy effect

$$\begin{cases} D^\alpha x_1(t) = & \lambda - \delta x_1(t) - (1-\gamma)\beta_1 x_1(t) x_3(t) \\ & -\beta_2 x_1(t) x_2(t), \\ D^\alpha x_2(t) = & (1-\gamma)\beta_1 x_1(t) x_3(t) + \beta_2 x_1(t) x_2(t) \\ & -a x_2(t), \\ D^\alpha x_3(t) = & (1-\eta) N a x_2(t) - u x_3(t), \end{cases} \tag{1.1}$$

where $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent the uninfected cells,

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the infected cells and the free virus, respectively. λ is the birth rate of the uninfected cells. δ, a and u represent the death rate of the uninfected cells, the infected cells and the virus, respectively. β_1 is the viral infection rate. β_2 is the contact rate between uninfected and infected cells. N is the number of virus produced by infected cells. $1-\gamma$ represents the reverse transcriptase inhibitor drug effect. $1-\eta$ is the protease inhibitor drug effect.

In this paper, our purpose is to investigate the dynamical properties of model (1.1), expressly the local and global stability of equilibria. By using the linearization method, we established the local stability of disease-free equilibrium and endemic equilibrium. By constructing Lyapunov functionals and using the fractional LaSalle's invariance principle, we demonstrated the global asymptotic stability of disease-free equilibrium and endemic equilibrium, respectively.

The organization of this paper is as follows. In the next section, we give some properties of the fractional calculus. In Section 3, we demonstrate the existence and uniqueness of positive solutions of model (1.1). In Section 4, we study the local and global stability of disease-free equilibrium and endemic equilibrium. In Section 5, the numerical method for fractional differential equation is discussed. In Section 6, the numerical simulations is given to further illustrate the main results obtained in this paper. In the last section, we offer a brief conclusion.

II. Basic results of fractional calculus

Definition 2.1 *([14]) The fractional integral of order $\alpha > 0$ of a function $f : R^+ \to R$ is given by*

$$I^\alpha f(x) = \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t)\,\mathrm{d}t.$$

Definition 2.2 *([14]) Let $\alpha \geq 0$, $n = [\alpha] + 1$, $n-1 < \alpha \leq n$, where $[\alpha]$ denotes the integer part of number α. The Caputo fractional derivative of order α for a function $f \in C^{n+1}([a,+\infty), R)$ is defined by*

$$D^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t \frac{f^{(n)}(s)}{(t-s)^{(\alpha+1-n)}}\,\mathrm{d}s, \quad t > 0,$$

$n-1 < \alpha < n$.

Lemma 2.3 *([19]) Assume that the vector function $f : R^+ \times R^3 \to R^3$ satisfies the following conditions:*

(1) Function $f(t, X(t))$ is Lebesgue measurable with respect to t on $\in R^+$;

(2) Function $f(t, X(t))$ is continuous with respect to $X(t)$ on R^3;

(3) $\frac{\partial f(t,X)}{\partial X}$ is continuous with respect to $X(t)$ on R^3;

(4) $\| f(t,X) - f(t,Y) \| \leq L \| X - Y \|, \forall t \in R^+,\ X, Y \in R^3$.

Then

$$\begin{cases} D^\alpha X(t) = f(t, X(t)), \\ X(0) = X_0,\ \alpha \in (0,1] \end{cases}$$

have a unique solution.

Lemma 2.4 *([16]) The equilibrium point (x^*, y^*) of the fractional 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

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

evaluated at the equilibrium satisfy the following condition:

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

III. The existence and uniqueness of positive solutions

For the proof of the non-negative solution, we consider the following two Lemmas.

Lemma 3.1 *(Generalized Mean Value Theorem)([17]) Suppose that $f(t) \in C[a,b]$ and $D^\alpha f(t) \in C[a,b]$ for $0 < \alpha \leq 1$, then we have*

$$f(t) = f(a) + \frac{1}{\Gamma(\alpha)} D^\alpha f(\xi)(t-a)^\alpha, a < \xi < t, \forall t \in (a,b].$$

Lemma 3.2 *([17]) Suppose that $f(t) \in C[a,b]$ and $D^\alpha f(t) \in C[a,b]$ for $0 < \alpha \leq 1$. If $D^\alpha f(t) \geq 0, \forall t \in [a,b]$, then $f(t)$ is non-decreasing for each $t \in [a,b]$. If $D^\alpha f(t) \leq 0, \forall t \in [a,b]$, then $f(t)$ is non-increasing for each $t \in [a,b]$.*

Theorem 3.3 *There is a unique solution $X(t) = (x_1(t), x_2(t), x_3(t))^T$ for model (1.1) at $t \geq 0$ and the solution will remain in R^3_+.*

Proof: Firstly, we prove that $\forall (x_1(0), x_2(0), x_3(0)) \in R^3_+$, model (1.1) has a unique solution. Obviously, vector function f of model (1.1) satisfies conditions (1)-(3) of Lemma 2.3. Next, we prove model (1.1) satisfies the last condition (4) of Lemma 2.3. Then model (1.1) becomes $D^\alpha X(t) = A_1 X(t) + x_1 A_2 X(t) + A_3$, where

$$A_1 = \begin{pmatrix} -\delta & 0 & 0 \\ 0 & -a & 0 \\ 0 & (1-\eta)Na & -u \end{pmatrix},$$

$$A_2 = \begin{pmatrix} 0 & -\beta_2 & -(1-\gamma)\beta_1 \\ 0 & \beta_2 & (1-\gamma)\beta_1 \\ 0 & 0 & 0 \end{pmatrix} \text{and} A_3 = \begin{pmatrix} \lambda \\ 0 \\ 0 \end{pmatrix}.$$

Denote $f(t, X(t)) = A_1 X(t) + x_1 A_2 X(t) + A_3$, then

$$\begin{aligned} & \| f(t,X(t)) - f(t,Y(t)) \| \\ = \ & \| A_1(X(t) - Y(t)) + x_1 A_2 X(t) - x_1 A_2 Y(t) \\ & + x_1 A_2 Y(t) - y_1 A_2 Y(t) \| \\ \leq \ & (\| A_1 \| + \| x_1 \| \| A_2 \| + \| A_2 \| \| Y(t) \|) \\ & \| X(t) - Y(t) \| \\ = \ & L \| X(t) - Y(t) \|, \end{aligned}$$

where $\| X(t) \| = \Sigma_{i=1}^3 \sup_t | x_i(t) |$ and $L = \| A_1 \| + \| A_2 \| (\| x_1 \| + \| Y(t) \|)$.

By Lemma 2.3, model (1.1) has a unique solution. Secondly, we prove the solution of model (1.1) is always non-negative. Based on model (1.1), we have

$$\begin{aligned} & D^\alpha x_1 \mid_{x_1=0} = \lambda \geq 0, \\ & D^\alpha x_2 \mid_{x_2=0} = (1-\gamma)\beta_1 x_1(t) x_3(t) \geq 0, \\ & D^\alpha x_3 \mid_{x_3=0} = (1-\eta) N a x_2(t) \geq 0. \end{aligned}$$

From Lemmas 3.1 and 3.2, the solution will remain in R^3_+.

IV. Stability of equilibria

In this section, we firstly discuss the existence of equilibria of model (1.1). The basic reproductive ratio of model (1.1) which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process is given by

$$R_0 = \frac{\lambda(\beta_1(1-\gamma)(1-\eta)Na + \beta_2 u)}{au\delta}.$$

By direct calculation we have that model (1.1) has possible two equilibria.

(i) There is always disease-free equilibrium $E_0 = (\bar{x_1}, 0, 0)$, where $\bar{x_1} = \frac{\lambda}{\delta}$.

(ii) If $R_0 > 1$, then there exists a unique endemic equilibrium $E_1 = (x_1^*, x_2^*, x_3^*)$, where

$$\begin{aligned} x_1^* &= \frac{au}{\beta_1(1-\gamma)(1-\eta)Na + \beta_2 u}, \\ x_2^* &= \frac{\lambda}{a} - \frac{u\delta}{\beta_1(1-\gamma)(1-\eta)Na + \beta_2 u}, \\ x_3^* &= \frac{(1-\eta)Nax_2^*}{u}. \end{aligned}$$

A. Locally asymptotically stable

Theorem 4.1 *If $R_0 \leq 1$, then disease-free equilibrium E_0 is locally asymptotically stable, and unstable if $R_0 > 1$.*

Proof: At equilibrium E_0, the characteristic equation for the corresponding linearized system of model (1.1) is

$$\begin{aligned} &(s+\delta)[s^2 + (a + u - \frac{\beta_2\lambda}{\delta})s + u(a - \frac{\beta_2\lambda}{\delta}) - (1 \\ &-\eta)Na(1-\gamma)\tfrac{\beta_1\lambda}{\delta}] = 0. \end{aligned} \tag{4.1}$$

One root of equation (4.1) is $s_1 = -\delta$. The remaining two roots are obtained by the following equation

$$s^2 + (a+u-\frac{\beta_2\lambda}{\delta})s + u(a-\frac{\beta_2\lambda}{\delta}) - (1-\eta)Na(1-\gamma)\frac{\beta_1\lambda}{\delta} = 0. \tag{4.2}$$

It is clear that

$$\begin{cases} s_2 + s_3 = \dfrac{\beta_2\lambda}{\delta} - a - u < 0, \\ s_2 s_3 = u(a - \dfrac{\beta_2\lambda}{\delta}) - (1-\eta)Na(1-\gamma)\dfrac{\beta_1\lambda}{\delta} > 0. \end{cases}$$

Hence, two roots of equation (4.2) have negative real parts. Therefore, according to Lemma 2.4, E_0 is locally asymptotically stable if $R_0 \leq 1$, and unstable if $R_0 > 1$.

Theorem 4.2 *If $R_0 > 1$, then endemic equilibrium E_1 is locally asymptotically stable.*

Proof: At equilibrium E_1, the characteristic equation for the corresponding linearized system of model (1.1) is

$$f(s) = s^3 + p_1 s^2 + p_2 s + p_3 = 0, \tag{4.3}$$

where

$$\begin{aligned} p_1 = &\ \delta + (1-\gamma)\beta_1 x_3^* + \tfrac{\beta_2\lambda}{a} + a + u \\ &- \tfrac{\beta_2 u(a+\delta)}{(1-\gamma)(1-\eta)\beta_1 Na + \beta_2 u}, \\ p_2 = &\ (a+u)(\delta + (1-\gamma)\beta_1 x_3^* + \beta_2 x_2^*) \\ &- \tfrac{\beta_2\delta au}{(1-\gamma)(1-\eta)\beta_1 Na + \beta_2 u}, \\ p_3 = &\ au((1-\gamma)\beta_1 x_3^* + \beta_2 x_2^*). \end{aligned}$$

Let $D(f)$ denote the discriminant of a polynomial $f(s) = s^3 + p_1 s^2 + p_2 s + p_3$, then

$$D(f) = 18p_1p_2p_3 + (p_1p_2)^2 - 4p_3p_1^3 - 4p_2^3 - 27p_3^2.$$

Using the proposition given in [23], we have the following result by using Routh-Hurwitz conditions.

Lemma 4.3 *Suppose that E_1 exists in R_+^3.*

(i) If $p_1 > 0,\ p_3 > 0,\ p_1p_2 > p_3$, then $\forall \alpha \in (0,1]$, E_1 is locally asymptotically stable.

(ii) If $D(f) < 0,\ p_1 \geq 0,\ p_2 \geq 0,\ p_3 > 0,\ p_1p_2 < p_3,\ \alpha < \frac{2}{3}$, then E_1 is locally asymptotically stable.

(iii) If $D(f) < 0,\ p_1 < 0,\ p_2 < 0,\ \alpha > \frac{2}{3}$, then E_1 is unstable.

(iv) If $D(f) < 0,\ p_1 > 0,\ p_2 > 0,\ p_1p_2 = p_3,\ \alpha \in (0,1]$, then E_1 is locally asymptotically stable.

(v) If $D(f) < 0,\ p_1 > 0,\ p_3 = 0,\ \alpha \in (0,1]$, then E_1 is locally stable.

B. Globally asymptotically stable

In this section, we first give sufficient conditions for the globally asymptotical stability of fractional system which generalize the result for ODEs. Then we will demonstrate the globally asymptotical stability of E_0 of model (1.1). Assume Ω is an open subset of R^n. Consider the following autonomous system

$$D^\alpha x(t) = f(x). \tag{4.4}$$

For $V \in C^1(\Omega, R^n)$, we define the α $(0 < \alpha \leq 1)$ order derivative of $V(x)$ along the solutions of equation (4.4) as the following form

$$D^\alpha V\mid_{(4.4)} = I^{1-\alpha} DV\mid_{(4.4)} = I^{1-\alpha}(\frac{dV}{dx}\frac{dx}{dt}). \tag{4.5}$$

To give sufficient conditions for the globally asymptotical stability of equilibria for the disease-free and the endemic, we put forward two important lemmas.

Lemma 4.4 *([15]) Suppose D is a bounded closed set. Every solution of $D^\alpha x(t) = f(x)$ starts from a point in D and remains in D for all time. If $\exists V(x) : D \to R$ with continuous first partial derivatives satisfies following condition:*

$$D^\alpha V\mid_{(4.4)} \leq 0.$$

Let $E = \{x \mid D^\alpha V\mid_{(4.4)} = 0\}$ and M be the largest invariant set of E. Then every solution $x(t)$ originating in D tends to M as $t \to \infty$. Particularly, when $M = 0$, then $x \to 0,\ as\ t \to \infty$.

Lemma 4.5 *([20]) Let $x(t) \in R^+$ be a continuous and derivable function. Then, for any time instant $t \geq t_0$,*

$$D_t^\alpha(x(t) - x^* - x^* \ln\frac{x(t)}{x^*}) \leq (1 - \frac{x^*}{x(t)})D_t^\alpha x(t),\ x^* \in R^+,$$

$\forall \alpha \in (0,1)$.

Theorem 4.6 *If $R_0 \leq 1$, then infection-free equilibrium E_0 is globally asymptotically stable.*

Proof: Define Lyapunov functional $V_1(t)$ as follows

$$\begin{aligned} V_1(t) = &\ x_1(t) - \bar{x_1} - \bar{x_1}\ln\frac{x_1(t)}{\bar{x_1}} + x_2(t) \\ &+ \tfrac{(1-\gamma)\beta_1\bar{x_1}}{u}x_3(t). \end{aligned}$$

Calculating the time derivative of $V_1(t)$ along solutions of model (1.1), we obtain

$$\begin{aligned} D^\alpha V_1(t) \leq\ & (1-\frac{\bar{x_1}}{x_1(t)})(\delta\bar{x_1}-\delta x_1(t)-(1\\ & -\gamma)\beta_1 x_1(t)x_3(t)-\beta_2 x_1(t)x_2(t))+(1\\ & -\gamma)\beta_1 x_1(t)x_3(t)+\beta_2 x_1(t)x_2(t)-ax_2(t)\\ & +\frac{(1-\gamma)\beta_1\bar{x_1}}{u}((1-\eta)Nax_2(t)-ux_3(t))\\ =\ & -\frac{\delta(x_1(t)-\bar{x_1})^2}{x_1(t)}+ax_2(t)(\beta_2\bar{x_1}-a\\ & +\tfrac{(1-\gamma)\beta_1\bar{x_1}(1-\eta)Na}{u})\\ =\ & -\frac{\delta(x(t)-\bar{x_1})^2}{x_1(t)}+ax_2(t)(R_0-1). \end{aligned}$$

Note that $D^\alpha V_1(t)=0$ if and only if $x_1(t)=\bar{x_1}$ and $x_2(t)=0$. By the third equation of model (1.1), we also have $x_3(t)=0$. Therefore, by the LaSalle's invariance principle [15], equilibrium E_0 is globally asymptotically stable.

Theorem 4.7 *If $R_0>1$, then endemic equilibrium E_1 is globally asymptotically stable.*

Proof: Define Lyapunov functional $V_2(t)$ as follows

$$\begin{aligned} V_2(t)=\ & x_1(t)-x_1^*-x_1^*\ln\frac{x_1(t)}{x_1^*}+x_2(t)-x_2^*\\ & -x_2^*\ln\tfrac{x_2(t)}{x_2^*}+\tfrac{\beta_1(1-\gamma)x_1^*x_3^*}{(1-\eta)Nax_2^*}(x_3(t)-x_3^*\\ & -x_3^*\ln\tfrac{x_3(t)}{x_3^*}). \end{aligned}$$

Calculating the derivative of $V_2(t)$ along solutions of model (1.1), we obtain that

$$\begin{aligned} D^\alpha V_2(t)\leq\ & (1-\frac{x_1^*}{x_1(t)})(\delta x_1^*+(1-\gamma)\beta_1 x_1^*x_3^*\\ & +\beta_2 x_1^*x_2^*-\delta x_1(t)-(1-\gamma)\beta_1 x_1(t)x_3(t)\\ & -\beta_2 x_1(t)x_2(t))+(1-\frac{x_2^*}{x_2(t)})((1\\ & -\gamma)\beta_1 x_1(t)x_3(t)+\beta_2 x_1(t)x_2(t)-ax_2(t))\\ & +\frac{\beta_1(1-\gamma)x_1^*x_3^*}{(1-\eta)Nax_2^*}(1-\frac{x_3^*}{x_3(t)})((1\\ & -\eta)Nax_2(t)-ux_3(t))\\ =\ & -\frac{\delta(x_1(t)-x_1^*)^2}{x_1(t)}+\beta_2 x_1^*x_2^*(2-\frac{x_1^*}{x_1(t)}\\ & -\frac{x_1(t)}{x_1^*})+(1-\gamma)\beta_1 x_1^*x_3^*(3-\frac{x_1^*}{x_1(t)}\\ & -\frac{x_2^*x_1(t)x_3(t)}{x_1^*x_3^*x_2(t)}-\frac{x_2(t)x_3^*}{x_2^*x_3(t)}). \end{aligned}$$

When $R_0>1$, we have $D^\alpha V_2(t)\leq 0$ and $D^\alpha V_2(t)=0$ if and only if $x_1(t)=x_1^*,\ x_2(t)=x_2^*$ and $x_3(t)=x_3^*$. By the LaSalle's invariance principle, E_1 is globally asymptotically stable.

V. Numerical method

In order to solve model (1.1), we shall use a numerical method introduced by Atanackovic and Stankovic [21,22] to solve the fractional-order nonlinear differential equation (FDE). In [21] it was shown that for a function $f(t)$, the Caputo fractional derivative of order α with $0<\alpha<1$ may be approximated as

$$\begin{aligned} D^\alpha f(t)=\ & \frac{1}{\Gamma(2-\alpha)}\{\frac{f^{(1)}(t)}{t^{\alpha-1}}[1+\sum_{p=1}^{M}\frac{\Gamma(p-1+\alpha)}{\Gamma(\alpha-1)p!}]\\ & -[\frac{\alpha-1}{t^\alpha}f(t)+\sum_{p=2}^{M}\frac{\Gamma(p-1+\alpha)}{\Gamma(\alpha-1)(p-1)!}(\frac{f(t)}{t^\alpha}\\ & +\frac{C_p(f)(t)}{t^{p-1+\alpha}})]\}, \end{aligned} \tag{5.1}$$

where

$$C_p(f)(t)=-(p-1)\int_0^t \tau^{p-2}f(\tau)\,\mathrm{d}\tau,\ p=2,3,\cdots, \tag{5.2}$$

with the following properties

$$\frac{d}{dt}C_p(f)=-(p-1)t^{p-2}f(t),\ p=2,3,\cdots. \tag{5.3}$$

We can rewrite equation (5.1) as follows:

$$\begin{aligned} & D^\alpha f(t)\simeq S(\alpha,t,M)f^{(1)}(t)+W(\alpha,t,M)f(t)\\ & +\sum_{p=2}^{M}A(\alpha,t,p)\tfrac{C_p(f)(t)}{t^{p-1+\alpha}}, \end{aligned} \tag{5.4}$$

where

$$\begin{aligned} S(\alpha,t,M)&=\frac{1+\sum_{p=1}^{M}\frac{\Gamma(p-1+\alpha)}{\Gamma(\alpha-1)p!}}{\Gamma(2-\alpha)t^{\alpha-1}},\\ R(\alpha,t)&=\frac{1-\alpha}{t^\alpha\Gamma(2-\alpha)},\\ A(\alpha,t,p)&=-\frac{\Gamma(p-1+\alpha)}{\Gamma(2-\alpha)\Gamma(\alpha-1)p!},\\ W(\alpha,t,M)&=R(\alpha,t)+\sum_{p=2}^{M}\frac{A(\alpha,t,p)}{t^\alpha}. \end{aligned}$$

Denote

$$\begin{aligned} & H_1(t)=x_1(t),\ H_{M+1}(t)=x_2(t),\ H_{2M+1}(t)=x_3(t),\\ & H_p(t)=C_p(x_1)(t),\ H_{M+p}(t)=C_p(x_2)(t),\\ & H_{2M+p}(t)=C_p(x_3)(t),\ p=2,3,\cdots. \end{aligned}$$

We can rewrite model (1.1) as the following form

$$\begin{aligned} & S(\alpha,t,M)H_1'(t)+W(\alpha,t,M)H_1(t)\\ & \quad+\sum_{p=2}^{M}A(\alpha,t,p)\tfrac{H_p(t)}{t^{p-1+\alpha}}\\ & =\lambda-\delta H_1(t)-(1-\gamma)\beta_1 H_1(t)H_{2M+1}(t)\\ & \quad-\beta_2 H_1(t)H_{M+1}(t),\\ & S(\alpha,t,M)H_{M+1}'(t)+W(\alpha,t,M)H_{M+1}(t)\\ & \quad+\sum_{p=2}^{M}A(\alpha,t,p)\tfrac{H_{M+p}(t)}{t^{p-1+\alpha}}\\ & =(1-\gamma)\beta_1 H_1(t)H_{2M+1}(t)+\beta_2 H_1(t)H_{M+1}(t)\\ & \quad-aH_{M+1}(t),\\ & S(\alpha,t,M)H_{2M+1}'(t)+W(\alpha,t,M)H_{2M+1}(t)\\ & +\sum_{p=2}^{M}A(\alpha,t,p)\tfrac{H_{2M+p}(t)}{t^{p-1+\alpha}}\\ & =(1-\eta)NaH_{M+1}(t)-uH_{2M+1}(t), \end{aligned} \tag{5.5}$$

where

$$\begin{aligned} H_p(t)=\ & -(p-1)\int_0^t\tau^{p-2}H_1(\tau)\,\mathrm{d}\tau,\\ H_{M+p}(t)=\ & -(p-1)\int_0^t\tau^{p-2}H_{M+1}(\tau)\,\mathrm{d}\tau, \end{aligned}$$

$$H_{2M+p}(t) = -(p-1)\int_0^t \tau^{p-2} H_{2M+1}(\tau)\,\mathrm{d}\tau, \quad p = 2, 3, \cdots M. \tag{5.6}$$

Now we can rewrite (5.5) and (5.6) as the following form

$$\begin{aligned}
H_1'(t) = & \frac{1}{S(\alpha,t,M)}(\lambda - \delta H_1(t) - (1 \\
& -\gamma)\beta_1 H_1(t) H_{2M+1}(t) - \beta_2 H_1(t) H_{M+1}(t) \\
& -W(\alpha,t,M) H_1(t) - \sum_{p=2}^{M} A(\alpha,t,p)\tfrac{H_p(t)}{t^{p-1+\alpha}}), \\
H_p'(t) = & -(p-1)t^{p-2} H_1(t),\ p = 2, 3, \cdots M, \\
H_{M+1}'(t) = & \frac{1}{S(\alpha,t,M)}((1-\gamma)\beta_1 H_1(t) H_{2M+1}(t) \\
& +\beta_2 H_1(t) H_{M+1}(t) - a H_{M+1}(t) \\
& -W(\alpha,t,M) H_{M+1}(t) \\
& -\sum_{p=2}^{M} A(\alpha,t,p)\tfrac{H_{M+p}(t)}{t^{p-1+\alpha}}), \\
H_{M+p}'(t) = & -(p-1)t^{p-2} H_{M+1}(t),\ p = 2, 3, \cdots M, \\
H_{2M+1}'(t) = & \tfrac{1}{S(\alpha,t,M)}((1-\eta) N a H_{M+1}(t) \\
& -u H_{2M+1}(t) - W(\alpha,t,M) H_{2M+1}(t) \\
& -\sum_{p=2}^{M} A(\alpha,t,p)\tfrac{H_{2M+p}(t)}{t^{p-1+\alpha}}), \\
H_{2M+p}'(t) = & -(p-1)t^{p-2} H_{2M+1}(t),\ p = 2, 3, \cdots M,
\end{aligned} \tag{5.7}$$

with the following initial conditions

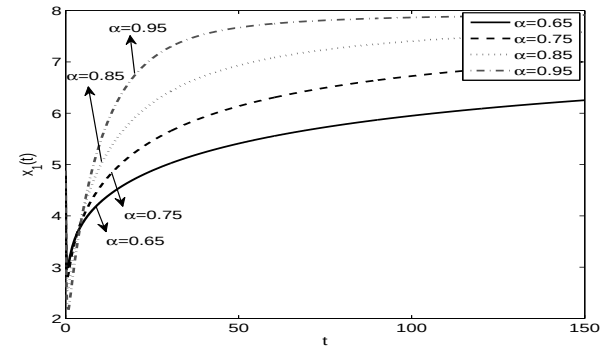
$$\begin{aligned}
H_1(\varphi) = & \ x_1(0), \\
H_p(\varphi) = & -\tfrac{p-1}{2}\Delta t^{p-1} x_1(0), \\
H_{M+1}(\varphi) = & \ x_2(0), \\
H_{M+p}(\varphi) = & -\tfrac{p-1}{2}\Delta t^{p-1} x_2(0), \\
H_{2M+1}(\varphi) = & \ x_3(0), \\
H_{2M+p}(\varphi) = & -\tfrac{p-1}{2}\Delta t^{p-1} x_3(0), \\
p = & \ 2, 3, \cdots M.
\end{aligned} \tag{5.8}$$

In section 6, we consider the numerical solution of system of ordinary differential equation (5.7) with the initial conditions (5.8) by using the well known Runge-Kutta method of order fourth.

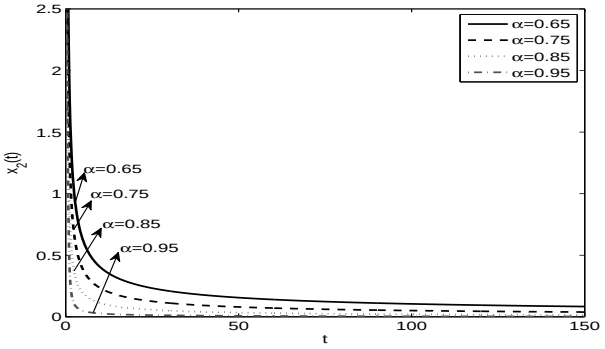
VI. Numerical simulations

In this section, to verify the effectiveness of the obtained results, some numerical simulations for fractional-order HIV model (1.1) have been conducted. All the differential equations are solved by using the method proposed in the previous section. In all numerical runs, the solution has been approximated at $\varphi = \Delta t = 0.01$. In Fig. 1, we display phase portrait of model (1.1). The values of parameters are $\alpha = 0.65,\ 0.75,\ 0.85,\ 0.95$, $\lambda = 0.8$, $\delta = 0.1$, $\gamma = 0.8$, $\beta_1 = 0.2$, $\beta_2 = 0.3$, $a = 5$, $\eta = 0.9$, $N = 1$, $u = 3$ and $M = 150$ with the initial conditions $x_1(0) = 8$, $x_2(0) = 16$, $x_3(0) = 12$. By calculating, $R_0 = 0.4907 < 1$, then disease-free equilibrium E_0 is globally asymptotically stable. In Fig. 2, we choose $\lambda = 10$, $\delta = 0.01$, $\gamma = 0.1$, $\beta_1 = 0.3$, $\beta_2 = 0.3$, $a = 0.5$, $\eta = 0.2$, $N = 1$, $u = 3$ and $M = 50$ with the initial conditions $x_1(0) = 8$, $x_2(0) = 16$, $x_3(0) = 12$.

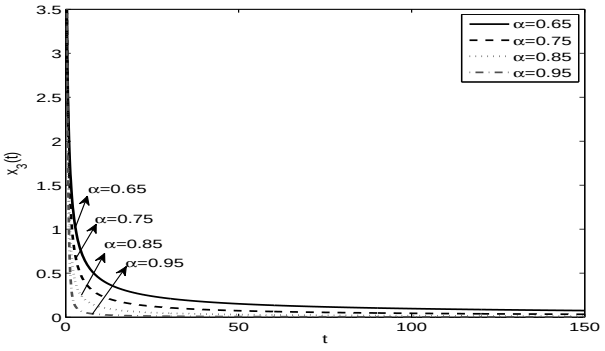
By calculating, $R_0 = 672 > 1$, then endemic equilibrium E_1 is globally asymptotically stable.



(a)

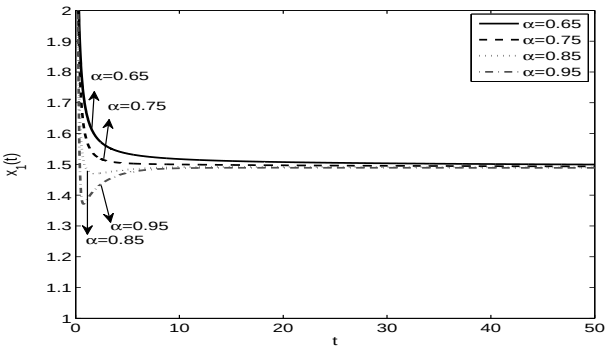


(b)

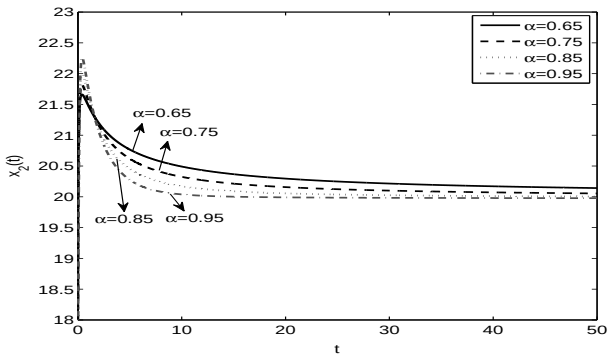


(c)

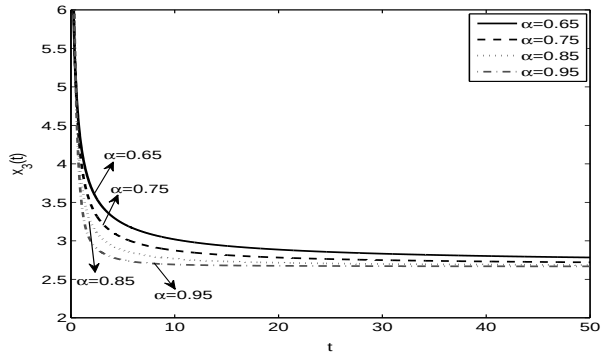
Fig.1. The diagrams show the approximate solutions of $x_1(t)$, $x_2(t)$ and $x_3(t)$ for $\alpha = 0.65,\ 0.75,\ 0.85,\ 0.95$, in condition of $R_0 = 0.4907 < 1$. It shows that $E_0 = (8, 0, 0)$ is globally asymptotically stable.



(a)



(b)



(c)

Fig.2. The diagrams show the approximate solutions of $x_1(t)$, $x_2(t)$ and $x_3(t)$ for $\alpha = 0.65,\ 0.75,\ 0.85,\ 0.95$, in condition of $R_0 = 672 > 1$. It shows that $E_1 = (1.4881, 19.9702, 2.6627)$ is globally asymptotically stable.

VII. Discussion

When a virus (HBV, HIV, HTLV-1, etc.) enters the human body, the salient features of the infection mechanism are as follows. First, the free virus enters its target, a susceptible cell. Inside this cell, it replicates itself. And this susceptible cell becomes an infected cell. Then the infected cell dies and releases new viruses, these viruses begin to infect other susceptible cells [26,28]. Besides the conventional HIV infection mode, we introduce cell-to-cell transmission mode inspired by recent studies [2,23]. This mode assumes that viral particles can be simultaneously transferred from infected $CD4^+T$ cells to uninfected ones through virological synapses [25]. In this paper, we have proposed a fractional order HIV model, as a generalization of the direct cell-to-cell transfer of HIV in addition virus-to-cell transmission by an integer order model. The premise of the proposed model is that fractional order system possesses memory while the main features of immune response involve memory.

By the serious analysis, we have shown that model (1.1) has a threshold dynamics. Such a threshold dynamics is fully determined by basic reproduction number R_0 in the sense that disease-free equilibrium E_0 is globally asymptotically stable if $R_0 < 1$, and when $R_0 > 1$, E_0 yields to a globally asymptotically stable endemic equilibrium E_1, implying the infection will persist.

Examining the formula for R_0, we demonstrated that R_0 should include two parts corresponding to virus-to-cell infection $R_{01} = \frac{\lambda\beta_1(1-\gamma)(1-\eta)Na}{au\delta}$ and cell-to-cell transmission $R_{02} = \frac{\lambda\beta_2}{a\delta}$. Meanwhile, we found that it is larger than that given in existing models that considered only one infection mode. Indeed, note that when $\beta_1 = 0$, meaning that infection is exclusively through cell-to-cell transmission, which is the scenario of the work in [2], R_0 reduces to R_{02}. This would be the basic reproduction number of the corresponding model that ignores the virus-to-cell infection mode. Similarly, when $\beta_2 = 0$, R_0 reduces to R_{01}, which is exactly the basic reproduction number for the corresponding model that neglects the cell-to-cell transmission mechanism. Therefore, we see that our model reveals that the basic reproduction number of the model that neglects either the cell-to-cell spread or virus-to-cell infection is underestimated.

We have also performed numerical experiments to demonstrate the theoretical results. The effect of parameter α (i.e. the order of model (1.1)) on the epidemic dynamics has been discovered. From the Figs.1-2 show that, as α increases, the trajectory of the model closes to the integer-order ODE. Also, the rate of convergence of the numerical solutions of model (1.1) for various values of α can be obtained as well.

Observing all obtained results in this paper, we can directly put forward the following open questions which need to be further studied in the future. In this paper, we obtain the global asymptotic stability of equilibria for the three-dimensional HIV model. Time delay can not be ignored in many biological model, time delays are always considered for the purpose of accurate representations of the phenomena. At the same time, immune response are the main host factors which determine viral load. Therefore, whether we also can obtain that the global asymptotic stability of equilibria for delayed fractional order HIV model with immune response will be a very estimable and significative subject.

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References

[1] M.A. Nowak and C.R.Bangham, "Population dynamics of immune responses to persistent viruses", *Science*, vol.272, pp.74-79, 2000.

[2] R.V. Culshaw, S. Ruan and G. Webb, "A mathematical model of cell-to-cell spread of HIV-1 that includes a time delay", *J. Math. Biol.*, vol.46, pp.425-444, 2003.

[3] A.S. Perelson, D.E. Kirschner, R.D. Boer, "Dynamics of HIV infection of CD4+ T cells", *Math. Biosci.*, vol.114, pp.81-125, 1993.

[4] A.S. Perelson, P.W. Nelson,"Mathematical analysis of HIV-I: dynamics in vivo", *SIAM Review*, vol.41, pp.3-44, 1999.

[5] D. Wodarz, A.L. Lloyd, V.A. Jansen, M.A. Nowak, "Dynamics of macrophage and T cell infection by HIV", *J. Theor. Biol.*, vol.196, pp.101-113, 1999.

[6] H. Dahari, A. Loa, R.M. Ribeiroa, A.S. Perelson, "Modeling hepatitis C virus dynamics: liver regeneration and critical drug efficacy", *J. Theor. Biol.*, vol.247, pp.371-381, 2007.

[7] S. Debroy, B.M. Bolker, M. Martcheva, "Bistability and long-term cure in a within-host model of hepatitis", *C. J. Biol. Syst.*, vol.19, pp.533-550, 2011.

[8] N.I. Stilianakis, J. Seydel, "Modeling the T-cell dynamics and pathogenesis of HTLV-I infection", *Bull. Math. Biol.*, vol.61, pp.935-947, 1999.

[9] D. Wodarz, M.A. Nowak, C.R. Bangham, "The dynamics of HTLV-I response and the CTL response", *Immunol. Today.*, vol.20, pp.220-227, 1999.

[10] D. Wodarz, "Hepatitis C virus dynamics and pathology: the role of CTL and antibody response", *J. General Virol.*, vol.84, pp.1743-1750, 2003.

[11] C.B. Sturdevant, S.B. Joseph, G. Schnell, R.W. Price, R. Swanstrom, "Compartmentalized replication of R5 T cell-tropic HIV-1 in the central nervous system early in the course of infection", *PLoS Pathog.*, vol.11, doi 10.1371.1004720, 2015.

[12] S. Gummuluru, C.M. Kinsey, M. Emerman, "An in vitro rapid-turnover assay for human immunodeficiency virus type 1 replication selects for cell-to-cell spread of virua", *J. Virol.*, vol.74, pp.10882-10891, 2000.

[13] X. Lai, X. Zou, "Modeling HIV-1 virus dynamics with both virus-to-cell infection and cell-to-cell transmission", *SIAM J. Appl. Math.*, vol.74, pp.898-917, 2014.

[14] I. Podlubny, "Fractional Differential Equations: An Introduction to Fractional Derivatives, Fractional Differential Equations, to Methods of their Solution and Some of their Applications", *Academic press*, 1998.

[15] J. Huo, H. Zhao, L. Zhu, "The effect of vaccines on backward bifurcation in a fractional order HIV model", *Nonlinear Anal: RWA.*, vol.26, pp.289-305, 2015.

[16] E. Ahmed, A.M.A. El-Sayed, H.A.A. El-Saka, "Equilibrium points, Stability and numerical solutions of fractional-order predator-prey and rabies models", *J. Math. Anal. Appl.*, vol.325(1), pp.542-553, 2007.

[17] Z.M. Odibat, N.T. Shawagfeh, "Generalized taylors formula", *Appl. Math. Comput.*, vol. 186(1), pp.286-293, 2007.

[18] E. Ahmed, A.S. Elgazzar, "On fractional order differential equations model for nonlocal epidemics", *Physica A.*, vol.379, pp.607-614, 2007.

[19] K. Diethelm, N.J. Ford, "Analysis of fractional differential equation", *J. Math. Anal. Appl.*, vol.265, pp.229-248, 2002.

[20] C. Vargas-De-Len, "Volterra-type Lyapunov functions for fractional-order epidemic", *Commun. Nonlinear Sci. Numer. Simulat.*, vol.24, pp.75-85, 2015.

[21] T.M. Atanackovic, B. Stankovic, "An expansion formula for fractional derivatives and its application", *Fract. Calculus Appl. Anal.*, vol.7, pp.365-378, 2004.

[22] T.M. Atanackovic, B. Stankovic, "On a numerical scheme for solving differential equations of fractional order", *Mech. Res. Commun.*, vol.7, pp.429-438, 2008.

[23] X. Wang, Y. He, M. Wang, "Chaos control of a fractional order modified coupled dynamos system", *Nonlinear Anal: RWA.*, vol.71, pp.6126-6134, 2009.

[24] V. Müller, A.F. Maree, R.J.D. Boer, "Release of virus from lymphoid tissue affects human immunodeficiency virus type 1 and hepatitis C virus kinetics in the blood", *J. Virol.*, vol.75, pp.2597-2603, 2001.

[25] Q. Sattentau, "The direct passage of animal viruses between cells", *Curr. Opin. Virol.*, vol.1, pp.396-402, 2011.

[26] H. Miao, Z. Teng, C. Kang, A. Muhammadhaji, " Stability analysis of a virus infection model with humoral immunity response and two time delays", *Math. Meth. Appl. Sci.*, vol.39, pp.3434-3449, 2016.

[27] C. Kang, H. Miao, X. Chen, " Global Stability Analysis for a Delayed HIV Infection Model with General Incidence Rate and Cell Immunity", *Engin. Letters*, vol.24, no. 4, pp.392-398, 2016.

[28] S. Olaniyi, M.A. Lawal and O.S. Obabiyi, "Stability and Sensitivity Analysis of a Deterministic Epidemiological Model with Pseudo-recovery", *IAENG Inter. J. Appl. Math.*, vol.46, no. 2, pp.160-167, 2016.