

A Fractional Order HIV Internal Viral Dynamics Model

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Abstract: In this paper, a fractional order model is established to describe HIV internal viral dynamics involving HAART effect. First, the model is proved to possess non-negative solutions as desired in any population dynamics. Then, a detailed analysis is carried out to study the stability of equilibrium points. Numerical simulations are presented to illustrate the stability analysis.

Keywords: HIV infection, HAART, Stability, Fractional differential equation, Non-negative solution.

1 Introduction

Since its discovery in 1981, human immunodeficiency virus (HIV) has spread relentlessly throughout the world and now is a major epidemic worldwide. HIV spreads by attacking the immune system, in particular by depleting the CD4 cells. The pathogenesis of HIV infection is a function of the virus life cycle, the host cellular environment, and quantity of virus in the infected individual. Factors such as age or genetic differences among individuals, the level of virulence of an individual strain of virus, and co-infection with other microbes may influence the rate and severity of disease progression. Cells with CD4 receptors at the site of HIV entry become infected and viral replication begins within them. The infected cells can then release virion or infected cells can undergo lysis to release new virion, which can then infect additional cells. CD4 cells, the primary targets of HIV, become infected as they encounter HIV. Active replication of HIV occurs at all stages of the infection. Over a period of years, even when little virus is detectable in the blood, significant amounts of virus accumulate within infected cells. This interaction between the virus and the immune system is called HIV internal viral dynamics.

In the literature mathematical and computer modeling has been found numerous applications in many fields such as finite element modeling of thin layers [Givoli

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(2004)], multiscale crystal plasticity modeling [Hasebe (2006)], acoustic waveguide modeling [Lu and Zhu (2007)] and so on. Referring to modeling of HIV infection, mathematical models have been proven valuable in understanding the dynamics of HIV infection. [Perelson, Kirschner, and De Boer (1993)] proposed an ordinary differential equation (ODE) model of cell-free viral spread of HIV in a wellmixed compartment such as the bloodstream. [Perelson, Neumann, Markowitz, Leonard and Ho (1996)] tried to estimate the length of the life cycle of the virus. [Korthals Altes, Wodarz and Jansen (2002)] concentrated on the question of whether it was advisable to stimulate CD4 cell response. They found that only when the virus has a low basic reproductive number does the number of CD4 cells at the moment of infection influence the outcome of infection. [Di Mascio, Ribeiro, Markowitz, Ho and Perelson (2004)] provided a statistical characterization of transient viraemia observed in 123 patients, suggesting that patients have different tendencies to show transient viraemia during the period of viral load suppression. [Ding and Wu (1999)] modeled the effect of Reverse Transcriptase Inhibitor drugs as inhibition rates of cell infection and Protease Inhibitor drugs as inhibition rates of infectious virus production based on the biological mechanisms of these two different types of drugs. They showed that the two viral decay rates are monotone functions of the treatment effects of these antiviral therapies. [Dalal, Greenhalgh and Mao (2008)] has proposed a stochastic model of viral dynamics including the effect of Highly Active Antiretroviral Treatment (HAART). The corresponding deterministic model has been analysed by [Tuckwell and Wan (2000)]. Given the basic reproduction number, R_0 , they showed that if $R_0 < 1$ then the disease-free equilibrium is the unique equilibrium and if $R_0 > 1$ then as well as the disease-free equilibrium there is a unique endemic equilibrium. Moreover if $R_0 < 1$ the disease-free equilibrium is locally asymptotically stable, whilst if $R_0 > 1$ then the disease-free equilibrium is unstable whilst the unique endemic equilibrium is locally asymptotically stable.

However, modeling the HIV infection has been mostly restricted to use a system of integer-order ordinary (or delay) differential equations without HAART (for example, [Perelson, Kirschner and De Boer (1993); Perelson, Neumann, Markowitz, Leonard and Ho (1996); Korthals Altes, Wodarz and Jansen (2002); Di Mascio, Ribeiro, Markowitz, Ho and Perelson (2004); Ding and Wu (1999)] and the references cited therein). Recently, fractional calculus has been extensively applied in many fields [Ahmed and Elgazzar (2007); Hartley, Lorenzo and Qammer (1995); El-Sayed, El-Mesiryb and El-Saka (2007); Podlubny (1999); Hilfer (2000)]. Many mathematicians and applied researchers have tried to model real processes using the fractional calculus. [Nigmatullin and Nelson (2006)] described in terms of fractional kinetics in complex systems. [Jesus, Machado and Cunha (2008)] ana-

lyzed the fractional order dynamics in botanical electrical impedances. [Petrovic, Spasic and Atanackovic (2005)] developed a fractional-order mathematical model of a human root dentin. In biology, it has been deduced that the membranes of cells of biological organism have fractional-order electrical conductance and then are classified in groups of non-integer order models. Fractional derivatives embody essential features of cell rheological behavior and have enjoyed greatest success in the field of rheology [Djordjević, Jarić, Fabry, Fredberg and Stamenović (2003)]. Particular emphasis is that a major difference between fractional order models and integer order models is that fractional order models possess memory [Ahmed and Elgazzar (2007); Hilfer (2000)], while the main features of immune response involve memory. To model HIV infection involving fractional order, [Ding and Ye (2009); Ye and Ding (2009)] introduced fractional-order into a model of HIV infection of CD4⁺ T-cells. They showed that the model possesses non-negative solutions and carried out a detailed analysis on the stability of equilibrium. To our knowledge, no works are contributed to the analysis for a model of fractional order differential equations (FODE) of describing the viral dynamics in the presence of HIV infection and HAART. Motivated by this situation, the idea of modeling HIV infection involving HAART effect by FODE arises.

This paper is organized as follows. In Section 2, a fractional order model of HIV internal viral dynamics is deduced. In Section 3, the established FODE model is proved to possess unique non-negative solutions as desired in any population dynamics. A detailed analysis on local stability of equilibrium is carried out in Section 4. Simulations and results are given in Section 5. Conclusions in Section 6 close the paper.

2 Model derivation

We first give the definition of fractional-order integration and fractional-order differentiation [Podlubny (1999)]. There are several forms of definitions of fractional integral and derivative, such as, Riemann-Liouville fractional integral and fractional derivative, Caputo's fractional derivative, Grünwald-Letnikov fractional derivative, and so on. It should be pointed out that applied problems require definitions of fractional derivatives allowing the utilization of physically interpretable initial conditions. In fact, Caputo's fractional derivative exactly satisfies these demands. The Caputo's fractional derivative was introduced [Caputo (1967); Podlubny (1999); Kilbas, Srivastava and Trujillo (2006)] to alleviate some of the difficulties associated with Riemann-Liouville approach to fractional differential equations when applied to the solution of physical problems. Therefore, in this article, we will adopt Caputo's derivative to deal with the systems of FODE.

Definition 1 The fractional integral of order $\alpha > 0$ of a function $f(t)$ is given by

$$I^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t \frac{f(\tau)}{(t-\tau)^{1-\alpha}} d\tau, \quad (1)$$

where $f(t)$ is an arbitrary integrable function.

Definition 2 The fractional derivative of $f(t)$ in Caputo's sense is defined as

$$D^\alpha f(t) = \frac{1}{\Gamma(m-\alpha)} \int_0^t \frac{f^{(m)}(\tau)}{(t-\tau)^{\alpha+1-m}} d\tau, \quad (2)$$

where $m-1 < \alpha \leq m$, $m \in N$, $t > 0$. In particular, when $0 < \alpha < 1$, we have

$$D^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(\tau)}{(t-\tau)^\alpha} d\tau. \quad (3)$$

This process of HIV pathogenesis can be slowed down or reversed to a certain extent by HAART. Primarily HAART inhibits the process of virus particle formation. This keeps the viral load down and in turn increases the quantity of CD4 cells. 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 [Ding and Wu (1999)]. To describe the viral dynamics in the presence of HIV-1 infection and HAART, the following system of ODE has been proposed [Dalal, Greenhalgh and Mao (2008); Tuckwell and Wan (2000)]:

$$\begin{cases} \frac{dx(t)}{dt} = \lambda - \delta x(t) - (1-\gamma)\beta x(t)z(t), \\ \frac{dy(t)}{dt} = (1-\gamma)\beta x(t)z(t) - ay(t), \\ \frac{dz(t)}{dt} = (1-\eta)Nay(t) - uz(t) - (1-\gamma)\beta x(t)z(t), \end{cases} \quad (4)$$

where $x(t)$ represents the concentration of uninfected cells, $y(t)$ represents the concentration of infected cells, $z(t)$ represents the concentration of virus particles.

Since $CD4^+$ cells posse memory, we now introduce fractional order into the previous ODE model (4), and obtain a new system described by the following set of

FODE:

$$\begin{cases} D^\alpha x(t) = \lambda - \delta x(t) - (1 - \gamma)\beta x(t)z(t), \\ D^\alpha y(t) = (1 - \gamma)\beta x(t)z(t) - ay(t), \\ D^\alpha z(t) = (1 - \eta)Nay(t) - uz(t) - (1 - \gamma)\beta x(t)z(t), \end{cases} \quad (5)$$

where λ is the total rate of production of healthy cells, δ is the nature death rate of healthy cells, $(1 - \gamma)$ is the reverse transcriptase inhibitor drug effect, β is the rate uninfected become infected with virus, $(1 - \eta)$ is the protease inhibitor drug effect, a is the nature death rate of infected cells, u is the nature death rate of infective virus particles, and N is the number of virus produced by infected cells. Here, $0.5 < \alpha \leq 1$ is restricted (see [Ding and Ye (2009)]). When $0 < \alpha \leq 0.5$, the solution of Eq.(5) is unbounded by numerical simulations, so we do not think fractional derivatives can approximately describe the rate of change in number.

3 Non-negative solutions

It is important that we do not have to worry about negative values when dealing with a model of population dynamics is concerned. Hence we first prove the positivity of the solutions. Denote $R_+^3 = \{X \in R^3 | X \geq 0\}$, and let $X(t) = (x(t), y(t), z(t))^T$.

Theorem 1 *Assume that $0 < \gamma, \eta < 1$ and that δ, λ, a, u, N and β are positive real numbers. Then for any initial value $X(0) > 0$, there is a unique solution $X(t)$ to equation (5) on $t \geq 0$ and the solution will remain in R_+^3 .*

Proof. According to Theorem 3.1 and Remark 3.2 of [Lin (2007)], we know the solution on $(0, +\infty)$ solving the equation (5) with any given initial value $X(0) > 0$ is not only existent but also unique. Next, we will show the solution with $X(0) > 0$ is always positive whenever the solution exists. Suppose that it is not true, *i.e.*, there exists $t^* > 0$ at which, at least, one of the elements of the solution becomes “0” and until which all elements of the solution are positive. There are three possibilities as follows.

(i) If $x(t^*) = 0$ holds, then $y(t) > 0, z(t) > 0$ when $t \in [0, t^*]$ and $x(t) > 0$ when $t \in [0, t^*)$. Let $m_1 = \min_{t \in [0, t^*]} z(t), c_1 = \delta + (1 - r)\beta m_1$, then it follows, from the first equation of Eq.(5), that

$$D^\alpha x(t) > -c_1 x(t), \quad t \in [0, t^*] \quad (6)$$

which implies

$$x(t) > x(0)E_\alpha(-c_1 t^\alpha), \quad t \in [0, t^*], \quad (7)$$

where

$$E_\alpha(t) = \sum_{k=0}^{\infty} \frac{t^k}{\Gamma(k\alpha + 1)}. \quad (8)$$

Since $x(0) > 0$, one has $x(t^*) > 0$ which is a contradiction.

(ii) If $y(t^*) = 0$ holds, then $x(t) > 0$, $z(t) > 0$ when $t \in [0, t^*]$ and $y(t) > 0$ when $t \in [0, t^*]$. Then it follows, from the second equation of Eq.(5), that

$$D^\alpha y(t) > -ay(t), \quad t \in [0, t^*] \quad (9)$$

which implies

$$y(t) > y(0)E_\alpha(-at^\alpha), \quad t \in [0, t^*]. \quad (10)$$

Since $y(0) > 0$, one has $y(t^*) > 0$ which is a contradiction.

(iii) If $z(t^*) = 0$ holds, then $x(t) > 0$, $y(t) > 0$ when $t \in [0, t^*]$ and $z(t) > 0$ when $t \in [0, t^*]$. Let $m_2 = \min_{t \in [0, t^*]} x(t)$, $c_2 = u + (1-r)\beta m_2$, then it follows, from the third equation of Eq.(5), that

$$D^\alpha z(t) > -c_2 z(t), \quad t \in [0, t^*] \quad (11)$$

which implies

$$z(t) > z(0)E_\alpha(-c_2 t^\alpha), \quad t \in [0, t^*]. \quad (12)$$

Since $z(0) > 0$, one has $z(t^*) > 0$ which is a contradiction.

Therefore, the solution of equation (5) will remain in R_+^3 . The proof is complete.

4 Local stability analysis

It is clear that the above system (5) has a disease-free equilibrium given by $E_0 = (\lambda/\delta, 0, 0)$, and in case that the basic reproduction number $R_0 = \frac{(1-\gamma)\beta\lambda N(1-\eta)}{\delta u + \beta\lambda(1-\gamma)} > 1$, there is an endemical equilibrium given by $E^* = (x^*, y^*, z^*)$, where

$$\begin{aligned} x^* &= \frac{u}{\beta(1-\gamma)[N(1-\eta)-1]}, \\ y^* &= \frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{a\beta(1-\gamma)[N(1-\eta)-1]}, \\ z^* &= \frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{(1-\gamma)\beta u}. \end{aligned} \quad (13)$$

Theorem 2 *The disease-free equilibrium E_0 is locally asymptotically stable if $0 < R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. The Jacobian matrix $J(E_0)$ for system (5) evaluated at E_0 is given by

$$J(E_0) = \begin{pmatrix} -\delta & 0 & -\frac{(1-\gamma)\beta\lambda}{\delta} \\ 0 & -a & \frac{(1-\gamma)\beta\lambda}{\delta} \\ 0 & (1-\eta)Na & -u - \frac{(1-\gamma)\beta\lambda}{\delta} \end{pmatrix}. \tag{14}$$

Denote

$$M_1 = a\delta + u\delta + (1-\gamma)\beta\lambda > 0, \quad M_2 = 4a\delta(u\delta + (1-\gamma)(1-N(1-\eta))\beta\lambda). \tag{15}$$

Hence, the eigenvalues of $J(E_0)$ are $\lambda_1 = -\delta$, $\lambda_{2,3} = \frac{1}{2\delta}(-M_1 \pm \sqrt{M_1^2 - M_2})$.

According to stability conditions in [Matignon (1996); Diethelm and Ford (2002)] the disease-free equilibrium E_0 is locally asymptotically stable if all of the eigenvalues λ_i ($i = 1, 2, 3$) satisfy $|\arg(\lambda_i)| > \alpha\pi/2$.

If $0 < R_0 < 1$, then $M_2 > 0$ and the above three characteristic roots will have negative real parts. Thus the disease-free equilibrium E_0 is locally asymptotically stable.

If $R_0 > 1$, then $M_2 < 0$, and thus at least one eigenvalue will be positive real root. Thus, the disease-free equilibrium E_0 is unstable and the endemical equilibrium E^* emerges. Therefore Theorem 2 is complete.

To discuss the local stability of the endemical equilibrium E^* for $R_0 > 1$, we consider the linearized system of (5) at E^* . The Jacobian matrix at E^* is given by

$$J(E^*) = \begin{pmatrix} -\delta - \frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{u} & 0 & -\frac{u}{N(1-\eta) - 1} \\ \frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{u} & -a & \frac{u}{N(1-\eta) - 1} \\ -\frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{u} & (1-\eta)Na & -u - \frac{u}{N(1-\eta) - 1} \end{pmatrix}. \tag{16}$$

Denote

$$M_3 = \frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{u}, \quad M_4 = \frac{u}{N(1-\eta) - 1}. \tag{17}$$

Then the characteristic equation of the linearized system of (5) at E^* is

$$\Phi(p) = p^3 + a_1p^2 + a_2p + a_3 = 0, \tag{18}$$

where

$$\begin{aligned} a_1 &= a + M_3 + M_4 + u + \delta, \\ a_2 &= M_3u + (M_4 + u)\delta + a(M_3 + M_4 - M_4N + u + \delta + M_4N\eta), \\ a_3 &= a(M_3u + \delta(M_4 - M_4N + u + M_4N\eta)). \end{aligned} \tag{19}$$

According to stability conditions in [Matignon (1996); Diethelm and Ford (2002)], we have the following proposition.

Proposition 1 *The endemical equilibrium E^* is locally asymptotically stable if all of the eigenvalues p of $J(E^*)$ satisfy $|\arg(p)| > \alpha\pi/2$.*

Denote

$$D(\Phi) = - \begin{vmatrix} 1 & a_1 & a_2 & a_3 & 0 \\ 0 & 1 & a_1 & a_2 & a_3 \\ 3 & 2a_1 & a_2 & 0 & 0 \\ 0 & 3 & 2a_1 & a_2 & 0 \\ 0 & 0 & 3 & 2a_1 & a_2 \end{vmatrix} \quad (20)$$

$$= 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2.$$

Utilizing the results of [Ahmed and Elgazzar (2007); Ahmed, El-Sayed and El-Saka (2006)], we have

Proposition 2 *Assume that E^* exists in R_+^3 .*

(i) *If the discriminant of $\Phi(p)$, $D(\Phi)$, is positive and Routh-Hurwitz conditions are satisfied, that is,*

$$a_1 > 0, a_3 > 0, a_1a_2 > a_3, D(\Phi) > 0, \quad (21)$$

then the endemical equilibrium E^ is locally asymptotically stable.*

(ii) *If $D(\Phi) < 0$, $a_1 > 0$, $a_2 > 0$, $a_1a_2 = a_3$, $\alpha \in (0.5, 1)$, then the endemical equilibrium E^* is locally asymptotically stable.*

(iii) *If $D(\Phi) < 0$, $a_1 \geq 0$, $a_2 \geq 0$, $a_3 > 0$, $\alpha \in (0.5, 2/3)$, then the endemical equilibrium E^* is locally asymptotically stable.*

(iv) *If $D(\Phi) < 0$, $a_1 < 0$, $a_2 < 0$, $\alpha > 2/3$, then the endemical equilibrium E^* is unstable.*

5 Simulations and results

In this section, we give some numerical simulations of system (5) to illustrate our results on stability, the values of the parameters are given in **Table 1**, more details can be found in [Dalal, Greenhalgh and Mao (2008)].

For the parameter values given in **Table 1**, we can get that $R_0 = N/202$, thus $0 < R_0 < 1$ if $0 < N < 202$ and $R_0 > 1$ if $N > 202$. Experimentally, N has been suggested to be hundreds and even thousands [Ding and Ye (2009)]. We first take $N = 100$, then $R_0 = 0.49505 < 1$, the condition of Theorem 2 is satisfied. Thus we expect the number of infected cells and infected virus particles to die out and the number of uninfected cells to approach λ/δ . Numerical simulations (see **Figure 1(A1-A3)**) show that the uninfected cells predominate.

Table 1: Parameters and values of system (5).

Parameters		Values
x_0	Initial concentration of uninfected cells	10000 dm^{-3}
y_0	Initial concentration of infected cells	10000 dm^{-3}
z_0	Initial concentration of virus particles	10000 dm^{-3}
$(1 - \gamma)$	The reverse transcriptase inhibitor drug effect	0.5
$(1 - \eta)$	The protease inhibitor drug effect	0.5
λ	The total rate of production of healthy cells	$10^6 \text{ day}^{-1} \text{ dm}^{-3}$
β	Rate uninfected become infected with virus	$1 \times 10^{-8} \text{ day}^{-1} \text{ dm}^3$
δ	Nature death rate of healthy cells	0.1 day^{-1}
a	Nature death rate of infected cells	0.5 day^{-1}
u	Nature death rate of infective virus particles	5 day^{-1}
N	Number of virus produced by infected cells	Varies

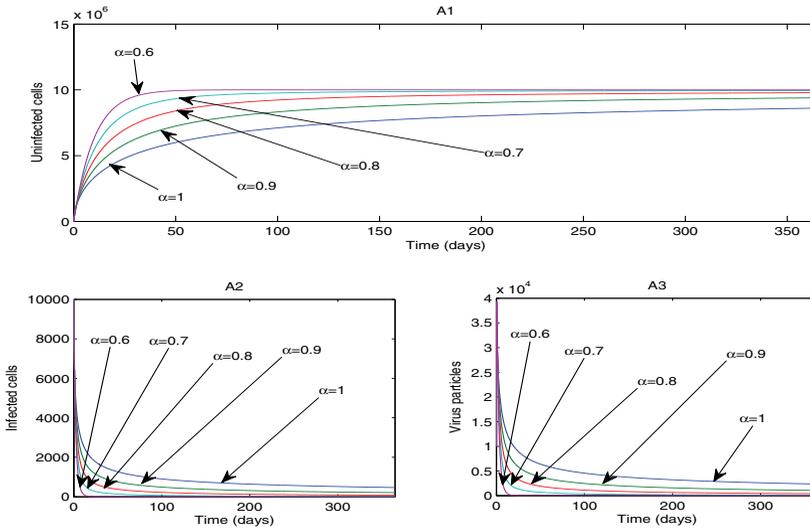


Figure 1: Fractional order HIV internal viral dynamics model, $N=100$.

However, we note that in reality it is unlikely that so few cells would survive la-

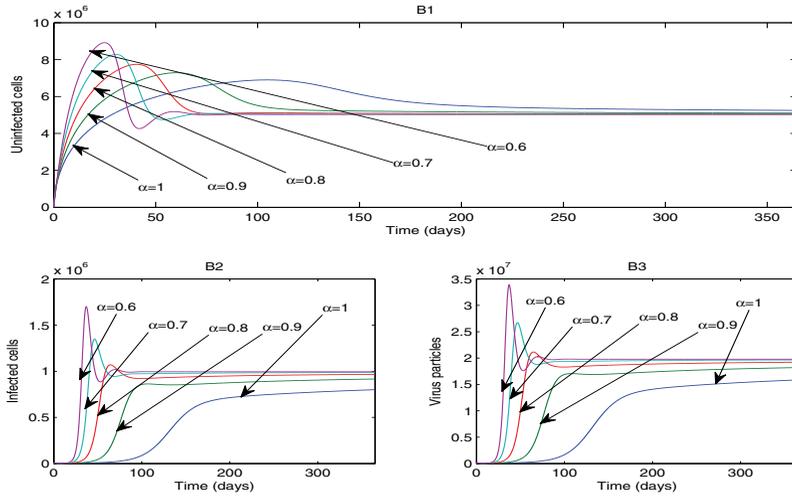


Figure 2: Fractional order HIV internal viral dynamics model, $N=400$.

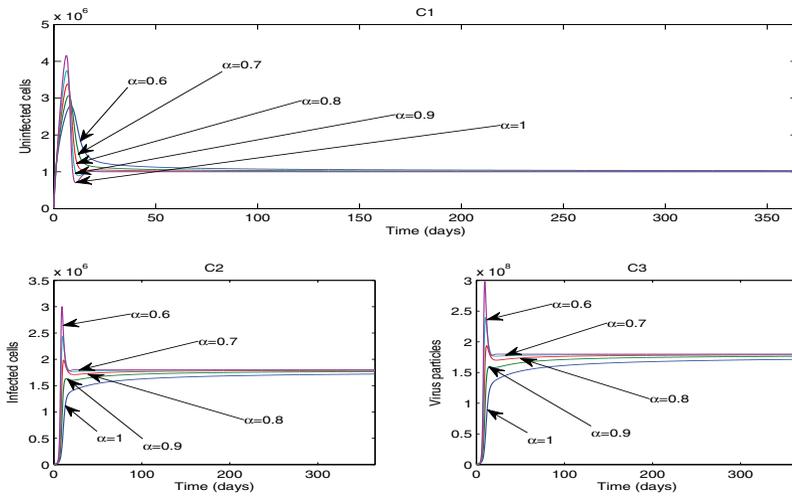


Figure 3: Fractional order HIV internal viral dynamics model, $N=2000$.

tency. Take $N = 205$, then $D(\Phi) = 6.92092 > 0$, and

$$a_1 = 5.65076, a_2 = 0.563176, a_3 = 0.00375, a_1 a_2 - a_3 = 3.17862 > 0. \quad (22)$$

Thus by Proposition 2(i), the endemical equilibrium E^* is locally asymptotically stable. Take $N = 400$, then the endemical equilibrium E^* is locally asymptotically stable by Proposition 1 (see **Figure 2**(B1-B3)). With $N = 2000$, the steady state E^* is also asymptotically stable (see **Figure 3**(C1-C3)). With increasing the N value, it will decrease the numbers of uninfected cells and increase the number of virus particles substantially, but does not change the stability of the steady state.

The above simulations are obtained by applying the PECE (Predict, Evaluate, Correct, Evaluate) method [Diethelm, Ford and Freed (2002)], and the approximate solutions are displayed in **Figure 1**, **Figure 2** and **Figure 3** for the step size 0.007 and different $0.6 \leq \alpha \leq 1$.

6 Conclusions

In this paper, a fractional order model has been proposed to describe the viral dynamics in the presence of HIV infection with HAART effect, as a generalization of an integer order model. First, the positivity of the solutions has been proved, as desired in any population dynamics. Then focus on the stability aspect of the model. By using stability analysis on a fractional order system, some sufficient conditions on the parameters for the local stability of equilibria has been given. Numerical simulations are carried out to confirm the analysis by applying PECE method.

The premise of the proposed model is the fact that fractional order models possess memory while the main features of immune response involve memory. It is an attempt to incorporate fractional order into the mathematical model of internal HIV dynamics. In particular, our work shows that FODE can give another option to model viral dynamics. Since fractional order models possess memory, FODE gives us a more realistic way to model viral dynamics. However, it is still an interesting exercise to determine, mathematically, and what the fractional order serves in the internal HIV dynamics with HAART. In addition, the global asymptotic behavior of FODE is still open since the chain rule is not valid in FODE. We will discuss these questions in our later studies.

Acknowledgement: The authors would like to thank the reviewers and editors for their valuable suggestions and hard work.

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