Global stability of a fractional order HIV infection model with cure of infected cells in eclipse stage

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RÉSUMÉ. La modélisation par des équations différentielles d'ordre fractionnaire présente plus d'avantages pour décrire la dynamique d'un phénomène à mémoire qui existe dans de nombreux systèmes biologiques. Dans cet article, nous proposons un modèle d'ordre fractionnaire pour l'infection par le virus de l'immunodéficience humaine (VIH) en incluant une classe de cellules infectées qui ne produisent pas encore de virus, c'est-à-dire, des cellules au stade de l'éclipse. Nous prouvons d'abord la positivité et la bornitude des solutions afin d'assurer que le modèle proposé est bien posé. En construisant des fonctions de Lyapunov appropriées, la stabilité globale de l'équilibre libre et de l'équilibre d'infection chronique est établi. Des simulations numériques sont présentées afin de valider nos résultats théoriques.

ABSTRACT. Modeling by fractional order differential equations has more advantages to describe the dynamics of phenomena with memory which exists in many biological systems. In this paper, we propose a fractional order model for human immunodeficiency virus (HIV) infection by including a class of infected cells that are not yet producing virus, i.e., cells in the eclipse stage. We first prove the positivity and boundedness of solutions in order to ensure the well-posedness of the proposed model. By constructing appropriate Lyapunov functionals, the global stability of the disease-free equilibrium and the chronic infection equilibrium is established. Numerical simulations are presented in order to validate our theoretical results.

MOTS-CLÉS : Infection par le VIH, stade de l'éclipse, taux d'incidence non linéaire, stabilité globale.

KEYWORDS : HIV infection, eclipse stage, nonlinear incidence rate, global stability.

1. Introduction

In recent years, many mathematical models used fractional order differential equations (FDEs) have been developed to better describe the dynamics of viral infections such as the human immunodeficiency virus (HIV), the hepatitis B virus (HBV) and the hepatitis C virus (HCV). In 2012, Arafa et al. [1] introduced fractional-order into a model of HIV infection of $CD4^+$ T cells and they studied the effect of the changing the average number of viral particles with different sets of initial conditions on the dynamics of the presented model. In 2016, Liu et al. [2] proposed a fractional mathematical model which includes cure rate and Beddington-DeAngelis functional response. They established only the local stability of equilibria, but not investigated the global stability of these equilibria. In 2017, Salman and Yousef [3] considered a fractional-order model for HBV infection with cure of infected cells and they discussed the local asymptotic stability of equilibria. In the same years, Boukhouima et al. [4] generalized all the above models by modeling the infection transmission process by Hattaf's incidence rate [5]. This incidence rate was used by many authors [6–9] and it covers many common types existing in the literature, such as the bilinear incidence function called also the mass action, the saturation incidence rate, the Beddington-DeAnglis functional response [10,11] and the Crowley-Martin functional response [12]. In the above fractional-order models [1–4], infected cells are assumed to produce new virions immediately after target cells are infected by a free virus. However, there are many biological steps between viral infection of target cells and the production of new virions. In our study, we extend and improve these fractional models by incorporating an eclipse phase, representing the stage in which infected cells have not started to produce new virions.

The rest of this paper is outlined as follows. In the next section, we formulate our fractional model and give their basic properties. In Section 3, by constructing suitable Lyapunov functionals, the global stability of equilibria is investigated. Numerical simulations are presented in Section 4. Finally, we conclude our results and give future work.

2. Model formulation and basic properties

The first aim of this paper is to extend and improve the fractional-order models [1–4] by proposing the following model

$$\begin{aligned} D^{\alpha}T(t) &= \lambda - \mu_T T(t) - f(T(t),V(t))V(t) + \rho E(t), \\ D^{\alpha}E(t) &= f(T(t),V(t))V(t) - (\mu_E + \rho + \gamma)E(t), \\ D^{\alpha}I(t) &= \gamma E(t) - \mu_I I(t), \\ D^{\alpha}V(t) &= kI(t) - \mu_V V(t), \end{aligned} \tag{1}$$

where D^{α} is fractional derivative in the Caputo sense and α is a parameter that describes the order of the fractional time-derivative with $0 < \alpha \leq 1$. The variables $T(t)$, $E(t)$, $I(t)$, $V(t)$ denote the concentrations of uninfected $CD4^+$ T cells, infected cells in the eclipse stage (unproductive infected cells), productive infected cells and free HIV particles at time t, respectively. The constant λ is the production rate of infected $CD4^+$ T cells and μ_T is their natural death rate, and $f(T,V)V =$

$\frac{\beta TV}{1+\alpha_1 T+\alpha_2 V+\alpha_3 TV}$ describes the incidence of HIV infection of health CD4$^+$T cells, where $\alpha_1, \alpha_2, \alpha_3 \geq 0$ are the saturation factors measuring the inhibitory or psychological effect, and β is the infection rate. The unproductive infected cells die at the rate μ_E, return to the uninfected cells at the rate ρ and become productive infected cells at the rate γ. Productive infected cells die at the rate μ_I. Free HIV particles are produced from infected cells at the rate k and cleared at the rate μ_V. It is very important to note when $\alpha = 1$, system (1) becomes a model with an ordinary derivative presented by Hattaf and al. in [8] which is the generalization of ODE models presented in [14, 16].

The use of fractional derivative in our model is justified by the fact that the membranes of cells of biological organisms have fractional order electrical conductance [17]. Further, the comparisons between the results of the fractional-order model, the results of the integer model and the measured real data obtained from 10 patients during HIV infection show that the results of the fractional-order model give predictions to the plasma virus load of the patients better than those of the integer model [18].

For biological reasons, we assume that the initial data for system (1) satisfy :

$$T(0) = T_0 \geq 0,\ E(0) = E_0 \geq 0,\ I(0) = I_0 \geq 0,\ V(0) = V_0 \geq 0. \tag{2}$$

First, we have the following result.

Theorem 2.1. *For any initial data satisfying (2), system (1) has a unique solution on $[0, +\infty)$. This solution remains non-negative and bounded for all $t \geq 0$. Moreover, we have*

(i) $N(t) \leq N(0) + \frac{\lambda}{\delta}$,

(ii) $V(t) \leq V(0) + \frac{k}{\mu_V}\|I\|_\infty$,

where $N(t) = T(t) + E(t) + I(t)$ *and* $\delta = \min\{\mu_T, \mu_E, \mu_I\}$.

Proof. From (1), we have

$$\begin{aligned} D^\alpha T\mid_{T=0} &= \lambda + \rho E \geq 0, \\ D^\alpha E\mid_{E=0} &= f(T,V)V \geq 0\ , \\ D^\alpha I\mid_{I=0} &= \gamma E \geq 0, \\ D^\alpha V\mid_{V=0} &= kI \geq 0. \end{aligned}$$

It follows from [13] that the set $\mathbf{R}^4_+ = \{(T, E, I, V) \in \mathbf{R}^4 : T \geq 0, E \geq 0, I \geq 0, V \geq 0\}$ is positively invariant.

It is not hard to see that the vector function of system (1) satisfies the first condition of Lemma 4 in [4]. It remains to show the second condition condition of this Lemma. Let

$$X(t) = \begin{pmatrix} T(t) \\ E(t) \\ I(t) \\ V(t) \end{pmatrix} \text{ and } \eta = \begin{pmatrix} \lambda \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

So, we discuss four cases :
If $\alpha_1 \neq 0$, then system (1) can be written as follows

$$D^\alpha X(t) = \eta + A_1 X + \frac{\alpha_1 T}{1+\alpha_1 T+\alpha_2 V+\alpha_3 TV} A_2 X,$$

where

$$A_1 = \begin{pmatrix} -\mu_T & \rho & 0 & 0 \\ 0 & -(\mu_E+\rho+\gamma) & 0 & 0 \\ 0 & \gamma & -\mu_I & 0 \\ 0 & 0 & k & -\mu_V \end{pmatrix} \text{ and } A_2 = \begin{pmatrix} 0 & 0 & 0 & \frac{-\beta}{\alpha_1} \\ 0 & 0 & 0 & \frac{\beta}{\alpha_1} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}. \tag{3}$$

Then

$$\|D^\alpha X(t)\| \leq \|\eta\| + (\|A_1\| + \|A_2\|)\|X\|. \tag{4}$$

If $\alpha_2 \neq 0$, we have

$$D^\alpha X(t) = \eta + A_1 X + \frac{\alpha_2 V}{1+\alpha_1 T + \alpha_2 V + \alpha_3 TV} A_3 X,$$

where

$$A_3 = \begin{pmatrix} \frac{-\beta}{\alpha_2} & 0 & 0 & 0 \\ \frac{\beta}{\alpha_2} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then

$$\|D^\alpha X(t)\| \leq \|\eta\| + (\|A_1\| + \|A_3\|)\|X\|.$$

If $\alpha_3 \neq 0$, we have

$$D^\alpha X(t) = \eta + A_1 X + \frac{\alpha_3 TV}{1+\alpha_1 T + \alpha_2 V + \alpha_3 TV} A_4 X,$$

where

$$A_4 = \begin{pmatrix} \frac{-1}{\alpha_3} & 0 & 0 & 0 \\ \frac{1}{\alpha_3} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then

$$\|D^\alpha X(t)\| \leq \|\eta\| + (\|A_1\| + \|A_4\|)\|X\|.$$

If $\alpha_1 = \alpha_2 = \alpha_3 = 0$, we have

$$D^\alpha X(t) = \zeta + A_1 X + V A_5 X,$$

where

$$A_5 = \begin{pmatrix} -\beta & 0 & 0 & 0 \\ \beta & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

Then

$$\|D^\alpha X(t)\| \leq \|\zeta\| + (\|V\|\|A_5\| + \|A_1\|)\|X\|.$$

Hence, the second condition of Lemma 4 in [4] is satisfied. Therefore, system (1) has a unique solution on $[0, +\infty)$.

By adding the first three equations of system (1), we obtain

$$D^\alpha N(t) \leq \lambda - \delta N(t),$$

which implies that

$$N(t) \leq N(0)E_\alpha(-\delta t^\alpha) + \frac{\lambda}{\delta}\left[1 - E_\alpha(-\delta t^\alpha)\right],$$

where $E_\alpha(z) = \sum_{k=0}^{\infty} \frac{z^\alpha}{\Gamma(\alpha k + 1)}$ is the Mittag-Leffler function of parameter α. Since $0 \leq E_\alpha(-\delta t^\alpha) \leq 1$, we deduce (i).

Now, we show (ii). The fourth equation of system (1) implies that

$$V(t) = V(0)E_\alpha(-\mu_V t^\alpha) + k\int_0^t \alpha I(s)(t-s)^{\alpha-1}E'_\alpha(-\mu_V(t-s)^\alpha)ds.$$

Then

$$V(t) \leq V(0)E_\alpha(-\mu_V t^\alpha) + \frac{k}{\mu_V}\left\|I\right\|_\infty\left[1 - E_\alpha(-\mu_V t^\alpha)\right].$$

Thus,

$$V(t) \leq V(0) + \frac{k}{\mu_V}\|I\|_\infty. \qquad \blacksquare$$

We begin the analysis of the equilibria by observing that system (1) has a disease-free equilibrium $Q_0(\frac{\lambda}{\mu_T}, 0, 0, 0)$. Then we define the basic reproduction number of (1) as follows

$$R_0 = \frac{\lambda\beta k\gamma}{\mu_I\mu_V(\lambda\alpha_1 + \mu_T)(\rho + \mu_E + \gamma)},$$

which represents the average number of secondary infections produced by one productive infected cell during the period of infection when all cells are uninfected.

Similarly to [8], it is not hard to get the following result.

Theorem 2.2.

(i) If $R_0 \leq 1$, then the system (1) has a unique disease-free equilibrium of the form $Q_0(T_0, 0, 0, 0)$, where $T_0 = \frac{\lambda}{\mu_T}$.

(ii) If $R_0 > 1$, then the disease-free equilibrium is still present and the system (1) has a unique chronic infection equilibrium of the form $Q_1(T_1, E_1, I_1, V_1)$ where $T_1 \in (0, \frac{\lambda}{\mu_T})$, $E_1 = \frac{\lambda - \mu_T T_1}{\mu_E + \gamma}$, $I_1 = \frac{\gamma(\lambda - \mu_T T_1)}{\mu_I(\mu_E + \gamma)}$ and $V_1 = \frac{k\gamma(\lambda - \mu_T T_1)}{\mu_I\mu_V(\mu_E + \gamma)}$.

3. Global stability

In this section, we establish the global stability of the disease-free equilibrium Q_0 and the chronic infection equilibrium Q_1.

Theorem 3.1. *If $R_0 \leq 1$, then the disease-free equilibrium Q_0 is globally asymptotically stable, and becomes unstable if $R_0 > 1$.*

Proof. Consider the following Lyapunov functional

$$\begin{aligned} L_0(t) &= \frac{T_0}{1+\alpha_1 T_0}\Phi\left(\frac{T}{T_0}\right) + \frac{\rho(T-T_0+E)^2}{2(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} \\ &\quad + \frac{\rho+\mu_E+\gamma}{\gamma} I + E + \frac{\mu_I(\rho+\mu_E+\gamma)}{k\gamma} V, \end{aligned}$$

where $\Phi(x) = x - 1 - \ln(x), x > 0$. By using the property of fractional derivatives given in [19], we can compute

$$\begin{aligned} D^\alpha L_0(t) &\leq \frac{1}{1+\alpha_1 T_0}\left(1-\frac{T_0}{T}\right) D^\alpha T + \frac{\rho(T-T_0+E)\left(D^\alpha T + D^\alpha E\right)}{2(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} \\ &\quad + \frac{\rho+\mu_E+\gamma}{\gamma} D^\alpha I + D^\alpha E + \frac{\mu_I(\rho+\mu_E+\gamma)}{k\gamma} D^\alpha V. \end{aligned}$$

Using $\lambda = \mu_T T_0$, we get

$$\begin{aligned} D^\alpha L_0(t) &\leq -\frac{\mu_T(T_0-T)^2}{(1+\alpha_1 T_0)\,T} + \frac{(1+\alpha_1 T)\,T_0 f(T,V)}{(1+\alpha_1 T_0)\,T} V + \rho\frac{(T-T_0)E}{(1+\alpha_1 T_0)\,T} \\ &\quad - \frac{\rho\mu_T(T-T_0)^2}{(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} - \frac{\rho(\mu_E+\gamma)E^2}{(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} \\ &\quad + \frac{\rho E}{(1+\alpha_1 T_0)T_0}\left(T_0 - T\right) - \frac{\mu_I\mu_V(\rho+\mu_E+\gamma)}{k\gamma} V. \end{aligned}$$

Hence,

$$\begin{aligned} D^\alpha L_0(t) &\leq -\left(\frac{1}{T} + \frac{\rho}{(\mu_T+\mu_E+\gamma)T_0}\right)\frac{\mu_T(T-T_0)^2}{1+\alpha_1 T_0} - \frac{\rho(\mu_E+\gamma)E^2}{(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} \\ &\quad - \frac{\rho(T-T_0)^2 E}{(1+\alpha_1 T_0)TT_0} + \frac{\mu_I\mu_V(\rho+\mu_E+\gamma)}{k\gamma}(R_0-1)V \\ &\quad - \frac{\beta T_0(\alpha_2+\alpha_3 T)V^2}{(1+\alpha_1 T_0)\left(1+\alpha_1 T+\alpha_2 V+\alpha_3 TV\right)}. \end{aligned}$$

Since $R_0 \leq 1$, we have that $D^\alpha L_0(t) \leq 0$. Furthermore, $D^\alpha L_0(t) = 0$ if and only if $T = T_0$, $E = 0$ and $V = 0$. From the last equation of (1), we get $I = 0$. Consequently, the largest invariant set of $\{(T,\ E,\ I,\ V) \mid D^\alpha L_0(t) = 0\}$ is the singleton $\{Q_0\}$. It follows from LaSalle's invariance principale [15] that the free equilibrium Q_0 is globally asymptotically stable when $R_0 < 1$.

By a simple computation, the characteristic equation at Q_0 is given by

$$(\mu_T+\xi)\left(\xi^3 + a_1\xi^2 + a_2\xi + a_3\right) = 0,$$

where

$$\begin{aligned} a_1 &= \rho+\gamma+\mu_E+\mu_I+\mu_V, \\ a_2 &= \mu_I(\rho+\gamma+\mu_E) + \mu_V(\rho+\gamma+\mu_E+\mu_I), \\ a_3 &= \mu_I\mu_V(\rho+\gamma+\mu_E)(1-R_0). \end{aligned}$$

Let

$$P(\xi) = \xi^3 + a_1\xi^2 + a_2\xi + a_3 \tag{5}$$

We have $\lim_{\xi\to+\infty} P(\xi) = +\infty$ and $P(0) = \mu_I\mu_V(\rho+\gamma+\mu_E)(1-R_0)$. If $R_0 > 1$, then $P(0) < 0$. So, there exists a $\xi_0 \in (0, +\infty)$ such that $P(\xi_0) = 0$, which implies that the characteristic equation at Q_0 has a positive root when $R_0 > 1$. Consequently, Q_0 is unstable if $R_0 > 1$. ■

Theorem 3.2. *The chronic infection equilibrium Q_1 is globally asymptotically stable if $R_0 > 1$ and*

$$R_0 \leq 1 + \frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma) + \alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma) + \rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}. \tag{6}$$

Proof. Consider the following Lyapunov functional

$$\begin{aligned} L_1(t) &= \frac{(1+\alpha_2V_1)\,T_1}{1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1}\Phi\left(\frac{T}{T_1}\right) \\ &\quad + \frac{\rho(1+\alpha_2V_1)}{2(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)(\mu_T+\mu_E+\gamma)T_1}(T-T_1+E-E_1)^2 \\ &\quad + \frac{\rho+\mu_E+\gamma}{\gamma}I_1\Phi\left(\frac{I}{I_1}\right) + E_1\Phi\left(\frac{E}{E_1}\right) + \frac{\mu_I(\rho+\mu_E+\gamma)}{k\gamma}V_1\Phi\left(\frac{V}{V_1}\right). \end{aligned}$$

The derivative of $L_1(t)$ along the positive solutions of (1) satisfies :

$$\begin{aligned} D^\alpha L_1(t) &\leq \left(1-\frac{f(T_1,V_1)}{f(T,V_1)}\right)D^\alpha T \\ &\quad + \frac{\rho(1+\alpha_2V_1)(T-T_1+E-E_1)}{(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)\ (\mu_T+\mu_E+\gamma)\ T_1}\,(D^\alpha T + D^\alpha E) \\ &\quad + \frac{\rho+\mu_E+\gamma}{\gamma}\ \left(1-\frac{I_1}{I}\right)\ D^\alpha I + \left(1-\frac{E_1}{E}\right)D^\alpha E \\ &\quad + \frac{\mu_I(\rho+\mu_E+\gamma)}{k\gamma}\left(1-\frac{V_1}{V}\right)D^\alpha V. \end{aligned}$$

By applying $\lambda = \mu_T T_1 - f(T_1, V_1)V_1 - \rho E_1 = \mu_T T_1 - (\gamma + \mu_E)E_1$, $\mu_I = \gamma\frac{E_1}{I_1}$ and $\mu_V = k\frac{I_1}{V_1}$, we get

$$\begin{aligned}
D^\alpha L_1(t) &\leq \left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right) D^\alpha T \\
&\quad + \frac{\rho(1+\alpha_2 V_1)(T - T_1 + E - E_1)}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)()\ (\mu_T + \mu_E + \gamma)\ T_1} (D^\alpha T + D^\alpha E) \\
&\quad + \frac{\rho + \mu_E + \gamma}{\gamma}\ \left(1 - \frac{I_1}{I}\right)\ D^\alpha I + \left(1 - \frac{E_1}{E}\right) D^\alpha E + \frac{\mu_I(\rho + \mu_E + \gamma)}{k\gamma}\left(1 - \frac{V_1}{V}\right) D^\alpha V \\
&\leq \left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right)\ (-\mu_T(T - T_1) + \rho(E - E_1) - f(T,V)V + f(T_1,V_1)V_1) \\
&\quad + (1 - \frac{E_1}{E})\left(f(T,V)V - \frac{f(T_1,V_1)V_1}{E_1}E\right) + \frac{\rho + \mu_E + \gamma}{\gamma}\left(1 - \frac{I_1}{I}\right)\ \left(\gamma E - \frac{\gamma E_1}{I_1}\right) \\
&\quad + \frac{\mu_I(\rho + \mu_E + \gamma)}{k\gamma}\left(1 - \frac{V_1}{V}\right)\left(kI - \frac{kI_1}{V_1}\right) \\
&\quad + \frac{\rho(1+\alpha_2 V_1)[(T - T_1) + (E - E_1)](-\mu_T(T - T_1) - (\mu_E + \gamma)(E - E_1))}{T_1(1 + \alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)(\mu_E + \gamma + \mu_T)}.
\end{aligned}$$

Thus,

$$\begin{aligned}
D^\alpha L_1(t) &\leq \frac{-\mu_T(1+\alpha_2 V_1)(T - T_1)^2}{TT_1(1 + \alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)}\left((\mu_T T_1 - \rho E_1) + \frac{\rho\mu_T T}{\mu_E + \gamma + \mu_T} + \rho E\right) \\
&\quad - \frac{\rho(1+\alpha_2 V_1)(\mu_E + \gamma)(E - E_1)^2}{T_1(1 + \alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)(\mu_E + \gamma + \mu_T)} \\
&\quad + f(T_1,V_1)V_1\left(5 - \frac{f(T_1,V_1)}{f(T,V_1)} - \frac{EI_1}{E_1 I} - \frac{f(T,V)}{f(T_1,V_1)}\frac{E_1 V}{EV_1} - \frac{IV_1}{I_1 V} - \frac{f(T,V_1)}{f(T,V)}\right) \\
&\quad - \frac{f(T_1,V_1)(1+\alpha_1 T_1)(\alpha_2 + \alpha_3 T)(V - V_1)^2}{(1 + \alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)(1 + \alpha_1 T + \alpha_2 V + \alpha_3 TV)}.
\end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that

$$5 - \frac{f(T_1,V_1)}{f(T,V_1)} - \frac{EI_1}{E_1 I} - \frac{f(T,V)}{f(T_1,V_1)}\frac{E_1 V}{EV_1} - \frac{IV_1}{I_1 V} - \frac{f(T,V_1)}{f(T,V)} \leq 0.$$

Therefore, $D^\alpha L_1(t) \leq 0$ if $\rho E_1 \leqslant \mu_T T_1$. It is not hard to show that $\rho E_1 \leqslant \mu_T T_1$ is equivalent to (6). Further, $D^\alpha L_1(t) = 0$ if and only if $E = E_1$, $V = V_1$ and $\frac{f(T_1,V_1)}{f(T,V_1)} = \frac{EI_1}{E_1 I} = \frac{IV_1}{I_1 V}$, which implies that $I = I_1$ and $T = T_1$. By the LaSalle's invariance principale, we conclude that Q_1 is globally asymptotically stable. ■

Since

$$\begin{aligned}
\lim_{\rho\to 0} \frac{[\mu_T\mu_I\mu_V(\mu_E + \gamma) + \alpha_2\mu_T\lambda k\gamma](\mu_E + \rho + \gamma) + \rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E + \rho + \gamma)(\mu_T + \alpha_1\lambda)} &= \infty, \\
\lim_{\gamma\to\infty} \frac{[\mu_T\mu_I\mu_V(\mu_E + \gamma) + \alpha_2\mu_T\lambda k\gamma](\mu_E + \rho + \gamma) + \rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E + \rho + \gamma)(\mu_T + \alpha_1\lambda)} &= \infty,
\end{aligned}$$

we have the following result.

Corollary 3.3.

(i) The chronic infection equilibrium Q_1 is globally asymptotically stable if $R_0 > 1$ and ρ is sufficiently small. In particular for $\rho = 0$.

(ii) The chronic infection equilibrium Q_1 is globally asymptotically stable if $R_0 > 1$ and γ is sufficiently large.

4. Numerical simulations

In this section, we present some numerical simulations in order to illustrate our analytical results. The initial conditions of system (1) are $T(0) = 800$ cells mm^{-3}, $E(0) = 100$ cells mm^{-3}, $I(0) = 24$ cells mm^{-3}, and $V(0) = 8000$ virions mm^{-3}.

First, we choose $\Lambda = 10$, $\mu_T = 0.0139$, $\beta = 0.000024$, $\alpha_1 = 0.1$, $\alpha_2 = 0.01$, $\alpha_3 = 0.00001$, $\rho = 0.01$, $\gamma = 1.1$, $\mu_I = 0.29$, $\mu_E = 0.0350$, $k = 600$ and $\mu_V = 3$. By calculation, we have $R_0 = 0.1568 < 1$. It follows from Theorem 2.2 that system (1) has a disease-free equilibrium $Q_0(719.4245, 0, 0, 0)$. By Theorem 3.1, we see that Q_0 is globally asymptotically stable which means that the virus is cleared and the infection die out. Figure 1 illustrates this result.

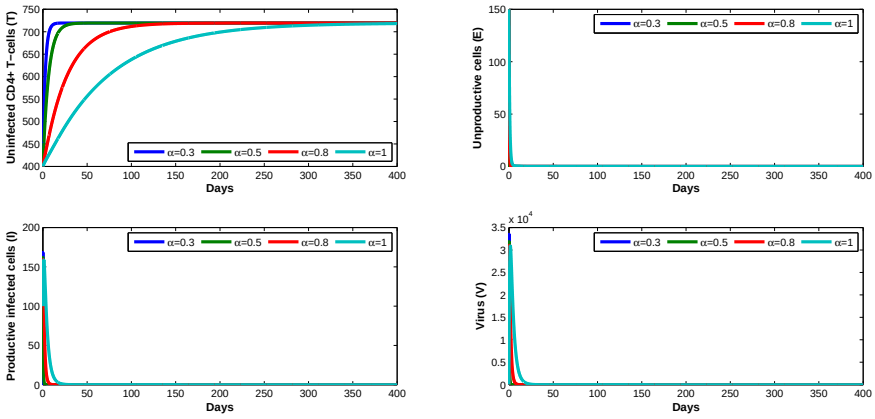

Figure 1. *Stability of the disease-free equilibrium Q_0.*

Next, we choose $\beta = 0.0005$ and we keep the other parameter values. We have $R_0 = 3.2673$ and

$$1 + \frac{[\mu_T\mu_I\mu_V(\mu_E + \gamma) + \alpha_2\mu_T\lambda k\gamma](\mu_E + \rho + \gamma) + \rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E + \rho + \gamma)(\mu_T + \alpha_1\lambda)} = 107.2121$$

Hence, the condition (6) is satisfied. From Theorem 2.2, the chronic infection equilibrium $Q_1(242.4, 5.842, 22.16, 4232)$ is globally asymptotically stable, which means that the virus persists in the host and the infection becomes chronic. This result is confirmed by Figure 2.

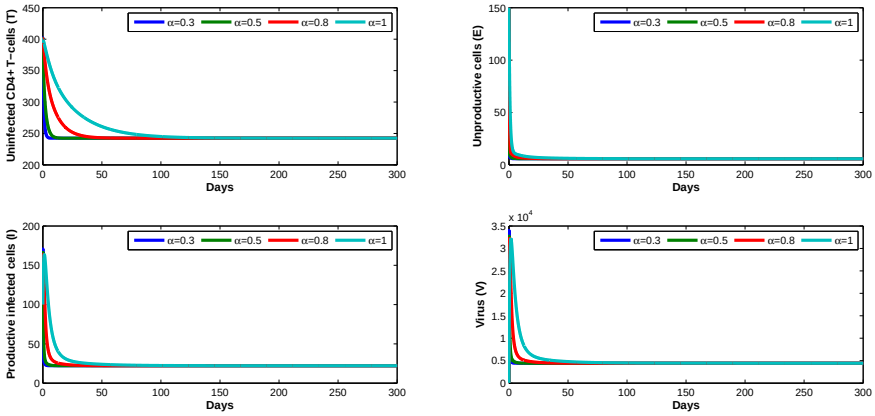

Figure 2. *Stability of the chronic infection equilibrium* Q_1.

Finally, we choose $\mu_I = 0.27$, $\mu_E = 0.0347$, $\beta = 0.0084$, $\gamma = 0.01$, $k = 200$ and we keep the other parameter values. We have $R_0 = 3.7397$ and $1 + \frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)} = 1.4443$. Hence, the dynamics of HIV infection converges to steady state Q_1, but the condition (6) is not satisfied. Therefore, the condition (6) is not necessary for the global stability of Q_1 (see Figure. 3).

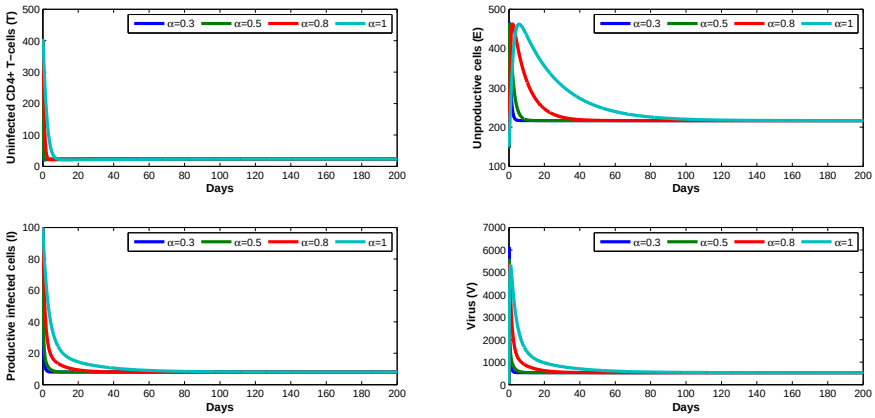

Figure 3. *Dynamics of HIV infection with the condition (6) not satisfied.*

5. Conclusion

In this work, we have proposed a fractional-order model to describe the dynamics of HIV infection by taking into account the cure of infected cells in eclipse

stage. We first proved that the proposed model is mathematically and virologically well-posed. In addition, we have proved that the disease-free equilibrium Q_0 is globally asymptotically stable if the basic reproduction number $R_0 \leq 1$, which means that the HIV particles are eradicated. When $R_0 > 1$, Q_0 becomes unstable and there occurs the HIV infection equilibrium Q_1 which is globally asymptotically stable provided that the condition (6) is satisfied. In this case, the HIV particles persist in the host. Numerically, we see that the condition (6) is not necessary (see Figure 3). So, it will be interesting to prove it mathematically in future work. From our analytical and numerical results, we conclude that the fractional order has no effect on the asymptotic properties of the equilibria, but it may affect the time for arriving at these equilibria. In addition, the fractional-order models presented in [1–4] are extended and improved.

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