LYAPUNOV FUNCTIONS FOR FRACTIONAL-ORDER SYSTEMS IN BIOLOGY: METHODS AND APPLICATIONS

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ABSTRACT. We prove new estimates of the Caputo derivative of order $\alpha \in (0, 1]$ for some specific functions. The estimations are shown useful to construct Lyapunov functions for systems of fractional differential equations in biology, based on those known for ordinary differential equations, and therefore useful to determine the global stability of the equilibrium points for fractional systems. To illustrate the usefulness of our theoretical results, a fractional HIV population model and a fractional cellular model are studied. More precisely, we construct suitable Lyapunov functionals to demonstrate the global stability of the free and endemic equilibriums, for both fractional models, and we also perform some numerical simulations that confirm our choices.

1. INTRODUCTION

Fractional calculus (FC) is the mathematical theory that generalizes the integrals and derivatives to real or complex order [7]. During the last decades, FC has gained popularity and importance in diverse fields of science and engineering, including biology, physics, chemistry, engineering, finance, and control theory, see, e.g., [15, 17, 18, 25, 30, 53, 65]. Recently, several works have appeared in the literature that deal with various applications of FC in real-life problems. In [32], the authors discuss general fractional optimal control problems (FOCPs) involving fractional derivatives (FD) with singular and non-singular kernels. They derive necessary optimality conditions and propose an efficient method for solving, numerically, these problems. Yildiz et al. [64] formulate new time FOCPs governed by Caputo–Fabrizio FD. To solve these problems, they firstly convert them into Volterra-type systems and then apply a new numerical scheme based on the approximation of Volterra integrals. Since most fractional-order problems cannot be solved explicitly,
their numerical simulations are of crucial importance to researchers. In the work of Veeresha et al. [62], the existence of solutions for fractional generalized Hirota–Satsuma coupled Korteweg-de-Vries (KdV) and coupled modified KdV equations are investigated with the aid of a fractional natural decomposition method. In a similar way, Singh et al. [57] perform a comparison between the reduced differential transform method and the local fractional series expansion method for solving local fractional Fokker–Planck equations on the Cantor set. They confirm that the two proposed methods are very successful and simple to solve differential equations with fractional derivative operators of local nature. The authors of [37] extend the fractional vibration equation for very large membranes, with distinct special cases, by considering the Atangana–Baleanu fractional derivative. They also employ a numerical algorithm, based on the homotopy technique, to examine the fractional vibration equation. For that, they show the effects of space, time, and order of the Atangana-Baleanu derivative on the graphical displacement, and confirm that the Atangana-Baleanu fractional derivative is very efficient in describing vibrations in large membranes.

The advantage of fractional differentiation is that it provides a powerful tool to model real-world processes with long-range memory, long-range interactions, and hereditary properties, which exist in most biological systems, as opposed to integer-order differentiation, where such effects are neglected [1, 50, 51, 66]. For these reasons, modeling with fractional differential equations (FDEs) has attracted the interest of researchers in biology [23, 27, 43]. In [33], the authors investigate a fractional version of the SIRS model for the human respiratory syncytial virus (HRSV) disease, involving a new derivative operator with Mittag–Leffler kernel in the Caputo sense. They confirm, from simulations, that fractional modeling is more realistic and effective than the proposed approach in the classical version of the model, to diminish the number of HRSV infected individuals. Sajjadi et al. [52] analyze hyperchaotic behaviors of a biological snap oscillator and study the chaos control and synchronization via a fractional-order model. They conclude that fractional calculus leads to more realistic and flexible models with memory effects, which could help to design more efficient controllers. Singh et al. [60] analyze the dynamical behavior of a fish farm model, related with the Atangana–Baleanu (AB) derivative. They discuss the influence of the derivative order on nutrients, fish, and mussels, and show that when this order tends to one, then the AB derivative gives interesting results. Elettreby et al. [24] propose a fractional-order species model to study the interaction of a system that consists of two-prey and one-predator. They study the stability of the equilibria and prove that the coexistence equilibrium points are stable without any conditions, in contrast with the corresponding ordinary differential equations (ODEs) model, where some conditions are imposed for the stability of the same points. This means that FDEs have a larger stability region than those of ODEs [24].

FDEs have been also successfully applied in epidemiology, as well as in virology [4, 48, 49]. Huo et al. [31] proposed a fractional homogeneous-mixing population model for human immunodeficiency virus (HIV), which incorporates anti-HIV preventive vaccines, and studied the backward bifurcation of the equilibrium points. They also generalize the integer-order LaSalle invariant theorem for fractional-order systems and demonstrate the global stability of the disease-free equilibrium point [31].
In the work [63] of Wojtak et al., the authors investigate the uniform asymptotic stability of the unique endemic equilibrium for a Caputo fractional-order tuberculosis (TB) model. They confirm that the proposed fractional-order model provides richer and more flexible results when compared with the corresponding integer-order TB model [49, 63].

In [28], González-Parra et al. propose a nonlinear fractional-order model to explain, and help to understand, the outbreak of influenza A(H1N1) worldwide. They show that the fractional-order model gives wider peaks and leads to better approximations of the real epidemic data [28].

Rihan et al. [46] develop a fractional-order model for hepatitis C dynamics, in order to describe the interactions between healthy liver cells \( H \), infected liver \( I \), and virus load \( V \). They confirm that the proposed model gives consistent results with the reality of the interactions [46].

In the study of Arafa et al. [3], the authors compare the results of the fractional-order model with the ones from the integer/classical model, taking into account real data obtained from 10 patients during primary HIV infection. They prove that the results of the fractional-order model give better predictions to the plasma virus load of the patients than those of the integer-order model [3].

In [59], the authors study diabetes and its complications with the help of the Caputo–Fabrizio fractional derivative. They observe, via numerical simulations, that when the derivative order is near to one, then the Caputo–Fabrizio non-integer order derivative reveals better absorbing characteristics. For other related works, see, e.g., [4, 12, 16, 36, 40, 45, 58].

Stability analysis of FDEs through Lyapunov functions is investigated by Delavari et al. [19]. Their method requires to construct a suitable function, which is not easy to find in the fractional case. In mathematical biology, the stability of equilibrium points, via Lyapunov method, is a very effective way to determine the global behavior of a system without solving it analytically. This is based on the construction of well-chosen Lyapunov functions, according to the nature of the system under study. In the literature, the most well-known Lyapunov functions are quadratic and Volterra-type functions. Accordingly, Aguila-Camacho et al. [2] extend such quadratic functions to the fractional case and then study the stability of fractional-order time-varying systems. In 2015, Duarte-Mermoud et al. [20] generalized the result of [2] to the vector case, in order to prove the stability of fractional-order models with reference adaptive control schemes.

Vargas-De-León uses Volterra-type Lyapunov functions to determine the stability of several fractional-order epidemic systems [61]. However, quadratic and Volterra-type Lyapunov functions can be successfully used to demonstrate the stability of the equilibrium points only in particular cases, and further work is needed.

Motivated by these works, we prove here a new result that estimates the Caputo fractional derivative for certain specific functions. Based on our result, we are able to construct Lyapunov functions for systems of FDEs in biology by using the Lyapunov functions of corresponding systems formulated by ODEs and, subsequently, to establish the global asymptotic stability of constant steady-state solutions.

The paper is organized as follows. In Section 2, new inequalities to estimate the FD of order \( \alpha \in (0,1] \), for specific functions, are rigorously proved and a detailed description of the proposed method is presented with proofs. Then, in Section 3, we apply our method to study the asymptotic stability of two models in virology and epidemiology. We end up with Section 4 of conclusions.
2. Description of the method

Consider an $n$-dimensional autonomous system formulated by ordinary differential equations,

$$
\begin{align*}
\frac{du}{dt} &= f(u), \\
u(t_0) &= u_0,
\end{align*}
$$

(1)

where $u$ is a non-negative vector of concentration $u_1, \ldots, u_n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$ is a $C^1$-function.

Let $V(u)$ be a $C^1$-function defined on some domain in $\mathbb{R}^n_+$. When $u(t)$ is a solution of (1), it is often necessary to compute the time derivative of $V(u(t))$:

$$
\frac{dV}{dt}(u(t)) = \nabla V(u(t)) \cdot \frac{du}{dt} = \nabla V(u(t)) : f(u(t)).
$$

We assume that the range of $u(t)$ is contained in the domain of $V(\cdot)$. The right-hand side is given by the gradient of function $V(\cdot)$ and the vector field $f(\cdot)$. Thus, the right-hand side is defined without the fact that $u(t)$ is a solution of (1), which is important for our construction of Lyapunov functions.

In the literature, many authors define explicit Lyapunov functions of the form

$$
V(u) = \sum_{i=1}^{n} a_i \Psi_i(u_i)
$$

(2)

with $a_i > 0$ and

$$
\Psi_i(u_i) = \int_{u_i^*}^{u_i} \frac{g_i(s) - g_i(u_i^*)}{g_i(s)} ds
$$

(3)

where $u^*(u_1, \ldots, u_n)$ is any equilibrium of (1), $u_i^* > 0$ for all $1 \leq i \leq n$, and $g_i$ is a non-negative, differentiable, and strictly increasing function on $\mathbb{R}^+_+$, see, e.g., [21, 22, 26, 29].

**Remark 1.** If $u_i^* = 0$, then function $\Psi_i(u_i)$ reduces to

$$
\Psi_i(u_i) = u_i.
$$

**Remark 2.** If $g_i(s) = s$, then function $\Psi_i(u_i)$ becomes

$$
\Psi_i(u_i) = u_i - u_i^* - \int_{u_i^*}^{u_i} \frac{g_i(u_i^*)}{g_i(s)} ds, \quad \forall i = 1, \ldots, n,
$$

with $u_i^* = (u_1^*, \ldots, u_n^*)$ is any equilibrium of (1), $u_i^* > 0$ for all $1 \leq i \leq n$, and $g_i$ is a non-negative, differentiable, and strictly increasing function on $\mathbb{R}^+_+$, see, e.g., [21, 22, 26, 29].

It is easy to see that function $\Psi_i$ is strictly positive in $\mathbb{R}^+_+ \setminus \{u_i^*\}$ with $\Psi_i(u_i^*) = 0$. In fact, $\Psi_i$ is differentiable and

$$
\frac{d\Psi_i}{du_i} = 1 - \frac{g_i(u_i^*)}{g_i(u_i)}.
$$

Since $g_i$ is a strictly increasing function, then $\Psi_i$ is strictly decreasing if $u_i < u_i^*$ and strictly increasing if $u_i > u_i^*$, with $u_i^*$ its global minimum. In this case, we have

$$
\frac{dV(u(t))}{dt} = \sum_{i=1}^{n} a_i \left( 1 - \frac{g_i(u_i^*)}{g_i(u_i)} \right) f_i(u_i),
$$

(4)
where
\[ f(u) = (f_1(u_1), \ldots, f_n(u_n))^T. \]

On the other hand, let us consider the following general type of fractional-order system:
\[
\begin{align*}
C_0 D_t^\alpha u(t) &= f(u(t)), \quad \alpha \in (0, 1], \\
u(t_0) &= u_0,
\end{align*}
\]
where \( C_0 D_t^\alpha \) denotes the Caputo fractional derivative of order \( \alpha \), defined for the function \( u \) by
\[
C_0 D_t^\alpha u(t) = \frac{1}{\Gamma(1-\alpha)} \int_{t_0}^{t} \frac{u'(y)}{(t-y)^\alpha} dy
\]
(see, e.g., [44]). Here, \( ' \) denotes \( \frac{d}{dy} \). We note that system (5) has the same equilibrium points as system (1).

The Caputo fractional derivative of \( V \) along the solution of (5) is given by
\[
C_0 D_t^\alpha V(u(t)) = \sum_{i=1}^{n} a_i C_0 D_t^\alpha \Psi_i(u_i).
\]

To extend the Lyapunov functions (2) to the Caputo fractional-order system (5), through an inequality that estimates the Caputo fractional derivative of these functions, we prove the following lemma, which is the main result of this section.

**Lemma 2.1.** Let \( x(t) \in \mathbb{R}^+ \) be a continuous and differentiable function. Then, for any \( t \geq t_0, 0 < \alpha \leq 1 \), and \( \bar{x} > 0 \), we have
\[
C_0 D_t^\alpha \Psi(x(t)) \leq \left( 1 - \frac{g(\bar{x})}{g(x(t))} \right) C_0 D_t^\alpha x(t),
\]
where
\[ \Psi(x) = x - \bar{x} - \int_{\bar{x}}^{x} \frac{g(s)}{g(\bar{x})} ds, \]
with \( g : \mathbb{R}^+ \to \mathbb{R}^+ \) a differentiable and strictly increasing function.

**Proof.** We start by reformulating inequality (8). By the linearity of the Caputo fractional derivative, we obtain that
\[
C_0 D_t^\alpha \Psi(x(t)) = C_0 D_t^\alpha x(t) - C_0 D_t^\alpha \left[ \int_{\bar{x}}^{x(t)} \frac{g(s)}{g(\bar{x})} ds \right].
\]
Hence, inequality (8) becomes
\[
C_0 D_t^\alpha x(t) - C_0 D_t^\alpha \left[ \int_{\bar{x}}^{x(t)} \frac{g(s)}{g(\bar{x})} ds \right] \leq \left( 1 - \frac{g(\bar{x})}{g(x(t))} \right) C_0 D_t^\alpha x(t).
\]
Because \( g \) is a non-negative function, we get
\[
g(x(t)) C_0 D_t^\alpha x(t) - g(x(t)) C_0 D_t^\alpha \left[ \int_{\bar{x}}^{x(t)} \frac{g(s)}{g(\bar{x})} ds \right] \leq g(x(t)) C_0 D_t^\alpha x(t) - g(\bar{x}) C_0 D_t^\alpha x(t).
\]
Thus,
\[
C_0 D_t^\alpha x(t) - g(x(t)) C_0 D_t^\alpha \left[ \int_{\bar{x}}^{x(t)} \frac{1}{g(s)} ds \right] \leq 0.
\]
Using the definition of Caputo fractional derivative (6), we have

\[ \frac{C_0^a D_t^a}{\Gamma(1-\alpha)} x(t) = \frac{1}{\Gamma(1-\alpha)} \int_{t_0}^{t} \frac{x'(y)}{(t-y)\alpha} dy \]

and

\[ \frac{C_0^a D_t^a}{\Gamma(1-\alpha)} \left[ \int_{x(t)}^{x(y)} \frac{1}{g(s)} ds \right] = \frac{1}{\Gamma(1-\alpha)} \int_{t_0}^{t} \frac{x'(y)}{(t-y)\alpha g(x(y))} dy. \]

Consequently, the inequality (9) can be written as follows:

\[ \frac{1}{\Gamma(1-\alpha)} \int_{t_0}^{t} \frac{x'(y)}{(t-y)\alpha} \left( 1 - \frac{g(x(t)))}{g(x(y))} \right) dy \leq 0. \] (10)

Now, we show that the inequality (10) is verified. Denoting

\[ H(t) = \frac{1}{\Gamma(1-\alpha)} \int_{t_0}^{t} \frac{x'(y)}{(t-y)\alpha} \left( 1 - \frac{g(x(t)))}{g(x(y))} \right) dy, \]

we integrate by parts by defining

\[ v(y) = \frac{(t-y)^{-\alpha}}{\Gamma(1-\alpha)}; \]
\[ v'(y) = \frac{\alpha(t-y)^{-(\alpha+1)}}{\Gamma(1-\alpha)}; \]

and

\[ w(y) = x(y) - x(t) - \int_{x(t)}^{x(y)} \frac{g(x(t))}{g(s)} ds; \]
\[ w'(y) = x'(y) \left( 1 - \frac{g(x(t)))}{g(x(y))} \right); \]

to obtain

\[ H(t) = \left[ \frac{(t-y)^{-\alpha}}{\Gamma(1-\alpha)} \left( x(y) - x(t) - \int_{x(t)}^{x(y)} \frac{g(x(t))}{g(s)} ds \right) \right]_{y=t}^{y=t} \]

(11)

\[ - \frac{(t-t_0)^{-\alpha}}{\Gamma(1-\alpha)} \left( x(t_0) - x(t) - \int_{x(t)}^{x(t_0)} \frac{g(x(t))}{g(s)} ds \right) \]

\[ - \int_{t_0}^{t} \frac{\alpha(t-y)^{-(\alpha+1)}}{\Gamma(1-\alpha)} \left( x(y) - x(t) - \int_{x(t)}^{x(y)} \frac{g(x(t))}{g(s)} ds \right) dy. \]

We can easily see that the first term in (11) is undefined at \( u = t \left( \frac{0}{t} \right) \). Let us analyze the corresponding limit. By L'Hôpital's rule, we get

\[ \lim_{y \to t} \frac{(t-y)^{-\alpha}}{\Gamma(1-\alpha)} \left( x(y) - x(t) - \int_{x(t)}^{x(y)} \frac{g(x(t))}{g(s)} ds \right) = \lim_{y \to t} \frac{x'(y) \left( 1 - \frac{g(x(t)))}{g(x(y))} \right)}{-\alpha \Gamma(1-\alpha)(t-y)^{\alpha-1}} = 0. \]

Hence,

\[ H(t) = - \frac{(t-t_0)^{-\alpha}}{\Gamma(1-\alpha)} \left( x(t_0) - x(t) - \int_{x(t)}^{x(t_0)} \frac{g(x(t))}{g(s)} ds \right) \]

\[ - \int_{t_0}^{t} \frac{\alpha(t-y)^{-(\alpha+1)}}{\Gamma(1-\alpha)} \left( x(y) - x(t) - \int_{x(t)}^{x(y)} \frac{g(x(t))}{g(s)} ds \right) dy. \]
From (3), we get

\[ H(t) = \frac{1}{\Gamma(1-\alpha)} \int_{t_0}^{t} x'(u) \left( 1 - \frac{g(x(t))}{g(x(u))} \right) du \leq 0 \]

and, as a result, the inequality (10) is satisfied. This completes the proof. \( \square \)

A particular case of Lemma 2.1 is given in the following corollary.

**Corollary 1.** Let \( x(t) \in \mathbb{R}^+ \) be a continuous and differentiable function. Then, for any \( t \geq t_0, 0 < \alpha \leq 1, \) and \( \bar{x} \geq 0, \) one has

\[ \frac{C_0^a D_t^\alpha}{\alpha} \left[ x(t) - \bar{x} - \bar{x} \ln \frac{x(t)}{\bar{x}} \right] \leq \left( 1 - \frac{\bar{x}}{x(t)} \right) \frac{C_0^a D_t^\alpha}{\alpha} x(t). \]

**Proof.** Define function \( g \) on \([0, +\infty)\) by \( g(s) = s. \) Obviously, function \( g \) is a non-negative and strictly increasing function on \([0, +\infty)\) with

\[ \psi(x(t)) = x(t) - \bar{x} - \bar{x} \ln \frac{x(t)}{\bar{x}}. \]

The result follows by Lemma 2.1. \( \square \)

**Remark 3.** We can see that the inequality obtained for Volterra-type Lyapunov functions in [61, Lemma 3.1] is a special case of our Lemma 2.1.

Finally, using Lemma 2.1, we estimate the Caputo fractional derivative of \( V \) in (7) through the following inequality:

\[ \frac{C_0^a D_t^\alpha}{\alpha} V(u(t)) \leq \sum_{i=1}^{n} a_i \left( 1 - \frac{g_i(u_i^*)}{g_i(u_i)} \right) \frac{C_0^a D_t^\alpha}{\alpha} u_i(t) = \sum_{i=1}^{n} a_i \left( 1 - \frac{g_i(u_i^*)}{g_i(u_i)} \right) f_i(u_i). \]

We summarize the above discussion in the following proposition.

**Proposition 1.** If \( V \) is a Lyapunov function for the ordinary differential equation (1) of the form described by (2), then \( V \) is also a Lyapunov function for the Caputo fractional-order system (5).

In other cases, some authors constructed a Lyapunov function for system (1) given by the composition of \( V \) and a quadratic function \( Q, \) that is, of the form

\[ L(u(t)) = V(u(t)) + Q(u(t)), \]

where

\[ Q(u) = \sum_{i=1}^{n} b_i(u_i - u_i^*)^2, \]

with \( b_i \geq 0 \) [6, 14, 41]. The time derivative of \( L \) is given by

\[ \frac{dL(u(t))}{dt} = \sum_{i=1}^{n} \left[ a_i \left( 1 - \frac{g_i(u_i^*)}{g_i(u_i)} \right) + b_i(u_i - u_i^*) \right] f_i(u_i). \]

Therefore, computing the fractional time derivative of \( L \) by using our Lemma 2.1 and Lemma 1 of [2], we obtain that

\[ \frac{C_0^a D_t^\alpha}{\alpha} L(u(t)) = \frac{C_0^a D_t^\alpha}{\alpha} V(u(t)) + \frac{C_0^a D_t^\alpha}{\alpha} Q(u(t)) \leq \sum_{i=1}^{n} \left[ a_i \left( 1 - \frac{g_i(u_i^*)}{g_i(u_i)} \right) + b_i(u_i - u_i^*) \right] f_i(u_i). \]
Thus, the following result holds.

**Corollary 2.** If $L$ is a Lyapunov function for the ordinary differential equation (1) of the form described by (12), then $L$ is also a Lyapunov function for the Caputo fractional-order system (5).

Let $D$ be a bounded closed set in $\mathbb{R}^n$. Assume that the largest invariant set in

$$\{ u \in D \mid C_t^\alpha D_t^\alpha L(u(t)) = 0 \}$$

is just the singleton $\{ u^* \}$. Then, we get the following result.

**Proposition 2.** If (4) (respectively (13)) is non-positive, then $C_t^\alpha D_t^\alpha V(u(t)) \leq 0$ (respectively, $C_t^\alpha D_t^\alpha L(u(t)) \leq 0$). It follows that the positive equilibrium $u^*$ of the fractional-order system (5) is globally asymptotically stable.

**Proof.** By Lemma 4.6 of [31], every solution originating in $D$ tends to the largest invariant set of

$$\{ u \in D \mid C_t^\alpha D_t^\alpha L(u(t)) = 0 \} = \{ u \in D \mid u = u^* \}.$$

Thus,

$$\lim_{t \to +\infty} u(t) = u^*.$$

This completes the proof.

3. Applications

In this section, we apply our method to study the stability of two fractional-order biological models. Our procedure is based on the construction of Lyapunov functions for FDEs using Lyapunov functions for ODEs.

**3.1. Example 1: an HIV population model.** In this example, we consider the SICA model of Silva and Torres [55], which contains four variables: the susceptible individuals ($S$), HIV-infected individuals with no clinical symptoms of AIDS ($I$), HIV-infected individuals under ART treatment ($C$), and HIV-infected individuals with AIDS clinical symptoms ($A$). The model is given by the following nonlinear system of differential equations:

$$\begin{align*}
\frac{dS}{dt} &= \Lambda - \mu S(t) - \beta S(t)I(t), \\
\frac{dI}{dt} &= \beta S(t)I(t) - (\rho + \phi + \mu)I(t) + \alpha A(t) + \omega C(t), \\
\frac{dC}{dt} &= \phi I(t) - (\omega + \mu)C(t), \\
\frac{dA}{dt} &= \rho I(t) - (\alpha + \mu + d)A(t).
\end{align*}$$

(14)

The basic reproduction number of system (14), which represents the expected average number of new HIV infections produced by a single HIV-infected individual when in contact with a completely susceptible population, is given by

$$R_0 = \frac{\beta \xi_1 \xi_2}{N},$$

where $\xi_1 = \alpha + \mu + d$, $\xi_2 = \omega + \mu$, and $N = \mu[\xi_2(\rho + \xi_1) + \xi_1 \phi + \rho d] + \rho \omega d$. Silva and Torres proved that if $R_0 > 1$, then system (14) has an endemic equilibrium.
The time derivative of $S$ is just the singleton $E$ given by constructing a Lyapunov function for system (15) at $E^*$ as follows:

$$V_1(S, I, C, A) = \Psi_1(S) + \Psi_2(I) + \frac{\omega}{\xi_2} \Psi_3(C) + \frac{\alpha}{\xi_1} \Psi_4(A)$$

$$= S - S^* - \int_{S^*}^{S} \frac{S}{X} dX + I^* - \int_{I^*}^{I} \frac{I}{X} dX$$

$$+ \frac{\omega}{\xi_2} \left( C - C^* - \int_{C^*}^{C} \frac{C}{X} dX \right) + \frac{\alpha}{\xi_1} \left( A^* - \int_{A^*}^{A} \frac{A}{X} dX \right).$$

The time derivative of $V_1$ is computed as

$$\frac{dV_1}{dt} = (\beta I^* S^* + \mu S^*) \left( 2 - \frac{S}{S^*} - \frac{S^*}{S} \right) + \alpha A^* \left( 2 - \frac{A I^*}{A^* I} - \frac{A^* I}{AI^*} \right)$$

$$+ \omega C^* \left( 2 - \frac{C I^*}{C^* I} - \frac{C^* I}{CI^*} \right) \leq 0.$$

However, when $R_0 < 1$, the global stability of the disease-free equilibrium $E_f = (S_0, 0, 0, 0)$, where $S_0 = \frac{A}{\mu}$, was determined without using a Lyapunov function. Here we discuss the global stability of $E_f$ when $R_0 \leq 1$. For this, we construct a Lyapunov function for system (14) at $E_f$:

$$V_0(S, I, C, A) = \Psi_1(S) + \Psi_2(I) + \frac{\omega}{\xi_2} \Psi_3(C) + \frac{\alpha}{\xi_1} \Psi_4(A)$$

$$= S - S_0 - \int_{S_0}^{S} \frac{S_0}{X} dX + I + \frac{\omega}{\xi_2} C + \frac{\alpha}{\xi_1} A.$$

The time derivative of $V_0$ along the solutions of system (14) satisfies

$$\frac{dV_0}{dt} = \left( 1 - \frac{S_0}{S} \right) \frac{dS}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dA}{dt}$$

$$\leq - \frac{\mu(S - S_0)^2}{S} + \frac{N}{\xi_1} I(R_0 - 1).$$

Therefore, $\frac{dV_0}{dt} \leq 0$ if $R_0 \leq 1$. Furthermore, the largest compact invariant set in $\left\{ (S, I, C, A) \mid \frac{dV_0}{dt} = 0 \right\}$ is just the singleton $E_f$. Using LaSalle’s invariance principle [39], we conclude that $E_f$ is globally asymptotically stable.

Now, we propose the following fractional-order SICA model defined by

\begin{align*}
\frac{d^\theta S(t)}{dt^\theta} &= \Lambda - \mu S(t) - \beta S(t)I(t), \\
\frac{d^\theta I(t)}{dt^\theta} &= \beta S(t)I(t) - (\rho + \phi + \mu)I(t) + \alpha A(t) + \omega C(t), \\
\frac{d^\theta C(t)}{dt^\theta} &= \phi I(t) - (\omega + \mu)C(t), \\
\frac{d^\theta A(t)}{dt^\theta} &= \rho I(t) - (\alpha + \mu + d)A(t),
\end{align*}

where $0 < \theta \leq 1$, subject to the initial conditions

\begin{align*}
S(0) &\geq 0, & I(0) &\geq 0, & C(0) &\geq 0, & A(0) &\geq 0.
\end{align*}
Remark 4. Following [11], one can easily prove that system (15)–(16) has a unique solution for any $t > 0$.

Applying Proposition 2, we have

$$C_0 D_t^\theta V_0(S, I, C, A) \leq 0, \quad \text{when } R_0 \leq 1$$

and

$$C_0 D_t^\theta V_1(S, I, C, A) \leq 0, \quad \text{when } R_0 > 1.$$ 

Then, the following result holds.

**Theorem 3.1.** Suppose that $0 < \theta \leq 1$.

(i) If $R_0 \leq 1$, then the disease-free equilibrium $E_f$ is globally asymptotically stable.

(ii) If $R_0 > 1$, then the endemic equilibrium $E^*$ is globally asymptotically stable.

**Proof.** (i) Obviously, the largest invariant set in

$$\{(S, I, C, A) \in \mathbb{R}_+^4 \mid C_0 D_t^\theta V_0(S, I, C, A) = 0\}$$

is just the singleton $E_f$. By LaSalle’s invariance principle in [31], $E_f$ is globally asymptotically stable.

(ii) It is easy to see that the largest invariant set in

$$\{(S, I, C, A) \in \mathbb{R}_+^4 \mid C_0 D_t^\theta V_1(S, I, C, A) = 0\}$$

is just the singleton $E^*$. Using LaSalle’s invariance principle, we conclude that $E_f$ is globally asymptotically stable.

Finally, we present some numerical simulations to illustrate the stability results of model (15)–(16), for different values of $\theta$. We consider the following parameter values:

$$\Lambda = 10724, \quad \mu = 1/69.54, \quad \beta = 0.066, \quad \rho = 0.1,$$

$$\phi = 1, \quad \alpha = 0.33, \quad \omega = 0.09, \quad d = 1.$$ 

A direct calculation gives $R_0 = 0.2900$, which satisfies item (i) of Theorem 3.1. Then, the disease-free equilibrium $E_f = (7.4575 \times 10^5, 0, 0, 0)$ is globally asymptotically stable, which leads to the eradication of HIV and AIDS from the population. Numerical simulations illustrate this result (see Figure 1).

In Figure 2, we choose $\beta = 0.866$, while keeping the other parameter values as before. In this case, we have $R_0 = 3.8049$ and system (15)–(16) has an endemic equilibrium $E^* = (0.8909 \times 10^5, 4.1489 \times 10^4, 3.9748 \times 10^5, 3.0861)$. Hence, by item (ii) of Theorem 3.1, $E^*$ is globally asymptotically stable, which means that the disease persists in the population.

3.2. **Example 2: an HIV cellular model.** We consider the HIV infection model with cure rate of infected cells in eclipse stage as proposed by Maziane et al. [42]. This model contains also four variables: the uninfected CD4$^+$ T cells $(T)$, infected cells in the eclipse stage (unproductive cells, denoted by $E$), productive infected cells
Figure 1. Stability of the disease-free equilibrium $E_f$ for the fractional-order SICA model (15) with $\theta = 0.5$ (blue), $\theta = 0.7$ (red), $\theta = 0.9$ (yellow), and $\theta = 1$ (green).

The model is given by the following non-linear system of ODEs:

$$
\begin{align*}
\frac{dT(t)}{dt} &= \lambda - \mu_T T(t) - f(T(t), V(t)) V(t) + \rho E(t), \\
\frac{dE(t)}{dt} &= f(T(t), V(t)) V(t) - (\mu_E + \rho + \gamma) E(t), \\
\frac{dI(t)}{dt} &= \gamma E(t) - \mu_I I(t), \\
\frac{dV(t)}{dt} &= k I(t) - \mu_V V(t),
\end{align*}
$$

where $\lambda$ is the recruitment rate of uninfected cells. The constants $\mu_T$, $\mu_E$, $\mu_I$, and $\mu_V$ represent the death rates of uninfected cells, unproductive cells, productive cells, and virus, respectively. The constant $\rho$ is the rate at which the unproductive infected cells may revert to the uninfected cells. The incidence of HIV infection of health CD4$^+$T cells has the form

$$
f(T, V) = \frac{\beta T}{1 + \alpha_1 T + \alpha_2 V + \alpha_3 TV},$$
where $\beta$ is the infection rate and $\alpha_1, \alpha_2, \alpha_3 \geq 0$ are non-negative constants. The constant $\gamma$ is the rate at which infected cells in the eclipse stage become productive infected cells and the constant $k$ is the rate of production of virions by infected cells. The basic reproduction number $R_0$ is given by

$$R_0 = \frac{\lambda \beta k \gamma}{\mu_1 \mu_2 (\lambda \alpha_1 + \mu_T) (\rho + \mu_E + \gamma)},$$

which is the average number of secondary infections produced by one productive infected cell during the period of infection when all cells are uninfected. Moreover, Maziane et al. [42] show that model (17) is globally asymptotically stable. The proof is done by using the following Lyapunov function in $\mathbb{R}_+^4$:

$$L(T, E, I, V) = \Psi_1(T) + \frac{\rho + \mu_E + \gamma}{\gamma} \Psi_2(I) + \Psi_3(E) + \frac{\mu_1 (\rho + \mu_E + \gamma)}{k \gamma} \Psi_4(V) + \frac{\rho(1 + \alpha_2 V)}{2(1 + \alpha_1 T + \alpha_2 V + \alpha_3 T V)} (T - T + E - E)^2.$$
\begin{equation}
T - T - \int_T^T f(T, V) d\theta + \frac{\rho + \mu E + \gamma}{\gamma} \left( I - \int_T^I \frac{I}{\theta} d\theta \right) + E + E + \int_E^E E d\theta + \frac{\mu_1 (\rho + \mu E + \gamma)}{k\gamma} \left( V - V + \int_V^V V d\theta \right) + \frac{\rho (1 + \alpha_2 V)}{2(1 + \alpha_1 T + \alpha_2 V + \alpha_3 T V)} (T - T + E - E)^2,
\end{equation}

where \( \mathbf{V} = (T, E, I, V) \) is an arbitrary equilibrium of system (17) and when \( \mathbf{V} \) is zero, for some equilibrium coordinate, the corresponding integral term vanishes.

Now, we propose the following fractional-order HIV infection model with cure rate of infected cells in eclipse stage:

\begin{equation}
\begin{cases}
\frac{D_t^\alpha}{5} T(t) = \lambda - \mu T(t) - f(T(t), V(t)) V(t) + \rho E(t), \\
\frac{D_t^\alpha}{5} E(t) = f(T(t), V(t)) V(t) - (\mu_E + \rho + \gamma) E(t), \\
\frac{D_t^\alpha}{5} I(t) = \gamma E(t) - \mu_1 I(t), \\
\frac{D_t^\alpha}{5} V(t) = k I(t) - \mu V(t),
\end{cases}
\end{equation}

subject to initial conditions

\begin{equation}
T(0) \geq 0, \quad E(0) \geq 0, \quad I(0) \geq 0, \quad V(0) \geq 0,
\end{equation}

where \( 0 < \alpha \leq 1 \).

**Remark 5.** It follows from the results of Boukhouima et al. [13] that system (19)–(20) has a unique global solution.

Let \( u(t) = (T(t), E(t), I(t), V(t)) \) be a solution of (19)–(20). According to our Corollary 2, since \( L \) given by (18) is a Lyapunov function for the ordinary differential equations (17) of the form described by (12), then \( L \) is also a Lyapunov function for the fractional-order system (19)–(20).

**4. Conclusion**

Mathematical models using ordinary differential equations have proved valuable to understand the interactions and the evolution of different biological phenomena [34]. However, such models ignore memory effects and long-range interactions, which exist in most biological systems. For this reason, fractional differential equations have recently been used to model more accurately such real processes: see, e.g., [5, 8, 35, 38]. As is well known, stability analysis is an important performance metric for any dynamical system [10, 47, 56]. The fractional-order extension of Lyapunov’s direct method becomes, naturally, one of main interesting techniques to study the global behavior of fractional-order models without solving explicitly such systems [9]. This method provides a way to determinate asymptotic stability by constructing a suitable Lyapunov function, which is not easy to find. Here, a new lemma for Caputo fractional derivatives of order \( 0 < \alpha \leq 1 \), of some functions, is presented. Our approach consists to construct Lyapunov functions for FDEs using Lyapunov functions for ODEs. This result is shown to be useful to determine the asymptotic stability of fractional-order systems in biology. In addition, the inequality obtained by Vargas-De-León [61] for Volterra-type Lyapunov functions is generalized and improved.
On the other hand, two proposed fractional HIV models are studied to show the effectiveness of our method. Firstly, we demonstrated the global stability of the endemic equilibrium of a fractional SICA model based on the Lyapunov functional proposed by Silva and Torres [55], when the basic reproduction number is greater than one, that is, $R_0 > 1$. Secondly, we have improved the global stability of the disease-free equilibrium by constructing an appropriate Lyapunov functional when $R_0 \leq 1$. To validate these theoretical results, we carried out some numerical simulations for different values of the order of the fractional derivative. We also remarked that when the value of this order is small, the solution of the fractional SICA model converges rapidly to the steady-states. The same approach is applied to prove the global stability of any arbitrary equilibrium point for a fractional HIV cellular model.

Time delay is a very important element in mathematical biology [23]. Generally, it represents the incubation time, the time needed for the activation of immunity or other biological effects [54]. To study the global stability of delayed systems, we often combine Volterra-type Lyapunov functions with others depending on the delays. Our method can be useful in biology to extend such functions to fractional systems with delays. This is under investigation and will be addressed elsewhere.

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