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UNIFORM ASYMPTOTIC STABILITY OF A FRACTIONAL TUBERCULOSIS MODEL

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Abstract. We propose a Caputo type fractional-order mathematical model for the transmission dynamics of tuberculosis (TB). Uniform asymptotic stability of the unique endemic equilibrium of the fractional-order TB model is proved, for any $\alpha \in (0, 1)$. Numerical simulations for the stability of the endemic equilibrium are provided.

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1. Introduction

When defining a differential operator, one often employs, besides ordinary derivatives, generalized derivatives, which appear in a natural way when considering extensions of differential operators defined on differentiable functions, and weak derivatives, related to the transition to the adjoint operator [9]. Derivatives of fractional and negative orders appear when the differentiation is defined by means of an integral transform, applicable to the domain of definition and range of such generalized differential operator [18]. This is often done in order to obtain the simplest possible representation of the corresponding differential operator of a function and to attain a reasonable generality in the formulation of problems and satisfactory properties of the objects considered [23]. Problems in the theory of differential equations, *e.g.*, problems of existence, uniqueness, regularity, continuous dependence of the solutions on the initial data or on the right-hand side, or the explicit form of a solution of a differential equation defined by a given differential expression, are readily interpreted in the theory of operators as problems on the corresponding differential operator defined on suitable function spaces [5]. One advantage of fractional order differential equations is that they provide a powerful instrument to incorporate memory and hereditary properties into the systems, as opposed to the integer order models, where such effects are neglected or difficult to incorporate [17]. Moreover, in order to precisely reproduce the nonlocal, frequency- and history-dependent properties of power law phenomena, some different modeling tools, based on fractional operators, have to be introduced: see, *e.g.*, [3] and references therein.

Keywords and phrases: Tuberculosis, fractional differentiation, ordinary differential equations, numerical solutions, stability.

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Communicable diseases have always been an important part of human history [6]. Fractional-order differential system models for infectious disease dynamics have been introduced in recent years [1, 14, 17, 28, 30, 44]. In [30], the authors propose a fractional-order model and show, through numerical simulations, that the fractional models fit better the first dengue epidemic recorded in the Cape Verde islands off the coast of west Africa, in 2009, when compared with the standard differential model. The authors of [17] show that a nonlinear fractional order epidemic model is well suited to provide numerical results that agree very well with real data of influenza A (H1N1) at the population level. In [28], a fractional model for malaria transmission is considered and numerical simulations are done for the variation of the values of the fractional derivative and of the parameter that models personal protection. In [44], fractional-order derivatives are introduced into an HIV infection model and local asymptotic stability is proved. The authors of [14] introduce fractional-order derivatives into a model of HIV infection of $CD4^+$ T-cells and analyze the local asymptotic stability of the equilibrium points. In [41], the uniform asymptotic stability is proved extending the Volterra-type Lyapunov functions to fractional-order epidemic systems. Fractional-order predator-prey models are investigated in [2]. In particular, existence and uniqueness of solutions are proved, and stability of equilibrium points studied. Numerical solutions of such models were obtained [2]. Here we are interested to investigate fractional calculus with respect to tuberculosis.

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis*, which is usually spread through the air by people with active TB. TB is one of the top ten causes of death worldwide, which justifies the amount of research on the area: see, *e.g.*, [35, 38, 42]. For a good survey on optimal models of TB, we refer the reader to [36]. In [38], delays are introduced in a TB model, representing the time delay on the diagnosis and commencement of treatment of individuals with active TB infection. Optimal control strategies to minimize the cost of interventions, considering reinfection and post-exposure interventions, are investigated in [35]. In [33], the potential of two post-exposure interventions, treatment of early latent TB individuals and prophylactic treatment/vaccination of persistent latent TB individuals, is investigated. A mathematical model for TB is studied in [11] from the optimal control point of view, using a multiobjective approach. For numerical simulations using TB data from Angola see [34]. Despite the numerous works on tuberculosis, the literature on fractional-order mathematical models for TB is scarce. In [39], the authors propose a multi-strain TB model of variable-order fractional derivatives and develop a numerical scheme to approximate the endemic solution numerically. Here, we propose a Caputo type fractional-order mathematical model for the transmission dynamics of tuberculosis (TB), based on the nonlinear differential system studied in [43], and investigate its stability.

The stability question is of main interest in epidemiological control systems [25, 32, 37]. For nonlinear fractional-order systems, stability analysis is a recent and interesting topic: see, *e.g.*, [4, 8, 10, 19, 20, 21, 22, 31, 41]. The direct Lyapunov method provides a way to determine (asymptotic, uniform, global asymptotic) stability of an equilibrium point without explicitly solving for integer-order nonlinear systems [41]. In [10], the authors extended the Lyapunov direct method to Caputo type fractional-order nonlinear systems using Bihari's inequality and Bellman–Grownwall's inequality. Different approaches for the extension of the Lyapunov direct method were proposed in [4, 21, 22]. See [20, 26, 27, 31, 40] for a survey on stability analysis of fractional differential equations. In [39], the stability of the endemic equilibrium of a fractional-order TB model is studied numerically. Here we prove, analytically, the uniform asymptotic stability of the unique endemic equilibrium of the fractional-order TB model, for any $\alpha \in (0, 1)$. Moreover, we illustrate the theoretical stability results through numerical simulations.

The paper is organized as follows. In Section 2, we present basic definitions and some known results about Caputo fractional calculus as well as results on uniform asymptotic stability and Volterra-type Lyapunov functions for fractional-order systems. In Section 3, we introduce Caputo fractional-order derivatives into the TB model proposed in [43] and study the existence of equilibrium points. In Section 4, we prove the uniform asymptotic stability of the unique endemic equilibrium of the fractional-order TB model. Numerical simulations are provided in Section 5, which illustrate the stability result proved in the previous section. We finish with Section 6 of conclusions.

2. Preliminaries on the Caputo fractional calculus

We begin by introducing the definition of Caputo fractional derivative and recalling its main properties.

Definition 2.1 (See [7]). Let $a > 0$, $t > a$, $\alpha, a, t \in \mathbb{R}$. The Caputo fractional derivative of order α of function $f \in C^n$ is given by

$$ {}_a^C D_t^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t \frac{f^{(n)}(\xi)}{(t-\xi)^{\alpha+1-n}} \mathrm{d}\xi, \qquad n-1 < \alpha < n \in \mathbb{N}. \tag{2.1} $$

Property 2.2 (Linearity, see, *e.g.*, [12]). *Let $f(t), g(t) : [a, b] \to \mathbb{R}$ be such that ${}_a^C D_t^\alpha f(t)$ and ${}_a^C D_t^\alpha g(t)$ exist almost everywhere and let $c_1, c_2 \in \mathbb{R}$. Then, ${}_a^C D_t^\alpha (c_1 f(t) + c_2 g(t))$ exists almost everywhere, and*

$$ {}_a^C D_t^\alpha (c_1 f(t) + c_2 g(t)) = c_1 {}_a^C D_t^\alpha f(t) + c_2 {}_a^C D_t^\alpha g(t). \tag{2.2} $$

Property 2.3 (Caputo derivative of a constant, see, *e.g.*, [29]). *The fractional derivative of a constant function $f(t) \equiv c$ is zero:*

$$ {}_{t_0}^C D_t^\alpha c = 0. \tag{2.3} $$

Let us consider the following general fractional differential equation involving the Caputo derivative:

$$ {}_a^C D_t^\alpha x(t) = f(t, x(t)), \qquad \alpha \in (0, 1), \tag{2.4} $$

with the initial condition $x_0 = x(t_0)$.

Definition 2.4 (See, *e.g.*, [21]). The constant x^* is an equilibrium point of the Caputo fractional dynamic system (2.4) if, and only if, $f(t, x^*) = 0$.

Next theorem is an extension of the Lyapunov direct method for Caputo type fractional-order nonlinear systems [10].

Theorem 2.5 (Uniform asymptotic stability [10]). *Let x^* be an equilibrium point for the nonautonomous fractional order system (2.4) and $\Omega \subset \mathbb{R}^n$ be a domain containing x^*. Let $L : [0, \infty) \times \Omega \to \mathbb{R}$ be a continuously differentiable function such that*

$$ W_1(x) \leq L(t, x(t)) \leq W_2(x) \tag{2.5} $$

and

$$ {}_a^C D_t^\alpha L(t, x(t)) \leq -W_3(x) \tag{2.6} $$

for all $\alpha \in (0, 1)$ and all $x \in \Omega$, where $W_1(\cdot)$, $W_2(\cdot)$ and $W_3(\cdot)$ are continuous positive definite functions on Ω. Then the equilibrium point of system (2.4) is uniformly asymptotically stable.

In what follows we recall a lemma proved in [41], where a Volterra-type Lyapunov function is obtained for fractional-order epidemic systems.

Lemma 2.6 (See [41]). *Let $x(\cdot)$ be a continuous and differentiable function with $x(t) \in \mathbb{R}_+$. Then, for any time instant $t \geq t_0$, one has*

$$ {}_{t_0}^C D_t^\alpha \left[x(t) - x^* - x^* \ln \frac{x(t)}{x^*} \right] \leq \left(1 - \frac{x^*}{x(t)} \right) {}_{t_0}^C D_t^\alpha x(t), \qquad x^* \in \mathbb{R}^+, \qquad \forall \alpha \in (0, 1). \tag{2.7} $$

3. Fractional-order tuberculosis (TB) model

In this section we propose a Caputo fractional-order version of a tuberculosis (TB) model in [43]. The model describes the dynamics of a population that is susceptible to infection by the *Mycobacterium tuberculosis* with incomplete treatment. The total population is partitioned into four compartments:

- susceptible individuals, S;
- latent individuals, L, which have been infected but are not infectious and do not have symptoms of the disease;
- infectious individuals, I, which have active TB, may transmit the infection but are not in treatment;
- and under treatment infected individuals, T.

The susceptible population is increased by the recruitment of individuals into the population, assumed susceptible, at a rate Λ. All individuals suffer from natural death, at a constant rate μ. Susceptible individuals acquire TB infection by the contact with individuals in the class I at a rate βIS, where β is the transmission coefficient. Individuals in the latent class L become infectious at a rate ϵ, and infectious individuals I start treatment at a rate γ. Treated individuals T leave their compartment at a rate δ. After leaving the treatment compartment, an individual may enter compartment L, due to the remainder of *Mycobacterium tuberculosis*, or compartment I, due to the failure of treatment. The parameter k, $0 \leq k \leq 1$, represents the failure of the treatment, where $k = 0$ means that all the treated individuals will become latent, while $k = 1$ means that the treatment fails and all the treated individuals will still be infectious. Infectious, I, and under treatment individuals, T, may suffer TB-induced death at the rates α_1 and α_2, respectively. The Caputo fractional-order system that describes the previous assumptions is

$$\begin{cases} {}_{t_0}^{C}D_t^{\alpha} S(t) = \Lambda - \beta I(t)S(t) - \mu S(t), \\ {}_{t_0}^{C}D_t^{\alpha} L(t) = \beta I(t)S(t) + (1-k)\delta T(t) - (\mu+\epsilon)L(t), \\ {}_{t_0}^{C}D_t^{\alpha} I(t) = \epsilon L(t) + k\delta T(t) - (\mu+\gamma+\alpha_1)I(t), \\ {}_{t_0}^{C}D_t^{\alpha} T(t) = \gamma I(t) - (\mu+\delta+\alpha_2)T(t). \end{cases} \tag{3.1}$$

The feasible region of system (3.1) is given by

$$\Omega = \left\{ (S, L, I, T) \in \mathbb{R}_+^4 : S + L + I + T \leq \frac{\Lambda}{\mu} \right\}. \tag{3.2}$$

Let $b_1 = \mu + \epsilon$, $b_2 = \mu + \gamma + \alpha_1$ and $b_3 = \mu + \delta + \alpha_2$. Consider the following endemic threshold [43]:

$$R_0 = \frac{\beta \epsilon b_3 \Lambda}{\mu b_1 b_2 b_3 - \mu\delta\gamma((1-k)\epsilon + k b_1)}. \tag{3.3}$$

According to Definition 2.4, system (3.1) has a disease-free equilibrium

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0 \right)$$

and, when $R_0 > 1$, an unique endemic equilibrium

$$E^* = (S^*, L^*, I^*, T^*)$$

with

$$S^* = \frac{\Lambda}{\mu + \beta I^*}, \quad L^* = \frac{1}{\epsilon}\left(b_2 - \frac{k\delta\gamma}{b_3}\right) I^*, \quad I^* = \frac{\mu}{\beta}\left(R_0 - 1\right), \quad T^* = \frac{\gamma}{b_3} I^*. \tag{3.4}$$

4. Uniform asymptotic stability of the endemic equilibrium

In this section we prove uniform asymptotic stability of the endemic equilibrium $E^* = (S^*, L^*, I^*, T^*)$ of the fractional order system (3.1).

Theorem 4.1. *Let $\alpha \in (0,1)$ and $R_0 > 1$. Then the unique endemic equilibrium E^* of the fractional order system (3.1) is uniformly asymptotically stable in the interior of Ω defined by (3.2).*

Proof. Consider the following Lyapunov function:

$$V(t) = m_1 V_1(S(t)) + m_1 V_2(L(t)) + m_2 V_3(I(t)) + m_3 V_4(T(t)),$$

where

$$\begin{aligned} V_1(S(t)) &= S(t) - S^* - S^* \ln \frac{S(t)}{S^*}, \\ V_2(L(t)) &= L(t) - L^* - L^* \ln \frac{L(t)}{L^*}, \\ V_3(I(t)) &= I(t) - I^* - I^* \ln \frac{I(t)}{I^*}, \\ V_4(T(t)) &= T(t) - T^* - T^* \ln \frac{T(t)}{T^*} \end{aligned}$$

and

$$m_1 = \epsilon, \quad m_2 = b_1, \quad m_3 = \frac{\delta T^*(b_1 k + \epsilon(1-k))}{\gamma I^*}.$$

Function V is defined, continuous and positive definite for all $S(t) > 0$, $L(t) > 0$, $I(t) > 0$ and $T(t) > 0$. By Lemma 2.6, we have

$${}^{C}_{t_0}D^{\alpha}_{t} V \leq m_1 \left(1 - \frac{S^*}{S}\right) {}^{C}_{t_0}D^{\alpha}_{t} S + m_1 \left(1 - \frac{L^*}{L}\right) {}^{C}_{t_0}D^{\alpha}_{t} L + m_2 \left(1 - \frac{I^*}{I}\right) {}^{C}_{t_0}D^{\alpha}_{t} I + m_3 \left(1 - \frac{T^*}{T}\right) {}^{C}_{t_0}D^{\alpha}_{t} T.$$

It follows from (3.1) that

$$\begin{aligned} {}^{C}_{t_0}D^{\alpha}_{t} V \leq\ & m_1 \left(1 - \frac{S^*}{S}\right)(\Lambda - \beta I S - \mu S) + m_1 \left(1 - \frac{L^*}{L}\right)(\beta I S + (1-k)\delta T - b_1 L) \\ & + m_2 \left(1 - \frac{I^*}{I}\right)(\epsilon L + k\delta T - b_2 I) + m_3 \left(1 - \frac{T^*}{T}\right)(\gamma I - b_3 T). \end{aligned}$$

At the endemic equilibrium $\Lambda = S^* (\mu + \beta I)$, we have

$$\begin{aligned} {}_{t_0}^{C}D_t^{\alpha} V \leq\ & m_1 \left[\mu S^* \left(2 - \frac{S}{S^*} - \frac{S^*}{S} \right) + \beta I^* S^* \left(1 - \frac{S^*}{S} - \frac{S}{S^*} \frac{I}{I^*} + \frac{I}{I^*} \right) \right] \\ & + m_1 \left(1 - \frac{L^*}{L} \right) (\beta I S + (1-k)\delta T - b_1 L) \\ & + m_2 \left(1 - \frac{I^*}{I} \right) (\epsilon L + k\delta T - b_2 I) + m_3 \left(1 - \frac{T^*}{T} \right) (\gamma I - b_3 T) . \end{aligned}$$

Let $m_1 = \varepsilon$. After some simplifications, one has

$$\begin{aligned} {}_{t_0}^{C}D_t^{\alpha} V \leq\ & \varepsilon \mu S^* \left(2 - \frac{S}{S^*} - \frac{S^*}{S} \right) + \varepsilon \beta I^* S^* \left(1 - \frac{S^*}{S} + \frac{I}{I^*} - \frac{L^*}{L} \frac{I}{I^*} \frac{S}{S^*} \right) \\ & + \varepsilon (1-k)\delta T - \varepsilon b_1 L - \varepsilon \frac{L^*}{L} (1-k)\delta T + \varepsilon L^* b_1 \\ & + m_2 \left(1 - \frac{I^*}{I} \right) (\epsilon L + k\delta T - b_2 I) + m_3 \left(1 - \frac{T^*}{T} \right) (\gamma I - b_3 T) . \end{aligned}$$

Let $m_2 = b_1$. Using

$$b_1 L^* = \beta I^* S^* + (1-k)\delta T^*$$

at the endemic equilibrium, we have

$$\begin{aligned} {}_{t_0}^{C}D_t^{\alpha} V \leq\ & \varepsilon \mu S^* \left(2 - \frac{S}{S^*} - \frac{S^*}{S} \right) + \varepsilon \beta I^* S^* \left(2 - \frac{S^*}{S} + \frac{I}{I^*} - \frac{L}{L^*} - \frac{L^*}{L} \frac{I}{I^*} \frac{S}{S^*} \right) \\ & + \varepsilon (1-k)\delta T^* \left(1 + \frac{T}{T^*} - \frac{L}{L^*} - \frac{L^*}{L} \frac{T}{T^*} \right) + m_3 \left(1 - \frac{T^*}{T} \right) (\gamma I - b_3 T)\, \epsilon b_1 L^* \frac{L}{L^*} \\ & + b_1 k\delta T - b_1 b_2 I - \epsilon b_1 L^* \frac{I^*}{I} \frac{L}{L^*} - b_1 \frac{I^*}{I} k\delta T + b_1 I^* b_2 . \end{aligned}$$

Moreover, since

$$b_1 L^* = \beta I^* S^* + (1-k)\delta T^*$$

at the equilibrium point, it follows that

$$\begin{aligned} {}_{t_0}^{C}D_t^{\alpha} V \leq\ & \varepsilon \mu S^* \left(2 - \frac{S}{S^*} - \frac{S^*}{S} \right) + \varepsilon \beta I^* S^* \left(2 - \frac{S^*}{S} + \frac{I}{I^*} - \frac{I^*}{I} \frac{L}{L^*} - \frac{L^*}{L} \frac{I}{I^*} \frac{S}{S^*} \right) \\ & + \varepsilon (1-k)\delta T^* \left(1 + \frac{T}{T^*} - \frac{I^*}{I} \frac{L}{L^*} - \frac{L^*}{L} \frac{T}{T^*} \right) + b_1 k\delta T^* \left(\frac{T}{T^*} - \frac{I^*}{I} \frac{T}{T^*} \right) \\ & - b_1 b_2 I + b_1 I^* b_2 + m_3 \left(1 - \frac{T^*}{T} \right) (\gamma I - b_3 T) . \end{aligned}$$

After some simplifications, and using again relations

$$b_2 I^* = \varepsilon L^* + k\delta T^*, \quad b_1 L^* = \beta I^* S^* + (1-k)\delta T^*,$$

we have

$$
\begin{aligned}
{}_{t_0}^{C}D_t^{\alpha}V \leq\ & \varepsilon\mu S^*\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right)+\varepsilon\beta I^*S^*\left(3-\frac{S^*}{S}-\frac{I^*}{I}\frac{L}{L^*}-\frac{L^*}{L}\frac{I}{I^*}\frac{S}{S^*}\right)\\
&+\varepsilon(1-k)\delta T^*\left(2+\frac{T}{T^*}-\frac{I}{I^*}-\frac{I^*}{I}\frac{L}{L^*}-\frac{L^*}{L}\frac{T}{T^*}\right)+b_1k\delta T^*\left(1+\frac{T}{T^*}-\frac{I}{I^*}-\frac{I^*}{I}\frac{T}{T^*}\right)\\
&+m_3\gamma I-m_3b_3T-m_3\frac{T^*}{T}\gamma I+m_3T^*b_3.
\end{aligned}
$$

TABLE 1. Parameter values taken from [43].

Parameter	Description	Value
Λ	Recruitment rate	792.8571
β	Transmission coefficient	5×10^{-5}
μ	Natural death rate	0.143
k	Treatment failure rate	0.15
δ	Rate at which treated individuals leave the T compartment	1.5
ϵ	Rate at which latent individuals L become infectious	0.00368
γ	Treatment rate for infectious individuals I	0.7
α_1	TB-induced death rate for infectious individuals I	0.3
α_2	TB-induced death rate for under treatment individuals T	0.05

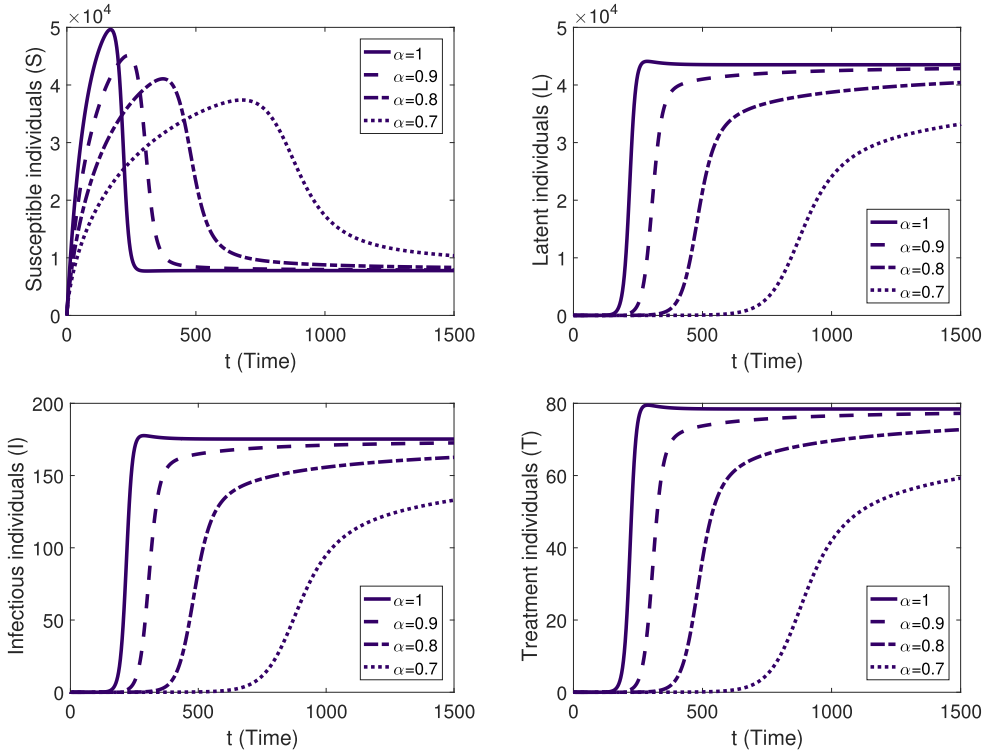

FIGURE 1. Numerical simulation of the Caputo TB system (3.1) with values as in Table 1, with exception of $b = 0.0005$, and initial conditions (5.1).

Let

$$m_3 = \frac{\delta T^*(b_1 k + \epsilon(1-k))}{\gamma I^*}.$$

Using $b_3 T^* = \gamma I^*$, and simplifying the previous inequality, we have

$$\begin{aligned} {}^{C}_{t_0}D^{\alpha}_{t} V \leq \varepsilon \mu S^* \left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) + \varepsilon \beta I^* S^* \left(3 - \frac{S^*}{S} - \frac{I^*}{I}\frac{L}{L^*} - \frac{L^*}{L}\frac{I}{I^*}\frac{S}{S^*}\right) \\ + \varepsilon(1-k)\delta T^* \left(3 - \frac{T^*}{T}\frac{I}{I^*} - \frac{I^*}{I}\frac{L}{L^*} - \frac{L^*}{L}\frac{T}{T^*}\right) + b_1 k \delta T^* \left(2 - \frac{T^*}{T}\frac{I}{I^*} - \frac{I^*}{I}\frac{T}{T^*}\right). \end{aligned}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then we have ${}^{C}_{t_0}D^{\alpha}_{t} V \leq 0$, with equality holding only if $S^* = S$, $L^* = L$, $I^* = I$ and $T^* = T$. Therefore, by Theorem 2.5 of uniform asymptotic stability, we conclude that the endemic equilibrium E^* (3.4) is uniformly asymptotically stable in the interior of Ω. □

5. Numerical simulations

In this section we study the dynamical behavior of our model (3.1), by variation of the noninteger order derivative α. The parameter values used in the simulations can be found in Table 1, with exception of $b = 0.0005$,

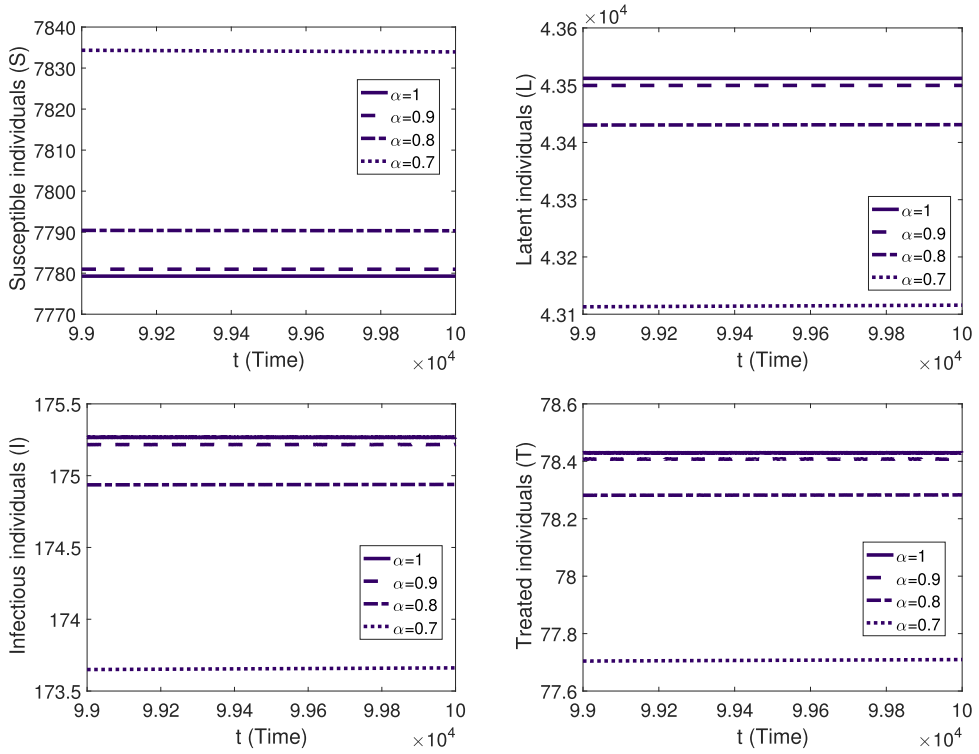

Figure 2. Numerical simulation of the Caputo TB system with parameters and initial conditions as in Figure 1, showing that the solutions converge to the endemic equilibrium $(7779.3, 43512, 175.2, 78.4)$ for $\alpha = 1$.

which we changed in order to get a value of R_0 bigger than one (endemic situation). Direct calculations, with these parameter values, give $R_0 = 7.1343 > 1$ and the endemic equilibrium

$$E^* = (7779.3, 43512, 175.2, 78.4).$$

We consider the initial conditions

$$S(0) = 0.8, \quad L(0) = 0.05, \quad I(0) = 0.1, \quad T(0) = 0.05 \tag{5.1}$$

and a fixed time step size of $h = 2^{-8}$.

For the numerical implementation of the fractional derivatives, we have used the Adams–Bashforth–Moulton scheme, which has been implemented in the Matlab code fde12 by Garrappa [16]. Regarding convergence and accuracy of the numerical method, we refer to [13]. The stability properties of the method implemented by fde12 have been studied in [15]. We consider, without loss of generality, the fractional-order derivatives $\alpha = 1.0, 0.9, 0.8$ and 0.7. In Figures 1 and 2, one can see that when $\alpha \to 1$ the solutions of our model converge to the solutions obtained in [43]. The simulation results confirm, numerically, the stability result of Theorem 4.1.

6. Conclusions

In this work we proposed a Caputo fractional-order tuberculosis (TB) model. Existence of equilibrium points has been investigated and the uniform asymptotic stability of the unique endemic equilibrium proved via a suitable Lyapunov function. Our analytical results were complemented by numerical simulations in Matlab, illustrating the obtained stability result. The proposed fractional order model provides richer and more flexible results when compared with the corresponding integer-order TB model.

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