



A fractional-order tuberculosis model with fast and slow progression

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Abstract. In this paper, we introduce a fractional-order tuberculosis model with fast and slow progression. We show the existence of non-negative solutions of the model, and also give a detailed stability analysis of the disease-free and endemic equilibria. Numerical simulations are presented to illustrate the results.

Keywords: fractional order, tuberculosis model, stability, predictor-corrector method

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1. Introduction

Recently, many mathematical models have been proposed to describe the dynamics of human infectious disease and understand the mechanism of disease transmission [1, 2]. The basic and important research subjects for these systems are the existence of the threshold value which distinguishes whether the infectious disease will die out, the local and global stability of the disease-free equilibrium and the endemic equilibrium, the persistence and extinction of the disease, etc.

Tuberculosis (TB) which is a deadly disease is on the rise and revisiting both developed and developing countries. It is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. It is an infectious disease caused by bacteria whose scientific name is *Mycobacterium tuberculosis*. It is spread through the air when people who have an active *Mycobacterium tuberculosis* infection cough, sneeze, or otherwise transmit their saliva through the air [3]. Only people who are sick with TB in their lungs are infectious.

Recently, mathematical models have played a key role in the formulation of TB control strategies. And mathematical models have established the interim goals for intervention programs [4, 5]. In 1962, Waaler et al. [4] introduced the first mathematical model for TB in ordinary differential equations. After the seminal models of Waaler et al., there were several numerical studies, primarily focusing on the dynamics of the mathematical model for TB transmission [6, 7]. The simplest TB transmission models include classes of susceptible, exposed and infective individuals, and hence are known as SEI models. More factors, such as drug-resistant strains, fast and slow progression, confection with HIV, relapse, reinfection, migration, treatment, seasonality and vaccination are incorporated into studying the transmission dynamics of TB by many authors [5, 6, 7, 8, 9, 10, 11, 12, 13]. In [5], C. Castillo-Chavez and Z.L. Feng formulated one-strain and two-strain TB models to determine possible mechanisms that may allow for the survival and spread of naturally resistant strains of TB as well as antibiotic-generated resistant strains of TB. In 1998, Dye et al. present a model with explicit fast and slow progression from two latent classes [8]. In [9], Y.C. Zhou et al. formulate a difference equation model to projection of TB incidence with increasing immigration trends. In [10], L.J. Liu et al. presented a TB model incorporating seasonality. Elad Ziv et al. [11] used mathematical models to predict the potential public health impact of new TB vaccines in high-incidence countries. C.P. Bhunu et al. presented a tuberculosis transmission model with chemoprophylaxis and treatment [12].

So far as we know, all the models have been restricted to integer order ordinary (or delay) differential equations. In recent decades, it has turned out that many phenomena in different fields can be described very successfully by the models using fractional-order differential equations [14, 15]. Fractional calculus has found wide applications in many areas of science and engineering. And fractional calculus plays a key role in superdiffusive and subdiffusive processes, which makes it a useful tool in epidemiology [16, 17]. There are two reasons for considering a fractional order tuberculosis system. One is the fractional order models are more accurate than

integer-order models as fractional order models allow more degrees of freedom. Another is that we like to argue that fractional order differential equations are more suitable than classic integer order ones in epidemic systems where memory effects are important [18].

In this paper, we will discuss a fractional-order tuberculosis model with fast and low progression.

2. Model derivation

Firstly, we present the definition of fractional-order integration and fractional-order differentiation [19]. For fractional-order differentiation, we will use Caputo's definition, due to its convenience for initial conditions of the differential equations.

Definition 2.1. The fractional integral of order $\alpha > 0$ of a function $f : \mathbb{R}^+ \rightarrow \mathbb{R}$ is given by

$$\mathcal{I}^\alpha = \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t) dt$$

provided the right side is pointwise defined on \mathbb{R}^+ . Here and elsewhere in this paper, Γ denotes the Gamma function. **Definition 2.2.** The Caputo fractional derivative of order $\alpha \in (n-1, n)$ of a continuous function $f : \mathbb{R}^+ \rightarrow \mathbb{R}$ is given by

$$D^\alpha f(x) = \mathcal{I}^{n-\alpha} D^n f(x), \quad D = \frac{d}{dt}.$$

In particular, when $0 < \alpha < 1$, we have

$$D^\alpha f(x) = \frac{1}{\Gamma(1-\alpha)} \int_0^x \frac{f'(t)}{(x-t)^\alpha} dt.$$

In [20], S.M. Blower et al. presented a tuberculosis model with fast and low progression in the following:

$$\begin{cases} \frac{dS}{dt} = A - \beta SI - \mu S, \\ \frac{dE}{dt} = (1-\rho)\beta SI - (k+\mu)E, \\ \frac{dI}{dt} = \rho\beta SI + kE - (d+\mu)I. \end{cases} \quad (1)$$

The model has a susceptible group designated by S , an exposed group E , and an infected group I . The parameters of system (2.1) have the following meaning: A is the recruitment rate of the population, β is the per capita contact rate, μ is the natural death rate of the population, ρ is proportion of new infections that develop TB within a year, k is the rate at which the exposed individuals become infective (so that $1/k$ is the mean latent period), d is the disease-related death rate. In [7], the global dynamics of system (2.1) is resolved through the use of Lyapunov functions.

Now we introduce fractional order into system (2.1). The new system is described by the following set of FODE:

$$\begin{cases} D^\alpha S = A - \beta SI - \mu S, \\ D^\alpha E = (1 - \rho)\beta SI - (k + \mu)E, \\ D^\alpha I = \rho\beta SI + kE - (d + \mu)I. \end{cases} \quad (2)$$

The initial conditions for system (2.2) are

$$S(0) = S^0 \geq 0, \quad E(0) = E^0 \geq 0, \quad I(0) = I^0 \geq 0. \quad (3)$$

We denote

$$\mathbb{R}_+^3 = \{(S, E, I) \in \mathbb{R}^3, S \geq 0, E \geq 0, I \geq 0\}.$$

3. Non-negative solutions

In order to prove that the solutions of system (2.2) are non-negative, we need the following lemmas.

Lemma 3.1. (Generalized Mean Value Theorem)[21]. Suppose that $f(x) \in \mathbb{C}[a, b]$ and $D_a^\alpha f(x) \in \mathbb{C}(a, b)$, for $0 < \alpha \leq 1$, then we have

$$f(x) = f(a) + \frac{1}{\Gamma(\alpha)}(D_a^\alpha f)(\xi)(x - a)^\alpha$$

with $a \leq \xi \leq x, \forall x \in (a, b]$.

Lemma 3.2. Suppose that $f(x) \in \mathbb{C}[a, b]$ and $D_a^\alpha f(x) \in \mathbb{C}(a, b)$, for $0 < \alpha \leq 1$. If $D_a^\alpha f(x) \geq 0, \forall x \in (a, b)$, then $f(x)$ is nondecreasing for each $x \in [a, b]$. If $D_a^\alpha f(x) \leq 0, \forall x \in (a, b)$, then $f(x)$ is nonincreasing for each $x \in [a, b]$.

Theorem 3.1. There is a unique solution $x(t) = (S, E, I)^\top$ to system (2.2) with initial condition (2.3) on $t \geq 0$ and the solution will remain in \mathbb{R}_+^3 . Furthermore, S, E, I are all bounded by $\frac{A}{\mu}$.

Proof. The existence and uniqueness of the solution of (2.2)-(2.3) in $(0, +\infty)$ can be obtained from Theorem 3.1 and Remark 3.2 in [22]. In the following, we will show that the domain \mathbb{R}_+^3 is positively invariant. Since

$$\begin{aligned} D^\alpha S|_{S=0} &= A \geq 0, \\ D^\alpha E|_{E=0} &= (1 - \rho)\beta SI \geq 0, \\ D^\alpha I|_{I=0} &= kE \geq 0, \end{aligned}$$

on each hyperplane bounding the non-negative orthant, the vector field points into \mathbb{R}_+^3 by using Lemma 3.2.

From system (2.2), we can obtain

$$D^\alpha(S + E + I) = A - \mu(S + E + I) - dI < A - \mu(S + E + I).$$

Hence,

$$D^\alpha(S + E + I)|_{S+E+I=\frac{A}{\mu}} < 0.$$

Thus, S, E, I are all bounded by $\frac{A}{\mu}$ by using Lemma 3.2.

4. Equilibria and their asymptotical stability

To prove the locally asymptotical stability of equilibria of system (2.2), the following lemma is useful.

Lemma 4.1.[15] The equilibrium (x, y) of the following frictional-order differential system

$$\begin{cases} D^\alpha x(t) = f_1(x, y), D^\alpha y(t) = f_2(x, y), \alpha \in (0, 1], \\ x(0) = x_0, y(0) = y_0 \end{cases}$$

is locally asymptotically stable if all the eigenvalues of the Jacobian matrix

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

evaluated at the equilibrium (x, y) satisfy the following condition:

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

The basic reproductive ratio of system (2.2) is $\mathcal{R}_0 = \frac{A\beta(k+\mu\rho)}{\mu(k+\mu)(d+\mu)}$. To evaluate the equilibria, we let

$$D^\alpha S = 0, D^\alpha E = 0, D^\alpha I = 0.$$

It is easily to know that if $\mathcal{R}_0 < 1$, then the disease-free equilibrium $P_0(S_0, 0, 0)$ is the unique steady state, where $S_0 = \frac{A}{\mu}$; if $\mathcal{R}_0 > 1$, then in addition to the disease-free equilibrium, there is only one endemic equilibrium $P^*(S^*, E^*, I^*)$, where $S^* = \frac{(k+\mu)(d+\mu)}{\beta(k+\rho\mu)}$, $I^* = \frac{A\beta(k+\mu\rho) - \mu(k+\mu)(d+\mu)}{\beta(\mu+k)(k+\rho\mu)}$, $E^* = \frac{(1-\rho)[A\beta(k+\mu\rho) - \mu(k+\mu)(d+\mu)]}{\beta(\mu+k)(k+\rho\mu)}$. In the following, we will discuss the local stability of the disease-free equilibrium and endemic equilibrium.

Theorem 4.1. The disease-free equilibrium P_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$ and is unstable if $\mathcal{R}_0 > 1$.

Proof. The Jacobian matrix $J(P_0)$ for system (2.2) evaluated at the disease-free equilibrium P_0 is given by

$$J(P_0) = \begin{pmatrix} -\mu & 0 & -\beta S_0 \\ 0 & -(k+\mu) & (1-\rho)\beta S_0 \\ 0 & k & \rho\beta S_0 - (d+\mu) \end{pmatrix}.$$

Hence, the characteristic equation about P_0 is given by

$$(\lambda + \mu)(\lambda^2 + A_1\lambda + A_2) = 0, \quad (4)$$

where $A_1 = \frac{1}{\mu}[k\mu + \mu d + \mu^2 - \rho\beta A]$ and $A_2 = \frac{1}{\mu}[\mu(k+\mu)(d+\mu) - A\beta(k+\mu\rho)]$.

Obviously, $\mathcal{R}_0 < 1 \Leftrightarrow A_2 > 0$ and $\mathcal{R}_0 > 1 \Leftrightarrow A_2 < 0$. All the eigenvalues are $\lambda_1 = -\mu < 0$, $\lambda_{2,3} = \frac{1}{2}[-A_1 \pm \sqrt{A_1^2 - 4A_2}]$.

If $\mathcal{R}_0 < 1$, then the three roots of the characteristic equation (4.1) will have negative real parts. Thus, if $\mathcal{R}_0 < 1$, the disease-free equilibrium P_0 is asymptotically stable.

If $\mathcal{R}_0 > 1$, at least one eigenvalue will be positive real root. Thus, if $\mathcal{R}_0 > 1$, the disease-free equilibrium P_0 is unstable.

In the following, we consider the local stability of the endemic equilibrium P^* . The Jacobian matrix $J(P^*)$ evaluated at the endemic equilibrium P^* is given as:

$$J(P^*) = \begin{pmatrix} -\beta I^* - \mu & 0 & -\beta S^* \\ (1 - \rho)\beta I^* & -(k + \mu) & (1 - \rho)\beta S^* \\ \rho\beta I^* & k & \rho\beta S^* - (d + \mu) \end{pmatrix}.$$

The characteristic equation of $J(P^*)$ is

$$f(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \quad (5)$$

where

$$\begin{aligned} a_1 &= d + k + 3\mu + \beta I^* - \rho\beta S^*, \\ a_2 &= kd + \beta k I^* + 2\beta\mu I^* + \beta d I^* + 2k\mu + 2\mu d + 3\mu^2 - 2\mu\beta\rho S^* - \beta k S^*, \\ a_3 &= \beta\mu^2 I^* + \beta\mu d I^* + \beta k\mu I^* + \beta k d I^* + k\mu^2 + \mu^2 d + \mu k d + \mu^3 - \mu^2\beta\rho S^* - \mu\beta k S^* \\ &= A\beta(k + \mu\rho) - \mu(k + \mu)(d + \mu). \end{aligned}$$

Hence, $a_3 > 0$ when $\mathcal{R}_0 > 1$. And we can easily obtain $a_1 > 0$.

Proposition 4.1. The endemic equilibrium P^* is locally asymptotically stable if all of the eigenvalues λ of $J(P^*)$ satisfy $\arg(\lambda) > \frac{\alpha\pi}{2}$.

Denote

$$\begin{aligned} D(f) &= - \begin{vmatrix} 1 & a_1 & a_2 & a_3 & 0 \\ 0 & 1 & a_1 & a_2 & a_3 \\ 3 & 2a_1 & a_2 & 0 & 0 \\ 0 & 3 & 2a_1 & a_2 & 0 \\ 0 & 0 & 3 & 2a_1 & a_2 \end{vmatrix} \\ &= 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2. \end{aligned}$$

Using the results of [23], we have the following proposition.

Proposition 4.2. Suppose $\mathcal{R}_0 > 1$.

(1) If $D(f) > 0$, then the endemic equilibrium P^* is locally asymptotically stable iff Routh-Hurwitz conditions are satisfied, i.e. $a_1a_2 > a_3$.

(2) If $D(f) < 0$, $a_2 \geq 0$ and $\frac{1}{2} < \alpha < \frac{2}{3}$, then the endemic equilibrium P^* is locally asymptotically stable.

(3) If $D(f) < 0$, $a_2 > 0$, $a_1a_2 = a_3$ and $0 \leq \alpha < 1$, then the endemic equilibrium P^* is locally asymptotically stable.

5. Numerical methods and simulations

According to the Adams predictor-corrector scheme shown in [24, 25], the numerical solution of the initial value problem for system (2.2) will be yielded as below.

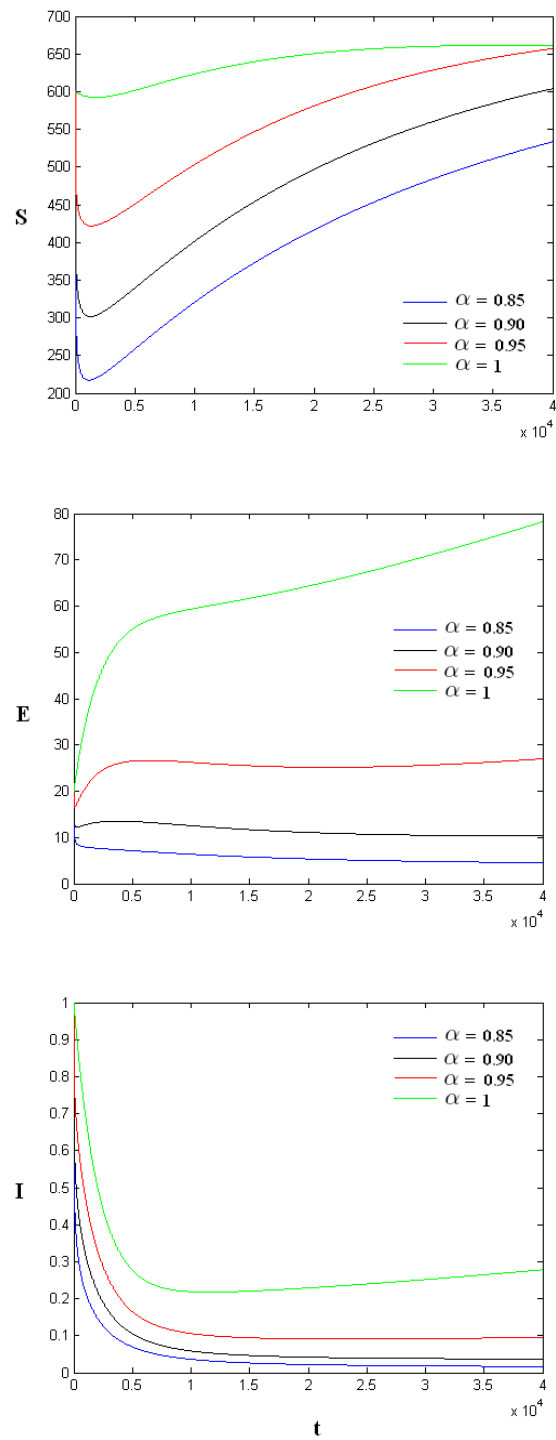


Fig.1: Time evolution of population of $S(t)$, $E(t)$, $I(t)$ when $A = 10$, $\beta = 5/750$, $\mu = 1/75$, $p = 0.0025$, $k = 0.0003$, $d = 0.08$ for $\alpha = 0.85, 0.9, 0.95, 1$.

Set $h = \frac{T}{N}$, $t_n = nh$, $n = 0, 1, 2, \dots, N \in \mathbb{Z}^+$, the system (2.2) can be discretized as follows:

$$\begin{cases} S_{n+1} = S^0 + \frac{h^\alpha}{\Gamma(\alpha+2)}(A - \beta S_{n+1}^p I_{n+1}^p - \mu S_{n+1}^p + S_{n+1}^q), \\ E_{n+1} = E^0 + \frac{h^\alpha}{\Gamma(\alpha+2)}[(1 - \rho)\beta S_{n+1}^p I_{n+1}^p - (k + \mu)E_{n+1}^p + E_{n+1}^q], \\ I_{n+1} = I^0 + \frac{h^\alpha}{\Gamma(\alpha+2)}[\rho\beta S_{n+1}^p I_{n+1}^p + kE_{n+1}^p - (d + \mu)I_{n+1}^p + I_{n+1}^q], \end{cases} \quad (6)$$

where

$$\begin{aligned} S_{n+1}^p &= S^0 + \frac{h^\alpha}{\Gamma(\alpha)} \sum_{j=0}^n \beta_{j,n+1} (A - \beta S_j I_j - \mu S_j), \\ E_{n+1}^p &= E^0 + \frac{h^\alpha}{\Gamma(\alpha)} \sum_{j=0}^n \beta_{j,n+1} [(1 - \rho)\beta S_j I_j - (k + \mu)E_j], \\ I_{n+1}^p &= I^0 + \frac{h^\alpha}{\Gamma(\alpha)} \sum_{j=0}^n \beta_{j,n+1} [\rho\beta S_j I_j + kE_j - (d + \mu)I_j], \\ S_{n+1}^q &= \sum_{j=0}^n \gamma_{j,n+1} (A - \beta S_j I_j - \mu S_j), \\ E_{n+1}^q &= \sum_{j=0}^n \gamma_{j,n+1} [(1 - \rho)\beta S_j I_j - (k + \mu)E_j], \\ I_{n+1}^q &= \sum_{j=0}^n \gamma_{j,n+1} [\rho\beta S_j I_j + kE_j - (d + \mu)I_j] \end{aligned}$$

and

$$\beta_{j,n+1} = \frac{h^\alpha}{\alpha} ((n - j - 1)^\alpha - (n - j)^\alpha),$$

$$\gamma_{j,n+1} = \begin{cases} n^{\alpha+1} - (n - \alpha)(n + 1)^\alpha, & j = 0, \\ (n - j + 2)^{\alpha+1} + (n - j)^{\alpha+1} - 2(n - j + 1)^{\alpha+1}, & 0 \leq j \leq n, \\ 1, & j = n + 1. \end{cases}$$

For the numerical simulations for system (2.2), using the above-mentioned method is appropriate. For the parameters $A = 10$, $\beta = 5/750$, $\mu = 1/75$, $p = 0.0025$, $k = 0.0003$, $d = 0.08$, we obtain $\mathcal{R}_0 = 1.309814879$. Furthermore, $a_1 = 0.1148875317$, $a_2 = 0.001740842644$, $a_3 = 0.000005256296269$, $a_1 a_2 - a_3 = 0.0001947448181$ and $D(f) = 0.1046724848 \times 10^{-7}$. System (2.2) exists a positive equilibrium $E^*(572.5999998, 173.0625919, 0.6196297597)$ and it is locally asymptotically stable. The approximate solutions are displayed in Fig. 1 for the step size 0.005 and $\alpha = 0.85, 0.9, 0.95, 1$. The initial conditions are $S(0) = 600$, $E(0) = 20$, $I(0) = 1$.

6. Conclusions

In this paper, we study a fractional-order tuberculosis model with fast and slow progression. We have obtained a stability condition for equilibrium points. Numerical

solutions of this model are given. One should note that although the equilibrium points are the same for both integer order and fractional order models, the solution of the fractional order model tends to the fixed point over a longer period of time. One also needs to mention that when dealing with real life problems, the order of the system can be determined by using the collected data.

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