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Dynamics of a Fractional Order Model for Mycobacterium Tuberculosis with Caputo-Fabrizio Derivatives

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Abstract: Tuberculosis is an infectious disease caused by the Mycobacterium tuberculosis (Mtb), bacteria that primarily attacks the lungs. Currently, tuberculosis remains a major public health challenge. This study develops a fractional-order mathematical model using the Caputo-Fabrizio derivatives to explore the growth dynamics of MTb in relation to vaccine administration. The methodology consists of the following steps: model formulation, equilibrium point determination, computation of the fundamental reproduction number R_0, equilibrium point stability analysis, and numerical simulation utilizing the Adam-Bashforth 3-step method. The main result reveals that the nonlinear dynamics of the model exhibits significant sensitivity to the fractional order. The model indicates that the infection-free equilibrium point is locally asymptotically stable if $R_0 < 1$, and the endemic equilibrium point is also locally asymptotically stable under specific circumstances. The fractional order can greatly influence the convergence rate towards equilibrium points, as numerical simulations further highlight that smaller fractional orders accelerate the convergence of immune response cells to stability, demonstrating the potential of fractional calculus to capture complex biological dynamics more effectively.

Keywords: *mycobacterium tuberculosis; fractional-order model; Caputo-Fabrizio derivatives; numerical simulation.*

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1 Introduction

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), a dangerous infectious disease that mostly affects the lungs. Despite treatment, tuberculosis is still one of the deadliest infectious diseases in the world, killing more people than HIV/AIDS combined [1]. One of the reasons why this disease still exists is the resistance of bacteria to the immune system, especially macrophages, which are essential for eliminating infections. Once TB germs enter the lungs, granulomas, a protective barrier that helps regulate bacterial development, are activated. The persistence of bacteria allows them to live inside these structures, postponing the immune response of the body and prolonging the illness. TB is difficult to control due to its rapid spread and drug resistance, even though it can be managed with the right antibiotics. Consequently, prevention, early detection, and effective management are essential in reducing the global burden of tuberculosis [2]. Governments, health organizations, and researchers around the world are working together to develop more comprehensive strategies to control the spread of tuberculosis and improve case management.

Various strategies and models have been explored in the investigation of TB. Recent research on TB prevention efforts at the cellular level can be found in several studies such as [3]. Another novel approach is to use fractional differential equations to model biological processes. Fractional models, as opposed to traditional models, take into account "memory" effects, which are situations in which previous occurrences impact future results. The fractional derivatives can be used to explain phenomena that show relaxation effects and memory retention since they incorporate memory and genetic characteristics [4]. This makes them especially helpful for tuberculosis, as the history of infection can affect the immune response and transmission rates. Fractional models provide a more accurate picture of TB dynamics by taking into consideration elements that are frequently missed in classical models. For example, Ibarguen-Mondragon et al. [5] formulate a model for the population dynamics of Mycobacterium tuberculosis (Mtb) to assess the impact of the competition among bacteria on the infection prevalence.

Recently, numerous fractional derivatives have also been investigated in recent works on tuberculosis epidemic modeling such as [6–8]. Zhang et al. [6] utilized the Caputo derivative to capture TB's transmission dynamics, incorporating the concept of memory behavior to illustrate how past infections affect disease progression and treatment. Meanwhile, Zafar et al. [7] explored machine learning approaches alongside fractional operators for various fractional orders. Recently, Olayiwola et al. [8] studied a mathematical model to investigate the impact of treatment on physical limitations in tuberculosis. Studies on TB control measures such as hospitalization, quarantine, and adherence to treatment, have used the Atangana-Baleanu-Caputo and Caputo-Fabrizio derivatives [9]. This broad variety of TB modeling is a result of continuous attempts to use fractional-order derivatives to better understand and treat TB. Based on the previous studies, in this study, we aim to develop a fractional-order-based mathematical model to analyze the interaction of MTb with host immune cells. This fractional-order approach was chosen to consider the memory effect on infection dynamics, which is not fully covered by models based on integer order [10].

The structure of this paper is as follows. Section 2 defines the methods; in particular, we describe the model formulation for the interaction between macrophages and Mycobacterium tuberculosis, the fractional model, and determine the existence and stability of the equilibrium point. Section 3 provides numerical results and discusses the

effect of a variation in order. Finally, Section 4 gives the conclusion.

2 Methods

2.1 Model description

In this section, we develop a mathematical model describing the interaction between macrophages and *Mycobacterium tuberculosis* (Mtb). The population is divided into four sub-populations: uninfected macrophages (M_U), infected macrophages (M_I), *Mycobacterium tuberculosis* bacteria (B), and T cells (T). The dynamics of *Mycobacterium tuberculosis* within granulomas are represented in the schematic diagram in Figure 1.

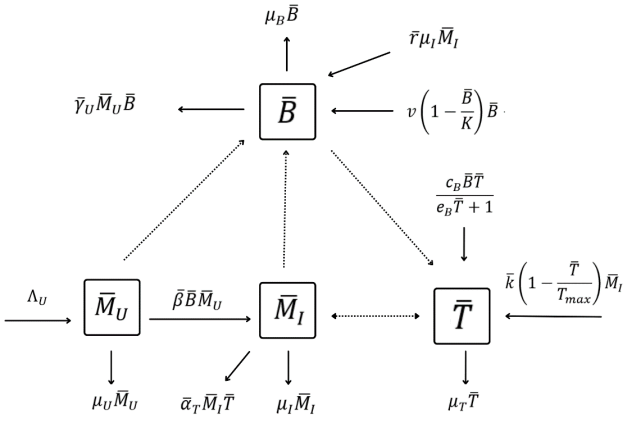

Figure 1: Schematic diagram of Mtb progression.

The population dynamics of uninfected macrophages ($M_U(t)$) are influenced by several factors, including the growth rate of uninfected macrophages per unit of time (Λ_U), the natural death rate of uninfected macrophages per unit of time ($\mu_U M_U(t)$), and the interaction between uninfected macrophages and bacteria per unit of time ($\beta B(t) M_U(t)$). This change in population is represented by the following equation:

$$\frac{dM_U(t)}{dt} = \Lambda_U - \beta B(t) M_U(t) - \mu_U M_U(t). \tag{1}$$

The population dynamics of infected macrophages ($M_I(t)$) are influenced by interactions between uninfected macrophages and bacteria per unit of time ($\beta B(t) M_U(t)$), interactions of T cells with infected macrophages per unit of time ($\alpha_T M_I(t) T(t)$), and the natural death rate of infected macrophages per unit of time ($\mu_I M_I(t)$):

$$\frac{dM_I(t)}{dt} = \beta B(t) M_U(t) - \alpha_T M_I(t) T(t) - \mu_I M_I(t). \tag{2}$$

The population of *Mycobacterium tuberculosis* bacteria ($B(t)$) is influenced by factors such as the bursting of infected macrophages when bacterial growth exceeds a threshold per unit of time ($r\mu_I M_I(t)$), the logistic growth of bacteria with the growth rate v

and maximum capacity K, phagocytosis by uninfected macrophages per unit of time ($\gamma_U M_U(t)B(t)$), and the natural death rate of bacteria per unit of time ($\mu_B B(t)$):

$$\frac{dB(t)}{dt} = r\mu_I M_I(t) + v\left(1 - \frac{B(t)}{K}\right)B(t) - \gamma_U M_U(t)B(t) - \mu_B B(t). \tag{3}$$

The T cell population ($T(t)$) is affected by T cell growth due to signals from infected macrophages per unit of time ($k(1 - T(t))M_I(t)$), immune memory from vaccination following a decay function per unit of time $\left(\frac{c_B BT}{e_B T+1}\right)$, and the natural death rate of T cells per unit of time ($\mu_T T(t)$):

$$\frac{dT(t)}{dt} = k\left(1 - \frac{T(t)}{T_{\max}}\right)M_I(t) + \frac{c_B BT}{e_B T + 1} - \mu_T T(t). \tag{4}$$

To simplify the model, we introduce the following non-dimensional variables:

$$M_U = \frac{M_U}{\Lambda_U/\mu_U}; \quad M_I = \frac{M_I}{\Lambda_U/\mu_U}; \quad B = \frac{B}{K}; \quad T = \frac{T}{T_{\max}}.$$

After substituting these variables into equations (1)–(4), the resulting system of differential equations becomes:

$$\begin{cases} \dot{M_U} &= \mu_U - \beta B M_U - \mu_U M_U, \\ \dot{M_I} &= \beta B M_U - \alpha_T M_I T) - \mu_I M_I, \\ \dot{B} &= r\mu_I M_I + v(1 - B)B - \gamma_U M_U B - \mu_B B, \\ \dot{T} &= k(1 - T)M_I + \frac{c_B BT}{e_B T+1} - \mu_T T, \end{cases} \tag{5}$$

where

$$\alpha_T = \alpha_T T_{\max}; \quad \beta = \beta K; \quad \gamma_U = \frac{\gamma_U \Lambda_U}{\mu_U}; \quad r = \frac{r\Lambda_U}{K\mu_U}; \quad k = \frac{k\Lambda_U}{\mu_U}.$$

2.2 Fractional model of Mycobacterium tuberculosis growth

Incorporating fractional calculus, we replace the integer-order derivatives $\frac{d}{dt}$ in equation (5) with the Caputo-Fabrizio fractional derivatives (${}_0^{CF}D_t^\alpha$) of order $\alpha \in (0, 1)$, we get:

$$\begin{cases} {}_0^{CF}D_t^\alpha M_U(t) &= \mu_U - \beta B M_U - \mu_U M_U, \\ {}_0^{CF}D_t^\alpha M_I(t) &= \beta B M_U - \alpha_T M_I T - \mu_I M_I, \\ {}_0^{CF}D_t^\alpha B(t) &= r\mu_I M_I + v(1 - B)B - \gamma_U M_U B - \mu_B B, \\ {}_0^{CF}D_t^\alpha T(t) &= k(1 - T)M_I + \frac{c_B BT}{e_B T+1} - \mu_T T, \end{cases} \tag{6}$$

with the initial conditions $M_U(0) \geq 0$, $M_I(0) \geq 0$, $B(0) \geq 0$, and $T(0) \geq 0$.

2.3 Equilibrium points

Equilibrium points can be found by setting each equation in system (6) to zero, so we have the infection-free equilibrium point

$$E_0 = (M_U, M_I, B, T) = (1, 0, 0, 0).$$

Next, the basic reproduction number, R_0, can be derived using the next-generation matrix method, where the classes responsible for infection are M_I and B. Thus, the differential equations used are

$$ {}_0^{CF}D_t^{\alpha} M_I = \beta B M_U - \alpha_T M_I T - \mu_I M_I, $$

$$ {}_0^{CF}D_t^{\alpha} B = r\mu_I M_I + v(1-B)B - \gamma_U M_U B - \mu_B B. $$

We can construct matrices $\mathcal{F}$ and $\mathcal{V}$, where $\mathcal{F}$ represents the rate of infection that increases the infected class, and $\mathcal{V}$ represents the rate of progression, recovery, and death that decreases the infected class. The matrices $\mathcal{F}$ and $\mathcal{V}$ are as follows:

$$ \mathcal{F} = \begin{pmatrix} \beta B M_U \\ v(1-B)B \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} \alpha_T M_I T + \mu_I M_I \\ -r\mu_I M_I + \gamma_U M_U B + \mu_B B \end{pmatrix}. $$

The Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at E_0 are

$$ F = \begin{pmatrix} 0 & \beta \\ 0 & v \end{pmatrix}, \quad V = \begin{pmatrix} \mu_I & 0 \\ -r\mu_I & \gamma_U + \mu_B \end{pmatrix}. $$

Then the matrix G is given by

$$ G = FV^{-1} = \begin{pmatrix} \frac{\beta r}{\gamma_U + \mu_B} & \frac{\beta}{\gamma_U + \mu_B} \\ \frac{vr}{\gamma_U + \mu_B} & \frac{v}{\gamma_U + \mu_B} \end{pmatrix}. $$

The basic reproduction number R_0 is the spectral radius of the matrix G, it is

$$ R_0 = \frac{\beta r + v}{\gamma_U + \mu_B}. $$

Furthermore, the endemic equilibrium E_1 of system (6) is given by

$$ E_1 = (M_U^*, M_I^*, B^*, T^*), \tag{7} $$

where

$$ M_U^* = \frac{\mu_U}{\beta B^* + \mu_U}, \quad M_I^* = \frac{\beta B^* \mu_U}{(\beta B^* + \mu_U)(\alpha_T T + \mu_I)}, $$
$$ T^* = \frac{\mu_I}{\alpha_T A}\left(B^*\beta v - B^{*2}\beta v - B^*(v\mu_U + \beta\mu_B^*) + \mu_U(\gamma_U + \mu_B^*)(R_0 - 1)\right), $$

and B^* is the root of

$$ 0 = k(1 - T^*)M_I^* + \frac{c_B B T^*}{e_B T^* + 1} - \mu_T T^*. $$

After further substitutions and simplifications, we find that the resulting polynomial equation is of degree 7. Based on Abel-Ruffini's theorem, polynomial equations of degree higher than 5 generally cannot be solved algebraically [11], so we will solve them numerically in Section 3.1.

2.4 Stability of equilibrium points

The stability of the equilibrium points in the system of equations (6) is provided by the following theorem.

Theorem 2.1 *The infection-free equilibrium point* $E_0 = (M_U, M_I, B, T) = (1, 0, 0, 0)$ *is locally asymptotically stable if* $R_0 < 1$*, and unstable if* $R_0 > 1$*.*

Proof. The Jacobian matrix of the linearized system (6) at $E_0 = (M_U, M_I, B, T) = (1, 0, 0, 0)$ is

$$J(E_0) = \begin{pmatrix} -\mu_U & 0 & -\beta & 0 \\ 0 & -\mu_I & \beta & 0 \\ 0 & r\mu_I & v - \gamma_U - \mu_B & 0 \\ 0 & k & 0 & -\mu_T \end{pmatrix}.$$

The characteristic equation is

$$0 = (\lambda + \mu_U)(\lambda + \mu_T)\left[(\lambda + \mu_I)(\lambda - v + \gamma_U + \mu_B) - \beta r \mu_I\right].$$

The first two eigenvalues are

$$\lambda_1 = -\mu_U, \quad \lambda_2 = -\mu_T,$$

and the other two are the roots of the quadratic equation

$$\lambda^2 + \lambda W_1 + W_2 = 0, \tag{8}$$

where $W_1 = \gamma_U + \mu_B - v + \mu_I$ and $W_2 = \mu_I(\gamma_U + \mu_B - v - \beta r)$.

Thus, we have $|\arg(\lambda_1)| = |\arg(\lambda_2)| = \pi > \frac{\alpha\pi}{2}$. According to the Routh-Hurwitz criterion, the roots of equation (8) are negative if $W_1, W_2 > 0$. Following Ahmed [12], the roots of the quadratic equation (8) are negative if and only if $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$ or, equivalently, $R_0 < 1$. Thus, the infection-free equilibrium $E_0 = (M_U, M_I, B, T) = (1, 0, 0, 0)$ is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.

Theorem 2.2 *Let* $D = \beta B^* + \mu_U$*,* $E = \beta B^*$*,* $F = \gamma_U B^*$*,* $G = \alpha_T T^* + \mu_I$*,* $H = r\mu_I$*,* $I = \beta M_U^*$*,* $K = \frac{c_B T^*}{e_B T^* + 1}$*,* $L = \alpha_T M_I^*$*,* $P = \frac{c_B e_B B^* T^*}{(e_B T^* + 1)^2} + k M_I^* + \mu_T$*,* $Q = \frac{c_B B^*}{e_B T^* + 1}$*, and* $R = \gamma_U M_U^* + 2vB^* + \mu_B$*. The endemic equilibrium point* E_1 *in* (7) *is locally asymptotically stable if* $s_1 > 0$*,* $s_4 > 0$*,* $s_1 s_2 - s_3 > 0$*,* $(s_1 s_2 - s_3)s_3 - s_1^2 s_4 > 0$*,* $A > 0$*, and* $B\beta v + \mu_U(\gamma_U + \mu_B)(R_0 - 1) > Y$*.*

Proof. Substituting the endemic equilibrium point E_1 into the Jacobian matrix of system (6), we get

$$J(E_1) = \begin{pmatrix} -D & 0 & -I & 0 \\ E & -G & I & -L \\ -F & H & -R + v & 0 \\ 0 & k - kT^* & K & Q - P \end{pmatrix}.$$

To ensure negative eigenvalues, we form the characteristic polynomial

$$p_1(\lambda) = \det(\lambda I - J(E_1)) = \lambda^4 + s_1\lambda^3 + s_2\lambda^2 + s_3\lambda + s_4,$$

where

$$
\begin{aligned}
s_1 &= D + G + P - Q + R - v,\\
s_2 &= (R - v + G + P - Q)D + (R - v + P - Q)G + (R - v)P + (v - R)Q - k(T^* - 1)L\\
&\quad - FI - HI,\\
s_3 &= ((R - v + P - Q)G + (R - v)P + (v - R)Q - k(T - 1)L - HI)\, D\\
&\quad + ((R - v)P + (v - R)Q - FI)\, G + (-FI - HI)P + (FI + HI)Q\\
&\quad + (-k(T - 1)R + k(T - 1)v + HK)\, L + EHI,\\
s_4 &= ((P - Q)(R - v)G - HPI + HQI - L(k(T - 1)R - k(T - 1)v - HK))\, D\\
&\quad - FGI(P - Q) + EHIP - EHIQ + kFIL(T - 1).
\end{aligned}
$$

By the Routh-Hurwitz criterion, the polynomial $p_1(\lambda)$ of order 4 will have all negative roots if and only if $s_1 > 0$, $s_4 > 0$, $s_1 s_2 - s_3 > 0$, $(s_1 s_2 - s_3)s_3 - s_1^2 s_4 > 0$,$A > 0$, and $B\beta v + \mu_U(\gamma_U + \mu_B)(R_0 - 1) > Y$. Thus, the endemic equilibrium $E_1 = (M_u^*, M_I^*, B^*, T^*)$ is locally asymptotically stable if these conditions are met.

3 Results and Discussion

3.1 Numerical simulation

In this section, we provided numerical simulations for the system of equations (6) using the Adams-Bashforth 3-step method.

We perform simulations for a first-order system using the possible parameter values from [3, 5]. We take the set of parameter values

$$
\begin{aligned}
\beta = 2.5 \times 10^{-5}, \alpha_T = 2.5 \times 10^{-5}, r = 0.1, v = 0.4, \gamma_U = 1.25 \times 10^{-8}, k = 0.4848, \quad (9)\\
c_B = 5 \times 10^{-3}, e_B = 10^{-4}, \mu_U = 0.02, \mu_I = 0.1, \mu_B = 0.42, \mu_T = 0.02.
\end{aligned}
$$

With this set of parameter values, we have $R_0 = 0.8571$ and the resulting interaction graph of M_U, M_I, B, T over time t is shown in Figure 2a. It can be seen that eventually the populations M_U, M_I, B, and T will move towards E_0.

Furthermore, we performed simulations using the parameter $\mu_B = 0.12$ and kept the values of the other parameters as before. With these parameter values, we have $R_0 = 3.0 > 1$ and the infective equilibrium points $E_1 = (0.9991673, 1.66529 \times 10^{-4}, 0.6666602, 4.82067 \times 10^{-3})$. The interaction graph of M_U, M_I, B, T over t is shown in Figure 2b. It is observed that the population of uninfected macrophages increases steadily towards the equilibrium point. Infected macrophages decrease as a result of interactions with T cells. Bacterial levels initially increase but eventually decrease due to interactions with uninfected macrophages. T cells increase in response to the presence of infected cells but decrease as infected macrophages decline.

Next, as for the stability of the equilibrium point E_0, Figure 3 shows that with varying initial conditions, the population will converge to E_0. In Figure 3, the simulation with various initial values shows that all growth graphs of uninfected macrophages, bacteria, and T cells converge towards the equilibrium point E_0, where the population of M_U approaches one, B approaches zero, and T approaches zero. This suggests that the equilibrium point E_0 is asymptotically stable and satisfies the condition $R_0 < 1$, which confirms Theorem 2.1. In this case, the bacteria cannot infect a sufficient number of

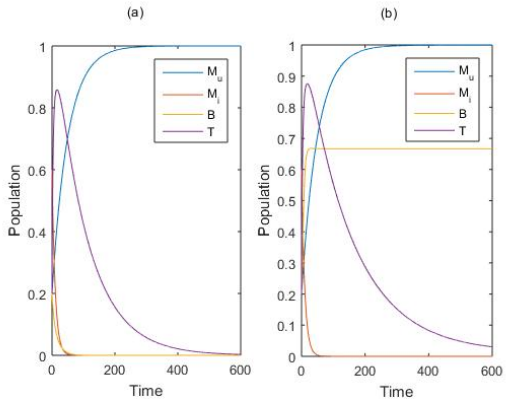

Figure 2: The dynamics interaction of M_U, M_I, B, T with respect to the set of parameter values in (9), (a) $R_0 = 0.8571$, (b)$R_0 = 3.00$.

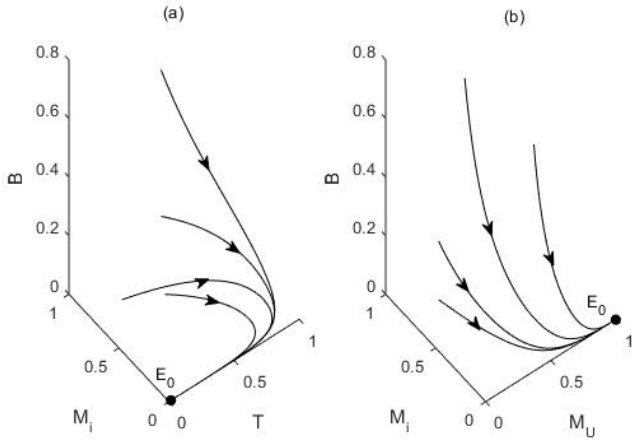

Figure 3: Phase portrait with different initial values confirms converge to E_0. (a) the phase portrait of M_I, B, T; (b) the phase portrait of M_U, M_I, B.

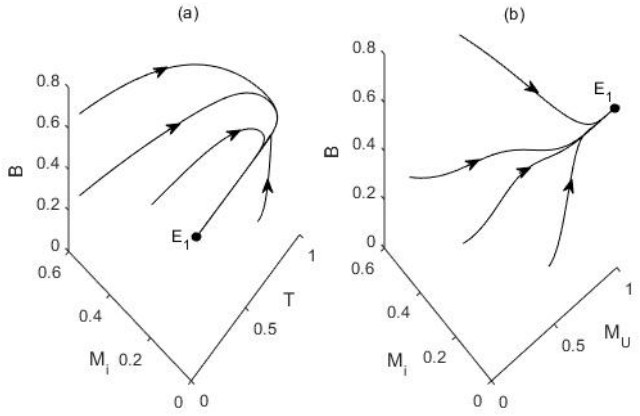

Figure 4: Phase portrait with different initial values confirm converge to E_1. (a) the phase portrait of M_I, B, T; (b) the phase portrait of M_U, M_I, B.

macrophages, the bacterial growth rate is low, or the immune response is capable of controlling the infection.

The graphical illustration related to the stability of the endemic equilibrium point is presented in Figure 4. In Figure 4a, the simulation with various initial values shows that the infected macrophages, bacteria, and T cells converge towards the endemic equilibrium point E_1. In Figure 4b, the simulation using various initial values shows that all growth graphs of uninfected macrophages, bacteria, and T cells converge towards the endemic equilibrium point E_1. The movement graphs of uninfected macrophages, infected macrophages, bacteria, and T cells show variables moving towards the equilibrium point $E_1 = (M_U^*, M_I^*, B^*, T^*)$ with $R_0 = 3.0$, indicating an average of 3 new infected macrophages per day. This suggests that the equilibrium point E_1 is asymptotically stable and satisfies the conditions $A > 0, B\beta v + (\gamma_U \Lambda_U + \mu_U \mu_B)(R_0 - 1) > Y, s_1 > 0, s_4 > 0, s_1 s_2 - s_3 > 0$, and $(s_1 s_2 - s_3)s_3 - s_1^2 s_4 > 0$, thus confirming Theorem 2.2.

The locally asymptotically stable equilibrium point E_1 implies that the number of uninfected macrophages remains significantly higher than the number of infected macrophages and bacteria, representing a latent state. This state suggests that bacterial growth exists but is still controllable by the immune system. If the immune system weakens, inactive bacteria may become active again, leading to active tuberculosis. This is consistent with [13], which states that the BCG tuberculosis vaccine has an efficacy of 60—80% against severe tuberculosis. According to [14], no tuberculosis vaccine has been shown to fully prevent and eliminate Mycobacterium tuberculosis infection, indicating that the bacteria remain in the human body.

Following [15], we calculate the sensitivity indices of each parameter with respect to the basic reproduction number R_0 presented in Table 1.

From Table 1, the most influential parameters on R_0 are the bacterial growth rate v and the bacterial death rate μ_B. The parameter v has a positive relationship with R_0,

Parameter	Sensitivity Index
β	$+6.25 \times 10^{-9}$
r	$+6.25 \times 10^{-9}$
v	$+1.000000000$
γ_U	-2.5×10^{-16}
μ_B	-1.00000000

Table 1: Sensitivity indices of R_0.

while μ_B has a negative relationship with R_0. If the parameter v is increased by 10% from 0.4 to 0.44, then R_0 increases from 0.8 to 0.88. Conversely, if v is decreased by 10% from 0.4 to 0.36, then R_0 decreases from 0.8 to 0.72. This result confirms that the sensitivity analysis aligns with the tested results on R_0.

3.2 Effect of variational order

In this section, we present numerical simulation results with fractional orders $\alpha = 0.6, 0.75, 0.85$, and 1 using the parameters in (9). The simulation results for uninfected macrophages, infected macrophages, bacteria, and T cells are illustrated in Figure 5.

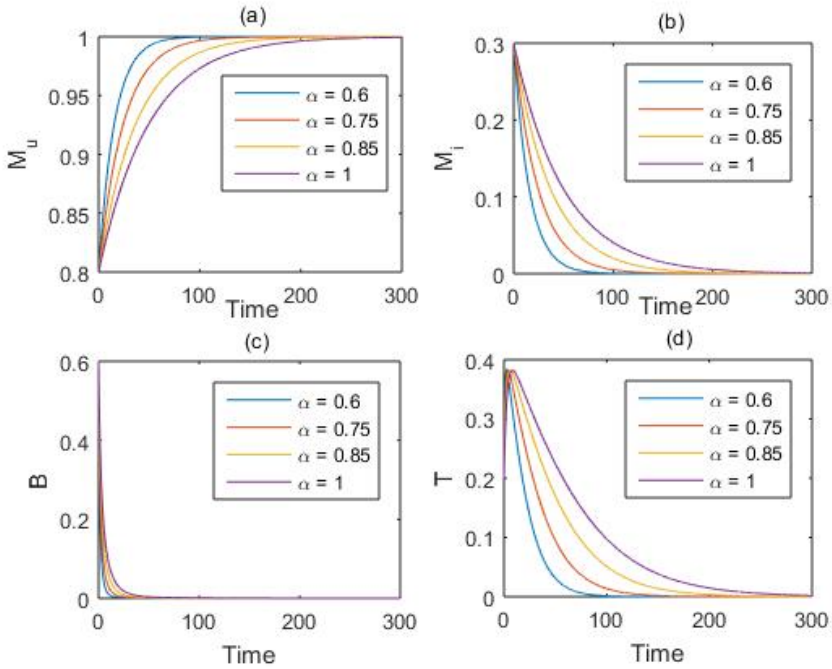

Figure 5: Graphs of uninfected macrophages, uninfected macrophages, bacteria Mtb, and T cells with different orders.

Figure 5a shows the population of uninfected macrophages with orders $\alpha = 0.6, 0.75, 0.85, 1$, all moving towards the equilibrium point with the same trend, regardless of the different orders used. The graph with order 0.6 reaches equilibrium faster

than with order 0.75, the graph with order 0.8 reaches equilibrium faster than with order 0.85, and so on. From the results of the numerical simulation, the graphs of uninfected macrophages, infected macrophages, bacteria and T cells converge to the equilibrium point, even when different orders are used, but follow the same trend as shown in Figure 5b-d. These figures indicate that the smaller the order used, the faster the immune response cells grow toward the equilibrium point.

4 Conclusion

This study presents a fractional-order mathematical model with the Caputo-Fabrizio derivative to understand the dynamics of Mycobacterium tuberculosis (Mtb) infection. The model offers a novel approach that incorporates memory effects, an aspect often overlooked in classical models. Key findings show that the fractional order value strongly influences the stability of the system and the rate of convergence of the immune response to a steady state. This provides new insights into how infections can persist or be controlled over time. Furthermore, the sensitivity of the model to certain parameters such as bacterial growth and death rates, demonstrates the importance of these elements in determining the overall behavior of the system. These results open up opportunities for broader applications in nonlinear dynamics, especially in studying other biological systems with similar characteristics, for example, chronic infections or complex ecological interactions. By integrating stability analysis, numerical simulations, and a memory effect-based approach, this study makes novel contributions to understanding complex biological interactions. This model is not only relevant for understanding TB dynamics, but also has the potential to develop more effective control strategies in the future.

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