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# Design of Optimal Control for the In-host Tuberculosis Fractional Model

**Sanaa L. Khalaf*, Mohammed S. Kadhim**
*Department of Mathematics, College of Science, University of Basrah , Basrah, Iraq*

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**Abstract**

In this article, we investigate a mathematical fractional model of tuberculosis that takes into account vaccination as a possible way to treat the disease. We use an in-host tuberculosis fractional model that shows how Macrophages and Mycobacterium tuberculosis interact to knowledge of how vaccination treatments affect macrophages that have not been infected. The existence of optimal control is proven. The Hamiltonian function and the maximum principle of the Pontryagin are used to describe the optimal control. In addition, we use the theory of optimal control to develop an algorithm that leads to choosing the best vaccination plan. The best numerical solutions have been discovered using the forward and backward fractional Euler method.

**Keywords:** Tuberculosis fractional model, Hamiltonian function, Optimal control, Pontryagin's maximum principle.

## تصميم التحكم الأمثل للنموذج الكسري لمرض السل داخل المضيف

**سناء لفته خلف* , محمد ساري كاظم**
قسم الرياضيات ,كلية العلوم,جامعة البصره,البصره,العراق

**الخلاصة**

في هذا البحث ، درسنا نموذجًا رياضيًا كسريًا لمرض السل الذي أخذ في الاعتبار التطعيم كطريقة ممكنة لعلاج المرض. استخدمنا نموذجًا كسريًا لمرض السل داخل المضيف الذي أظهر كيفية تفاعل البلاعم والسل المتفطرة لمعرفة كيف تؤثر علاجات التطعيم على الضامة التي لم تُصاب بالعدوى. تم إثبات وجود السيطرة المثلى. يتم استخدام دالة هاميلتونين والمبدأ الأقصى لبونترياكن لوصف التحكم الأمثل. بالإضافة إلى ذلك ، نستخدم نظرية التحكم الأمثل لتطوير خوارزمية تتيح لنا اختيار أفضل خطة تطعيم. تم اكتشاف أفضل الحلول العددية باستخدام طريقة أويلر الكسرية الأمامية والخلفية.

## 1. Introduction

Tuberculosis is an infectious disease with a high death rate in many countries. It is caused by an agent called Mycobacterium tuberculosis. Tuberculosis is still one of the leading causes of death in the world today. According to the World Health Organization's 2019 Global Tuberculosis Report [1], eight countries are responsible for two-thirds of the total number of TB cases worldwide: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), and Nigeria (4%).

*Email: mohammed.sari@uobasrah.edu.iq

The bacteria that cause tuberculosis is called Mycobacterium tuberculosis, it attacks mainly the alveolar macrophages [2]. When Mycobacterium tuberculosis bacteria are presented, the immune system responds by forming granulomas of immune cells called macrophages, which are in charge of managing and separating the pathogens that infect the lungs. Several organs in a person's body have macrophages. These cells are where Mycobacterium tuberculosis grows and stays alive [3, 4]. The bacteria that causes tuberculosis is called Mycobacterium tuberculosis, that is eaten by macrophages, which then lock the bacteria away in cellular compartments where they cannot come back. Antibiotics and chemotherapy have become powerful tools for getting rid of the disease since the 20th century. Most TB-related deaths can be stopped if they are early caught and treated well, which saved about 54 million lives between 2000 and 2017 [5].

Over the past few decades, mathematical models have become increasingly important in the fight against the disease. The dynamic system can be used to explain how tuberculosis spreads. When studying tuberculosis, complex network models are used to show how complicated the disease is because of its topology. Five different complex network models have been made to help understand how the disease spreads and help get rid of it [6]. Data fitting provides a good balance of theoretical analysis and practical situations. Population growth, randomness, contact clustering, and age structure have all been studied to see how they affect tuberculosis dynamics [7]. There are now several studies on tuberculosis that have been studied through various factors such as fast and slow progression [8], drug-resistant strains [9], reinfection [10, 11], co-infection [12], migration and seasonality [13, 14]. The model developed with isolation [15], treatment [16], immunization [17] or a combination of various control strategies [18, 19, 20] is discussed for the prevention of tuberculosis. On the other hand, the effect will be enhanced if people take the initiative to increase their awareness of prevention and control. Das et al. [21] investigate the effect of widespread media awareness on the transmission dynamics of tuberculosis and provide the optimal control strategy with the lowest cost. The optimal control theory is applied in a variety of fields, such as the design of therapy [22], the optimal control of the disease among animals [23], and the best tuberculosis prevention strategy [24, 25], in order to improve control. Additionally, the theory and application of fractional calculus have been extensively utilized in order to model dynamic processes in a variety of fields, including but not limited to the fields of science and engineering [26, 27, 28]. Fractional order derivatives have an important property known as the memory effect. This study aims to identify the therapeutic approaches in a fractional within-host tuberculosis model and use Pontryagin's maximum principle to find the best control function.

The rest of this article is organized as follows. In section two, we give a general formulation of the tuberculosis fractional model, and we use the maximum Ponntryagin principle to infer the necessary conditions. In section three, we discuss the numerical results. Finally, section four summarizes the conclusions.

## 2. The optimal control problem of the tuberculosis fractional model

Fractional optimal control theory is a widely used method for determining the extreme value of a dynamically variable objective function. In this section, fractional optimal control theory is used to determine the best vaccination as a function of time. There are many interesting definitions of fractional derivatives in fractional calculus [29], but for this purpose, we will use the famous Caputo derivatives due to their advantage on initial value problems.

**Definition 1 [29]** The Riemann-Liouville fractional integral of order $0<\alpha<1,\ t>0$ is defined by

$$J^{\alpha} f(t)=\frac{1}{\Gamma(\alpha)}\int_0^t \frac{f(x)}{(t-x)^{1-\alpha}}dx \tag{1}$$

**Definition 2 [29]** Let $n-1<\alpha<n$, the Caputo fractional derivative of order $\alpha$ is given by

$${}^{C}D^{\alpha} f(t)=\frac{1}{\Gamma(\mathrm{n}-\alpha)}\int_0^t \frac{f^{n}(x)}{(t-x)^{\alpha+1-n}}dx \tag{2}$$

The fractional tuberculosis model is presented as a system of fractional differential equations as follows.

$$\begin{aligned}
{}_0^C D_t^{\alpha} M_u &= \Lambda^{\alpha}-\mu^{\alpha}M_u-\frac{\beta^{\alpha}M_u}{1+\rho B}B,\\
{}_0^C D_t^{\alpha} M_i &= \frac{\beta^{\alpha}M_u}{1+\rho B}B-c^{\alpha}M_i-\frac{k^{\alpha}M_i}{1+\varepsilon M_i},\\
{}_0^C D_t^{\alpha} B &= r\,c^{\alpha}M_i-\gamma^{\alpha}M_u B-d^{\alpha}B.
\end{aligned} \tag{3}$$

Where $0<\alpha\leq 1$. In fact, some biological constants in model (3) have been powered to alpha (the fractional order) in order to unify the time unit on both sides of each equation. The within-host tuberculosis fractional model (3) consists of three components: uninfected macrophages $(M_u)$, infected macrophages $(M_i)$, and mycobacterium tuberculosis bacteria $(B)$. Table 1 describes the parameters of the tuberculosis fractional model.

**Table 1:** parameters used in the tuberculosis fractional model and their meaning

| Parameter | Description |
|---|---|
| $\Lambda$ | The constant production rate of $M_u$. |
| $\mu$ | The death rate of healthy macrophages. |
| $\beta$ | The maximum macrophage infection rate. |
| $\rho$ | The inhibition effect. |
| $c$ | The rate of macrophage explosion. |
| $k$ | The maximum killing rate. |
| $\varepsilon$ | The half-saturation constant. |
| $r$ | The average number of the $B$ released by $M_i$. |
| $\gamma$ | The mycobacterium tuberculosis bacteria death rate by $M_u$. |
| $d$ | The natural mortality rate of $B$. |

To determine the optimal trajectories of $M_u$, $M_i$, and $B$ in response to the optimal strategy, we now reformulate and analyze an optimal control problem for the model (3). We present a control function which is denoted by the symbol $u(t)$, which stands for the amount of effort put into preventing tuberculosis, such as through vaccination. The control model is presented in the following format:

$$
\begin{aligned}
{}_0^C D_t^{\alpha} M_u &= \Lambda^{\alpha} - \mu^{\alpha} M_u - \frac{(1-u(t))\beta^{\alpha} M_u}{1+\rho B} B, \\
{}_0^C D_t^{\alpha} M_i &= \frac{(1-u(t))\beta^{\alpha} M_u}{1+\rho B} B - c^{\alpha} M_i - \frac{k^{\alpha} M_i}{1+\varepsilon M_i}, \\
{}_0^C D_t^{\alpha} B &= r\, c^{\alpha} M_i - \gamma^{\alpha} M_u B - d^{\alpha} B.
\end{aligned} \tag{4}
$$

Where $0 \le u(t) \le 1$ is a control strategy that slows the rate at which macrophages migrate from uninfected classes to infected classes while curing a portion of uninfected macrophages. The admissible controls are defined as follows:

$$\Psi = \{u(t) \,|\, 0 \le u \le 1, t \in [0, T_f]\} \tag{5}$$

The goal is to find the optimal value of the control $u(t)$ so that the state trajectories $M_u$, $M_i$, and $B$ are solutions of the system (2) with the initial conditions:

$$M_u(0) \ge 0, M_i(0) \ge 0, B(0) \ge 0 \tag{6}$$

and $u(t)$ maximizes the cost function given by:

$$J(u) = \int_0^{T_f} (M_u(t) - M_i(t) - u^2(\mathrm{t}))\, dt \tag{7}$$

Our problem with optimal control is to find the values $(M_u^*, M_i^*, B^*)$ that are related to a control $u(t)$ on the time interval $[0, T_f]$ that satisfies Eq. (4) and the initial condition of Eq. (6), while also maximizing the cost function of Eq. (7) in a way that ensures that

$$J(u^*) = \max_{\Psi} J(u) \tag{8}$$

The Hamiltonian functional $H$ is as follows:

$$H = M_u(t) - M_i(t) - u^2(\mathrm{t}) + p_1\, {}_0^C D_t^{\alpha} M_u(t) + p_2\, {}_0^C D_t^{\alpha} M_i(t) + p_3\, {}_0^C D_t^{\alpha} B \tag{9}$$

Then

$$
\begin{aligned}
H = {} & M_u(t) - M_i(t) - u^2(\mathrm{t}) + p_1\left(\Lambda^{\alpha} - \mu^{\alpha} M_u - \frac{(1-u(t))\beta^{\alpha} M_u}{1+\rho B} B\right) \\
& + p_2\left(\frac{(1-u(t))\beta^{\alpha} M_u}{1+\rho B} B - c^{\alpha} M_i - \frac{k^{\alpha} M_i}{1+\varepsilon M_i}\right) \\
& + p_3(r\, c^{\alpha} M_i - \gamma^{\alpha} M_u B - d^{\alpha} B)
\end{aligned} \tag{10}
$$

where $p_1, p_2$ and $p_3$ are the adjoin variables associated with the state variables $M_u^*, M_i^*, B^*$. In Theorem 1, we summarize the necessary conditions for optimal control $u^*(t)$.

**Theorem 1:** There is optimal control $u^*(t)$ corresponding to the optimal solutions $M_u^*, M_i^*$, and $B^*$ that maximize the cost function $J(u)$ over $\Psi$. Moreover, there exist adjoint variables,

$p_i$, $i=1,2,3$ that satisfy ${}_t^C D_{T_f}^{\alpha} p = \frac{\partial H}{\partial X}$, where $X=(M_u^*, M_i^*, B^*)$ with transversality condition $p_i(T_f)=0$, $i=1,2,3$. Furthermore, the optimal control $u^*(t)$ is given by

$$u^* = \min\{1, \max\{0, \frac{(p_1-p_2)\beta^{\alpha} M_u^*}{2(1+\rho B^*)} B^*\}\}. \tag{11}$$

**Proof:** By applying the results of fractional optimal control problems in [30, 31], the Hamiltonian equation (10) will be derived with respect to $M_u^*, M_i^*$ and $B^*$ as follows:

$$\begin{aligned} {}_t^C D_{T_f}^{\alpha} p_1 &= \frac{\partial H}{\partial M_u^*} \\ &= 1 - p_1\mu^{\alpha} + (p_2-p_1)\frac{(1-u(t))\beta^{\alpha}}{1+\rho B^*} B^* - p_3\gamma^{\alpha} B^* \end{aligned} \tag{12}$$

$$\begin{aligned} {}_t^C D_{T_f}^{\alpha} p_2 &= \frac{\partial H}{\partial M_i^*} \\ &= -1 - p_2(c^{\alpha} + \frac{k^{\alpha}}{(1+\varepsilon\ M_i^*)^2}) + p_3 r\, c^{\alpha} \end{aligned} \tag{13}$$

$$\begin{aligned} {}_t^C D_{T_f}^{\alpha} p_3 &= \frac{\partial H}{\partial B^*} \\ &= (p_2-p_1)\frac{(1-u(t))\beta^{\alpha} M_u^*}{(1+\rho B^*)^2} - p_3(\gamma^{\alpha} M_u^* + d^{\alpha}) \end{aligned} \tag{14}$$

And the transversality conditions $p_1(T_f) = p_2(T_f) = p_3(T_f) = 0$.

By solving $\frac{\partial H}{\partial u^*} = 0$ , we can find the condition of optimal control as follows:

$$\begin{aligned} &\frac{\partial H}{\partial u^*} = 0 \\ &-2u^* + (p_1-p_2)\frac{\beta^{\alpha} M_u^*}{1+\rho B^*} B^* = 0 \\ &u^* = (p_1-p_2)\frac{\beta^{\alpha} M_u^*}{2(1+\rho B^*)} B^* \end{aligned} \tag{15}$$

Since $0 \le u^* \le 1$ then we can rewrite $u^*$ in Eq. (15) as follow

$$u^*(t) = \min(1, \max(0, (p_1-p_2)\frac{\beta^{\alpha} M_u^*}{2(1+\rho B^*)} B^*)). \tag{16}$$

The proof is completed.

## 3. Numerical results

To illustrate the theoretical findings from the previous section, this section provides some numerical simulations using Maple software. Using the forward and backward Euler method, we compute Theorem 1 numerically. The parameter values used in numerical simulations are shown in Table 2 [2].

**Table 2:** parameter values in the tuberculosis fractional model

| Parameter | Value |
|---|---|
| $\Lambda$ | 3500 |
| $\mu$ | 0.01 |
| $\beta$ | $0.8\times10^{-8}$ |
| $\rho$ | 0.01 |
| $c$ | 0.3 |
| $k$ | 1 |
| $\varepsilon$ | 30 |
| $r$ | 30 |
| $\gamma$ | $0.125\times10^{-8}$ |
| $d$ | 0.05 |

Also, we will use the proposed initial values of the state variables in Table 3 [2].

**Table 3:** the initial values in the tuberculosis fractional model

| Variable | Initial values |
|---|---|
| $M_u(t)$ | $M_u(0)=300000$ |
| $M_i(t)$ | $M_i(0)=20$ |
| $B(t)$ | $B(0)=500$ |

To find the optimal vaccination strategy, we construct the following algorithm based on applying the forward and backward Euler method to solve state Eq. (3) and co-state equations Eq. (12)-Eq. (14), respectively, and on the optimal control law in Eq. (16). The primary findings have been graphically illustrated with the help of the results of numerical simulations. The approximate solution with control and without of $M_u(t)$, $M_i(t)$ and $B(t)$ are displayed in Figures 1, 2, and 3, respectively. Indeed, each figure includes three different approximate solutions with and without control corresponding with three different values of $\alpha$ ($\alpha=1,\ 0.9$, and $0.8$). While, Figure 4 indicates the behavior of the approximate optimal control solution, $u(t)$, with three different values of $\alpha$ ($\alpha=1,\ 0.9$, and $0.8$). These figures demonstrate that the number of infected macrophages, as well as the population of Mycobacterium tuberculosis bacteria, is decreasing. In this case, almost no macrophages will be infected by the Mycobacterium tuberculosis bacteria, and the Mycobacterium tuberculosis bacteria will die out completely.

**Algorithm:**

**Step 1:** Insert the values of fractional order $\alpha$, and the biological parameters $\Lambda,\mu,\beta,\rho,c,k,\varepsilon,r,\gamma$ and $d$. Also, insert the initial conditions of $M_u(0),M_i(0),B(0)$ and terminal conditions $p_1(N)=p_2(N)=p_3(N)=0$.

**Step 2:** Suppose the time interval is $[0,T_f]$ and compute the step size $h=\frac{T_f}{N}$, where $N$ is positive integer number.

**Step 3:** Set $u(\kappa h)=0$, for all $\kappa=0,1,2,...,N$.

**Step 4:** Compute the coefficients $C_{j,\kappa}$ as follows:

$C_{j,\kappa} = \frac{h^\alpha}{\Gamma(\alpha+1)}((j+1-\kappa)^\alpha - (j-\kappa)^\alpha)$, for all $j = \kappa, ..., N-1$, and $\kappa = 0, ..., N-1$.

**Step 5:** Compute the coefficients $B_{j,\kappa}$ as follows:

$B_{j,\kappa} = \frac{h^\alpha}{\Gamma(\alpha+1)}((\kappa-j)^\alpha - (\kappa-j-1)^\alpha)$, for all $j = 0,1,...,\kappa-1$, and $\kappa = 1,2,...,N$.

**Step 6:** For all $\kappa = 1,2,...,N$, compute $M_u(\kappa h), M_i(\kappa h)$, and $B(\kappa h)$ by applying the forward fractional Euler method [32] as follows:

$$M_u(\kappa h) = M_u(0) + \sum_{j=0}^{\kappa-1} B_{j,\kappa}[\Lambda^\alpha - \mu^\alpha M_u(jh) - \frac{(1-u(jh))\beta^\alpha M_u(jh)}{1+\rho B(jh)} B(jh)],$$

$$M_i(\kappa h) = M_i(0) + \sum_{j=0}^{\kappa-1} B_{j,\kappa}[\frac{(1-u(jh))\beta^\alpha M_u(jh)}{1+\rho B(jh)} B(jh) - c^\alpha M_i(jh) - \frac{k^\alpha M_i(jh)}{1+\varepsilon M_i(jh)}],$$

$$B(\kappa h) = B(0) + \sum_{j=0}^{\kappa-1} B_{j,\kappa}[r c^\alpha M_i(jh) - \gamma^\alpha M_u(jh) B(jh) - d^\alpha B(jh)].$$

**Step 7:** For all $\kappa = N-1, N-2, ..., 0$, compute $p_1(\kappa h), p_2(\kappa h)$, and $p_3(\kappa h)$ by applying the backward fractional Euler method as follows:

$$p_1(\kappa h) = p_1(T_f) - \sum_{j=\kappa}^{N-1} C_{j,\kappa}[1 - p_1((j+1)h)\mu^\alpha + (p_2((j+1)h) - p_1((j+1)h))\frac{(1-u((j+1)h))\beta^\alpha}{1+\rho B^*((j+1)h)} B^*((j+1)h)$$
$$- p_3\gamma^\alpha B^*((j+1)h)]$$

$$p_2(\kappa h) = p_2(T_f) - \sum_{j=\kappa}^{N-1} C_{j,\kappa}[-1 - p_2((j+1)h)(c^\alpha + \frac{k^\alpha}{(1+\varepsilon M_i^*((j+1)h))^2}) + p_3((j+1)h) r^\alpha c^\alpha]$$

$$p_3(\kappa h) = p_3(T_f) - \sum_{j=\kappa}^{N-1} C_{j,\kappa}(p_2((j+1)h) - p_1((j+1)h))\frac{(1-u((j+1)h))\beta^\alpha M_u^*((j+1)h)}{(1+\rho B^*((j+1)h))^2}$$
$$- p_3((j+1)h)(\gamma^\alpha M_u^*((j+1)h) - d^\alpha)]$$

**Step 8:** Apply the optimal control law to compute $u(\kappa h)$ for all $\kappa = 1,2,...,N$ as follows:

$$u^*(\kappa h) = \min(1, \max(0, \frac{(p_1(\kappa h) - p_2(\kappa h))\beta^\alpha M_u^*(\kappa h)}{2(1+\rho B^*(\kappa h))} B^*(\kappa h)))$$

**Step 9:** If the stopping criterion (the absolute value of optimal control of the current and the previous iterations) is held, then the algorithm ends, else return to Step 4.

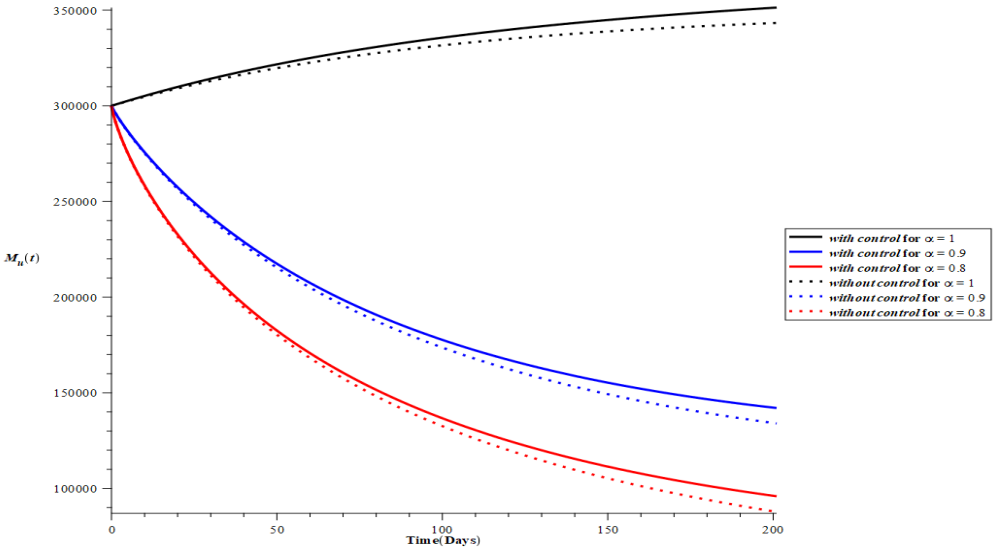


**Figure 1:** The uninfected macrophages with and without control.

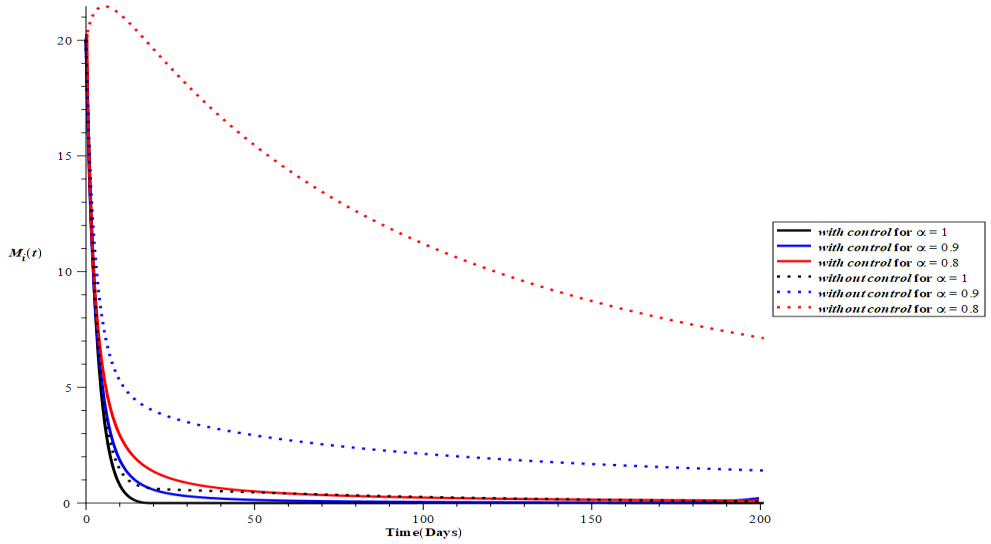


**Figure 2:** The infected macrophages with and without control.

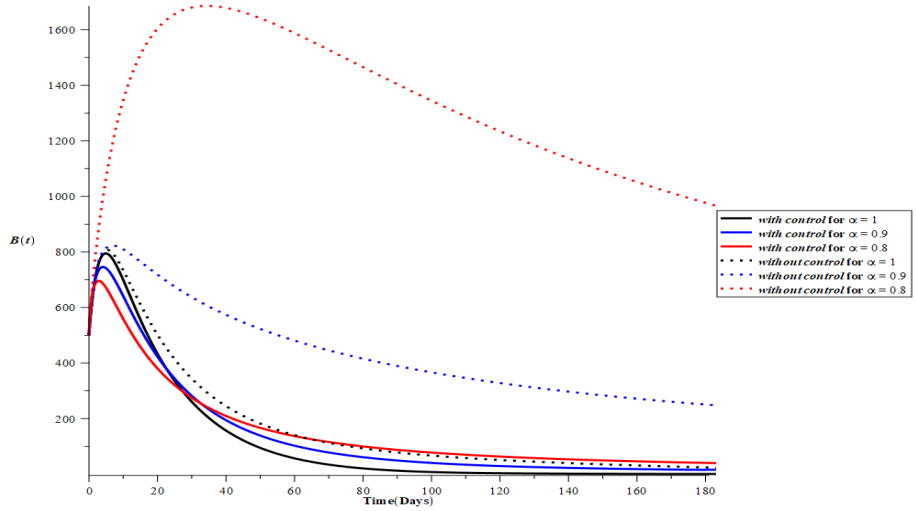


**Figure 3:** The mycobacterium tuberculosis bacteria with and without control.

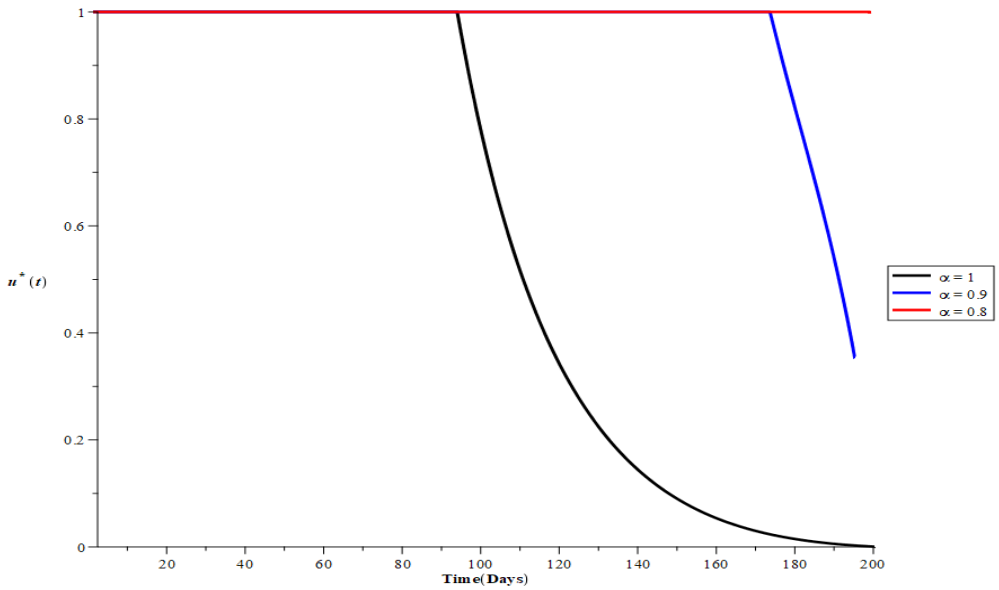


**Figure 4:** The optimal control.

However, according to Theorem 1, we prove that in Equation (11), there is optimal control. That is to say, the value of the cost function corresponding to the optimal control in Equation (11) will be the maximum value (the optimal solution). Therefore, the value of the cost function corresponding with any arbitrary control will be certainly greater than the optimal solution. See the following illustrated tables to confirm our result:

**Table 4:** The value of the cost function for different control $u(t)$ for $\alpha = 1$.

| Some control variable $u(t)$ | The value of the cost functions $J(u(t))$ |
|---|---|
| **The optimal control $u^*(t)$ which is given in Eq. (11)** | $6.576060533\times10^7$ |
| $u(t)=0, \quad \forall t\in[0,1]$ | $6.575908208\times10^7$ |
| $u(t)=0.5, \quad \forall t\in[0,1]$ | $6.576007315\times10^7$ |
| $u(t)=0.7, \quad \forall t\in[0,1]$ | $6.576029727\times10^7$ |
| $u(t)=1, \quad \forall t\in[0,1]$ | $6.576052718\times10^7$ |
| $u(t)=\lvert\sin(t)\rvert, \quad \forall t\in[0,1]$ | $6.576021579\times10^7$ |
| $u(t)=e^{-t}, \quad \forall t\in[0,1]$ | $6.575910458\times10^7$ |
| $u(t)=\begin{cases}0, & 0\le t<0.5\\ 1, & 0.5\le t\le 1\end{cases}$ | $6.575929430\times10^7$ |

**Table 5:** The value of the cost function for different control $u(t)$ for $\alpha = 0.9$.

| Some control variable $u(t)$ | The value of the cost functions $J(u(t))$ |
|---|---|
| The optimal control $u^*(t)$ which given in Eq. (11) | $3.732470389\times10^7$ |
| $u(t)=0,\quad \forall t\in[0,1]$ | $3.731842731\times10^7$ |
| $u(t)=0.5,\quad \forall t\in[0,1]$ | $3.732199779\times10^7$ |
| $u(t)=0.7,\quad \forall t\in[0,1]$ | $3.732326311\times10^7$ |
| $u(t)=1,\quad \forall t\in[0,1]$ | $3.732469753\times10^7$ |
| $u(t)=\lvert\sin(t)\rvert,\quad \forall t\in[0,1]$ | $3.732286912\times10^7$ |
| $u(t)=e^{-t},\quad \forall t\in[0,1]$ | $3.731851578\times10^7$ |
| $u(t)=\begin{cases}0, & 0\le t<0.5\\ 1, & 0.5\le t\le 1\end{cases}$ | $3.731996206\times10^7$ |

**Table 6:** The value of the cost function for different control $u(t)$ for $\alpha = 0.8$.

| Some control variable $u(t)$ | The value of the cost functions $J(u(t))$ |
|---|---|
| The optimal control $u^*(t)$ which given in Eq. (11) | $2.977634641\times10^7$ |
| $u(t)=0,\quad \forall t\in[0,1]$ | $2.975186035\times10^7$ |
| $u(t)=0.5,\quad \forall t\in[0,1]$ | $2.976477957\times10^7$ |
| $u(t)=0.7,\quad \forall t\in[0,1]$ | $2.976980129\times10^7$ |
| $u(t)=1,\quad \forall t\in[0,1]$ | $2.977634592\times10^7$ |
| $u(t)=\lvert\sin(t)\rvert,\quad \forall t\in[0,1]$ | $2.976824325\times10^7$ |
| $u(t)=e^{-t},\quad \forall t\in[0,1]$ | $2.975221574\times10^7$ |
| $u(t)=\begin{cases}0, & 0\le t<0.5\\ 1, & 0.5\le t\le 1\end{cases}$ | $2.975806232\times10^7$ |

## 4 Conclusions

This research introduces the in-host tuberculosis fractional model. The goal of this paper is to build an algorithm for solving the tuberculosis fractional model. Also, the fractional-order optimal necessary conditions were derived using the Pontryagin maximum principle. We used the forward and backward Euler methods to get the optimal solution. The numerical simulation was done by using the optimization technique in Maple 20 to study the behavior of how the combination of control $u(t)$ affects the proposed model. Also, we studied the effect of the order of the fractional derivative (the memory property of fractional derivatives) on this model.

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