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A within-host tuberculosis model with optimal control

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ABSTRACT

We considered an in-host tuberculosis model that described the interaction between macrophages and Mycobacterium tuberculosis and investigated the effect of vaccination treatments on uninfected macrophages. Optimal control is applied to show the optimal vaccination and effective strategies to control the disease. The optimal control formula is obtained using the Hamiltonian function and Pontryagin's maximum principle. Finally, we perform numerical simulations to support the analytical results.

A. INTRODUCTION

We consider a within-host tuberculosis model in (Adi & Thobirin, 2020) with three components: uninfected macrophages, infected macrophages (M_i), and MTb bacteria, denoted by M_u, M_i, and B, respectively, given in the following form of ordinary differential equation system

$$\begin{aligned}\frac{dM_u}{dt} &= \Lambda - \mu M_u - \frac{\beta M_u B}{1+\alpha B},\\ \frac{M_i}{dt} &= \frac{\beta M_u B}{1+\alpha B} - cM_i - \frac{kM_i}{1+\varepsilon M_i},\\ \frac{dB}{dt} &= rcM_i - \gamma M_u B - dB.\end{aligned} \tag{1.1}$$

In this model (1.1), Λ and μ are a constant production rate and a natural death rate of uninfected macrophages, respectively. Parameter β is the maximal transmission of infection rate at which macrophages became infected at a saturated incidence rate of $\frac{\beta M_u B}{1+\alpha B}$, whit $\frac{1}{1+\alpha B}$ is an inhibition effect. Parameter r and c are the average numbers of the MTb bacteria released by infected macrophages and the rate of macrophages burst, respectively. The parameters γ is the MTb bacteria death rate by uninfected macrophages, and d is MTb bacteria natural death rate. The infected macrophages die due to an adaptive immune response modeled in a density-

dependent term, $\frac{kM_i}{1+\varepsilon M_i}$, whereas k is the maximum killing rate, and ε is a half-saturation constant.

In many works of literature of tuberculosis models, it is usually considered drug administration or vaccination, as in (Baba et al., 2020; Blaser et al., 2016; Brooks-Pollock et al., 2014; Byrne et al., 2015; Kim et al., 2018; Kuddus et al., 2020; Kyu et al., 2018). Many of the TB models use optimal control theory regarding their treatment strategies (Agusto & Adekunle, 2014; Baba et al., 2020; Bowong, 2010; Choi et al., 2015; Emvudu et al., 2011; Fatmawati et al., 2020; Gao & Huang, 2018; Moualeu et al., 2015). In a within-host tuberculosis model, the immune response to bacteria is generally assumed, as in (Adi & Thobirin, 2020; Zhang, 2020; Zhang et al., 2020). This paper will apply the optimal control theory to a within-host tuberculosis model by considering the vaccination that affects macrophages.

We organize this paper as follows. We begin by briefly review the basic concept of optimal control in Section 2. In Section 3, we are formulating the optimal control model. To support the theoretical results, we give some numerical simulations in Section 5. Finally, the discussion and conclusion are provided in Section 5.

B. BASIC CONCEPT OF OPTIMAL CONTROL

In this section, we recall the basic theory of optimal control (Chambers et al., 1965). We consider a system of ordinary differential equations

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}(t)), \mathbf{x}(0) = \mathbf{x}_0, \tag{2.1}$$

where $\mathbf{x}_0 \in \mathbb{R}$, $\mathbf{f}: \mathbb{R}^n \to \mathbb{R}^n$, and $\mathbf{x}: [0,\infty) \to \mathbb{R}^n$. Suppose that the right-hand side depends on a parameter $u: [0,\infty) \to A$, where $A \subset \mathbb{R}^m$. Then the system becomes

$$\dot{\mathbf{x}} = \mathbf{f}\big(\mathbf{x}(t), u(t)\big), \mathbf{x}(0) = \mathbf{x}_0, \ \mathbf{x}(T) \text{ free} . \tag{2.2}$$

In this system, the solution $\mathbf{x}(t)$ depends on the control $u(t)$. The corresponding response of the system is a trajectory that corresponds to the control $u(t)$. In system (2.2), the control may be arbitrary, so the problem does not have a solution. Therefore, we need to find the best control to minimize or maximize the performance measure as an objective function. In a disease-control model, we need to find the control to minimize the cost of controlling the disease. For that purpose, a payoff functional is defined as follows

$$J[u] = \int_0^T g(\mathbf{x}(t), u(t))dt, \tag{2.3}$$

where $\mathbf{x}(t)$ solves (2.2) for the specified control $u(t)$, with the given function $g: \mathbb{R}^n \times A \to \mathbb{R}$ and terminal time T as well. The function g is called the running payoff. Now, introduce the admissible controls

$$\Omega = \{u(t) \in L^1(0,T): u(t) \in A\}. \tag{2.4}$$

The optimal control problem is to find a control $u^*(t) \in \Omega$ that minimizes or maximizes the payoff functional (2.3). A corresponding solution together with the optimal control gives the pair of optimal control $(\mathbf{x}^*, u^*)$.

If such a control $u(t)$ exists, it is called the optimal control. For maximum problem, the solution $(\mathbf{x}^*, u^*)$, if exits, can be found by Pontryagin's maximum principle. According to the constraint in the Lagrangian problem, the time-varying Lagrange multiplier $\lambda(t)$ was introduced. The function $\lambda(t)$ is usually called an adjoint variable of the system. The comparable function, in this case, is the Hamiltonian function H, defined for all $t \in [0,T]$ by

$$H(\mathbf{x}(t), u(t), \lambda(t)) = g(\mathbf{x}(t), u(t)) + \sum_{i=1}^n \lambda_i(t) f_i(\mathbf{x}(t), u(t)). \tag{2.5}$$

The Pontryagin maximum principle is precisely formulated as follows .

Theorem 1. *Let $u^*(t)$ be a piecewise control defined on $[0,T]$ and $\boldsymbol{x}^*(t)$ be the associated trajectory. Then there exists a nonzero adjoint vector function $\lambda^*(t)$ that is a solution to the adjoint system*

$$\begin{aligned} \dot{\lambda}(t) &= -\frac{\partial H(\mathbf{x}(t),u(t),\lambda(t))}{\partial x} \\ \lambda(T) &= 0, \end{aligned} \tag{2.6}$$

so that $\mathbf{x}^*(t)$ maximizes $H(\mathbf{x}^*(t), u(t), \lambda(t))$ for $u(t) \in \Omega$, that is

$$H(\mathbf{x}^*(t), u^*(t), \lambda^*(t)) \geq H(\mathbf{x}^*(t), u(t), \lambda^*(t)), for\ \ all \quad u(t) \in \Omega. \tag{2.7}$$

Thus, the necessary conditions for optimizing the Hamiltonian are:

$$\begin{aligned} \frac{\partial H}{\partial u} &= 0 \Rightarrow g_u + \sum_{i=1}^{n} \lambda_i(t)(f_i)_u = 0, \\ \dot{\lambda}_i(t) &= -\frac{\partial H(\mathbf{x}(t),u(t),\lambda(t))}{\partial x_i} \Rightarrow \dot{\lambda}_i(t) = -g_{x_i} - \sum_{i=1}^{n} \lambda_i(t)(f_i)_{x_i}, \\ \lambda(T) &= 0. \end{aligned} \tag{2.8}$$

Please refer to Pontryagin's book (Kaufman, 1964) and some extensions book, such as (Becker et al., 1989; Seierstad & Sydsaeter, 1977) for more details.

C. RESULT AND DISCUSSION

1. Optimal control problem

This section reformulates and analyzes an optimal control problem for the model (1.1) to determine the optimal trajectories of uninfected macrophages, infected macrophages, and MTb bacteria in response to the optimal strategy. The control is chosen basis on the significant parameter used as the bifurcation parameter (Adi & Thobirin, 2020). We introduce a control function $u(t)$, which represents the effort of tuberculosis prevention, such as vaccination. The control model is given as follows

$$\begin{aligned} \frac{dM_u}{dt} &= \Lambda - \mu M_u - \frac{(1-u(t))\beta M_u B}{1+\alpha B}, \\ \frac{M_i}{dt} &= \frac{(1-u(t))\beta M_u B}{1+\alpha B} - cM_i - \frac{kM_i}{1+\varepsilon M_i}, \\ \frac{dB}{dt} &= rcM_i - \gamma M_u B - dB, \end{aligned} \tag{3.1}$$

where $u(t)$ represents a control strategy that cures a fraction of uninfected macrophages and reduces the rate at which macrophages leaves uninfected class towards the infected class. The control is bounded between 0 and u_{max}. From a medical point of view, it is realistic to assume that $u_{max} < 1$, since the vaccination is not completely effective. Let us define the set of admissible control as

$$\Omega = \{u(t) \in L^1(0,T): 0 \leq u(t) \leq u_{max}, \forall t \in [0,T]\}. \tag{3.2}$$

Then, optimal control theory is applied to determine the optimal treatment administration that will maximize the effort on tuberculosis prevention measures and the cost associated with this support. We define the set of state variables $X(t) = (M_u(t), M_i(t), B(t))$ and the objective functional as

$$J[u] = \int_0^T (M_u(t) - M_i(t) - u^2(t))dt. \tag{3.3}$$

which consider the fraction of the uninfected macrophages (M_u) and the infected macrophages (M_i) and the cost associated with the support of transmission measure (u).

The optimal control problem is to find the control u^* with corresponding state trajectories $X^* = (M_u^*, M_i^*, B^*)$ on the time interval $[0, T]$, that maximizes the objective functional (3.3) subject to dynamical system constraints (3.1), that is

$$J[u^*] = \max_{\Omega} J[u]. \tag{3.4}$$

Then, to apply Pontryagin's maximal principle in Theorem 1, we define the Hamiltonian as

$$\begin{aligned} H(M_u, M_i, B, u, \lambda) &= M_u(t) - M_i(t) - u^2(t) + \lambda_1 \frac{dM_u}{dt} + \lambda_2 \frac{dM_i}{dt} + \lambda_3 \frac{dB}{dt} \\ &= M_u(t) - M_i(t) - u^2(t) + \lambda_1 (\Lambda - \mu M_u - \frac{(1-u(t))\beta M_u B}{1+\alpha B}) \\ &+ \lambda_2 (\frac{(1-u(t))\beta M_u B}{1+\alpha B} - cM_i - \frac{kM_i}{1+\varepsilon M_i}) \\ &+ \lambda_3 (rcM_i - \gamma M_u B - dB). \end{aligned} \tag{3.5}$$

According to Pontryagin's maximum principle, for u^* to be an optimal solution with corresponding optimal states X^*, the following conditions must be satisfied.

$$\begin{aligned} \frac{dX}{dt} &= -\frac{\partial H}{\partial \lambda_i}, \\ \frac{\partial H}{\partial u} &= 0, \\ \frac{d\lambda_i}{dt} &= -\frac{\partial H}{\partial x}. \end{aligned} \tag{3.6}$$

According to the optimal condition (3.6), we claim the optimal solution of system (3.1) in the following theorem.

Theorem 2. *There exists an optimal control u^* corresponding to the optimal solution M_u^*, M_i^*, B^* that maximizes the objective function $J[u]$ over Ω. Moreover, there exist adjoint variables λ_i, $i = 1,2,3$, along with the transversality conditions $\lambda_i(T) = 0$ such that*

$$\begin{aligned} \frac{d\lambda_1}{dt} &= -1 + \lambda_1 \mu - (\lambda_1 - \lambda_2) \frac{(1-u(t))\beta B^*(t)}{1+\alpha B^*(t)} - \lambda_3 \gamma B^*(t), \\ \frac{d\lambda_2}{dt} &= 1 + \lambda_2 (c + \frac{k}{(1+\varepsilon M_i^*(t))^2} - \lambda_3 rc, \\ \frac{d\lambda_3}{dt} &= (\lambda_1 - \lambda_2)\beta \frac{(1-u^*(t))M_u^*(t)}{(1+\alpha B^*(t))^2} - \lambda_3 d. \end{aligned} \tag{3.7}$$

Furthermore, associated optimal control u^* is given by

$$u^*(t) = \min\{u_{\max}, \max\{0, \frac{\beta(\lambda_1 - \lambda_2) M_u^*(t) B^*(t)}{2(1+\alpha B^*(t))}\}\} \tag{3.8}$$

Proof. The adjoint system (3.7) is derived by taking partial derivatives of the Hamiltonian (3.5) with respect to the associated state variables so that

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial M_u}, \quad \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial M_i}, \quad \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial B},$$

together with the transversality conditions $\lambda_i(T) = 0, i = 1,2,3$. The optimal control u^* is defined by solving $\frac{\partial H}{\partial u} = 0$. This lead to the condition of optimal control: $-2u(t) + \beta(\lambda_1 - \lambda_2)\frac{M_u(t)B(t)}{1+\alpha B(t)} = 0$. Hence, we have

$$u(t) = \frac{\beta(\lambda_1 - \lambda_2)M_u(t)B(t)}{2(1 + \alpha B(t))}.$$

Since u^* must belong to Ω, we obtain

$$u^* = \begin{cases} 0 & if\ u \leq 0 \\ u & if\ 0 \leq u \leq 1, \\ 1 & if\ u \geq 1 \end{cases}$$

which can also be characterized as

$$u^*(t) = \min\{u_{\max}, \max\{0, \frac{\beta(\lambda_1 - \lambda_2)M_u^*(t)B^*(t)}{2(1 + \alpha B^*(t))}\}\}.$$

This completes the proof.

2. Numerical simulations

This section gives some numerical simulations by using the ode45 solver in MATLAB to demonstrate the previous section's theoretical results. We compute numerically the Theorem 2 by implementing a forward-backward fourth-order Runge-Kutta method, as described in (Campos et al., 2020). The iterative method is starting with a guess on a control variable over the time interval $[0, T]$ using a forward scheme. Then, using the transversality conditions $\lambda_i(t) = 0$, the co-state equation (3.7) are solved by a backward scheme. Furthermore, we update the control by using the state's new values and the value from (3.8). The iterative processes are stopped if the values reach convergence.

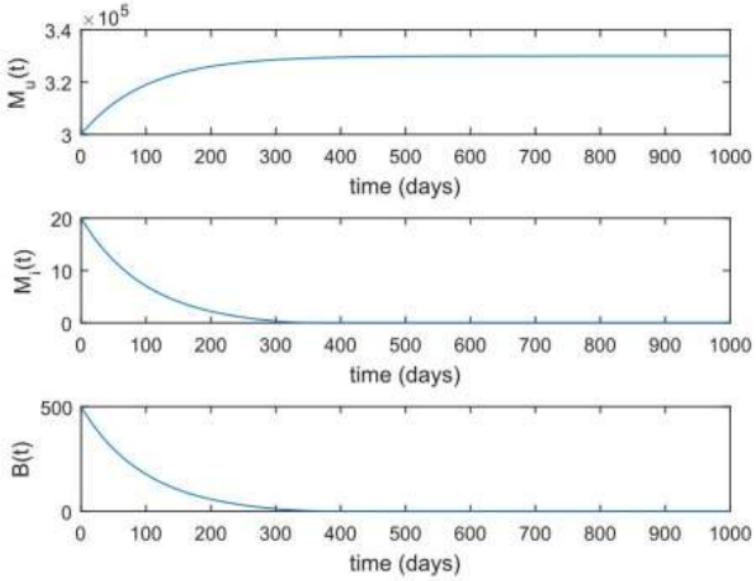

Figure 1. Solution of the System (3.4) with low transmission rates β so that it does not require optimal control.

For the simulation, we consider a set of parameter values obtained from the literature (Adi & Thobirin, 2020; Zhang et al., 2020), with the unit volume in milliliters and time in days as follows

$$\Lambda = 3300, \mu = 0.01, \alpha = 0.01, c = 0.01, k = 0.1, \varepsilon = 10,$$
$$r = 100,\ \gamma = 0.125 \times 10^{-8}, d = 0.05, \qquad (4.1)$$

with variation of parameter β. The initial value for the uninfected macrophage, infected macrophage, and MTb bacteria are taken as $M_u(0) = 300000, M_i(0) = 20$, and $B(0) = 500$, respectively. Now, we consider the case of low transmission of infection rate at which the uninfected macrophages became infected and choose parameter $\beta = 1.5 \times 10^{-8}$. Figure 1 shows that the infected macrophages and the MTb bacteria population are reduced, and in this case, almost no macrophages will be infected by the MTb bacteria, and the MTB bacteria become extinct. This means, in cases of very low transmission, vaccination or control is not needed, and the Mtb bacteria and infected macrophages will disappear from the body. Figure 1 shows that infected macrophages and MTb bacteria disappear from the body in about a year (after about the 300th day).

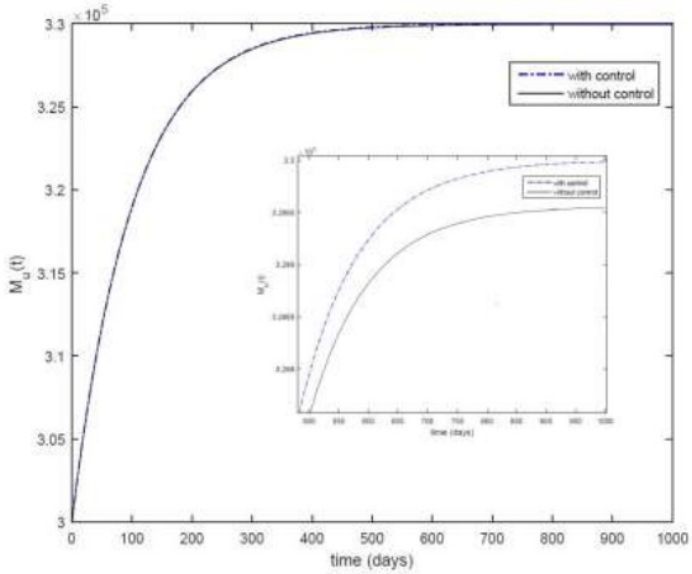

Figure 2. Results from optimal control with a set of parameter (4.1) and $\beta = 1.5 \times 10^{-7}$ of uninfected macrophages, in dashed, compared with that of no control (solid).

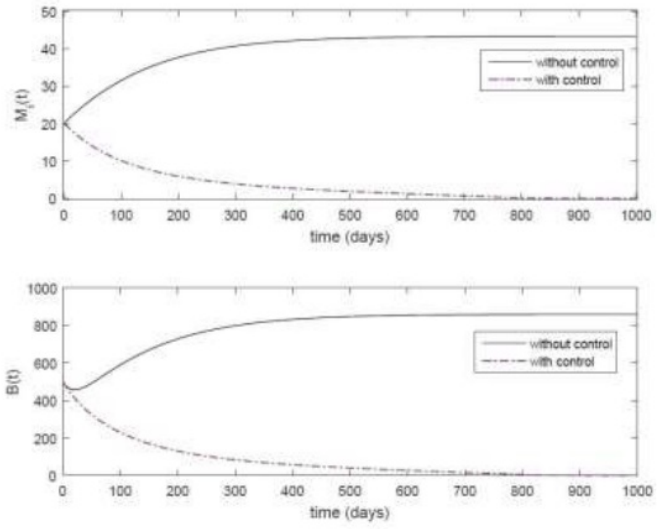

Figure 3. Results from optimal control with a set of parameter (4.1) and $\beta = 1.5 \times 10^{-7}$ of infected macrophages and MTb bacteria, in dashed, compared with that of no control (solid).

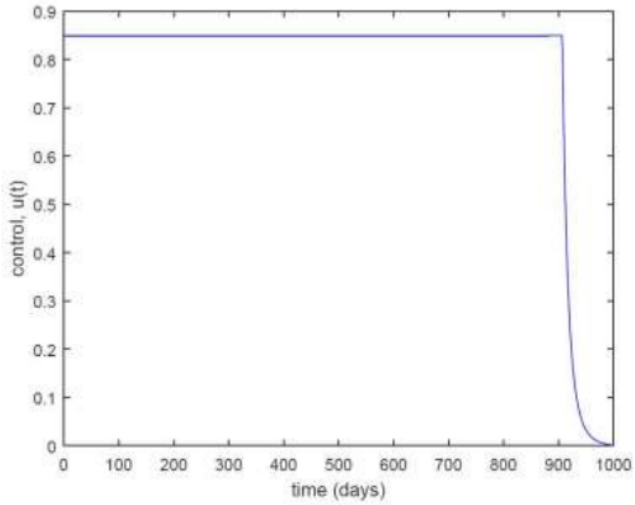

Figure 4. Optimal control u^* for the optimal control problem (3.4) subject to the initial condition $M_u(0) = 300000$, $M_i(0) = 20$, and $B(0) = 500$ and the admissible control Ω.

Now, we vary β with a much higher transmission rate, which is about ten times as much, and keep all other parameter values as in (??). Since vaccination is not completely effective, in this simulation, we set $u_{max} = 0.85$. Figure 2-3 show comparison trajectories for uninfected macrophages, infected macrophages, and MTb bacteria with and without control. Meanwhile, Figure 4 shows control variate over time. With the control, the number of uninfected macrophage populations is higher than without control. The increase in the number of uninfected macrophages is proportional to the decrease in the number of infected macrophages. As shown in Figure 3, with the initial condition of infected macrophages 20, without control, this number will increase to its maximum level in less than two years. Likewise, MTb bacteria's population continued to grow until it was at a constant level for less than two years. Meanwhile, if given control, both population infected macrophages and MTb Bacteria will decrease and disappear from the body in about two years. Appropriate control is shown in Figure 4, and a control policy is obtained; in this case, the complete vaccination is given for approximately 900 days (30 months) then decreases within 100 days later.

D. CONCLUSION AND SUGGESTIONS

This paper has studied an optimal control problem for a within-host tuberculosis model describing the interaction between Microbacterium tuberculosis and macrophages. We determine the existence of optimal control analytically and characterize them using Pontryagin's maximum principle. From our results, we suggest that for the tuberculosis disease to be successfully eradicated, it is necessary to optimize the treatment of vaccination. In other words, there is still a need to improve medical methods and technology. From the point of view of mathematical modeling, it is still necessary to develop a more realistic in-host TB model that considers the most relevant treatment methods and uses actual data to help doctors determine the right treatment for TB patients. Our future research will learn more about this.

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