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Optimal control for a tuberculosis model with reinfection and post-exposure interventions

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ABSTRACT

We apply optimal control theory to a tuberculosis model given by a system of ordinary differential equations. Optimal control strategies are proposed to minimize the cost of interventions, considering reinfection and post-exposure interventions. They depend on the parameters of the model and reduce effectively the number of active infectious and persistent latent individuals. The time that the optimal controls are at the upper bound increase with the transmission coefficient. A general explicit expression for the basic reproduction number is obtained and its sensitivity with respect to the model parameters is discussed. Numerical results show the usefulness of the optimization strategies.

1. Introduction

Mycobacterium tuberculosis is the cause of most occurrences of tuberculosis (TB) and is usually acquired via airborne infection from someone who has active TB. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). Only approximately 10% of people infected with *M. tuberculosis* develop active TB disease. Therefore, approximately 90% of people infected remain latent. Latent infected TB people are asymptomatic and do not transmit TB, but may progress to active TB through either endogenous reactivation or exogenous reinfection [21,22].

Without treatment, mortality rates are high, but the anti-TB drugs developed since 1940 dramatically reduce mortality rates (in clinical cases, cure rates of 90% have been documented) [26]. However, TB remains a major health problem. In 2010 there were an estimated 8.5 to 9.2 million cases and 1.2 to 1.5 million deaths. TB is the second leading cause of death from an infectious disease worldwide after HIV [26].

One can distinguish three types of TB treatment: vaccination to prevent infection; treatment to cure active TB; treatment of latent TB to prevent endogenous reactivation [12]. The treatment of active infectious individuals can have different timings [16]. Here we consider treatment with the duration of six months. In these treatments one of the difficulties to their success is to make sure that the patients complete the treatment. Indeed, after two months, patients no longer have symptoms of the disease and feel healed, and many of them stop taking the medicines. When the treatment is not concluded, the patients are not cured and reactivation can occur and/or the patients may develop resistent TB. One way to prevent patients of not completing the treatment is based on supervision and patient support. In fact, this is one of the measures proposed by the Direct Observation Therapy (DOT) of World Health Organization (WHO) [25]. One example of treatment supervision consists in recording each dose of anti-TB drugs on the patients treatment card [25]. These measures are very expensive since the patients need to stay longer in the hospital or specialized people are to be payed to supervise patients till they finish their treatment. On the other hand, it is recognized that the treatment of latent TB individuals reduces the chances of reactivation, even if it is still unknown how treatment influences reinfection [12].

Optimal control is a branch of mathematics developed to find optimal ways to control a dynamic system [6,11,18]. While the usefulness of optimal control theory in epidemiology is nowadays well recognized [17,19,20], results in tuberculosis are scarce [14]. Recently, different optimal control problems applied to TB have been proposed and analyzed [3,9,13]. The first paper appeared in 2002 [14], and considers a mathematical model for TB based on [5] with two classes of infected and latent individuals (infected with typical TB and with resistant strain TB) where the aim is to reduce the number of infected and latent individuals with resistant TB. In [9] the model considers the existence of a class called *the lost to follow up individuals* and they propose optimal control strategies for the reduction of the number of individuals in this class. In [13] the authors adapt a model from [10] where exogenous reinfection is considered and wish to minimize the number of infectious individuals. In [3] a TB model that incorporates exogenous reinfection, chemoprophylaxis of latently infected individuals and treatment of infections is proposed. Optimal control strategies based on

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chemoprophylaxis of latently infected individuals and treatment of infectious individuals are analyzed for the reduction of the number of active infected individuals. Our aim is to study optimal strategies for the minimization of the number of active TB infectious and persistent latent individuals, taking into account the cost of the measures for the treatments of these individuals. For that, we study the mathematical model for TB dynamics presented in [12], where reinfection and post-exposure interventions are considered. The importance of considering reinfection and post-exposure interventions is justified in [2,4,12,24]. In Section 2 we modify the model of [12] adding two controls $u_1(t)$ and $u_2(t)$, which are functions of time t, and two real positive parameters, ϵ_1 and ϵ_2. We also explain the meaning of these and the other parameters of the TB model. A sensitivity analysis for the basic reproduction number is given in Section 3. In Section 4 we formulate the optimal control problem. We prove that the problem has a unique solution, and finally we apply to it the celebrated Pontryagin Maximum Principle [18]. In Section 5 we propose optimal control strategies, obtained by numerical simulations, considering several variations of some of the parameters of the TB model. We end with Section 6 of conclusion.

2. TB model with controls

We study the mathematical model from [12] where reinfection and post-exposure interventions are considered. We add to that model two control functions $u_1(\cdot)$ and $u_2(\cdot)$ and two real positive parameters ϵ_1 and ϵ_2. The resulting model is given by the following system of nonlinear ordinary differential equations:

$$\begin{cases} \dot{S}(t) = \mu N - \frac{\beta}{N} I(t) S(t) - \mu S(t) \\ \dot{L_1}(t) = \frac{\beta}{N} I(t)(S(t) + \sigma L_2(t) + \sigma_R R(t)) - (\delta + \tau_1 + \mu) L_1(t) \\ \dot{I}(t) = \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \epsilon_1 u_1(t) + \mu) I(t) \\ \dot{L_2}(t) = (1-\phi)\delta L_1(t) - \sigma \frac{\beta}{N} I(t) L_2(t) - (\omega + \epsilon_2 u_2(t) + \tau_2 + \mu) L_2(t) \\ \dot{R}(t) = (\tau_0 + \epsilon_1 u_1(t)) I(t) + \tau_1 L_1(t) + (\tau_2 + \epsilon_2 u_2(t)) L_2(t) - \sigma_R \frac{\beta}{N} I(t) R(t) - (\omega_R + \mu) R(t). \end{cases} \tag{1}$$

The population is divided into five categories (i.e., control system (1) has five state variables): susceptible (S); early latent (L_1), i.e., individuals recently infected (less than two years) but not infectious; infected (I), i.e., individuals who have active TB and are infectious; persistent latent (L_2), i.e., individuals who were infected and remain latent; and recovered (R), i.e., individuals who were previously infected and treated. The control u_1 represents the effort that prevents the failure of treatment in active TB infectious individuals I, e.g., supervising the patients, helping them to take the TB medications regularly and to complete the TB treatment. The control u_2 represents the fraction of persistent latent individuals L_2 that is identified and put under treatment. The parameters $\epsilon_i, \epsilon_i \in (0,1), i = 1,2$, measure the effectiveness of the controls $u_i, i = 1,2$, respectively, i.e., these parameters measure the efficacy of treatment interventions for active and persistent latent TB individuals, respectively.

Following [12], we assume that at birth all individuals are equally susceptible and differentiate as they experience infection and respective therapy. Moreover, the total population, N, with $N = S + L_1 + I + L_2 + R$, is assumed to be constant, i.e., the rate of birth and death, μ, are equal (corresponding to a mean life time of 70 years [12]) and there are no disease-related deaths. The assumption that the total population N is constant, allows to reduce the control system (1) from five to four state variables. We decided to maintain the TB model in form (1), using relation $S(t) + L_1(t) + I(t) + L_2(t) + R(t) = N$ as a test to confirm the numerical results. The proportion of population change, in each category, is described by system (1). The initial value of each category, $S(0), L_1(0), I(0), L_2(0)$ and $R(0)$, are given in Table 1 and are based on [14].

The values of the rates $\delta, \phi, \omega, \omega_R, \sigma$ and τ_0 are taken from [12] and the references cited therein (see Table 1 for the values of the parameters). The parameter δ denotes the rate at which individuals leave L_1 compartment; ϕ is the proportion of individuals going to compartment I; ω is the rate of endogenous reactivation for persistent latent infections (untreated latent infections); ω_R is the rate of endogenous reactivation for treated individuals (for those who have undergone a therapeutic intervention). The parameter σ is the factor that reduces the risk of infection, as a result of acquired immunity to a previous infection, for persistent latent individuals, i.e., this factor affects the rate of exogenous reinfection of untreated individuals; while σ_R represents the same parameter factor but for treated patients. In our simulations we consider the case where the susceptibility to reinfection of treated individuals equals that of latents: $\sigma_R = \sigma$.

The parameter τ_0 is the rate of recovery under treatment of active TB (assuming an average duration of infectiousness of six months). The parameters τ_1 and τ_2 apply to latent individuals L_1 and L_2, respectively, and are the rates at which chemotherapy or a post-exposure vacine is applied. In [12] different values for these rates are considered: the case where no treatment of latent infections occur ($\tau_1 = \tau_2 = 0$); the case where there is an immediate treatment of persistent latent infections ($\tau_2 \to \infty$); or there is a moderate treatment of persistent latent infections ($\tau_2 \in [0.1, 1]$). The first and second cases are not interesting from the optimal control point of view. In our paper we consider, without loss of generality, that the rate of recovery of early latent individuals under post-exposure interventions is equal to the rate of recovery under treatment of active TB, $\tau_1 = \tau_0 = 2\ yr^{-1}$, and greater than the rate of recovery of persistent latent individuals under post-exposure interventions, $\tau_2 = 1\ yr^{-1}$.

Table 1
Parameter values.

Symbol	Description	Value
β	Transmission coefficient	$75, 100, 150, 175$
μ	Death and birth rate	$1/70\, yr^{-1}$
δ	Rate at which individuals leave L_1	$12\, yr^{-1}$
ϕ	Proportion of individuals going to I	0.05
ω	Rate of endogenous reactivation for persistent latent infections	$0.0002\, yr^{-1}$
ω_R	Rate of endogenous reactivation for treated individuals	$0.00002\, yr^{-1}$
σ	Factor reducing the risk of infection as a result of acquired immunity to a previous infection for L_2	0.25
σ_R	Rate of exogenous reinfection of treated patients	0.25
τ_0	Rate of recovery under treatment of active TB	$2\, yr^{-1}$
τ_1	Rate of recovery under treatment of latent individuals L_1	$2\, yr^{-1}$
τ_2	Rate of recovery under treatment of latent individuals L_2	$1\, yr^{-1}$
N	Total population	$30000, 40000, 60000$
$S(0)$	Initial number of susceptible individuals	$\frac{76}{120}N$
$L_1(0)$	Initial number of early latent L_1 individuals	$\frac{37}{120}N$
$I(0)$	Initial number of infectious individuals	$\frac{4}{120}N$
$L_2(0)$	Initial number of persistent latent L_2 individuals	$\frac{2}{120}N$
$R(0)$	Initial number of recovered individuals	$\frac{1}{120}N$
T	Total simulation duration	5 yr
ϵ_1	Efficacy of treatment of active TB I	$0.25, 0.5, 0.75$
ϵ_2	Efficacy of treatment of latent TB L_2	$0.25, 0.5, 0.75$
W_1	Weight constant on control $u_1(t)$	$150, 250, 500$
W_2	Weight constant on control $u_2(t)$	$50, 150, 250$