Applied Mathematical Sciences, Vol. 3, 2009, no. 5, 231 - 240

Optimal Control of Tuberculosis with Exogenous Reinfection

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Abstract

The aim of this work is the application of optimal control for the system of ordinary differential equations modeling a tuberculosis disease with exogenous reinfection. Seeking to reduce the infectious group by the reduction of the contact between infectious and exposed individuals, we use control representing the prevention of exogenous reinfection. The Pontryagin's maximum principle is used to characterize the optimal control. The optimality system is derived and solved numerically.

Keywords: Optimal control, exogenous reinfection, Tuberculosis, TB model with exogenous reinfection

1 Introduction

Tuberculosis (TB) is a bacterial disease with about one third of the world human population as its reservoir (see [1]and [9]) but only a small proportion (approximately 10%) of individuals develop the progressive disease (active TB). Most people are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli and leads to long-lasting partial immunity both to further infection and to the reactivation of latent bacilli remaining from the original infection (see [10]). Individuals who have a latent infection are not clinically ill or capable of transmitting TB (see [9]). Exposed individuals may remain in this latent stage for long and variable periods of time (in fact, many die without ever developing active TB). At greater ages,

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the immunity of persons who have been previously infected may wane, and they may be then at risk of developing active TB as a consequence of either exogenous reinfection (i.e., acquiring a new infection from another infectious individual) or endogenous reactivation of latent bacilli (i.e., re-activation of a pre-existing dormant infection) (see [11] and [10]).

The exogenous reinfection plays a key role in tuberculosis transmission in high-incidence regions, particularly in Africa (where HIV is high) and in inner cities of developed countries.

In literature, Zhilan Feng, Carlos Castillo-Chavez and Angel F. Capurro (see [3]) have incorporated exogenous reinfection into a epidemiological model for the transmission dynamics of tuberculosis and have discussed control of the disease by looking at the role of disease transmission parameters in the reduction of R_0 and the prevalence of the disease. However, this model did not account for time dependent control strategies since their discussions are based on prevalence of the disease at equilibria.

In this article we consider optimal control strategies associated with preventing exogenous reinfection based on a exogenous reinfection tuberculosis model developed in [3]. This model is governed by the following system of ordinary differential equations

$$\frac{dS}{dt} = \Lambda - \mu S - \beta c S \frac{I}{N}, \tag{1}$$
$$\frac{dE}{dt} = \beta c S \frac{I}{N} - p\beta c E \frac{I}{N} - (\mu + k)E + \sigma \beta c T \frac{I}{N}, \tag{2}$$
$$\frac{dI}{dt} = p\beta c E \frac{I}{N} + kE - (\mu + d + r)I, \tag{3}$$
$$\frac{dT}{dt} = rI - \mu T - \sigma \beta c T \frac{I}{N}, \tag{4}$$

where the four epidemiological classes and parameters model are defined in section 2.

The term $p\beta c E\frac{I}{N}$ models exogenous reinfection, that is, the potential reactivation of TB by continuous exposure of latently-infected individuals to those who have active infections, and p represents the level of reinfection. When $p = 0$, system (1)-(4) reduces to our earlier TB model (Castillo-Chavez and Feng, 1997). A value of $p \in [0, 1]$ implies that reinfection is less likely than a new infection. In fact, a value of $p \in [0, 1]$ implies that a primary infection provides some degree of cross immunity to exogenous reinfections. A value of $p \in [1, +\infty[$ implies that TB infection increases the likelihood of active TB.

We introduce into this model a control to the above mentioned model simulating effect of exogenous reinfection. This exogenous reinfection effect is incorporated by adding a term that may lower the exogenous reinfection rate reducing the contact between infectious and exposed individuals so that the number of infectious individuals with tuberculosis will be reduced. Our objective functional balances the effect of minimizing the cases of infectious TB and minimizing the cost of implementing the control.

The paper is organized as follows. Section 2 describes a model with exogenous reinfection with control variable. The analysis of optimization problems is presented in section 3. In section 4, we present a numerical appropriate method and the simulation corresponding results. Finally, the conclusion are summarized in Section 5.

2 A TB model with exogenous reinfection

In this section, we present a TB model with exogenous reinfection [3]. The host population is divided into the four epidemiological classes: namely susceptible $S(t)$, exposed (infected but not infectious) $E(t)$, infectious $I(t)$ and treated (removed) $T(t)$. We assume that an individual can be infected only through contacts with infectious individuals. Our TB model with exogenous reinfection is given by the following nonlinear system of differential equations

$$\frac{dS}{dt} = \Lambda - \mu S - \beta c S \frac{I}{N}, \tag{5}$$

$$\frac{dE}{dt} = \beta c S \frac{I}{N} - p\beta c(1-u)E\frac{I}{N} - (\mu + k)E + \sigma \beta c T \frac{I}{N}, \tag{6}$$

$$\frac{dI}{dt} = p\beta c(1-u)E\frac{I}{N} + kE - (\mu + d + r)I, \tag{7}$$

$$\frac{dT}{dt} = rI - \mu T - \sigma \beta c T \frac{I}{N}, \tag{8}$$

where $S(0) = S_0$, $E(0) = E_0$, $I(0) = I_0$, $T(0) = T_0$ are given and the definitions of above model parameters are listed in Tab. 1.

The control variables, $u(t)$, is bounded, Lebesgue integrable function [7]. The coefficient, $1 - u(t)$, represents the effort that prevents the exogenous reinfection in order to reduce the contact between the infectious and exposed individuals, then we decease the number of infectious individuals.
If $u = 1$, the prevention of exogenous reinfection is 100% effective, whereas if $u = 0$, we find the model for tuberculosis with exogenous reinfection (see, [3]).

Parameter	Definition
Λ	Recruitment rate
μ	Natural mortality rate
d	TB induced mortality rate
β	Average number of susceptible individual infected by one infectious individual per contact per unit of time
$\sigma\beta$, $0 \leq \sigma \leq 1$	Average number of treated individual infected by one infectious individual per contact per unit of time
c	Per-capita contact rate
k	Rate of progression to active TB
r	Per-capita treatment rate
N	Total population $N = S + E + I + T$
p	level of exogenous reinfection

Table 1: Parameter definitions

3 The optimal control problems

The problem is to minimize the objective functional

$$J(u) = \int_{t_0}^{t_f} [I(t) + Au^2(t)]dt \tag{9}$$

where the parameter A represents the weight on the benefit and cost (A balance the size of the terms). Our target is to minimize the objective functional defined in equation (9) by minimizing the number of the infectious classes. In other words, we are seeking optimal control u^* such that

$$J(u^*) = \min\{J(u) : u \in U\}, \tag{10}$$

where U is the control set defined by

$$U = \{u \in L^1(0, t_f) : 0 \leq u \leq 1\}.$$

Pontryagin's Maximum Principle[12] provides necessary conditions for an optimal control problem. This principle converts (5) - (8), (9) and (10) into a problem of minimizing an Hamiltonian, H, pointwisely with respect to u :

$$H = I(t) + Au^2(t) + \sum_{i=1}^{4} \lambda_i f_i, \tag{11}$$

where f_i is the right hand side of the differential equation of i-th state variable. By applying Pontryagin's Maximum Principle [12] and the existence result for the optimal control from [4], we obtain the following theorem.

Theorem 3.1 *There exists an optimal control $u^*(t)$ and corresponding solution S^*, E^*, I^*, T^* and J^*, that minimizes $J(u)$ over U. Furthermore, there exists adjoint functions, λ_1, λ_2, λ_3, λ_4 satisfying the equations*

$$\begin{aligned}
\lambda_1^{'} &= \lambda_1\mu + (\lambda_1 - \lambda_2)\beta c\frac{I^*}{N}, \\
\lambda_2^{'} &= \lambda_2\mu + (\lambda_2 - \lambda_3)(k + p(1-u)\beta c\frac{I^*}{N}), \\
\lambda_3^{'} &= -1 + \lambda_3(\mu + d) + (\lambda_1 - \lambda_2)\beta c\frac{S^*}{N} + (\lambda_2 - \lambda_3)p(1-u)\beta c\frac{E^*}{N} \\
&\quad + (\lambda_4 - \lambda_2)\sigma\beta c\frac{T^*}{N} + (\lambda_3 - \lambda_4)r, \\
\lambda_4^{'} &= \lambda_4\mu + (\lambda_4 - \lambda_2)\sigma\beta c\frac{I^*}{N},
\end{aligned}$$

with transversality conditions

$$\lambda_i(t_f) = 0, i = 1, ..., 4.$$

Moreover, the optimal control is given by

$$u^* = min(1, max(0, \frac{1}{2AN}(\lambda_3 - \lambda_2)p\beta cE^*I^*)) \tag{12}$$

Proof.

Due to the convexity of integrand of J with respect to u, a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. The existence of an optimal control has been given by [4] (see Corollary 4.1). The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle such that

$$\begin{aligned}
\lambda_1^{'} &= -\frac{\partial H}{\partial S}, \quad \lambda_1(t_f) = 0, \\
\lambda_2^{'} &= -\frac{\partial H}{\partial E}, \quad \lambda_2(t_f) = 0, \\
\lambda_3^{'} &= -\frac{\partial H}{\partial I}, \quad \lambda_3(t_f) = 0, \\
\lambda_4^{'} &= -\frac{\partial H}{\partial T}, \quad \lambda_4(t_f) = 0.
\end{aligned}$$

The optimal control u can be solve from the optimality condition,

$$\frac{\partial H}{\partial u} = 0.$$

That is

$$\frac{\partial H}{\partial u} = 2Au + (\lambda_2 - \lambda_3)p\beta cE^*I^*/N = 0.$$

By the bounds in U of the controls, it is easy to obtain u^* in the form of (12). ■

4 Numerical simulations

The numerical algorithm presented below is a semi-implicit finite difference method.
We discretize the interval $[t_0, t_f]$ at the points $t_i = t_0 + ih$ $(i = 0, 1, ..., n)$, where h is the time step such that $t_n = t_f$, [5]. Next, we define the state and adjoint variables S(t), E(t), I(t), T(t), $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$, $\lambda_4(t)$, and the control u in terms of nodal points S_i, E_i, I_i, T_i, λ_1^i, λ_2^i, λ_3^i, λ_4^i and u_i. Now a combination of forward and backward difference approximation is used as follows :

The Method, developed by [6] and presented in [8], is then read as :

$$\begin{aligned}
\frac{S_{i+1}-S_i}{h} &= \Lambda - \mu S_{i+1} - \beta c S_{i+1}\frac{I_i}{N}, \\
\frac{E_{i+1}-E_i}{h} &= \beta c S_{i+1}\frac{I_i}{N} - p(1-u_i)\beta c E_{i+1}\frac{I_i}{N} - (\mu+k)E_{i+1} + \sigma\beta c T_i\frac{I_i}{N}, \\
\frac{I_{i+1}-I_i}{h} &= p(1-u_i)\beta c E_{i+1}\frac{I_{i+1}}{N} + kE_{i+1} - (\mu+d+r)I_{i+1}, \\
\frac{T_{i+1}-T_i}{h} &= rI_{i+1} - \mu T_{i+1} - \sigma\beta c T_{i+1}\frac{I_{i+1}}{N}.
\end{aligned}$$

By using a similar technique, we approximate the time derivative of the adjoint variables by their first- order backward-difference and we use the appropriated scheme as follows

$$\begin{aligned}
\frac{\lambda_1^{n-i}-\lambda_1^{n-i-1}}{h} &= \lambda_1^{n-i-1}\mu + (\lambda_1^{n-i-1}-\lambda_2^{n-i})\beta c\frac{I_{i+1}}{N}, \\
\frac{\lambda_2^{n-i}-\lambda_2^{n-i-1}}{h} &= \lambda_2^{n-i-1}\mu + (\lambda_2^{n-i-1}-\lambda_3^{n-i})(k + p(1-u_i)\beta c\frac{I_{i+1}}{N}), \\
\frac{\lambda_3^{n-i}-\lambda_3^{n-i-1}}{h} &= -1 + \lambda_3^{n-i-1}(\mu+d) + (\lambda_1^{n-i-1}-\lambda_2^{n-i-1})\beta c\frac{S_{i+1}}{N} \\
&\quad + (\lambda_2^{n-i-1}-\lambda_3^{n-i-1})p(1-u_i)\beta c\frac{E_{i+1}}{N} \\
&\quad + (\lambda_4^{n-i}-\lambda_2^{n-i-1})\sigma\beta c\frac{T_{i+1}}{N} + (\lambda_3^{n-i-1}-\lambda_4^{n-i})r, \\
\frac{\lambda_4^{n-i}-\lambda_4^{n-i-1}}{h} &= \lambda_4^{n-i-1}\mu + (\lambda_4^{n-i-1}-\lambda_2^{n-i-1})\sigma\beta c\frac{I_{i+1}}{N}.
\end{aligned}$$

The algorithm describing the approximation method for obtaining the optimal control is the following
Algorithm

step 1 :
$S(0) = S_0$, $E(0) = E_0$, $I(0) = I_0$, $T(0) = T_0$, $\lambda_i(t_f) = 0$ (i=1, ..., 4), $u(0) = 0$.

step 2 :

for i=1, ..., n-1, do :

$$S_{i+1} = \frac{S_i + h\Lambda}{1 + h(\mu + \beta c\frac{I_i}{N})}$$

$$E_{i+1} = \frac{E_i + h(\beta c S_{i+1}\frac{I_i}{N} + \sigma\beta c T_i\frac{I_i}{N})}{1 + h(\mu + k + p(1-u_i)\beta c\frac{I_i}{N})}$$

$$I_{i+1} = \frac{I_i + hkE_{i+1}}{1 + h(\mu + d + r - p(1-u_i)\beta c\frac{E_{i+1}}{N})}$$

$$T_{i+1} = \frac{T_i + hrI_{i+1}}{1 + h(\mu + \sigma\beta c\frac{I_{i+1}}{N})}$$

$$\lambda_1^{n-i-1} = \frac{\lambda_1^{n-i} + h\lambda_2^{n-i}\beta c\frac{I_{i+1}}{N}}{1 + h(\mu + \beta c\frac{I_{i+1}}{N})}$$

$$\lambda_2^{n-i-1} = \frac{\lambda_2^{n-i} + h\lambda_3^{n-i}(k + p(1-u_i)\beta c\frac{I_{i+1}}{N})}{1 + h(\mu + k + p(1-u_i)\beta c\frac{I_{i+1}}{N})}$$

$$\lambda_3^{n-i-1} = [\lambda_3^{n-i} + h(1 + (\lambda_2^{n-i-1} - \lambda_1^{n-i-1})\beta c\frac{S_{i+1}}{N}$$

$$-\lambda_2^{n-i-1}p(1-u_i)\beta c\frac{E_{i+1}}{N} + (\lambda_2^{n-i-1} - \lambda_4^{n-i})\sigma\beta c\frac{T_{i+1}}{N}$$

$$+\lambda_4^{n-i}r)]/[1 + h(\mu + d + r - p(1-u_i)\beta c\frac{E_{i+1}}{N})]$$

$$\lambda_4^{n-i-1} = \frac{\lambda_4^{n-i} + h\lambda_2^{n-i-1}\sigma\beta c\frac{I_{i+1}}{N}}{1 + h(\mu + \sigma\beta c\frac{I_{i+1}}{N})},$$

$$R_{i+1} = \frac{(\lambda_3^{n-i-1} - \lambda_2^{n-i-1})r_1 E_{i+1}I_{i+1}}{2AN},$$

$$u_{i+1} = min(1, max(R_{i+1}, 0))$$

end for

step 3 :

for i=1, ..., n-1, write

$S^*(t_i) = S_i$, $E^*(t_i) = E_i$, $I^*(t_i) = I_i$, $T^*(t_i) = T_i$, $u^*(t_i) = u_i$.

end for

The following parameters and initial values are used for the simulation which we have taken from [2], [3] and [7]:
$\mu = 0.016$, $\Lambda = \mu * N = 192$, $d = 0.1$, $k = 0.005$, $c = 1$, $\beta = 13$, $p = 0.4$, $\sigma = 0.9$, $r = 2$, $N = 12000$, $S_0 = 7600$, $E_0 = 3800$, $I_0 = 500$ and $T_0 = 100$.
the period of the prevention effort is 12 months, and we take $A = 400$. In figure 1, we remark that in absence of prevention the number I (solid curve) of individuals infectious with Tuberculosis increase in the first five months start to grow after.
Whereas, in presence of prevention, the number I (dashed curve) of individuals infectious decreases, in addition the number of individuals I infectious with TB at the final time $t_f = 1$ (years) is 256 in the case with control and 584 without control, and the total cases of TB prevented at the end of the control program is 319 (= 584 − 256). Finally, the figure 1 represents the control optimal u^* for the effort that prevents the exogenous reinfection in order to reduce the number of infectious individuals.

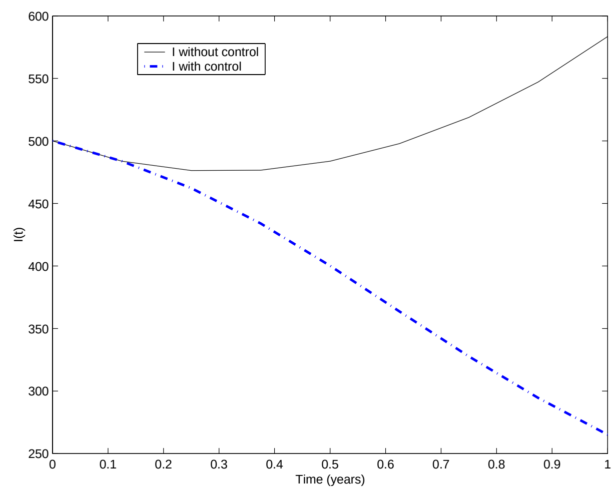

Figure 1: Function I with and without control

5 Conclusion

Our numerical results show the effectiveness to introduce the control that prevents the exogenous reinfection which reactivates the bacterium tuberculosis at the latent individuals. This objective is realizable by sensitizing the latent individuals not to contact the infectious individuals with TB active , particularly in the closed places. As says the proverb "to prevent better than to cure".

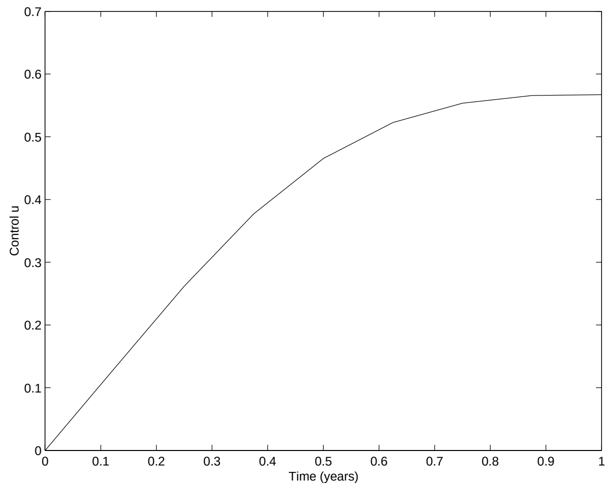

Figure 2: The control u

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Received: July, 2008