Optimal Treatment Strategies for Tuberculosis with Exogenous Reinfection

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Abstract

Tuberculosis (TB) is a disease found in about one third of the world population. There is some controversy on the role of exogenous reinfection; with some epidemiologists supporting it while others consider it irrelevant. However, even at a minimal level, the presence of exogenous reinfection is capable of generating hysteresis and supporting multiple endemic states when the basic reproduction number (R_0) is less than one. In this manuscript, we study the use of control in areas where TB is prevalent ($R_0 > 1$) as well as in areas where some additional effort ($R_0 < 1$) may be able to eliminate the disease. In this model, controls on social distancing, disease relapse, and treatment are incorporated to reduce the latently infected and actively infected populations, via the application of optimal control theory.

1 Introduction

Tuberculosis (TB) is an infectious disease caused by various strains of Mycobacteria. Specifically, Mycobacterium tuberculosis attacks the lungs and is spread through the air. Unique from other infectious diseases (e.g. influenza, measles, etc), only a small portion of individuals develop active TB after primary infection. In fact, most individuals infected with TB remain in the latent stage and never become infectious or show symptoms of TB. In perspective, 30% of individuals in contact with active TB patients are infected (latent and active) while 10% of this infected group will become infectious (active). TB is the leading cause of death among infectious diseases with 2 billion infections and 3 million deaths in the world each year. Factors like age of infection and chronological age are important in TB progression because it is less likely for the development of active TB when the individual has carried the bacteria for a long time. Unfortunately, progression towards active TB may accelerate from repeated contact with active TB individuals [1]. Consequently, the source for TB progression is not only primary infection but also the possibility of exogenous reinfection. Exogenous reinfection has occurred, in the past, on public transportation systems such as airplanes, buses, and subways in crowded cities. There is a high possibility for individuals with latent TB to be exposed to exogenous reinfection through infectious surroundings due to mass-transportation. Therefore, exogenous reinfection plays a key role in the progression from latent to active TB for individuals living in regions with a high incidence rate.

In this paper, we consider optimal control strategies based on an exogenous reinfection TB model. The theory of optimal control has been applied to many areas such as economics [2, 3, 4], engineering [5, 6, 7], biology [8, 9, 10, 11, 12, 13] and medicine [14, 15]. The development of the mathematical theory for optimal control began in the early 1950's, partially in response to problems in various branches of engineering and economics. Despite its modern origins, optimal control theory, from a mathematical point of view, is a variant of one of the oldest and most important subfields in mathematics-the

calculus of variations. Optimal control is the standard method for solving dynamic optimization problems, which deal with finding a control law for a given system such that a certain optimality criterion is achieved. Playing an increasingly important role in modern system design, the main purpose of optimal control theory is to maximize the return from or minimize the cost of the operation of physical, social, economical, and biological processes. It was developed by a group of Russian mathematicians; with Pontryagin as the central character. A basic optimal control problem consists of finding a piecewise continuous control and the associated state variable to maximize or minimize an objective functional. This maximizing or minimizing process is accomplished by adjusting the control variable until the maximum or minimum is achieved. The optimal control can be derived using Pontryagin's maximum principle (a necessary condition) [18]. Details of the derivation is provided in Appendix A.

A TB model with exogenous reinfection assumes that individuals in the latent stage of TB progress into the active stage at some given exogenous reinfection rate. The model further assumes there is an amount of individuals with active TB that fail to complete treatment. With these assumptions, we introduce the three control mechanisms to represent distancing, relapse and treatment efforts. The goal is to minimize the number of infectious individuals while reducing the cost to implement the control treatments. The optimal treatment strategies for different R_0 scenarios ($R_0 > 1$ or $R_0 < 1$) are illustrated through numerical simulation.

This paper is organized as follows: The introduction is given in Section 1. Section 2 describes a mathematical TB model with exogenous reinfection and a TB model with controls. The objective functional and characteristics of optimal controls are also presented in this section. Section 3 includes numerical studies of optimal controls and discusses our results based on the optimal treatment strategy. Conclusions are presented in the final section.

2 Mathematical Model

2.1 Tuberculosis with exogenous reinfection

We consider a tuberculosis model with exogenous reinfection that was developed by Feng and Castillo-Chavez [16]. The host population is divided into four epidemiological classes: susceptibles (S), exposed (infected but not infectious) (E), infectious (I), and treated (removed) (T). N denotes the total population size. We assume that an individual can be infected only through contacts with infectious individuals. The state system is governed by a system of ordinary differential equations (ODEs) as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta c S\frac{I}{N} - \mu S,\\
\frac{dE}{dt} &= \beta c S\frac{I}{N} - p\beta c E\frac{I}{N} - (\mu + k)E + \sigma\beta c T\frac{I}{N},\\
\frac{dI}{dt} &= p\beta c E\frac{I}{N} + kE - (\mu + r + d)I,\\
\frac{dT}{dt} &= rI - \sigma\beta c T\frac{I}{N} - \mu T,\\
\frac{dN}{dt} &= \Lambda - \mu N - dI.
\end{aligned} \tag{1}$$

Λ is the constant recruitment rate; β and $\sigma\beta$ are the average numbers of susceptible and treated individuals infected by one infectious individual per contact per unit of time, $0 < \sigma < 1$; c is the per-capita contact rate; μ is the per-capita natural death rate; k is the rate at which an individual leaves the latent class and becomes infectious; d is the per-capita disease-induced death rate; r is the per-capita treatment rate. The term $p\beta cE\frac{I}{N}$ models the exogenous reinfection rates with p representing the level of reinfection.

The basic reproduction number, R_0, is the expected number of secondary cases produced from a completely susceptible population by a typical infectious individual [17]. In the typical case, if $R_0 < 1$ then, on average, an infected individual produces less than one new infected individual over the course of his/her infectious period, thus the infection

cannot spread. Conversely, if $R_0 > 1$, then each infected individual produces, on average, more than one new infection, which may lead to outbreak of the disease. In other words, if $R_0 < 1$ then the disease free equilibrium is locally asymptotically stable; whereas if $R_0 > 1$ then it is unstable. Thus, R_0 is a threshold parameter for the model. This is not the case in the context of this TB model if the proportion of exogenous reinfection (p) and the initial number of infectious (I_0) are large enough. In the TB model with exogenous reinfection, the basic reproductive number can be written as follows [16]:

$$R_0 = \left(\frac{\beta c}{\mu + r + d}\right)\left(\frac{k}{\mu + k}\right)$$

The incorporation of exogenous reinfection into our basic TB model shows the possibilitiy of a subcritical bifurcation, that is, a "backwards" bifurcation. This bifurcation implies that our system can sustain multiple endemic equilibria even when R_0 <1, if the proportion of exogenous reinfection (p) and the initial number of infectious individual (I_0) are large enough. Due to exogenous reinfection, the "ends" (at an endemic or at the infection-free state) of system (1) depend not just on the parameters, but also on the initial conditions of the system. Figure 1 shows the backwards bifurcation and its dependence. In Figure 1, the top frame shows a bifurcation diagram of endemic steady states. The blue solid curve represents the stable steady state and the red dashed curve represents the unstable steady state. In the bottom frame, the numbers of infectious individuals are displayed as functions of time for various I_0's; (50, 300, 750, 900, 1100). The following parameter values were considered: $\mu = 0.016$, $d = 0.1$, $p = 0.4$, $\sigma = 0.9$, $\Lambda = 417$ ($\frac{\Lambda}{\mu}$ =25000), $k = 0.005$, $r = 2$, $R_0 = 0.87$. The cases with large values of I_0 $(750, 900, 1100)$ have solutions that approach the endemic equilibrium point; note that $R_0 = 0.87$. This result suggests that a sudden influx of infectious individuals (immigrants, for example) may give rise to epidemic outbreaks that could stabilize at

an endemic level, which would have been unstable (or non-existent) in the absence of exogenous reinfections.

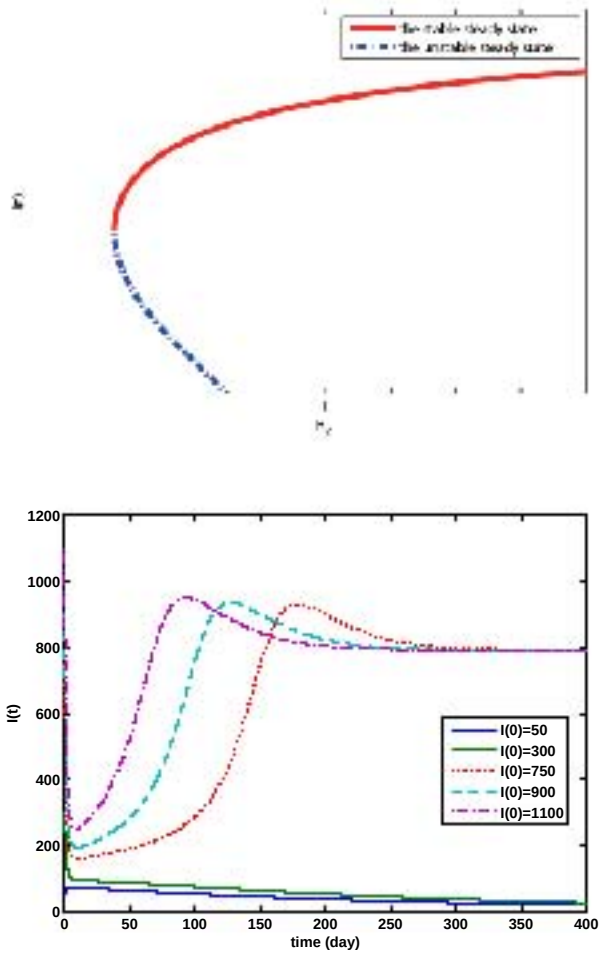

Figure 1: The top frame is a bifurcation diagram of endemic steady states and the bottom frame shows the numbers of infectious individuals as functions of time with various I_0. In the bottom frame, the basic reproductive number $R_0 = 0.87$ is considered.

2.2 The exogenous TB model with controls

In this subsection, three controls are introduced into system (1). The first control, $u_1(t)$, is incorporated into the term that represents the progression from susceptible to latent and latent to active TB due to contact with infectious individuals. Because susceptible and exposed individuals cannot be distinguished in real life, the same control

$u_1(t)$ is assumed to be incorporated into both S and E terms. The second control, $u_2(t)$, is incorporated into the term that represents the treated individuals infected by contacting infectious individuals. The third control, $u_3(t)$, is associated into the term that represents the individuals that received successful treatments.

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - (1-u_1(t))\beta cS\frac{I}{N} - \mu S, \\
\frac{dE}{dt} &= (1-u_1(t))\beta cS\frac{I}{N} - (1-u_1(t))p\beta cE\frac{I}{N} - (\mu+k)E + (1-u_2(t))\sigma\beta cT\frac{I}{N}, \\
\frac{dI}{dt} &= (1-u_1(t))p\beta cE\frac{I}{N} + kE - (\mu+u_3(t)r+d)I, \\
\frac{dT}{dt} &= u_3(t)rI - (1-u_2(t))\sigma\beta cT\frac{I}{N} - \mu T, \\
\frac{dN}{dt} &= \Lambda - \mu N - dI.
\end{aligned} \tag{2}$$

The control fuctions, $u_1(t)$, $u_2(t)$ and $u_3(t)$ are bounded, Lebesgue integrable functions. The first control, $u_1(t)$, is a distancing control, which is the effort that prevents infection of susceptible individuals and exogenous reinfection of exposed individuals. This reduces the number of individuals that could develop active TB. The second control, $u_2(t)$, is a relapse control, which is the effort to prevent the reinfection of treated individuals in the typical TB infection. The third control, $u_3(t)$, is a treatment control, which is the effort on treatment of actively infected individuals to increase the number of treated individuals. Note that the efforts are fully effective when $u_i(t) = 1$ for $i = 1, 2, 3$ whereas no effort is effective when $u_i(t) = 0$

We first consider minimizing the number of infectious individuals and the cost of implementing such a control. The objective functional is defined as follows:

$$J(u_1, u_2, u_3) = \int_0^{t_f} [I(t) + \frac{B_1}{2}{u_1}^2(t) + \frac{B_2}{2}{u_2}^2(t) + \frac{B_3}{2}{u_3}^2(t)]dt$$

In the numerical results, the optimal control strategy showed that the infectious individuals, I(t), are dramatically reduced, but not the exposed individuals, E(t). A large E(t) implies that I(t) is not truly eliminated because some of the exposed individuals can still become infectious (see Figure 2 in Appendix B).

As a result, we now consider the following objective functional, in order to minimize the numbers of exposed and infectious class with exogenous reinfection of TB, while keeping the effort low.

$$J(u_1, u_2, u_3) = \int_0^{t_f} [E(t) + I(t) + \frac{B_1}{2}{u_1}^2(t) + \frac{B_2}{2}{u_2}^2(t) + \frac{B_3}{2}{u_3}^2(t)]dt \tag{3}$$

where t_f is the final time and the coefficients B_1, B_2, B_3 are the weighting parameters, balancing the relative importance and the size of the terms in the objective functional. We assume that the costs of using the controls are nonlinear and take a quadratic form. We seek to find an optimal control, u_1^*, u_2^* and u_3^*, such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{\Omega} J(u_1, u_2, u_3) \tag{4}$$

where $\Omega = \{(u_1, u_2, u_3) \in L^1(0, t_f) | a_i \leq u_i \leq b_i, i = 1, 2, 3\}$ and $a_i, b_i, i = 1, 2, 3$ are positive constants. Pontryagin's maximum principle [18] is used to solve the optimality system, which is derived in Appendix A.

3 Numerical Results and Discussion

In this section, we study, numerically, the optimal treatment strategies of our TB model with exogenous reinfection. The optimal treatment strategy is obtained by solving the optimality system; consisting of the state and adjoint systems with transversality and

optimality equations. The optimality system is solved using an iterative method. The state system with an initial guess is solved forward in time and then the adjoint system with transversality conditions is solved backward in time. The controls are updated at the end of each iteration using the optimal equations. The iterations continue until convergence is achieved. The parameters are given in Table 1 and 2.

Table 1: Computational parameters

Computational parameters	Symbol	
Final time	t_f	5 years
Timestep duration	dt	0.01 years
Upper bound for controls		1
Lower bound for controls		0
weight factor associated with $u_1(t)$	B_1	$1, 10, 100$
weight factor associated with $u_2(t)$	B_2	$1, 10, 100$
weight factor associated with $u_3(t)$	B_3	$1, 10, 100$

Table 2: Epidemical parameters

Parameters	Values
β	80
μ	0.0167
σ	0.9
c	0.1, 0.3
d	0.1
k	0.005
p	0.4
r	2
Λ	417
N	25000 (Λ/μ)
$S(0)$	13250
$E(0)$	10500
$I(0)$	1000
$T(0)$	250

Note that the simulated period is 5 years, which is determined from Figure 1. The curves in Figure 1 illustrate two behaviors, one approaching zero and another approaching

a steady state (endemic). Without utilizing the entire simulation of 400 years, a 5 year period is enough time to show if the solution approaches zero or an endemic equilibrium. We consider the two cases of epidemic outbreaks: $R_0 < 1$ with large enough p and I_0, and $R_0 > 1$.

In order to find more meaningful and efficient controls, we consider various scenarios using the following cases.

- $R_0 < 1$
  - **Strategy 1** distancing, relapse, and treatment controls ($u_1(t), u_2(t)$ and $u_3(t)$)
  - **Strategy 2** distancing and relapse controls ($u_1(t)$ and $u_2(t)$)
  - **Strategy 3** distancing and treatment controls ($u_1(t)$ and $u_3(t)$)
  - **Strategy 4** relapse and treatment controls ($u_2(t)$ and $u_3(t)$)
  - **Strategy 5** distancing control ($u_1(t)$)
- $R_0 > 1$
  - **Strategy 6** distancing, relapse, and treatment controls ($u_1(t), u_2(t)$ and $u_3(t)$)
  - **Strategy 7** distancing and relapse controls ($u_1(t)$ and $u_2(t)$)
  - **Strategy 8** distancing control ($u_1(t)$)
  - **Strategy 9** relapse control ($u_2(t)$)

Strategies $1-5$ correspond to the cases when R_0 is less than 1, while Strategies $6-9$ correspond to the cases when R_0 is greater than 1.

3.1 $R_0 < 1$ with large enough p and I_0

In this subsection, the optimal treatment strategies are investigated using Strategies 1 through 5 and note that $R_0 = 0.8070 < 1$. We considered the three cases, using three controls in Strategy 1. Since the cost of using controls may differ depending on country and/or government, we consider three different sets of cost coefficients: ($B_1 = B_2 = B_3 = 10$), ($B_1 = 100, B_2 = 10, B_3 = 100$) and ($B_1 = 100, B_2 = 100, B_3 = 10$). In

Figure 3, the top three frames illustrate the optimal controls. The blue dotted curves represent the controls with weight parameters ($B_1 = B_2 = B_3 = 10$), the red dashed curves represent the controls with weight parameters ($B_1 = 100, B_2 = 10, B_3 = 100$) and the green dot-dashed curves represent the controls with weight parameters ($B_1 = 100, B_2 = 100, B_3 = 10$) In the bottom five frames, the black solid curve represents the state variables without control while the blue dotted, red dashed and green dot-dashed curves represent the state variables with controls for ($B_1 = B_2 = B_3 = 10$), ($B_1 = 100, B_2 = 10, B_3 = 100$) and ($B_1 = 100, B_2 = 100, B_3 = 10$), respectively. The main results from Figure 3 are as follows: for the first case, when the costs of $u_1(t)$, $u_2(t)$ and $u_3(t)$ (B_1, B_2, and B_3 respectively) are equal to 10, all three controls are used to near full force with $u_1(t)$ being used frequently within the five year period. In the second case, when the costs of $u_1(t)$ and $u_3(t)$ are increased by a factor of 10 while maintaining the same cost for $u_2(t)$, the effort of using $u_1(t)$ remains the largest. For the third case ($B_1 = 100, B_2 = 100, B_3 = 10$), $u_3(t)$ is seemingly used the most because of its cheap cost, the difference among the costs of all three controls reveal that $u_1(t)$ is actually the most effective control. Further, this control strategy seems to work well because the number of both exposed $E(t)$ and infectious $I(t)$ individuals are noticeably reduced with $I(t)$ approaching zero. However, if the cost of using $u_3(t)$ is too high, then $I(t)$ increases again at the end of simulation (See red dotted curve of I(t) in Figure 3). Note that $I(t)$ seems to decrease without control within the given time of 5 years, but it actually increases and stays at an endemic steady-state (see Figure 1). Next we consider the use of two controls.

In Strategies $2-4$, all cost coefficients are assumed to be of the same order ($B_1 = B_2 = B_3 = 10$ or 100). Notice that E(t) is not shown for the remaining figures in this section because E(t) has the same behavior as that of Figure 2 (i.e. E(t) behaves similarly to the curves with controls when the control is working). In Strategy 2, the distancing and relapse controls ($u_1(t)$ and $u_2(t)$) are introduced. Figure 4 illustrates the distancing

control $u_1(t)$, relapse control $u_2(t)$ and infectious individuals $I(t)$. The control strategy is effective; the distancing control, $u_1(t)$, requires near full effort for the whole simulated time, but the relapse control, $u_2(t)$, requires less effort. In Strategy 3, the distancing and treatment controls ($u_1(t)$ and $u_3(t)$) are considered. Figure 5 shows two controls and infectious individuals as functions of time. The results illustrate that when the cost of both $u_1(t)$ and $u_3(t)$ are equal to 10, the controls are used at near full effort. However, when the cost of the controls increase to 100, only $u_1(t)$ requires near full effort for almost the entire simulated time period while the required effort for $u_3(t)$ starts to decrease after 2 years. In Strategy 4, the relapse and treatment control ($u_2(t)$ and $u_3(t)$) are applied. It is interesting to note that the optimal control strategy dose not work in this case. The number of infectious individuals $I(t)$ with controls (dotted curve) and without controls (solid curve) are almost the same (see bottom frame in Figure 6). Even though near full effort for $u_2(t)$ and $u_3(t)$ are applied for the whole period, the control program does not work. This finding indicates that the controls $u_2(t)$ and $u_3(t)$ alone are not enough to reduce the exposed and infectious individuals in this TB model.

Overall, the distancing control $u_1(t)$ is the most effective control if the costs are of the same order. For this reason, we consider only one control program with the distancing control, $u_1(t)$, associated with the exogenous rate (Strategy 5). Figure 7 displays the control $u_1(t)$ and $I(t)$ as functions of time in the top and bottom frames, respectively. The two weight constants, $B_1 = 10$ and 100, are considered. As expected, a larger B_1 leads to less effort from $u_1(t)$ This optimal treatment strategy shows the reduction of $E(t)$ and $I(t)$.

Note that the basic reproductive number $R_0 = \left(\frac{\beta c}{\mu+r+d}\right)\left(\frac{k}{\mu+k}\right)$ and the level of exogenous reinfection p is not involved in R_0. This resulting optimal treatment strategy changes the endemic outbreak state with $R_0 < 1$ to the disease free state by applying the effort to reduce the exogenous reinfection rate, $p\beta cE\frac{I}{N}$. However, if $R_0 < 1$ with p and I_0 large enough, then the most effective control is the distancing control for exogenous

reinfection.

3.2 $R_0 > 1$

This subsection discusses the optimal control treatment strategies for $R_0 = 2.6125$. We first consider the three controls with three sets of the weight constants, $(B_1 = 10, B_2 = 100, B_3 = 10)$, $(B_1 = 100, B_2 = 100, B_3 = 10)$ and $(B_1 = 100, B_2 = 100, B_3 = 100)$ in Strategy 6. Figure 8 displays the controls $u_1(t)$, $u_2(t)$ and $u_3(t)$ and the state variables as functions of time in the top three and bottom five frames, respectively. In each frame, the red dashed curve represents the case with ($B_1 = 10$, $B_2 = 100$, and $B_3 = 10$), the blue dotted curve represents the case with ($B_1 = 100$, $B_2 = 100$, and $B_3 = 10$) and the green dot-dashed curve represents the case with ($B_1 = 100$, $B_2 = 100$, and $B_3 = 100$). The black solid curves represent the state variables without controls in the bottom five frames. The main results are as follows: first, the distancing control, $u_1(t)$, is less effective than the relapse and treatment controls because a small amount of $u_1(t)$ is used even though the costs of using $u_1(t)$, $u_2(t)$ and $u_3(t)$ are the same. Second, in all three cases, $(B_1 = 10, B_2 = 100, B_3 = 10)$, $(B_1 = 100, B_2 = 100, B_3 = 10)$ and $(B_1 = 100, B_2 = 100, B_3 = 100)$, almost full effort of $u_2(t)$ is needed during the whole simulation. This implies that the most effective control mechanism is to prevent the reinfection of treated individuals. Third, while the number of exposed $E(t)$ and infectious $I(t)$ individuals initially increase, both ultimately approach zero, which suggests that these control strategies are effective. Fourth, only $u_2(t)$ is used at near full effort for the entire simulation while the usage $u_1(t)$ and $u_3(t)$ begins at 2 and 0.5 years respectively. Next, we consider two control strategies; $u_1(t)$ and $u_2(t)$.

In Figure 9, the controls $u_1(t)$ and $u_2(t)$ and $I(t)$ as functions of time are shown in the top, middle and bottom frames, respectively. Considering cost coefficients of the same order, $B_1 = B_2 = 100$ (blue dotted curves), almost full control $u_2(t)$ is used while $u_1(t)$ is not used until approximately 2.5 years. So, we increase the cost of using $u_2(t)$ and

maintaining the same cost for using $u_1(t)$, $(B_1 = 100, B_2 = 1000)$. Although the cost of using $u_2(t)$ increased significantly, $u_2(t)$ is still used much more than $u_1(t)$. In both cases, the optimal treatment strategies are effective; with the number of E(t) and $I(t)$ approaching to zero (E(t) behaves similarly to the results displayed in Figure 9). These results show that the most important control is, again, relapse control, $u_2(t)$. One of the most important results from Figure 8 and Figure 9 is that the control $u_2(t)$ is the most effective.

Now we consider the mitigation strategies with only one control. Figure 10 displays the control $u_1(t)$, $E(t)$ and $I(t)$ as functions of time, respectively. Even though the optimal treatment program with only $u_1(t)$ effectively reduces I(t), the control has less effect on E(t). This suggests that I(t) is not truly reduced because some exposed individuals may become infected. Let's consider the optimal treatment program with only the relapse control, $u_2(t)$. Figure 11 displays the control $u_2(t)$, $E(t)$ and $I(t)$ as functions of time. The cost constant B_2 is considered as 100 and 1000. Unlike $u_1(t)$ from Figure 10, $u_2(t)$ alone can effectively reduce both $E(t)$ and $I(t)$.

Overall, under the implementation of $u_1(t)$ solely, infectious individuals are reduced effectively, but exposed individuals are still maintained at a high level. The implementation of only $u_2(t)$ manages to reduce exposed individuals and infectious individuals effectively. Under two controls ($u_1(t)$ and $u_2(t)$), it is observed that $u_1(t)$ is delayed (zero up to 2 years) until exposed individuals are reduced significantly enough while $u_2(t)$ is applied from the beginning. This result suggests that $u_2(t)$ is the most effective control strategy when $R_0 > 1$.

4 Conclusions

The purpose of this work is to introduce the optimal control strategies for a model of TB with exogenous reinfection. Since the TB model with exogenous reinfection has

multiple endemic equilibria even when $R_0 < 1$, we considered the optimal strategies for both cases when $R_0 > 1$ and $R_0 < 1$. In our work, three controls have been introduced in our state system to minimize the number of exposed and infectious individuals. The distancing control, $u_1(t)$, associated with the transmission rate(βc), represents the effort to reduce the susceptible and exposed individuals from being in contact with infectious individuals (e.g. an isolation policy or a vaccination policy for infection). The relapse control, $u_2(t)$, represents the effort to prevent reinfection of the treated individuals. An example of this control is a vaccination policy for reinfection during treatment. The treatment control, $u_3(t)$, represents the effort to treat actively infected individuals, which increases the number of treated individuals. Different combination of these controls were evaluated through two cases. For the case when $R_0 < 1$, 5 strategies were evaluated: (1) combination of $u_1(t)$, $u_2(t)$, and $u_3(t)$; (2) combination of $u_1(t)$ and $u_2(t)$; (3) combination of $u_1(t)$ and $u_3(t)$; (4) combination of $u_2(t)$ and $u_3(t)$; (5) $u_1(t)$ alone. In contrast, when $R_0 > 1$, 4 strategies were evaluated: (1)combination of $u_1(t)$, $u_2(t)$, and $u_3(t)$; (2) combination of $u_1(t)$ and $u_2(t)$; (3) $u_1(t)$ alone; (4) $u_2(t)$ alone.

Overall, we have identified optimal control strategies for both cases when $R_0 > 1$ and $R_0 < 1$. The distancing control, $u_1(t)$, is the most effective control when $R_0 < 1$ while the relapse control, $u_2(t)$, is the most effective control when $R_0 > 1$. Further, the results suggest that when $R_0 < 1$, the control strategy is not effrective without the presence of $u_1(t)$. Similarly, when $R_0 > 1$, $u_2(t)$ must be present. With the presence of $u_1(t)$ when $R_0 < 1$ and the presence of $u_2(t)$ when $R_0 > 1$, the optimal control programs will effectively reduce the number of exposed and infectious individuals

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A Characteristics of optimal controls

Pontryagin's Maximum Principle converts (2) - (4) into a problem of minimizing a pointwise Hamiltonian, H, with respect to u_1, u_2 and u_3:

$$H = E + I + \frac{B_1}{2}{u_1}^2(t) + \frac{B_2}{2}{u_2}^2(t) + \frac{B_3}{2}{u_3}^2(t) + \sum_{i=1}^{5}\lambda_i g_i$$

where g_i is the right hand side of the differential equation of the ith state variable.

To find the optimal solutions, we apply the Pontryagin's maximum principle, which gives the necessary conditions that the adjoint equations must satisfy. We obtain the following theorem.

Theorem A.1 *Given optimal controls ${u_1}^*, {u_2}^*, {u_3}^*$ and solutions S^*, E^*, I^*, T^*, N^* of the corresponding state system (1), there exists adjoint variables $\lambda_1, ..., \lambda_5$ satisfying*

$$\begin{aligned}
\dot{\lambda_1} &= \lambda_1((1-u_1(t))\beta c\frac{I}{N} + \mu) - \lambda_2(1-u_1(t))\beta c\frac{I}{N},\\
\dot{\lambda_2} &= -1 + \lambda_2((1-u_1(t))p\beta c\frac{I}{N} + \mu + k) - \lambda_3((1-u_1(t))p\beta c\frac{I}{N} + k),\\
\dot{\lambda_3} &= -1 + \lambda_1(1-u_1(t))\beta c\frac{S}{N} - \lambda_2((1-u_1(t))\beta c\frac{S}{N} - (1-u_1(t))p\beta c\frac{E}{N} + (1-u_2(t))\sigma\beta c\frac{T}{N})\\
&\quad - \lambda_3((1-u_1(t))p\beta c\frac{E}{N} - (\mu + u_3(t)r + d)) - \lambda_4(u_3(t)r - (1-u_2(t))\sigma\beta c\frac{T}{N})\\
&\quad + \lambda_5 d, \qquad (5)\\
\dot{\lambda_4} &= -\lambda_2(1-u_2(t))\sigma\beta c\frac{I}{N} + \lambda_4((1-u_2(t))\sigma\beta c\frac{I}{N} + \mu),\\
\dot{\lambda_5} &= -\lambda_1(1-u_1(t))\beta cS\frac{I}{N^2} + \lambda_2((1-u_1(t))\beta cS\frac{I}{N^2} - (1-u_1(t))p\beta cE\frac{I}{N^2} + (1-u_2(t))\sigma\beta cT\frac{I}{N^2})\\
&\quad + \lambda_3(1-u_1(t))p\beta cE\frac{I}{N^2} - \lambda_4(1-u_2(t))\sigma\beta cT\frac{I}{N^2} + \lambda_5\mu
\end{aligned}$$

and $\lambda_1(t_f) = ... = \lambda_5(t_f) = 0$, the transversality conditions. Furthermore

$$
\begin{aligned}
u_1^* &= min\Big\{max\Big\{a, \frac{1}{B_1 N^*}(\beta c S^* I^*(\lambda_2 - \lambda_1) + p\beta c E^* I^*(\lambda_3 - \lambda_2))\Big\}, b\Big\}, \\
u_2^* &= min\Big\{max\Big\{a, \frac{1}{B_2 N^*}(\sigma\beta c T^* I^*(\lambda_2 - \lambda_4))\Big\}, b\Big\}, \\
u_3^* &= min\Big\{max\Big\{a, \frac{1}{B_3}(r I^*(\lambda_3 - \lambda_4))\Big\}, b\Big\}.
\end{aligned} \tag{6}
$$

Proof: Corollary 4.1 of [19] gives the existence of an optimal control pair due to the convexity of integrand of J with respect to u_1, u_2, u_3, a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. The form of the adjoint equations and transversality conditions are standard results from the Pontryagin's Maximum Principle [18]. We differentiate the Hamiltonian with respect to states, S, E, I, T and N respectively.

$$
\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial H}{\partial S} \\
&\cdots \\
\frac{d\lambda_5}{dt} &= -\frac{\partial H}{\partial N},
\end{aligned}
$$

and then the adjoint system can be written as (5). By considering the optimality conditions,

$$
\frac{\partial H}{\partial u_1} = 0, \frac{\partial H}{\partial u_2} = 0, \frac{\partial H}{\partial u_3} = 0 \qquad \text{at } u_1^*, u_2^*, u_3^*,
$$

which can then be solved for our optimal u_1^*, u_2^*, u_3^*, giving us:

$$\begin{aligned}
\frac{dH}{du_1} &= B_1 u_1 + \lambda_1 \beta c S \frac{I}{N} - \lambda_2 \beta c S \frac{I}{N} + \lambda_2 p \beta c E \frac{I}{N} - \lambda_3 p \beta c E \frac{I}{N} = 0, \\
\frac{dH}{du_2} &= B_2 u_2 - \lambda_2 \sigma \beta c T \frac{I}{N} + \lambda_4 \sigma \beta c T \frac{I}{N} = 0, \\
\frac{dH}{du_3} &= B_3 u_3 - \lambda_3 r I + \lambda_4 r I = 0,
\end{aligned}$$

at ${u_1}^*$ on the set $\{t | a < {u_i}^*(t) \text{ for } i = 1, 2, 3\}$. On this set,

$$\begin{aligned}
u_1^* &= \frac{1}{B_1 N^*}(\beta c S^* I^* (\lambda_2 - \lambda_1) + p \beta c E^* I^* (\lambda_3 - \lambda_2)), \\
u_2^* &= \frac{1}{B_2 N^*}(\sigma \beta c T^* I^* (\lambda_2 - \lambda_4)), \\
u_3^* &= \frac{1}{B_3}(r I^* (\lambda_3 - \lambda_4)).
\end{aligned}$$

Taking into account the bounds on controls, we obtain the characterization of u_1^*, u_2^* and u_3^* in (6).

B Simulation Figures

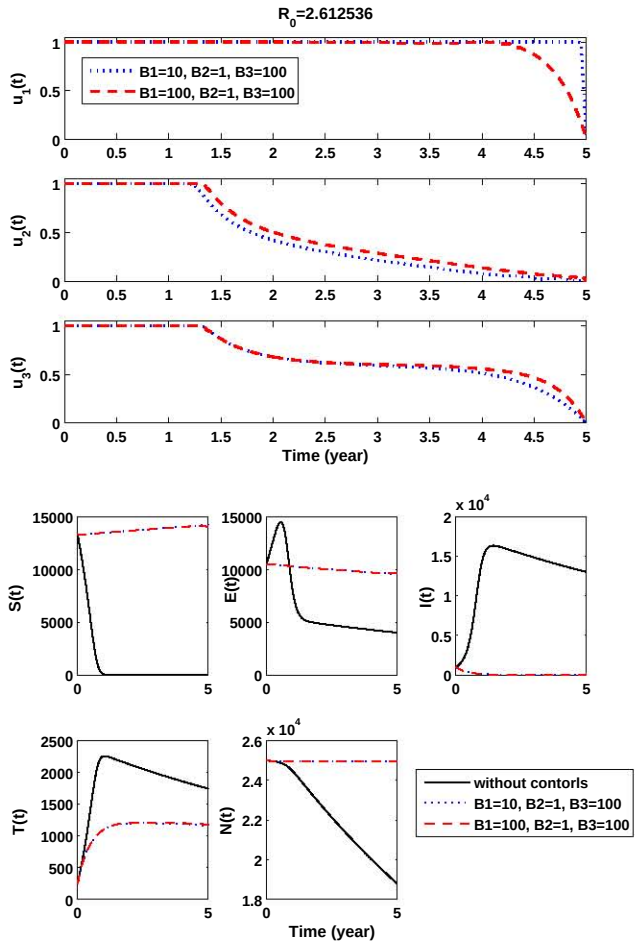

Figure 2: The optimal controls ($u_1(t)$, $u_2(t)$ and $u_3(t)$) and state variables are displayed as functions of time when objective functional is minimize $J(u_1, u_2, u_3) = \int_0^{t_f}[I(t) + \frac{B_1}{2}{u_1}^2(t) + \frac{B_2}{2}{u_2}^2(t) + \frac{B_3}{2}{u_3}^2(t)]dt$. The black solid , blue dotted, red dashed curves represent the cases of without controls, $(B_1 = 10, B_2 = 1, B_3 = 100)$ and $(B_1 = 100, B_2 = 1, B_3 = 100)$ with controls, respectively.

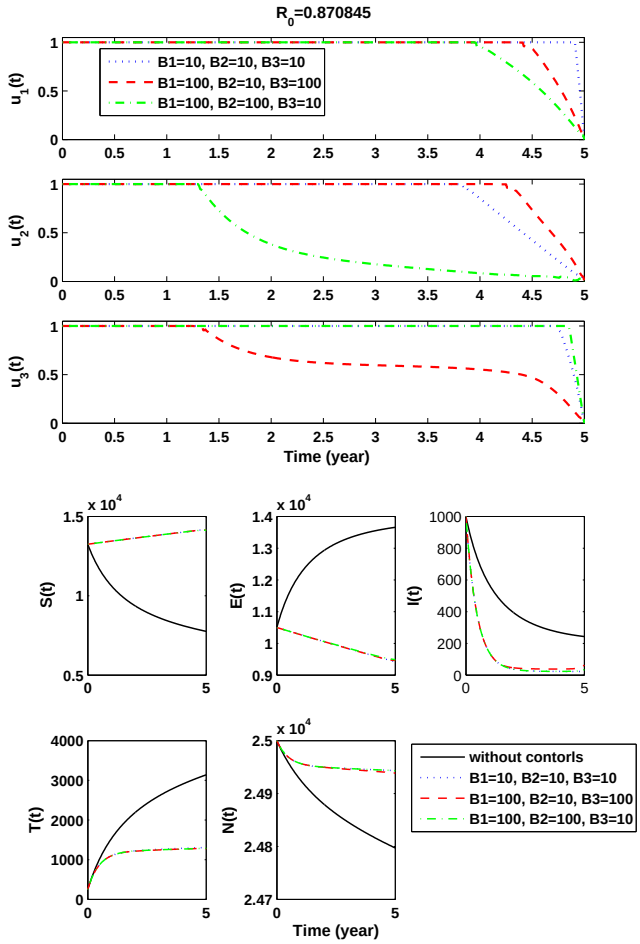

Figure 3: The optimal controls ($u_1(t)$, $u_2(t)$ and $u_3(t)$) and state variables of Strategy 1 are displayed as functions of time. The black solid, blue dotted, red dashed, green dot-dashed curves represent the cases without controls, $(B_1 = 10, B_2 = 10, B_3 = 10)$, $(B_1 = 100, B_2 = 10, B_3 = 100)$ and $(B_1 = 100, B_2 = 100, B_3 = 10)$ with controls, respectively.

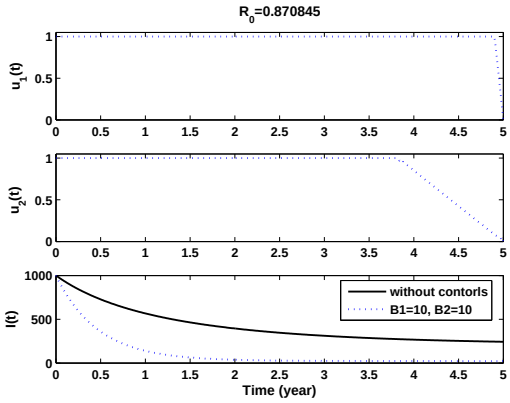

Figure 4: The optimal controls $u_1(t)$, $u_2(t)$ and the infectious individuals of Strategy 2 as functions of time are displayed. The black solid and blue dotted curves represent the cases without controls and with controls $(B_1 = 10, B_2 = 10)$ respectively.

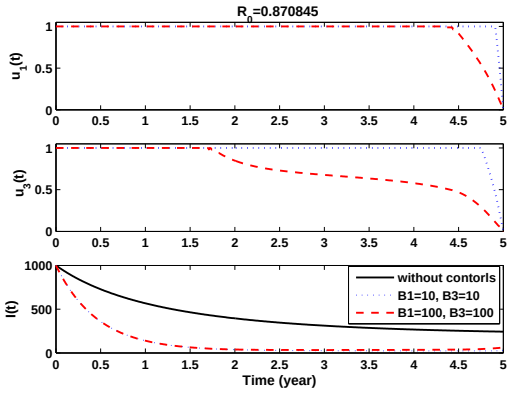

Figure 5: The optimal controls $u_1(t)$, $u_3(t)$ and the infectious individuals of Strategy 3 as functions of time are displayed. The black solid, blue dotted and red dashed curves represent the cases without controls, $(B_1 = 10, B_3 = 10)$ and $(B_1 = 100, B_3 = 100)$ with controls, respectively.

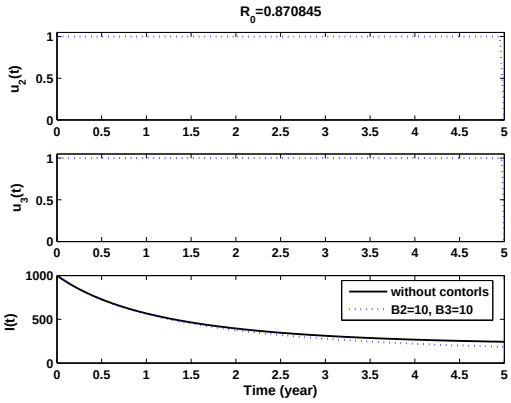

Figure 6: The optimal controls $u_2(t)$, $u_3(t)$ and the infectious individuals of Strategy 4 as functions of time are displayed. The black solid and blue dotted curves represent the cases without controls and with controls $(B_2 = 10, B_3 = 10)$ respectively.

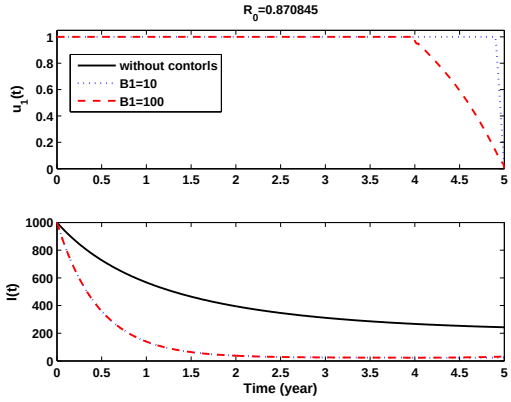

Figure 7: The optimal controls $u_1(t)$ and the infectious individuals of Strategy 5 as functions of time are displayed. The black solid, blue dotted and red dashed curves represent the cases without controls, $(B_1 = 10)$ and $(B_1 = 100)$ with controls, respectively.

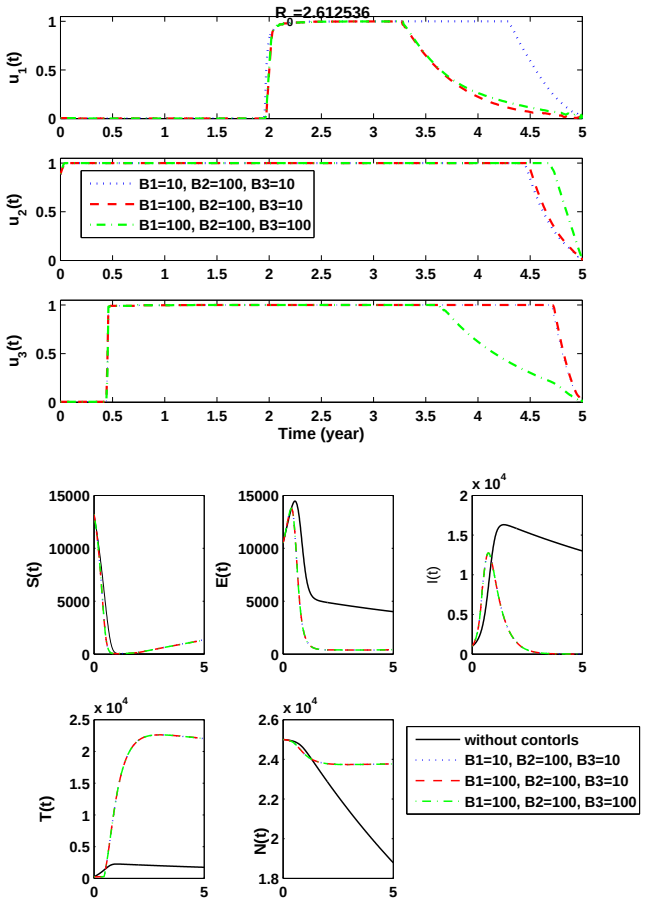

Figure 8: The optimal controls ($u_1(t)$, $u_2(t)$ and $u_3(t)$) and state variables of Strategy 6 as functions of time are displayed. The black solid, blue dotted, red dashed, green dot-dashed curves represent the cases without controls, $(B_1 = 10, B_2 = 100, B_3 = 10)$, $(B_1 = 100, B_2 = 100, B_3 = 10)$ and $(B_1 = 100, B_2 = 100, B_3 = 100)$ with controls, respectively.

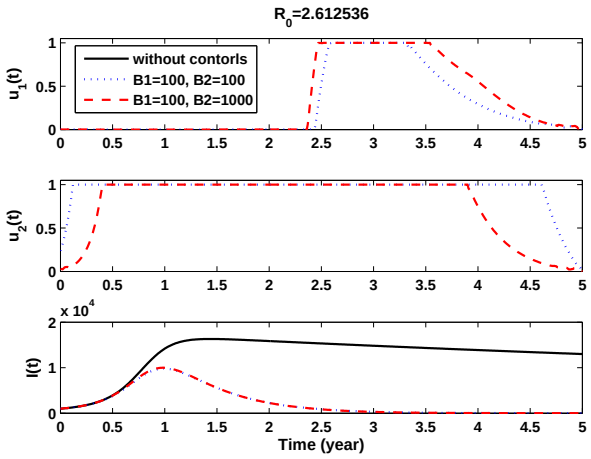

Figure 9: The optimal controls $u_1(t)$, $u_2(t)$ and t he infectious individuals of Strategy 7 as functions of time are displayed. The black solid, blue dotted and red dashed curves represent the cases without controls, $(B_1 = 100, B_2 = 100)$ and $(B_1 = 100, B_2 = 1000)$ with controls, respectively.

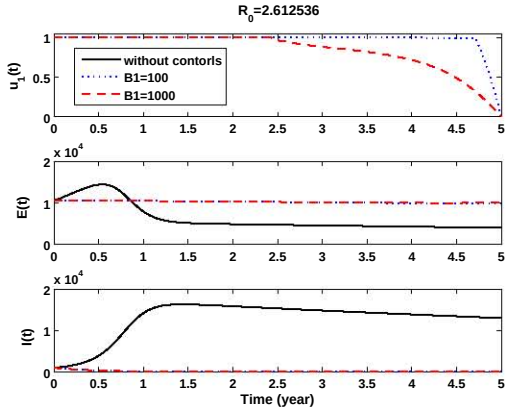

Figure 10: The optimal controls $u_1(t)$ and the infectious individuals of Strategy 8 as functions of time are displayed. The black solid, blue dotted and red dashed curves represent the cases without controls, $(B_1 = 100)$ and $(B_1 = 1000)$ with controls, respectively.

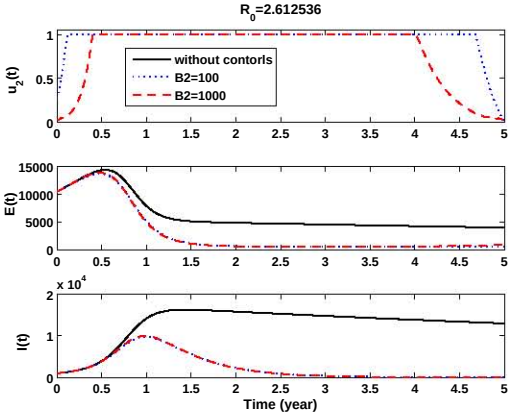

Figure 11: The optimal controls $u_2(t)$ and the infectious individuals of Strategy 9 as functions of time are displayed. The black solid, blue dotted and red dashed curves represent the cases without controls, $(B_2 = 100)$ and $(B_2 = 1000)$ with controls, respectively.