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Mathematical modelling of Tuberculosis in a logistically growing human population with optimal control *

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Abstract. Tuberculosis (TB) is a common deadly infectious disease caused mainly by Mycobacterium tuberculosis. Approximately, one-third of the world's population is infected by TB. Therefore, the effectiveness of treatment and control strategies to reduce the spread of TB is still needed. In this paper, we proposed and analyzed a mathematical modelling of TB transmission considering logistically growing human population. The model also incorporates TB prevention and anti-TB treatment efforts as control strategies to minimize the number of latent and infectious populations. For model without controls, we obtain the basic reproduction number which determines the stability of the equilibriums of the model. The disease free equilibrium is locally asymptotically stable whenever the reproduction number is less than unity. Using the Pontryagin Maximum Principle, the optimal control theory is then deduced analytically. Numerical simulations are further conducted to confirm the effectiveness of the optimal treatments. According to the simulation results, the combination TB prevention and anti-TB treatment give better result in term minimizing the number of the latent and infected populations. However, as shown by the numerical results, the anti-TB treatment strategy is more effective than TB prevention if we use only one control.

Keywords: mathematical model, tuberculosis, logistically growing, optimal control

1 Introduction

Tuberculosis (TB) is a common deadly infectious disease caused mainly by Mycobacterium tuberculosis, which most commonly affects the lung. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease[18]. According to WHO, one-third of the world's population has latent TB (no symptoms), which means have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease[19]. The symptoms of active TB of the lung are coughing, sometimes with sputum or blood, chest pains, weakness, weight loss, fever and night sweats. This can lead to delays in seeking care, and results in transmission of bacteria to others. Tuberculosis mostly affects young adults, in their most productive years.

Tuberculosis is a preventable and treatable disease. For prevention of TB, the BCG vaccine is widely used, which is 80% effective in preventing TB[23]. Tuberculosis is treatable with a six month course of antibiotics[18]. There are two types of the treatment. The treatment of latent TB is called chemoprophylaxis and treatment of active TB is called therapeutics. The treatment for an active TB lasts long. Therefore control strategies have been developed for compliance to TB treatment. DOTS (Directly Observed Treatment, Short-Course) are a treatment program used for compliance with treatment of drug-sensitive TB. Another control program is DOTS-plus, which is developed for compliance with treatment of drug-resistant TB[20]. If not treated, active-

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TB can be fatal, killing up to 60% of patients. In 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease[19].

Mathematical models of transmission dynamics of TB is an important tool in analyzing the disease control as they provide short and long term prediction of TB incidence. Mathematical models may be helpful to improve our understanding of the major contributing factors to the epidemic. The dynamics of the transmission TB model have been addressed by researchers[1, 6, 8, 12]. These models assume that the recruitment rate is constant. In order to study disease dynamics for the model with more demographic effects, it should be assumed that the recruitment is density-dependent. Motivated by infectious diseases models in the literature[15, 17], we propose a new model to investigate the spread of TB infection in a population with the assumed that the recruitment rate is a logistic growth.

Studies of dynamic systems with optimal control theory to the epidemiological models such as malaria[4, 10], TB-HIV co-infection [2, 11] and also TB infection[1, 3, 5, 13, 21] have been done. For instance, the impact of optimal control on the model that describes the dynamics of the spread of TB by a factor of resistance to anti-TB drugs and also the migration of healthy sub-population in the two regions was depicted in [3]. The optimal control strategies associated with case holding and case finding based on a two-strain TB model was proposed in [13]. In [21], the authors used the optimal control strategies to minimize the cost of interventions, considering re-infection and post-exposure interventions. Recently, the optimal control of TB model with case detection and treatment was demonstrated in [5]. In this paper, we also applied the optimal control to the mathematical model of TB transmission with logistic growth human population. Our goal is to minimize the number of latent and infectious individual and the cost of implementing the optimal prevention and treatment controls of TB infection on the model.

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2 Model formulation

We consider the population dynamic of TB corresponding to logistic growth of human population is assumed homogeneous and closed. The total population density N is divided into four class, namely, the susceptible class (S), the latent class (L), infected with TB class (I), and the recovered with temporary immunity class (R). The growth rate constant and the carrying capacity of the environment corresponding to the human population are denoted by r and K respectively.

Natural mortality is proportional to the size of subpopulation with the rate μ. Additional mortality due to TB disease only affects the class I with the rate δ. Transmission of Mycobacterium TB occurs after adequate contact between vulnerable populations with the infected population. In each unit of time, susceptible individuals have an average contact βI that will be sufficient to transmit the disease. Thus the rate of the population is susceptible to latent infection βSI. The latently infected individuals progress to infectious class at rate α. The controls u_1 and u_2 represents the efforts of the TB prevention (vaccination) and the anti-TB treatment at rate a respectively. The natural recovery of the class I is denoted by γ. The immunity of the recovered class is lost at a rate of b per unit time. All parameters and variables used in the nonnegative value in order to have biological significance.

We use the transmission diagram as in Fig. 1 for deriving our model, where $N = S + L + I + R$.

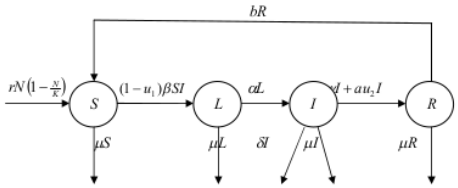

Fig. 1: Tuberculosis transmission diagram

2.1 TB model without controls

Based on the above assumption, the model of tuberculosis transmission with logistic growth human population without control variables is given as:

$$\begin{cases} \frac{dS}{dt} = rN\left(1-\frac{N}{K}\right) + bR - \beta SI - \mu S \\ \frac{dL}{dt} = \beta SI - (\mu+\alpha)L \\ \frac{dI}{dt} = \alpha L - (\delta+\mu+\gamma)I \\ \frac{dR}{dt} = \gamma I - (\mu+b)R. \end{cases} \tag{1}$$

Therefore, the change rate of the total population is given by following equation

$$\frac{dN}{dt} = rN\left(1-\frac{N}{K}\right) - \delta I - \mu N.$$

Since $N = S + L + I + R$ the model (1) can now be written as:

$$\begin{cases} \frac{dN}{dt} = rN\left(1-\frac{N}{K}\right) - \delta I - \mu N \\ \frac{dL}{dt} = \beta(N - L - I - R)I - (\mu+\alpha)L \\ \frac{dI}{dt} = \alpha L - (\delta+\mu+\gamma)I \\ \frac{dR}{dt} = \gamma I - (\mu+b)R \end{cases} \tag{2}$$

The region of biological interest of model (2) is $\Omega = \left\{(N,\ L,\ I, R) \in \Re_+^4\right\}$

Model (2) is well-posed in the non-negative region because the vector field on the boundary does not point to the exterior. So, if it is given an initial condition in the region, the solution is defined for all time $t \geq 0$ and remains in the region.

2.2 TB model with controls

The model (1) is now modified with control functions u_1 and u_2 as control for the system to reduce the spread of TB using logistic growth human population model. The TB model (1) becomes

$$\begin{cases} \frac{dS}{dt} = rN\left(1-\frac{N}{K}\right) + bR - (1-u_1)\beta SI - uS \\ \frac{dL}{dt} = (1-u_1)\beta SI - (u+\alpha)L \\ \frac{dI}{dt} = \alpha L - (\delta+u+\gamma+au_2)I \\ \frac{dR}{dt} = (\gamma+au_2)I - (u+b)R. \end{cases} \tag{3}$$

In this case, u describe the natural mortality.

The control functions u_1 and u_2 are defined on interval $[0, t_f]$, where $0 \leq u_i(t) \leq 1,\ t \in [0, t_f], i = 1, 2$, and t_f denotes the end time of the controls. Our goal is to minimize the number of individuals with latent and active tuberculosis infections and the cost of applying prevention and treatment controls as low as possible. For this, we consider the objective functional

$$J(u_1,\ u_2) = \int_0^{t_f} \left\{ L + I + \frac{1}{2}\, c_1 {u_1}^2 + \frac{1}{2}\, c_2 {u_2}^2 \right\} dt \tag{4}$$

where c_1 and c_2 are the weighting positive constants for TB prevention and anti-TB treatment efforts respectively. Here, we choose a quadratic cost on the controls for measuring the cost of epidemic controls[6, 13]. The term $c_1u_1^2$ and $c_2u_2^2$ describe the relative cost of interventions associated with TB prevention and anti-TB treatment controls respectively. Larger values of c_1 and c_2 will imply more expensive implementation cost for TB prevention and anti-TB treatment. We seek an optimal control u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = \min_{\Gamma} J(u_1, u_2) \tag{5}$$

where $\Gamma = \{u_i \,|0 \leq u_i \leq 1,\ i = 1, 2\}$.

3 Model analysis

In this section, we present the equilibrium and stability analysis of the model (2).

3.1 Equilibria of the model

The disease-free equilibrium of the model (2) is given by $E_0 = (N_0, 0, 0, 0)$ with $N_0 = \frac{K(r-u)}{r}$. The equilibrium E_0 exists if $r-u > 0$. The stability of this equilibrium will be investigated using the next generation operator [22]. Using the operator, we calculate the basic reproduction ratio R_0 of the model (2). It is given by

$$R_0 = \frac{\alpha\beta K(r-u)}{(u+\alpha)(\delta+u+\gamma)r}$$

This ratio describes the average number of new cases of an infection caused by one typical infected individual, in a population consisting of susceptible only[9].

The model (2) also has endemic equilibrium $E_1 = (N_1, L_1, I_1, R_1)$ where

$$\begin{aligned}
N_1 &= \tfrac{1}{R_0}\,\tfrac{K(r-u)}{r} + \left(\tfrac{\delta+u+\gamma}{\alpha} + 1 + \tfrac{\gamma}{u+b}\right) I_1,\\
L_1 &= \tfrac{\delta+u+\gamma}{\alpha} I_1,\\
R_1 &= \tfrac{\gamma}{u+b}\, I_1,\\
I_1 &= \tfrac{r}{\delta} N_1 \left(1 - \tfrac{N_1}{K}\right) - \tfrac{u}{\delta} N_1.
\end{aligned}$$

The equilibrium E_1 exist if $r-u > 0$ and $0 < N_1 < \frac{K(r-u)}{r}$.

3.2 Local stability analysis

Now, let us analyze the local stability of the equilibriums.

Theorem 1. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$.*

Proof. Linearizing model (2) near the equilibrium E_0 gives eigenvalues $-(r-u)$, $-(u+b)$ and the roots of quadratic equation $x^2 + a_1x + a_2 = 0$ where

$$\begin{aligned}
a_1 &= 2u + \alpha + \delta + \gamma,\\
a_2 &= (u+\alpha)(\delta+u+\gamma)(1-R_0).
\end{aligned}$$

We can see that based on the existence of the equilibrium E_0, the all eigenvalues are negative. While the quadratic equation has negative roots if $a_1 > 0$, $a_2 > 0$ or equivalently $R_0 < 1$.

Stability of the endemic equilibrium E_1 is not easy to confirm analytically because it is not really tractable mathematically. Numerically, the endemic equilibrium is locally asymptotically stable. This can be seen in Fig. 2. We use three different initial conditions for the simulation. Those orbits tend to a same point as time evolves.

Theorem 2. *The endemic equilibrium E_1 is locally asymptotically stable if $R_0 > 1$.*

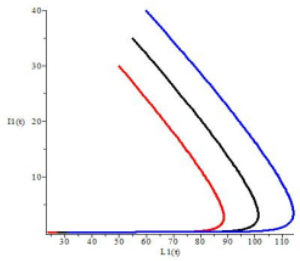

Fig. 2: Phase portrait of model (2) in $L-I$ plane

4 Analysis of optimal control

In this section, we analyze model (3), that is, model of the spread of TB in population using optimal control strategy. Consider the objective function (4) to model (3) as the state system. Necessary conditions to determine the optimal control u_1^* and u_2^* that satisfy the condition (5) with constraint model (3) will be solved by the Pontryagin's Maximum Principle[7]. This principle converts (3), (4) and (5) into a problem of minimizing pointwise a Hamiltonian H, with respect to (u_1, u_2), that is

$$\begin{aligned} H = {} & L + I + \tfrac{1}{2}\, c_1 {u_1}^2 + \tfrac{1}{2}\, c_2 {u_2}^2 + \lambda_1 \left(rN\left(1-\tfrac{N}{K}\right) + bR - (1-u_1)\beta SI - uS \right) \\ & + \lambda_2 \left((1-u_1)\,\beta SI - (u+\alpha)\, L \right) \\ & + \lambda_3 \left(\alpha L - (\delta + u + \gamma + a u_2)\, I \right) + \lambda_4 \left((\gamma + a u_2)\, I - (u+b)\, R \right). \end{aligned}$$

The variable λ_i, $i = 1,\ 2,\ 3,\ 4$, are called adjoint variables satisfying the following co-state equations TB model (1) becomes

$$\begin{aligned} \tfrac{d\lambda_1}{dt} &= \lambda_1 \left((1-u_1)\,\beta I + u \right) - \lambda_2 (1-u_1)\,\beta I \\ \tfrac{d\lambda_2}{dt} &= -1 + \lambda_2 (u+\alpha) - \lambda_3 \alpha \\ \tfrac{d\lambda_3}{dt} &= -1 + \lambda_1 (1-u_1)\,\beta S - \lambda_2 (1-u_1)\,\beta S + \lambda_3 (\delta + u + \gamma + a u_2) - \lambda_4 (\gamma + a u_2) \\ \tfrac{d\lambda_4}{dt} &= -\lambda_1 b + \lambda_4 (u+b) \end{aligned} \tag{6}$$

where the transversality conditions

$$\lambda_1(t_f) = 0, \quad \lambda_2(t_f) = 0, \quad \lambda_3(t_f) = 0, \quad \lambda_4(t_f) = 0$$

.

By applying Pontryagin's Maximum Principle and the existence result for the optimal control pairs[14, 16], we obtain the following theorem.

Theorem 3. *The optimal control pair (u_1^*, u_2^*) that minimizes $J(u_1, u_2)$ over Γ is given by*

$$u_1^* = \min\left\{ \max\left\{ 0,\ \frac{\beta SI}{c_1}\,(\lambda_2 - \lambda_1) \right\},\ 1 \right\} \tag{7}$$

$$u_2^* = \min\left\{ \max\left\{ 0,\ \frac{aI}{c_2}\,(\lambda_3 - \lambda_4) \right\},\ 1 \right\}. \tag{8}$$

where λ_i, $i = 1,\ 2,\ 3,\ 4$, is the solution of the co-state equation (6) with the transversality conditions $\lambda_1(t_f) = 0, \quad \lambda_2(t_f) = 0, \quad \lambda_3(t_f) = 0, \quad \lambda_4(t_f) = 0$.

Proof. Using the result of Pontryagins Maximum Principle, there exist adjoint variables satisfying

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S},\ \lambda_1(t_f) = 0, \ldots, \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial R},\ \lambda_4(t_f) = 0$$

.

The optimal control (u_1, u_2) can be solve from the optimality condition,

$$\frac{\partial H}{\partial u_1} = 0, \ \frac{\partial H}{\partial u_2} = 0,$$

and we have

$$0 = \frac{\partial H}{\partial u_1} = c_1 u_1 + (\lambda_1 - \lambda_2)\,\beta SI$$
$$0 = \frac{\partial H}{\partial u_2} = c_2 u_2 + (\lambda_4 - \lambda_3)\,aI.$$

Hence, we obtain

$$\mu_1^* = \frac{\beta SI}{c_1}(\lambda_2 - \lambda_1), u_2^* = \frac{aI}{c_2}(\lambda_3 - \lambda_4)$$

Then, by the bounds on the controls, it is easy to obtain and in the form (7) and (8) respectively.

Next we discuss the numerical solutions of the optimality system. The optimality system is the state and adjoint systems coupled with the optimal control characterization.

5 Numerical simulation

In this section, we present the numerical simulations of model (3) with and without optimal control. An iterative scheme is used for solving the optimality system. We start to solve the state equations by the forward Runge-Kutta method of order 4. Then we use the backward Runge-Kutta method of order 4 to solve the co-state equations with the transversality conditions. Finally, the controls are updated by using a convex combination of the previous controls and the value from the characterizations for u_1^* and u_2^*. This iterative process is stopped when current state, co-state and control values converge sufficiently[14].

Three scenarios of the control strategies are explored. In the first scenarios, we consider only the TB preventive treatment (control u_1^* alone). In the second scenario, we use only the anti-TB treatment (control u_2^* alone). Finally, we implement the combination of the TB preventive and anti-TB treatments (controls u_1^* and u_2^*). The numerical parameters are shown in Table 1. In these simulations, we use initial condition $(S(0), L(0), I(0), R(0)) = (500,\ 50,\ 30,\ 20)$, weighting constants $c_1 = c_2 = 50$ and the carrying capacity $K = 100000$.

Table 1: Parameters values for simulations

Parameter	Value	Ref.	Parameter	Value	Ref.
r	0.02	assumed	α	0.00023	[12]
b	0.08182	assumed	γ	0.2	[5]
β	0.001	[12]	δ	0.0575	[12]
u	0.0154	[3]	α	2	[5]

5.1 First scenario

For this scenario, the TB preventive treatment (u_1^*) is used to optimize the objective function J while we set the anti-TB treatment control u_2^* to zero. The profile of the optimal prevention control u_1^* could be seen in Fig. 3. To eradicate the TB infected in 10 years, the prevention control should be given intensively almost 6 years before dropping to the lower bound in the end of 10th year.

The dynamic of the latent and infected TB populations of this scenario are given in Fig. 4. We observe in the left of Fig. 4, that the control strategy decreases the number of latent population significantly compared with the case without control. On the contrary, the result in the right of Fig. 4 shows that there is no significant difference in the number of TB infected populations with and without control. This may be due to the absence of the anti-TB treatment against TB infection.

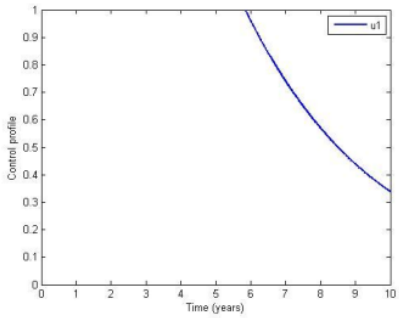

Fig. 3: The profile of the optimal prevention control u_1^*

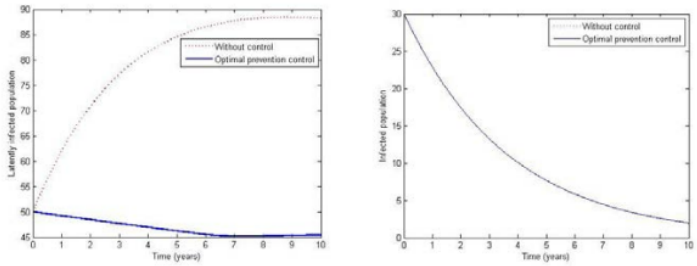

Fig. 4: The dynamic of latent and infected populations using control u_1^*

5.2 Second scenario

For the second scenario, we set the prevention control u_1^* to zero and use only the anti-TB treatment control u_2^* to optimize the objective function J. The control profile of anti-TB treatment is shown in Fig. 5. We see that, to reduce the TB infection in 10 years, the anti-TB treatment should be given intensively in almost one year before dropping gradually to lower bound at the end 10th year. The Fig. 6 are showing the effects of the optimal anti-TB treatment strategy on the latent and infected TB populations respectively. From these figures it can be observed that the optimal anti-TB treatment control has positive impact on decreasing the number of latent and infected TB populations compared to numbers without control.

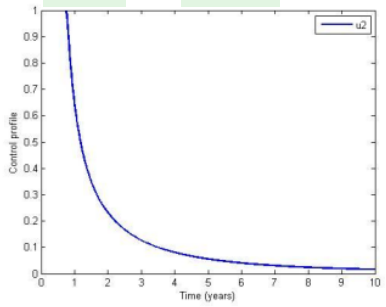

Fig. 5: The profile of the optimal treatment control u_2^*

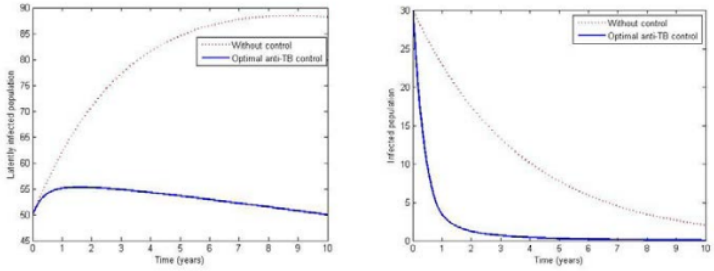

Fig. 6: The dynamic of latent and infected populations using control u_2^*

5.3 Third scenario

For this scenario, we use all two controls u_1^* and u_2^* to optimize the objective function J. The profile of the optimal controls u_1^* and u_2^* of this scenario is in Fig. 7. To reduce TB cases in 10 years, the preventive and anti-TB treatment controls should give full effort in the beginning of the TB disease spread and then the effort can be smoothly reduced after one and the middle year respectively. We observed in Fig. 8 that the optimal control strategies resulted in a decrease in the numbers of latent L and infected I populations compared to the numbers without control. This scenario shows that the combination of the prevention and anti-TB treatment controls the most effectively to minimize the number of the latent and infected TB populations.

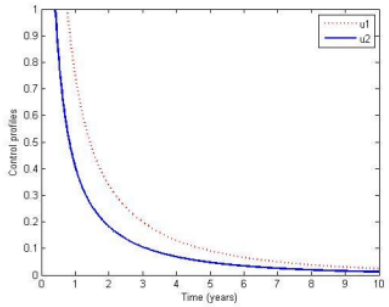

Fig. 7: The profile of the optimal controls u_1^* and u_2^*

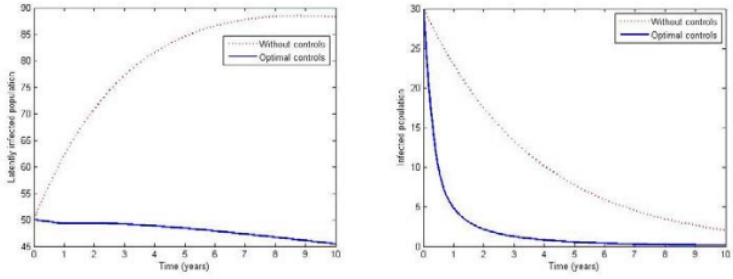

Fig. 8: The dynamic of latent and infected populations using controls u_1^* and u_2^*

Numerical simulations of the model suggest that if we have to use only one control, then the anti-TB treatment strategy is more effective than TB prevention.

6 Conclusion

In this paper, we have devoted a deterministic model of tuberculosis transmission considering logistically growing human population. The model also incorporates TB prevention and anti-TB treatment efforts as control strategies to reduce the spread of the disease. For the model without controls, we obtain the basic reproduction number R_0 which determines the stability of the equilibriums of the model. The disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and the endemic equilibrium is tend to locally asymptotically stable if $R_0 > 1$. Using the Pontryagin Maximum Principle, the optimal control theory is then derived analytically. Numerical simulations of the control model (3) showed that the control strategy of the TB prevention only has positive impact on decreasing the number of latent TB populations. On the contrary, there is no significant difference in the number of TB infected populations with and without control using the TB prevention only. This may be due to the absence of the anti-TB treatment against TB infection. The simulation results of the optimal control indicate that the combination TB prevention and anti-TB treatment give better result in term minimizing the number of the latent and infected populations. The numerical analysis also indicates that the anti-TB treatment strategy is more effective than TB prevention if we use only one control strategy.

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