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Optimal Control Strategy of a Tuberculosis Epidemic Model with Drug Resistant TB

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Abstract: **In *this paper, we present an optimal control approach for a Susceptible-Exposed-Infected- Recovered (SEIR) epidemic model of tuberculosis disease. Seeking to reduce the infected group, we use a control representing drug-resistant TB. Pontryagin's maximum principle is used to characterize the optimal control. Numerical simulations solved to show the effectiveness of the optimal approach.***

Keywords: SEIR epidemic models, optimal control, Pontryagin's maximum principle, numerical simulations.

1. Introduction

Epidemiology is the science of public health; the relationship between mathematics and epidemiology has continually increased. For the mathematician it provides new and exciting branches, while for the epidemiologist, mathematical modeling offers an important research tool in the study of the evolution of diseases.

The first mathematical model of an infectious disease was proposed by Daniel Bernoulli, a Swiss Mathematician and Physicist. In 1760, Daniel Bernoulli developed a differential equation model to quantitatively analyze how cowpox inoculation affects the spread of smallpox [8]. Theoretical papers by Kermack and McKendrinck, between 1927 and 1933 about infectious disease models, have had a great influence in the development of mathematical epidemiology models. Mathematical models are being increasingly used to elucidate the transmission of several diseases. These models, usually based on compartment models, may be rather simple, but studying them is crucial in gaining important knowledge of the underlying aspects of the infectious diseases spread out, and to evaluate the potential impact of control programs in reducing morbidity and mortality [12].

One of the transmissible disease that was studied in works we have Tuberculosis (TB): it's a disease bacterial found in about one third of the world human population, caused by various strains of Mycobacteria. Specifically, Mycobacterium tuberculosis. TB primarily affects the lungs, but it can also affect organs in the central nervous system, lymphatic system, and circulatory system among others.

World Health Organization (WHO) declared TB as global epidemic in 1993. Tuberculosis is a contagious disease that spreads like the common cold [14]. Active tuberculosis develops primarily in people with weakened immune systems, especially in people with HIV. TB is also more common among men than women, and affects mostly adults in the economically productive age groups; arounds two-thirds of cases are estimated to occur among people aged 15-59 years.

The infection can remain in an inactive (dormant) state for years without causing symptoms or spreading to other people. When a patient immune system with dormant TB is weakened, the TB can become active (reactivate) and cause infection in the lungs or other parts of the body. The risk factors for acquiring TB include close- contact situations, alcohol and drug abuse, and certain diseases (such as diabetes, cancer, and HIV) and occupations (such as health-care workers). The most common symptoms and signs of TB are fatigue, fever, weight loss, cough, and night sweat. The diagnosis of TB involves skin tests, chest X-rays, sputum analysis (smear and culture), and Polymerase Chain Reaction (PCR) tests to detect the genetic material of the causative bacteria. Antibiotics such as isoniazid (INH) maybe used to treat inactive (dormant) TB to prevent the TB infection from becoming active. Combining INH with one or more of several drugs, including rifampicin (Rifadin), ethambutol (Myambutol), pyrazinamide, and streptomycin can usually successfully treat active TB. Drug-resistant TB is a serious, as yet unsolved, public-health problem, especially in south-east Asia, the countries of the former Soviet Union, Africa, and in prison populations.

Given an optimal control approach, it produces valuable theoretical results, which can be used to suggest or design epidemic control programs. Having as aim a goal (or goals), various objective criteria may be adopted [17]. Although the implementation of the control policies, suggested by the mathematical analysis, can be difficult, they can be a support for the public health authorities and simulation of optimal control problems applied to mathematical models may become a powerful tool in their hands (see [17] and references cited therein).

The paper is organized as follows. In Section 2 mathematical models for TB dynamic is presented without control in first time, the model with control is introduced in second paragraph to form the control system of the optimal control problems on TB epidemics under consideration. It's in section 3, where we explain how to obtain the analytic expression for the optimal controls, using the Pontryagin maximum principle [2]. In Section 4, we recall the numerical methods used to compute the optimal controls and associated

dynamics, presented with illustrations derived from the Matlab graphs program. The conclusions, derived from the numerical simulations, are resumed in section5.

2. Mathematical Model

As any infection disease model, the total population is divided into epidemiological subgroups, we consider in this model, four disease-state compartments: susceptible individuals (S), people who can catch the disease; exposed individuals (E) are people who have come into contact with the disease but are not yet infective or infectious, infective individuals (I), people who have the disease and can transmit the disease; recovered individuals (R) people who have recovered from the disease. We assume that an individual can be infected only through contacts with infectious individuals and that immunity is permanent. The parameters used in the model considered are identified by:

- β is the rate of contact. It is defined as the average number of effective contacts with other individuals (susceptible) per infective unit time;
- ε is the rate at which the exposed individuals become infective or infectious;
- γ is the rate at which the infectious individuals recover per unit time;
- μ is the birth and death rate.

We consider the tuberculosis model developed by I.K. Dontwi1 [1]. The dynamics of the model are governed by the following system of differential equations subject to non-negative initial conditions

$$\begin{cases} \dfrac{dS}{dt} = \mu N - \mu S - \beta \dfrac{SI}{N} \\ \dfrac{dE}{dt} = \beta \dfrac{SI}{N} - (\mu + \varepsilon)E \\ \dfrac{dI}{dt} = \varepsilon E - (\mu + \gamma)I \\ \dfrac{dR}{dt} = \gamma I - \mu R \end{cases} \quad (1)$$

We also denote by N (t) the total number individuals at time t and is given by

$$N(t) = S(t) + E(t) + I(t) + R(t)$$

As mechanism of control, we use treatment of the infected individuals. We represent this action by a control u into the model (1) that for mathematical reason is taken as Lebesgue measurable function. The control u represents the rate at which infectious individuals are treated at each time period.

We assume that all infected individuals that we treat are transfered directly to the removed class. The mathematical system with control is given by the nonlinear differential equations

$$\begin{cases} \dfrac{dS}{dt} = \mu N - \mu S - \beta \dfrac{SI}{N} \\ \dfrac{dE}{dt} = \beta \dfrac{SI}{N} - (\mu + \varepsilon)E \\ \dfrac{dI}{dt} = \varepsilon E - (\mu + \gamma)I - uI \\ \dfrac{dR}{dt} = \gamma I - \mu R + uI \end{cases} \quad (2)$$

With $S(0) \geq 0$, $I(0) \geq 0$, $E(0) \geq 0$, and $R(0) \geq 0$ are given.

3. Optimal Control Problem

Our goal in this optimal control problem is to find the best strategy in terms of efforts in treatment that would minimize the number of people who die from Tuberculosis while at the same time minimizing the cost of treatment of the population, considering the initial population sizes of all four classes, S(0), E(0) , I(0) and R(0) given. Naturally, there are various ways of expressing such a goal mathematically. In this paper, for a fixed terminal time t_f, we consider the following objective function:

$$J(u) = \int_0^{t_f} (I(t) + \frac{A}{2}u^2(t))dt \quad (3)$$

Where A>0 represents the weight constant of the control and time respectively. We seek an optimal control u^* such that

$$J(u^*) = \min\{J(u) : u \hat{\imath} U\} \quad (4)$$

Where U is the set of admissible controls defined by

$$U = \{u(t) : 0 \leq u \leq 1, t \in [0, t_f]\}$$

With u is measurable.

Pontryagin's Maximum Principal converts (2), (3) and (4) into a problem of minimizing a Hamiltonian, defined by

$$H = I + \frac{A}{2}u^2 + \sum_{i=1}^{4} \lambda_i f_i \quad (5)$$

Where f_i is the right side of the differential equation of the i^{th} state variable.

By applying the Pontryagin's maximum principle [2], we obtain the following theorem:

Theorem 1 Given an optimal control u^* an optimal terminal time t_f, and solutions S^*, I^*, E^* and R^* of the corresponding state system, there exists an adjoint vector $\lambda = [\lambda_1, \lambda_2, \lambda_3, \lambda_4]$ satisfying

$$\dot{\lambda}_1 = (\lambda_1 - \lambda_2)\beta\frac{I}{N} + \lambda_1\mu$$

$$\dot{\lambda}_2 = \lambda_2\mu + (\lambda_2 - \lambda_3)\varepsilon$$

$$\dot{\lambda}_3 = (\lambda_1 - \lambda_2)\beta\frac{S}{N} + \lambda_3\mu + (\lambda_3 - \lambda_4)\gamma + (\lambda_3 - \lambda_4)u - 1$$

$$\dot{\lambda}_4 = \lambda_4\mu$$

With the transversality conditions

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

Furthermore, the optimal control u^* is given by

$$u^* = \min(1, \max(0, \frac{(\lambda_3 - \lambda_4)I^*}{A})) \quad (6)$$

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle such that

$$\begin{cases} \dot{\lambda}_1 = -\frac{\partial H}{\partial S}, \lambda_1(t_f) = 0 \\ \dot{\lambda}_2 = -\frac{\partial H}{\partial E}, \lambda_2(t_f) = 0 \\ \dot{\lambda}_3 = -\frac{\partial H}{\partial I}, \lambda_3(t_f) = 0 \\ \dot{\lambda}_4 = -\frac{\partial H}{\partial R}, \lambda_4(t_f) = 0 \end{cases}$$

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

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

that is

$$\frac{\partial H}{\partial u} = Au - \lambda_3 I + \lambda_4 I = 0$$

By the bounds in the control U, it is easy to obtain u^* in the form of (6).

4. Numerical Simulations

The optimality system is solved using an iterative method [16]. 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 $t_n = t_f$, [11]. Next, we define the state and adjoint variables $S(t), E(t), I(t), R(t), \lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t)$; And the control $u(t)$.

In addition, the algorithm we used proceeds as follows:

Algorithm 2

- Choose initial guess of the state variables, the adjoint variables and the control;
- Forward solving of the state system;
- Backward solving of the adjoint system;
- Update the control using the characterization (6);

The following parameters and initial values are used for the simulation, which we have taken from [1]:

The period of the treatment efforts is 250 days

- Initial conditions:
  $S(0) = 300, E(0) = 400, I(0) = 12, R(0) = 2$
- Parameter values:

$\mu = 0,00875 \quad \gamma = 0,5 \quad \varepsilon = 0,1666 \quad \beta = 0,5853$

- The weight constant of the control: $A = 100$

In figure 1, we remark that in absence of treatment the number I of infectious individuals with Tuberculosis increases in the first 50 days to grow highly after.

Whereas, in presence of treatment, the number I of individuals infectious decreases from the first day, in addition the number of individuals I infectious with TB at the final time $t_f = 250$ days is 1400 infection in the case without control and 0 infection with control.

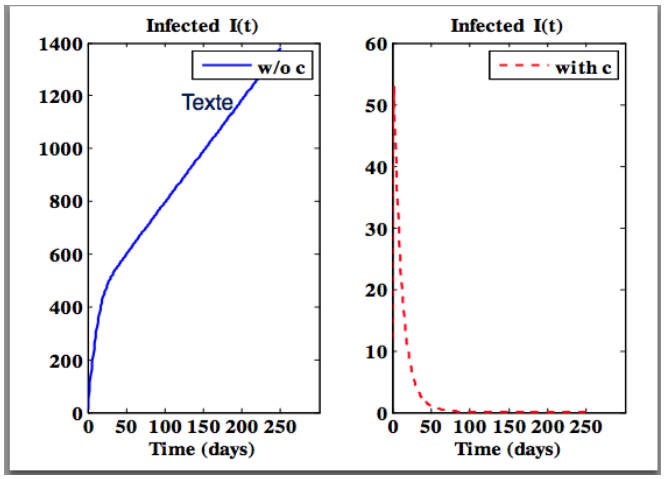

Figure 1: The infected group with and without control

Figure 2, gives a representation of the optimal control u^* for the treatment representing the effort to treat actively infected individuals with drug-resistant TB, in order to reduce the number of infected individual.

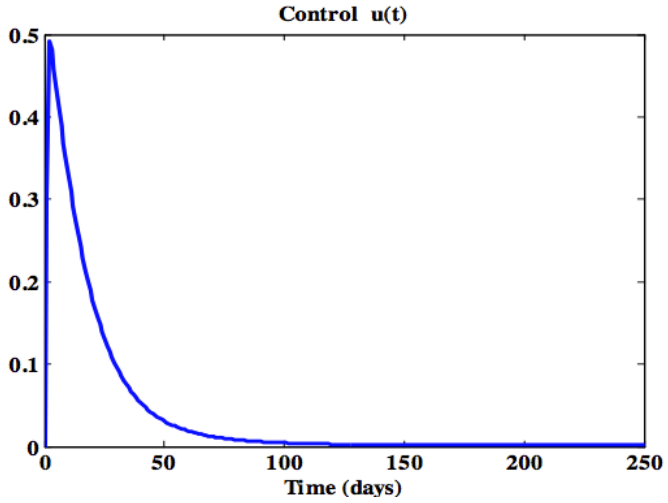

Figure 2: The control u^*

5. Conclusion

In search for the possible way of eradicating tuberculosis, there is the need to address the issue of the mechanism of the transmission of the disease. Many communicable diseases as Tuberculosis have been modeled using differential equations. The purpose of this work was to give an optimal control strategy considering a treatment program in order to reduce tuberculosis infections because there is a need to detect new cases as early as possible so as to provide early treatment for the disease. In our work, a control has been introduced in our state system representing drug-resistant TB with aim to minimize the number of infectious individuals. The numerical simulations show that this implementation of the control has a positive impact on the reduction of infectious individuals, which confirm the effectiveness of the approach.

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