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Optimal control of tuberculosis with case detection and treatment

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Abstract. It is well known that the treatment is an effective way to control the transmission of an infectious disease and any delay in treatment can lead to many new infections. Hence, it is important to identify the infectives at early stages and to provide proper treatment. Since the disease TB has a long latent period, the early case detection of TB plays a critical role in reducing the transmission of the disease. This paper presents an optimal control problem using the case detection strategy to reduce the transmission of tuberculosis. A non-linear S-E-I-R mathematical model for tuberculosis is considered for the analysis. The optimal control theory is applied to the model by assuming the case detection parameter as time dependent. The optimality of the system is deduced analytically and solved numerically. The effectiveness of optimal control is exhibited by comparing the levels of exposed and infected populations with and without optimal control. It has been observed that the optimal control strategy gives better result in terms of minimizing the number of infectives.

Keywords: tuberculosis, case detection, optimal control, treatment

1 Introduction

Infectious diseases are major cause of concern world-wide as they affect both humans and animals. They cause significant level of financial losses and loss of human lives and animal stock every year. These losses seriously impact the economic growth, more so in case of the developing countries. The 'Tubercle Bacillus (TB)' is second most fatalistic human killer disease after the 'Human Immunodeficiency Virus (HIV)'/'Acquired Immunodeficiency Syndrome (AIDS)', in the developing countries, and as per current available data it causes millions of death every year[1].

The eradication of the disease is not easy as there are several factors which are hindering the success of control policies, e.g. the difficulty of developing an effective vaccine, the expensive and time-consuming diagnostic process, and the necessity of many months of expensive treatments with potential harmful side effects, etc. In a developing country like India, there are many unreported cases of TB and the people in general have a tendency to avoid visiting medical practitioner until it becomes intolerable and/or unavoidable. This delay causes an increase in the infection prevalence of this disease. As the TB has a long latency period, early case detection can reduce the risk of transmission of this disease to others. Hence, there is a need of obtaining the cost-effective optimal case detection strategy to minimize the number of infectives. This paper is motivated by this idea.

The mathematical modeling is an important tool for analyzing the transmission and control of any infectious disease. The evolution of disease, control strategies and efficacy of drugs, etc., can be analyzed using mathematical models. There exist several research works in which the simple compartment models for different infectious diseases have been proposed and analyzed and in some of them optimal control technique has been incorporated. The case detection and its effectiveness in the dynamics of TB are discussed in [2].

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In [3], the optimal control theory is applied to a two-strain tuberculosis model to reduce the latent and infectious groups with the resistant-strain tuberculosis. Here the authors used optimal control theory where control parameters were involved in treatment. Recently, in [4] optimal parameters for the mathematical model of tuberculosis are obtained by using tuberculosis data of China from January 2005 to December 2012. Here authors also obtained the effective basic reproduction numbers. In [5], the optimal control strategies of a 'Susceptible Infected Recovered (SIR)' epidemic model with time delay was discussed by using the treatment as control parameter and the authors used optimal control approach to minimize the probability of infection transmission and to maximize the total number of susceptible and recovered individuals. A simple epidemic model with vaccination and treatment is analyzed in [6] where authors focused on incorporation of non-linear force of infection and two types of controls: an imperfect preventive vaccine and therapeutic treatment. Effect of optimal control on HIV/AIDS is depicted in [7]. The impact of optimal control on a model of biological control of malaria is demonstrated in [8, 9]. In [10] a tuberculosis model is considered and analyzed using optimal control theory by introducing control terms on the chemoprophylaxis and detection to reduce the number of individuals infected with active TB. Epidemic models for vector-borne diseases are formulated and analyzed by introducing optimal control in [11–14]. An optimal control parameter representing the effort that prevents the exogenous reinfection of tuberculosis in order to reduce the contact between the infectious and exposed individuals is used in [15]. Recently, in [16] a TB and HIV/AIDS co-infection model is studied by incorporating nine control parameters. Similarly, a co-infection model of malaria and cholera diseases is analyzed in [17] by considering different types of controls. An optimal control model for TB with 3 supporting controls corresponding to reduction in the transmission rate, decrease in the treatment failure rate and increase in the screening and treatment rate had been depicted in [18]. A mathematical model for tuberculosis incorporating both frequency dependent and density dependent force of infection for TB transmission is studied in [19]. Here authors also considered optimal control of tuberculosis through diagnosis campaign, education and chemoprophylaxis of latently infected. Impact of reinfection in the transmission dynamics of tuberculosis in Korea is investigated in [20]. Here authors found that the case finding effort is the most significant component in the reduction of active tuberculosis cases.

A tuberculosis model with the effects of case detection and treatment has been presented in [21] and the authors have considered the case detection as a constant (fixed) parameter.

However, in reality it is observed that it varies with time depending upon severity of the disease and the region under consideration. Hence, there should be proper health network covering whole population under consideration irrespective of their class, color, creed, ethnic race, and religion, etc. Unfortunately, in developing countries, the population who lives in slum areas does not have access to proper health centers. In general they are delayed in approaching the medical practitioner even when they are seriously infected and sick. Though, in case of an outbreak of any epidemic, health authority are expected to provide additional support to stop the transmission of the disease, but it rarely happens well in time in developing countries. This support can be in terms of number of beds, number of doctors, and number of diagnostic centers, etc.. The case detection is an important parameter which is essential to control the transmission of any infectious disease and to provide proper treatment to infectious individuals.

Our proposed model focuses on this aspect and in our model this parameter is made time dependent. This can help the health policy makers to target the elimination of TB from the population under consideration in fixed duration of time depending upon the cost of control. In our present work we have tried to project the optimal case detection strategy so that the number of TB infectives can be minimized. In the earlier works, mostly optimal control parameters were associated with treatment. But in our model treatment comes after detection. Additionally, in our model, the case detection is helping in reducing the transmission of the disease as we assume that the transmission due to detected group of individuals is less compared to the transmission due to undetected group of individuals. So we take our case detection parameter as an optimal control parameter and analyze the optimal control model using the well known Pontryagin's maximum principle[22].

The remaining of this paper is organized: Section 2 describes the basic model; Section 3 presents the optimal control problem; Section 4 discusses the numerical simulation and results; and finally Section 5 concludes the paper.

2 The model

We consider an SEIR model studied in [21] and apply optimal control theory to it. Here we consider the case detection parameter η which represents the fraction of infected individuals that are detected as the control parameter. It is assumed that the rate of transmission of tuberculosis in group of detected infectives will be much less than the rate of transmission in group of undetected infectives. Here $S(t)$, $E(t)$, $I(t)$ and $R(t)$ are the fractions of the susceptible individuals, the exposed (latent) individuals, the TB infectious individuals and the treated/recovered individuals in the population, respectively, at time t. It is assumed that the total population is varying and homogeneously mixed, i.e., all people are equally likely to be infected by the infectious individuals in a case of contact. The mathematical model discussed in [21] is given below:

$$\begin{aligned}
\frac{dS}{dt} &= A - dS - [\alpha_1\eta + \alpha_2(1-\eta)]IS, \\
\frac{dE}{dt} &= (1-p)[\alpha_1\eta + \alpha_2(1-\eta)]IS - \beta EI - (d+\nu_1+\theta)E, \\
\frac{dI}{dt} &= p[\alpha_1\eta + \alpha_2(1-\eta)]IS + \beta EI - (d+d_1+\nu_2\eta)I + \theta E, \\
\frac{dR}{dt} &= \nu_1 E\nu_2\eta I - dR.
\end{aligned} \tag{1}$$

The parameters used in the model (1) are described in Tab. 1. For more details one can refer [21], however

Table 1. Description of parameters

Parameter	Description
A	Recruitment rate
d	Natural death rate
η	Fraction of total TB infected individuals who are detected
α_1	Rate of transmission (detected)
α_2	Rate of transmission (undetected)
p	Rate of fast progression to infection
β	Contact rate b/w E and I
θ	Rate of progression to I from E
$\nu_1,\ \nu_2$	Recovery rates due to treatment
d_1	Death rate due to infection

for the completeness of this paper some basic results of [21] are extracted below. The model (1) is simplified as follows:

$$\begin{aligned}
\frac{dS}{dt} &= A - dS - k_1IS, \\
\frac{dE}{dt} &= (1-p)k_1IS - \beta EI - k_2E, \\
\frac{dI}{dt} &= pk_1IS + \beta EI - k_3I + \theta E, \\
\frac{dR}{dt} &= \nu_1E + \nu_2\eta I - dR,
\end{aligned} \tag{2}$$

where $k_1 = (\alpha_1 - \alpha_2)\eta + \alpha_2,\ k_2 = (d+\nu_1+\theta),\ k_3 = (d+d_1+\nu_2\eta)$. The basic reproduction number for this model is computed as

$$\mathcal{R}_0 = \frac{[(1-p)\theta + pk_2]k_1A}{dk_2k_3}.$$

This system has two types of equilibria, namely the disease-free equilibrium $E_0 = (S^0, E^0, I^0, R^0) = \left(\frac{A}{d}, 0, 0, 0\right)$, and the endemic equilibrium

$$E = (S^*, E^*, I^*, R^*) = \left(\frac{A}{d + k_1 I^*}, \frac{(1-p)k_1 I^* S^*}{\beta I^* + k_2}, I^*, \frac{\nu_1 E^* + \nu_2 \eta I^*}{d} \right),$$

where I^* is given by the roots of the following quadratic equation which is obtained in [21] as Eq. (4),

$$\beta k_1 k_3 I^{*2} + \beta d k_3 + (k_1 k_2 k_3 - \beta k_1 A) I^* + d k_2 k_3 (1 - \mathcal{R}_0) = 0.$$

In [21], it is shown that the model has unique endemic equilibrium for $\mathcal{R}_0 > 1$. For $\mathcal{R}_0 < 1$, there is a possibility of backward bifurcation depending upon the choice of parameters and this leads to existence of two endemic equilibria corresponding to the two distinct positive roots of the last quadratic equation in I^*.

3 Optimal control problem

The main aim of mathematical modelling of infectious diseases is to reduce the infection prevalence in the population under consideration. Application of optimal control theory to epidemiological modelling has emerged as a potential tool to achieve this goal. It helps in minimizing the total number of infectives over a finite time interval at a minimal cost of effort. In the basic tuberculosis model analyzed in [21] and described in previous section, authors have considered the case detection parameter as constant. But practically, one can achieve greater success in reducing the infection prevalence if this parameter becomes time dependent. So here we make our case detection parameter as time dependent parameter by applying optimal control theory. From this analysis we will come to know what percentage of population should be detected as time evolves, to minimize the number of infectives and the cost of implementing the strategy. We shall use Pontryagin's Maximum Principle (see [23–25]) to achieve our goal. The optimal control system with the objective functional are given below:

$$\begin{aligned} \frac{dS}{dt} &= A - dS - k_1 IS, \\ \frac{dE}{dt} &= (1-p)k_1 IS - \beta EI - k_2 E, \\ \frac{dI}{dt} &= p k_1 IS + \beta EI - k_3 I + \theta E, \\ \frac{dR}{dt} &= \nu_1 E + \nu_2 \eta I - dR, \end{aligned} \tag{3}$$

where $k_1 = (\alpha_1 - \alpha_2)\eta(t) + \alpha_2,\ k_2 = (d + \nu_1 + \theta),\ k_3 = d + d_1 + \nu_2 \eta(t)$. Here $\eta(t)$ models the fraction of infected individuals getting detected per unit time.

We formulate an optimal control problem with the objective (cost) functional given by

$$J = \int_0^T \left(C_1 E + C_2 I + \frac{1}{2} C_3 (I\eta)^2 \right) dt. \tag{4}$$

subject to the state system given by (3).

Our objective is to find a control η^* such that $J(\eta^*) = \min_{\eta \in \Omega} J(\eta)$, where Ω = $\{\eta$: measurable and $0 \leq \eta(t) \leq 1$ for $t \in [0, T]\}$ is the set for the controls.

Here, the value $\eta(t) = 1$ represents the maximal control of detection and the quantities $C_1,\ C_2$ represent, respectively, the weight constants. The term $C_3(I\eta)^2$ describes the cost associated with case detection control of TB infectives.

The Lagrangian of this problem is given by

$$L(E, I, \eta) = C_1 E + C_2 I + \frac{1}{2} C_3 (I\eta)^2. \tag{5}$$

Next we form the Hamiltonian H for our problem as follows:

$$H = L(E, I, \eta) + \lambda_1 \tfrac{dS}{dt} + \lambda_2 \tfrac{dE}{dt} + \lambda_3 \tfrac{dI}{dt} + \lambda_4 \tfrac{dR}{dt}, \tag{6}$$

where λ_i, $i = 1,\ 2,\ 3,\ 4$ are the adjoint variables or the co-state variables and can be determined by solving the following system of differential equations:

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial H}{\partial S} = \lambda_1[d + k_1 I] - \lambda_2[(1-p)k_1 I] - \lambda_3 p k_1 I, \\
\frac{d\lambda_2}{dt} &= -\frac{\partial H}{\partial E} = -C_1 + \lambda_2[\beta I + k_2] - \lambda_3[\beta I + \theta] - \lambda_4 \nu_1, \\
\frac{d\lambda_3}{dt} &= -\frac{\partial H}{\partial I} = -C_2 - C_3 I \eta^2 + \lambda_1 k_1 S - \lambda_2[(1-p)k_1 S - \beta E] \\
&\qquad - \lambda_3[p k_1 S + \beta E - k_3] - \lambda_4 \nu_2 \eta, \\
\frac{d\lambda_4}{dt} &= -\frac{\partial H}{\partial R} = \lambda_4 d,
\end{aligned} \tag{7}$$

satisfying the transversality condition

$$\lambda_i(T) = 0, \quad \text{for} \quad i = 1, 2, \cdots, 4.$$

Let S^*, E^*, I^* and R^* be the solution of the corresponding state system (3). Also let $\{\tilde{\lambda}_1, \tilde{\lambda}_2, \tilde{\lambda}_3, \tilde{\lambda}_4\}$ be the solutions of the system (7).

Following [26] we now state and prove the following theorem.

Theorem 1. *There exists an optimal control $\eta^* \in \Omega$ such that*

$$J(\eta^*) = \min_{\eta \in \Omega} J(\eta)$$

subject to the system (3).

Proof. We use the result by Lukes[26] to prove this theorem. Here the control and the state variables are non-negative. The necessary convexity of the objective functional in η is satisfied for this minimizing problem. The control variable set $\{\eta \in \Omega\}$ is also convex and closed by definition. The system (3) with control parameter applied (i.e. values of state variables at the optimal control parameter η) is bounded which determines the compactness needed for the existence of the optimal control. This completes the proof of this theorem.

Since there exists an optimal control for minimizing the functional subject to Eqs. (3) and (7), we use Pontryagin's Maximum Principle to derive the necessary conditions to find the optimal solution as follows: If (x, u) is an optimal solution of an optimal control problem, then there exists a non trivial vector function $\lambda = (\lambda_1, \lambda_2, \cdots, \lambda_n)$ satisfying the following equalities.

$$\begin{aligned}
\frac{dx}{dt} &= \frac{\partial H(t, x, u, \lambda)}{\partial \lambda}, \\
\frac{d\lambda}{dt} &= -\frac{\partial H(t, x, u, \lambda)}{\partial x}.
\end{aligned} \tag{8}$$

With the help of Pontryagin's Maximum Principle [22] and the theorem (1) we now state and prove the following theorem.

Theorem 2. *The optimal control (η^*) which minimizes J over the region Ω given by*

$$\eta^* = \max\{0, \min(\tilde{\eta}, 1)\}$$

where

$$\tilde{\eta} = \frac{(\alpha_2 - \alpha_1) S^*[(1-p)\tilde{\lambda}_2 + p\tilde{\lambda}_3 - \tilde{\lambda}_1] + (\tilde{\lambda}_3 - \tilde{\lambda}_4)\nu_2}{C_3\, I^*}.$$

Proof. Using the optimality condition i.e.

$$\frac{\partial H}{\partial \eta} = 0,$$

we get

$$(I^*)^2 \tilde{\eta} = \frac{(\alpha_2 - \alpha_1) I^* S^*[(1-p)\tilde{\lambda}_2 + p\tilde{\lambda}_3 - \tilde{\lambda}_1] + (\tilde{\lambda}_3 - \tilde{\lambda}_4)\nu_2 I^*}{C_3},$$

and

$$\tilde{\eta} = \frac{(\alpha_2 - \alpha_1)S^*[(1-p)\tilde{\lambda}_2 + p\tilde{\lambda}_3 - \tilde{\lambda}_1] + (\tilde{\lambda}_3 - \tilde{\lambda}_4)\nu_2}{C_3\, I^*}.$$

Again this control is bounded and the upper and the lower bounds are respectively 0 and 1 i.e. $\eta = 0$ if $\tilde{\eta} < 0$ and $\eta = 1$ if $\tilde{\eta} > 1$, otherwise $\eta = \tilde{\eta}$. Hence for this control η^* we get the optimum value of the functional J given by Eq. (4). Hence the theorem.

4 Numerical simulation

The values of the parameters used in the simulation of our problem are described in Tab. 2. The time

Table 2. Description of parameters with their values

Parameter	Description	Values	Sample-Range	Ref.
d	Natural death rate		(0.0143, 0.04)	[2, 27]
A	Recruitment rate	$d \times 10^5$	—	[2, 28]
α_1	Rate of trans.(det.)	0.17 or (8.557)	(0.12, 0.23) or (4.4769, 15.1347)	[2, 29, 30]
α_2	Rate of trans.(undet.)	$0.9 \times \alpha_1$	—	[2]
p	Frac. of fast prog.	0.1	(0.05, 0.3)	[2, 31, 32]
β	Contact rate b/w E and I	1.5	(1.5, 3.5)	[2]
θ	Rate of prog. to I from E	0.05	(0.005, 0.04)	[2, 29, 33]
ν_1	Recovery rate due to treatment	0.2	(0.14, 0.25)	[2, 29, 34, 35]
ν_2	Recovery rate due to detection and treatment	1.5	(1.5, 2.5)	[2, 28, 31, 36–38]
d_1	TB-induced death	0.365	(0.22, 0.39)	[2, 29, 30, 39, 40]

interval for which the optimal control is applied is taken as 5 years with initial population for susceptible, exposed, infected, recovered as 1000, 200, 100 and 56 respectively. We compare our optimal control results with the results of the model in [21] with constant rate of detection. The weight constants for the optimal control problem are taken as $C_1 = 1, C_2 = 1, C_3 = 10$. We solve the optimality system in Section 3 by iterative method with the help of Runge-Kutta fourth order procedure (see [3, 41]). At first we solve the state equations by the forward Runge-Kutta fourth order procedure in the time interval [0, 5] starting with an initial guess for the control. Then we use the backward Runge–Kutta fourth order procedure to solve the adjoint variables in the same time interval with the help of the solutions of the state variables and the transversality conditions. The plot of the control profile of the control parameter η is given in Fig. 1. Here it is observed that the control strategy starts nearly at 0.3 and after three years it reaches the value somewhere close to 0.7 and then starts declining. Finally it reaches to 0 at the end of five years. From this we come to the conclusion that when the case detection reaches the reasonable level (i.e. when most of the infectives are detected), then there will not be much detection needed and hence it starts declining. Here Fig. 2 demonstrates the comparison between constant detections and time dependent detection (optimal control). The variations of infective population with time for different rates of constant control and with optimal control are shown in this figure which clearly reflects the benefit of optimal control over the constant detection control. It is observed that the optimal control makes better impact on decreasing the infected population compared to constant control.

Fig. 3 shows similar plot where effects of different rates of constant control and optimal control on exposed population are shown.

From Figs. 2–3 we see that the optimal control gives better result(i.e. in case of optimal control, the decrease in both the exposed and the infected populations is more compared to the decrease in case of constant detection η. The higher value of η gives better result but optimal control seems to be the best.

Figs. 4–7 are displaying the impression of adjoint variables on developing the optimal control strategy. It is very important observation that the adjoint variables λ_i, $i = 1$ to 4 are taking their charge on making the

variation of Hamiltonian function because these Figs. 4–7 show that the adjoint variables slowly decreases to zero as the time period goes to the end of optimal strategy. Finally in Fig. 8, we depicted the effect of weight constant C_3 on the control profile of η. The Figs. 9-10 are showing the effects of weight constant C_3 on the infected population and the exposed population respectively. From these figures it can be observed that when we increase the weight constant C_3, the cost of efforts (detection) increases and optimal control decreases, leading to higher morbidity. Thus increase in the cost of detection leads to increase in the number of infectives and the number of exposed individuals due to reduction in the intensity of intervention. These facts are evidently showing that the suitable optimal control program is needed to detect the infectives to minimize the morbidity due to tuberculosis.

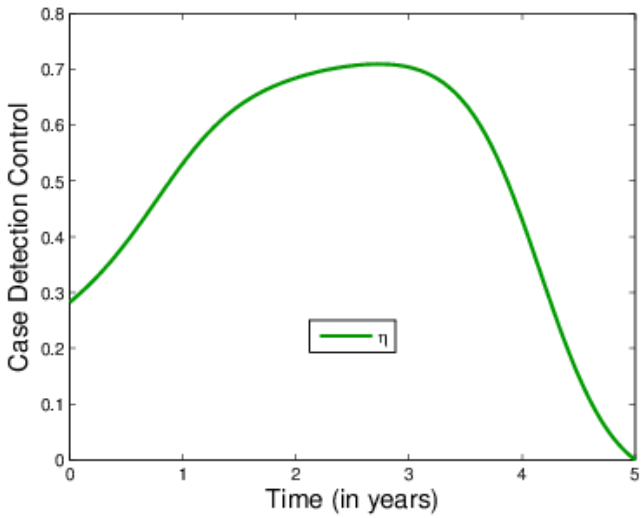

Fig. 1. Plot of optimal control parameter η.

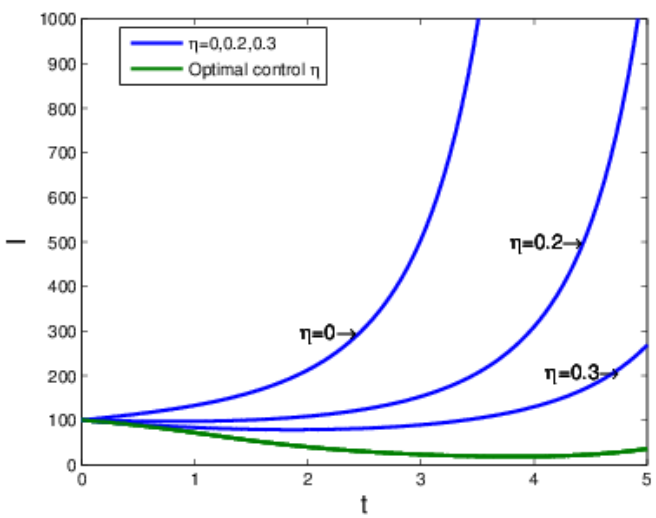

Fig. 2. Comparison of variation in Infected population with time for different values of detection parameter (η) and optimal control ($\eta(t)$).

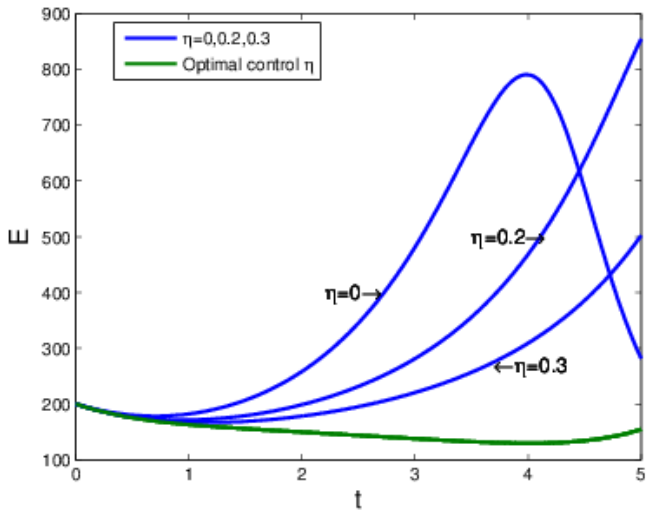

Fig. 3. Comparison of variation in Exposed population with time for different values of detection parameter (η) and optimal control ($\eta(t)$).

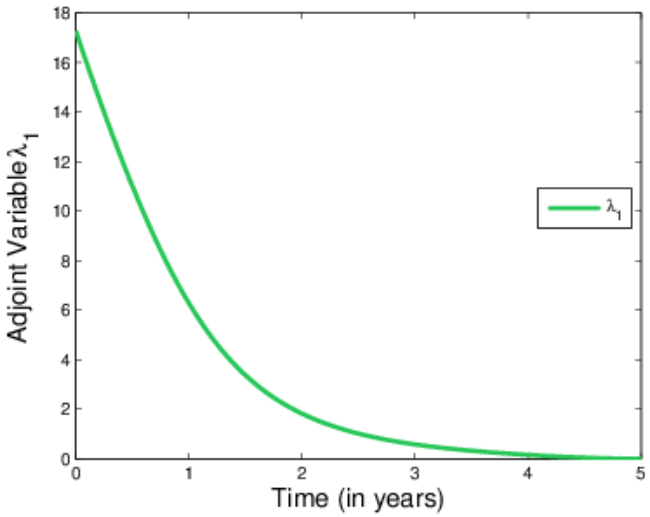

Fig. 4. Plot of Adjoint variable λ_1.

5 Conclusion

In this paper we analyzed an optimal control model for TB by considering the case detection of TB infectives as optimal control parameter. The result of this optimal control model is compared with the results of the model with fixed control and it is observed that optimal control gives better result than fixed control. In the fixed control model, the number of infectives starts increasing after some interval of time, where as in optimal control it always keeps decreasing. It has been observed from this study that the time dependent case detection parameter has positive impact on decreasing the number of exposed and infected populations. The proposed model helps in obtaining the time dependent optimal control profile in appropriate time interval for a given set of parameters. Additionally, it is found that the optimal control profile of the detection parameter is very much dependent on the cost associated with the case detection of TB infectives. When the weight constant associated with detection parameter increases, optimal control decreases leading to increase in the number of infectives. This fact clearly suggests that the suitable optimal control program is needed to detect the number of TB infectives to minimize the morbidity due to this disease.

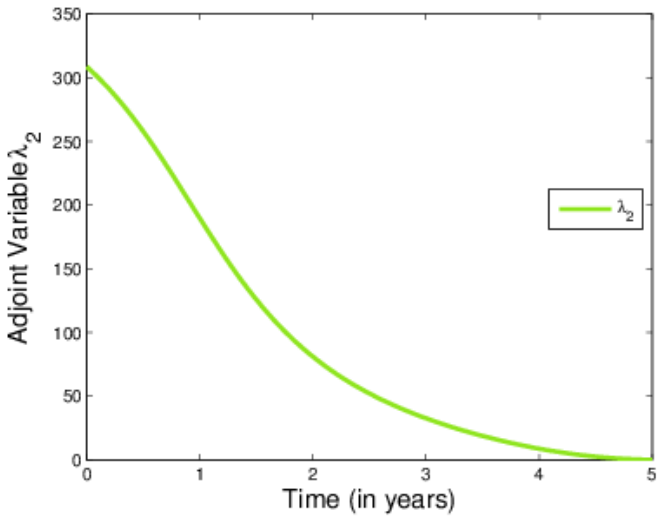

Fig. 5. Plot of Adjoint variable λ_2.

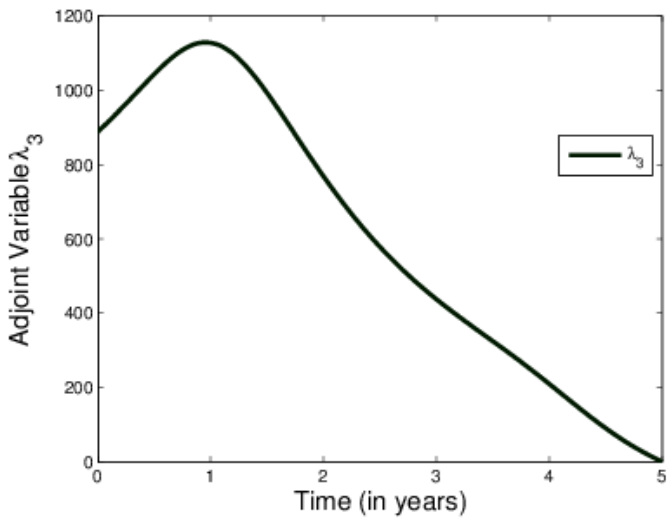

Fig. 6. Plot of Adjoint variable λ_3.

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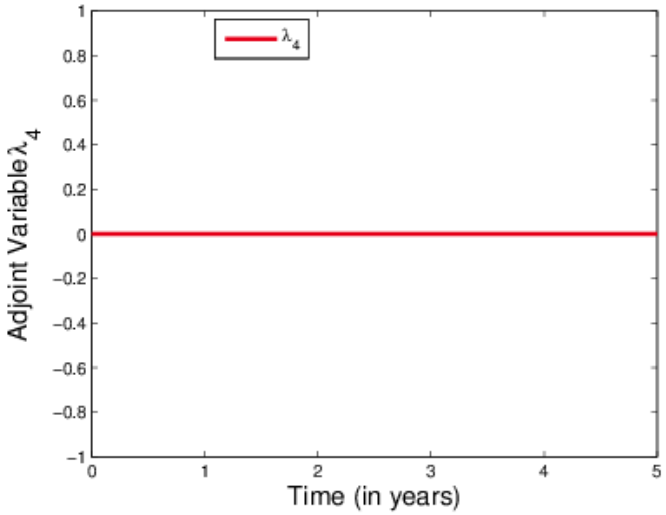

Fig. 7. Plot of Adjoint variable λ_4.

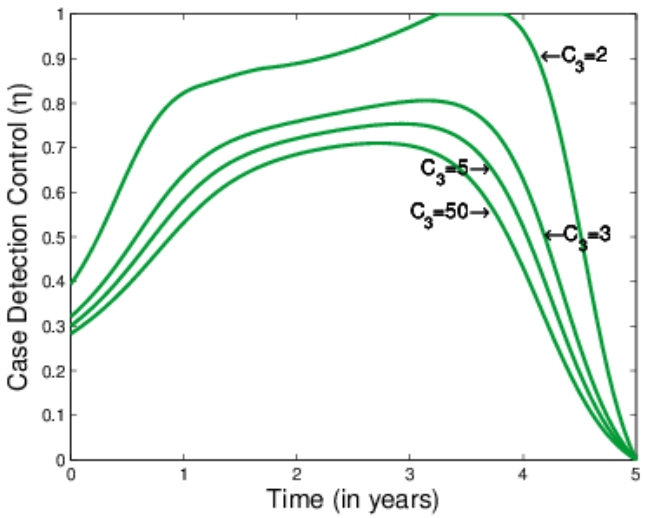

Fig. 8. Optimal control profile of η for different costs of control C_3.

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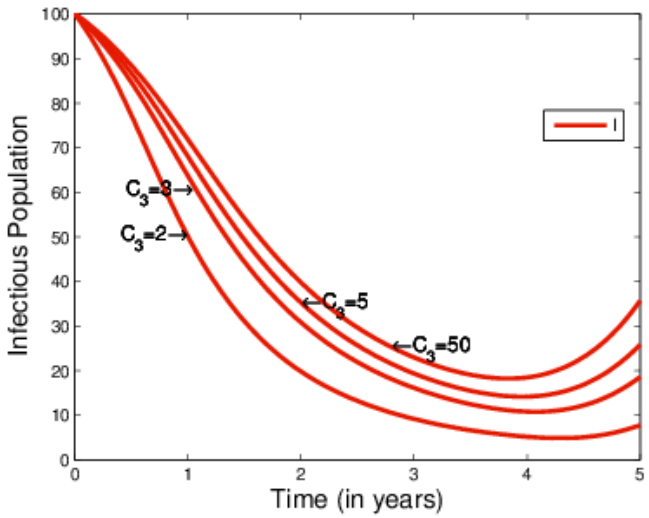

Fig. 9. Variation of I with time for different values of weight constant C_3.

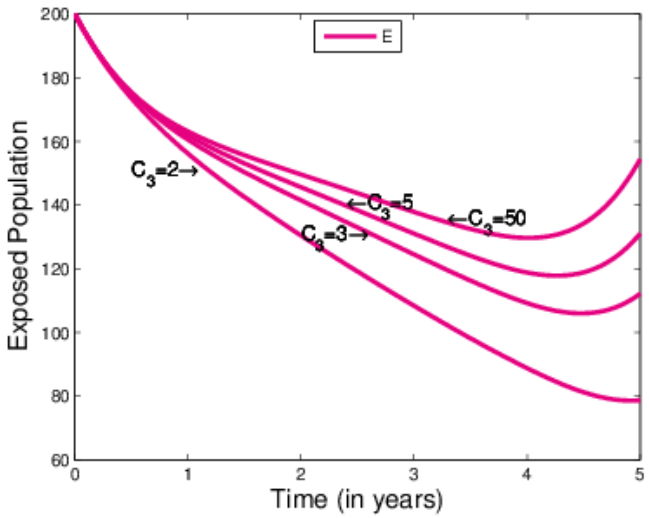

Fig. 10. Variation of E with time for different values of weight constant C_3.

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