OPTIMAL CONTROL STRATEGIES FOR TUBERCULOSIS TREATMENT

Shuo Tian

University of Waterloo department of system design engineering. Email: s33tian@uwaterloo.ca
UW ID: 20800262

Abstract:

Mycobacterium tuberculosis is transmitted by airborne particles and tuberculosis (TB) infection results when the mycobacterium is deposited in the lungs of exposed persons. TB is an important health issue all over the world, particularly in many African countries. This paper focused on Angola, it is recognized by authorities that TB is the most serious public health problems. Efforts to control TB in Angola have been underway since 1981, but results are still not satisfactory, and minimizing the effects caused by TB is an important challenge. Implemented measures to control these problems are having a positive effect. In this article the optimal control theory was applied to a tuberculosis model given by a system of ordinary differential equations. Optimal control strategies are proposed to minimize the cost of interventions. Numerical simulations are given using data from Angola Luanda Sanatorium Hospital.

1. Introduction:

Mycobacterium tuberculosis is transmitted by airborne particles and tuberculosis (TB) infection results when the mycobacterium is deposited in the lungs of exposed persons. One-third of the world population is currently infected with Mycobacterium tuberculosis, the vast majority harboring a latent infection. Recent data from Luanda Sanatorium Hospital makes it clear that TB is one of the leading causes of death in Angola. Optimal control is a branch of mathematics that involves finding optimal ways of controlling a dynamic system [L. Cesari (1983), W. H. Fleming (1975)]. While the usefulness of optimal control theory in epidemiology is nowadays well recognized [A. d'Onofrio (2009), U. Ledzewicz (2010), U. Ledzewicz (2011), H. S. Rodrigues (2010), H. S. Rodrigues (2012)], results pertaining to tuberculosis are a rarity [E. Jung (2002)], and specific studies for the situation of Angola nonexistent. Our aim in this paper is thus to use real data from Angola to study optimal strategies for the minimization of the number of active TB infectious and persistent latent individuals, taking into account the cost of the measures for the treatment of these individuals.

2. TB model with controls:

A mathematical model is posed, based on the assumption that all individuals are equally susceptible at birth and differentiate as they experience infection and in its case therapy. The population is divided into five categories: (S) susceptible, who have never encountered the mycobacterium; (L_1) early latent, representing individuals that were recently infected (typically within less than two years) and have not yet developed active TB; (I) infected, who have active TB and are infectious; (L_2) persistent latent, representing individuals

who were infected and remain latent; (R) recovered individuals who were previously infected and treated. Two control functions $u_1(\cdot)$ and $u_2(\cdot)$ and two real positive model constants E1 and E2 were added. The resulting model is given by the following system of nonlinear ordinary differential equations:

The control u_1 represents the effort in preventing the failure of treatment in active. The control u_2 governs the fraction of persistent latent individuals L_2 that is put under treatment. The parameters $E_i \in (0,1)$, i = 1,2, measure the effectiveness of the controls u_i, i = 1,2, respectively, i.e., these parameters measure the efficacy of treatment interventions for active and persistent latent TB individuals, respectively. The total population N, with N = $S(t)+L_1(t)+I(t)+L_2(t)+R(t)$ is constant in time. In this paper, the TB model in form (1), using relation $S(t)+L_1(t)+I(t)+L_2(t)+R(t) = N$ as a test to check the numerical results.

$$\begin{cases} \dot{S}(t) = \mu N - \frac{\beta}{N} I(t) S(t) - \mu S(t) \\ \dot{L_1}(t) = \frac{\beta}{N} I(t) \left(S(t) + \sigma L_2(t) + \sigma_R R(t)\right) - (\delta + \tau_1 + \mu) L_1(t) \\ \dot{I}(t) = \phi\delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \epsilon_1 u_1(t) + \mu) I(t) \\ \dot{L_2}(t) = (1-\phi)\delta L_1(t) - \sigma\frac{\beta}{N} I(t) L_2(t) - (\omega + \epsilon_2 u_2(t) + \tau_2 + \mu) L_2(t) \\ \dot{R}(t) = (\tau_0 + \epsilon_1 u_1(t)) I(t) + \tau_1 L_1(t) + (\tau_2 + \epsilon_2 u_2(t)) L_2(t) - \sigma_R \frac{\beta}{N} I(t) R(t) \\ \qquad\qquad - (\omega_R + \mu) R(t)\,. \end{cases}$$

The values of the rates δ, φ, ω, ωR, σ and τ_0 are taken from [M. Gomes (2007)] and the references cited therein (Table 1). The parameter δ denotes the rate at which individuals leave the L_1 category; φ is the proportion of individuals going to category I; ω is the rate of endogenous reactivation for persistent latent infections; and ω_R is the rate of endogenous reactivation for treated individuals. The parameter σ is a factor that measures the reduction in the risk of infection, as a result of acquired immunity to a previous infection, for persistent latent individuals; while σ_R represents the same parameter factor but for treated patients.

3. The optimal control problem:

Consider the state system (1) of ordinary differential equations in R^5 with the set of admissible control functions given by

$$\Omega = \{(u_1(\cdot), u_2(\cdot)) \in (L^\infty(0,T))^2 \,|\, 0 \le u_1(t), u_2(t) \le 1, \forall\, t \in [0,T]\,\}.$$

The objective functional is given by

$$J(u_1(\cdot), u_2(\cdot)) = \int_0^T \left[I(t) + L_2(t) + \tfrac{1}{2} W_1 u_1^2(t) + \tfrac{1}{2} W_2 u_2^2(t)\right] dt\,, \tag{2}$$

where the constants W_1 and W_2 are a measure of the relative cost of the interventions associated with the controls u_1 and u_2, respectively.

In our numerical simulations we consider the weight W_1 associated with the control u_1 to be greater than the weight W_2 associated with u_2: W_1 = 500 and W_2 = 50. The reason for this is that the cost associated with u_1 includes the cost of holding active infected patients I in the hospital or paying professionals to supervise them, ensuring that they finish their treatment, which is costly to implement.

The optimal control problem of determining $(S^*(\cdot), L^*_1(\cdot), I^*(\cdot), L^*_2(\cdot), R^*(\cdot))$, associated with an admissible control pair $(u^*_1(\cdot), u^*_2(\cdot)) \in \Omega$ on the time interval [0, T], satisfying (1), the initial conditions S(0), $L_1(0)$, I(0), $L_2(0)$ and R(0) (Table 1), and minimizing the cost functional (2), i.e.,

$$J(u_1^*(\cdot), u_2^*(\cdot)) = \min_{\Omega} J(u_1(\cdot), u_2(\cdot))\,.$$

Theorem 3.1. The problem (1), (3) with fixed initial conditions S(0), L1(0), I(0), L2(0) and R(0), and fixed final time T , admits a unique optimal solution ($S^*(\cdot)$, $L^*_1(\cdot)$, $I^*(\cdot)$, $L^*_2(\cdot)$, $R^*(\cdot)$) associated with an optimal control pair ($u^*_1(\cdot)$, $u^*_2(\cdot)$) on [0, T]. Moreover, there exist adjoint functions, $\lambda^*_1(\cdot)$, $\lambda^*_2(\cdot)$, $\lambda^*_3(\cdot)$, $\lambda^*_4(\cdot)$ an $\lambda^*_5(\cdot)$, such that

$$\begin{cases} \dot{\lambda}^*_1(t) = \lambda^*_1(t)\left(\frac{\beta}{N}I^*(t)+\mu\right) - \lambda^*_2(t)\frac{\beta}{N}I^*(t) \\ \dot{\lambda}^*_2(t) = \lambda^*_2(t)(\delta+\tau_1+\mu) - \lambda^*_3(t)\phi\delta - \lambda^*_4(t)(1-\phi)\delta - \lambda^*_5(t)\tau_1 \\ \dot{\lambda}^*_3(t) = -1 + \lambda^*_1(t)\frac{\beta}{N}S^*(t) - \lambda^*_2(t)\frac{\beta}{N}(S^*(t)+\sigma L^*_2(t)+\sigma_R R^*(t)) \\ \quad +\lambda^*_3(t)(\tau_0+\epsilon_1 u^*_1(t)+\mu) + \lambda^*_4(t)\sigma\frac{\beta}{N}L^*_2(t) - \lambda^*_5(t)\left(\tau_0+\epsilon_1 u^*_1(t) - \sigma_R\frac{\beta}{N}R^*(t)\right) \\ \dot{\lambda}^*_4(t) = -1 - \lambda^*_2(t)\frac{\beta}{N}I^*(t)\sigma - \lambda^*_3(t)\omega + \lambda^*_4(t)\left(\sigma\frac{\beta}{N}I^*(t)+\omega+\epsilon_2 u^*_2(t)+\tau_2+\mu\right) \\ \quad -\lambda^*_5(t)\left(\tau_2+\epsilon_2 u^*_2(t)\right) \\ \dot{\lambda}^*_5(t) = -\lambda^*_2(t)\sigma_R\frac{\beta}{N}I^*(t) - \lambda^*_3(t)\omega_R + \lambda^*_5(t)\left(\sigma_R\frac{\beta}{N}I^*(t)+\omega_R+\mu\right), \end{cases}$$

with transversality conditions $\lambda^*_i(T) = 0$, i = 1, … ,5. Furthermore,

$$u^*_1(t) = \min\left\{\max\left\{0, \frac{\epsilon_1 I^*(\lambda^*_3-\lambda^*_5)}{W_1}\right\}, 1\right\},$$
$$u^*_2(t) = \min\left\{\max\left\{0, \frac{\epsilon_2 L^*_2(\lambda^*_4-\lambda^*_5)}{W_2}\right\}, 1\right\}.$$

Proof. The existence of optimal controls ($u^*_1(\cdot)$, $u^*_2(\cdot)$) and associated optimal solution (S^*, L^*_1, I^*, L^*_2, R^*) comes from the convexity of the integrand of the cost function (2) with respect to the controls (u_1, u_2) and the Lipschitz property of the state system with respect to state variables (S, L_1, I, L_2, R). According to the Pontryagin Maximum Principle [L. Pontryagin (1962)], if ($u^*_1(\cdot)$, $u^*_2(\cdot)$) $\in \Omega$ is optimal for the problem (1), (3) with the initial conditions given in Table 1 and fixed final time T, then there exists a nontrivial absolutely continuous mapping $\lambda : [0, T] \longrightarrow R^5$, $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t))$, called the adjoint vector, such that

$$\begin{cases} \dot{S} = \frac{\partial H}{\partial \lambda_1}, \\ \dot{L}_1 = \frac{\partial H}{\partial \lambda_2}, \\ \dot{I} = \frac{\partial H}{\partial \lambda_3}, \\ \dot{L}_2 = \frac{\partial H}{\partial \lambda_4}, \\ \dot{R} = \frac{\partial H}{\partial \lambda_5} \end{cases}$$

and

$$\begin{cases} \dot{\lambda}_1 = -\frac{\partial H}{\partial S}, \\ \dot{\lambda}_2 = -\frac{\partial H}{\partial L_1}, \\ \dot{\lambda}_3 = -\frac{\partial H}{\partial I}, \\ \dot{\lambda}_4 = -\frac{\partial H}{\partial L_2}, \\ \dot{\lambda}_5 = -\frac{\partial H}{\partial R}, \end{cases}$$

where the Hamiltonian H is defined by

$$\begin{aligned} H &= H(S, L_1, I, L_2, R, \lambda, u_1, u_2) \\ &= I + L_2 + \frac{W_1}{2}u_1^2 + \frac{W_2}{2}u_2^2 \\ &\quad + \lambda_1\left(\mu N - \frac{\beta}{N}IS - \mu S\right) \\ &\quad + \lambda_2\left(\frac{\beta}{N}I(S+\sigma L_2+\sigma_R R) - (\delta+\tau_1+\mu)L_1\right) \\ &\quad + \lambda_3(\phi\delta L_1 + \omega L_2 + \omega_R R - (\tau_0+\epsilon_1 u_1+\mu)I) \\ &\quad + \lambda_4\left((1-\phi)\delta L_1 - \sigma\frac{\beta}{N}IL_2 - (\omega+\epsilon_2 u_2+\tau_2+\mu)L_2\right) \\ &\quad + \lambda_5\left((\tau_0+\epsilon_1 u_1)I + \tau_1 L_1 + (\tau_2+\epsilon_2 u_2)L_2 - \sigma_R\frac{\beta}{N}IR - (\omega_R+\mu)R\right) \end{aligned}$$

and the minimization condition

$$\begin{aligned} &H(S^*(t), L^*_1(t), I^*(t), L^*_2(t), R^*(t), \lambda^*(t), u^*_1(t), u^*_2(t)) \\ &\qquad = \min_{0\le u_1, u_2\le 1} H(S^*(t), L^*_1(t), I^*(t), L^*_2(t), R^*(t), \lambda^*(t), u_1, u_2) \end{aligned}$$

4. Numerical results and discussion.

Different optimal control strategies for the TB model (1) under the parameter values given in Table 1 were presented. All the initial values of state borrowed from E Jung (2002).

Three control strategies are explored:

- Strategy 1, which implements measures that prevent the failure of treatment in active TB individuals I (control u_1 alone);

• Strategy 2, which considers treatment of persistent latent individuals L_2 with anti-TB drugs (control u_2 alone);

• Strategy 3, which implements measures for preventing treatment failure inactive TB individuals and variation of the fraction of persistent latent individuals that are put under treatment (controls u_1 and u_2).

The numerical results were calculated by the PROPT Matlab Optimal Control ToolBox. The optimal treatment strategy is obtained by solving the optimality system, consisting of 10 ODEs from the state and adjoint equations. An iterative method is used for solving the optimality system. We start to solve the state equations with a guess for the controls over the simulated time using a forward fourth order Runge-Kutta scheme. Because of the transversality conditions (6), the adjoint equations are solved by a backward fourth order Runge-Kutta scheme using the current iteration solution of the state equations. Then, the controls are updated by using a convex combination of the previous controls and the value from the characterizations (7). This process is repeated and iteration is stopped if the values of unknowns at the previous iteration are very close to the ones at the present iteration.

Symbol	Description	Value
β	Transmission coefficient	100
μ	Death and birth rate	$1/52\,yr^{-1}$
δ	Rate at which individuals leave L_1	$12\,yr^{-1}$
ϕ	Proportion of individuals going to I	0.05
ω	Endogenous reactivation rate for persistent latent infections	$0.0002\,yr^{-1}$
ω_R	Endogenous reactivation rate for treated individuals	$0.00002\,yr^{-1}$
σ	Factor reducing the risk of infection as a result of acquired immunity to a previous infection for L_2	0.25
σ_R	Rate of exogenous reinfection of treated patients	0.25
τ_0	Rate of recovery under treatment of active TB	$2\,yr^{-1}$
τ_1	Rate of recovery under treatment of latent individuals L_1	$2\,yr^{-1}$
τ_2	Rate of recovery under treatment of latent individuals L_2	$1\,yr^{-1}$
N	Total population	30,000
T	Total simulation duration	$5\ yr$
ϵ_1	Efficacy of treatment of active TB I	0.5
ϵ_2	Efficacy of treatment of latent TB L_2	0.5
W_1	Weight constant of control u_1	500
W_2	Weight constant of control u_2	50

Runge-Kutta 4th order method is a numerical technique used to solve ordinary differential equation. The Runge-Kutta 4th order method is based on the following

$y_{i+1} = y_i + \frac{1}{6}(k_1+2k_2 + 2k_3 + k_4)\, h$

Where knowing the value of $y = y_i$ at x_i, we can find the value of $y= y_{i+1}$ at x_{i+1}, and

$$h = x_{i+1} - x_i$$

$$k_1 = f(x_i, y_i)$$
$$k_2 = f\left(x_i + \frac{1}{2}h, y_i + \frac{1}{2}k_1 h\right)$$
$$k_3 = f\left(x_i + \frac{1}{2}h, y_i + \frac{1}{2}k_2 h\right)$$
$$k_4 = f(x_i + h, y_i + k_3 h)$$

4.1. Strategy 1 versus Strategy 3.

Comparing strategy 1 with strategy 3, we observe that the optimal control u^*_1 stays at the upper bound for almost the same duration in both situations (Figure 1).

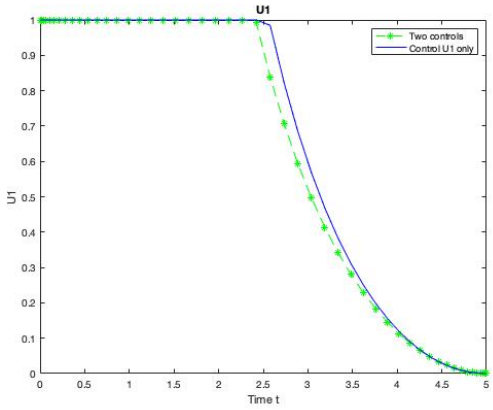

Figure 1. The optimal control u^*_1 for Strategy 1 and Strategy 3 in a time scale in units of years

When only the control u_1 is considered, the fraction of persistent latent individuals

L_2 is greater than the respective fraction associated with Strategy 3, for the entire five years. This implies a higher value of the cost functional (2) associated with Strategy 1 when compared to the cost associated with Strategy 3. When one compares the change in the fraction of susceptible (S), early latent (L_1) and infected (I) individuals, no difference is observed between Strategies 1 and 3 (Figure 2).

4.2. Strategy 2 versus Strategy 3.

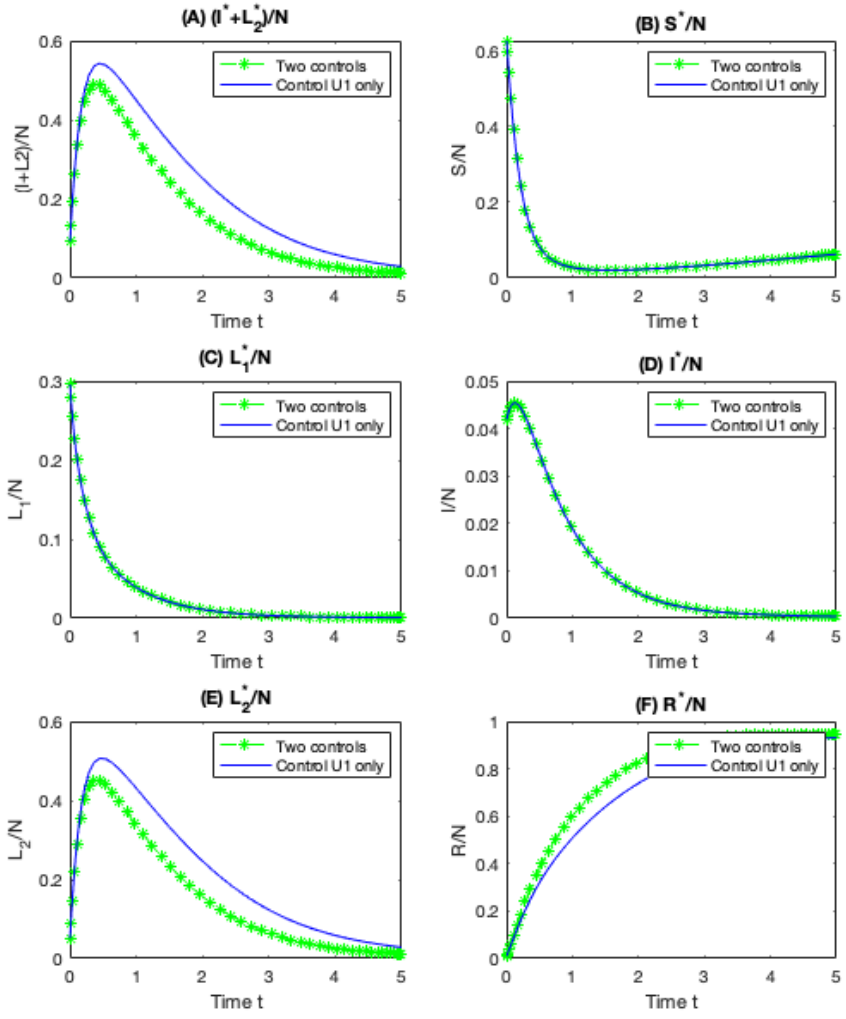

Figure 2. Optimal states for Strategy 1 and Strategy 3 in a time scale in units of years

With Strategy 3, there is a lower fraction of early and persistent latent individuals as well as infected individuals (see Figure 3). The fraction of susceptible and recovered individuals is higher when two controls are applied at the same time. The value of the cost functional (2) associated with Strategy 3 is lower than that of Strategy 2.

5. Conclusion.

Two control functions u_1 and u_2 were introduced to an existing mathematical model for TB developed in [M. Gomes (2007)]. These controls are associated with measures that help to reduce the number of active infected and persistent latent TB individuals: the control u_1 represents the effort that prevents the failure of treatment in active TB infectious individuals I, e.g., supervising the patients, helping them to take the TB medications regularly and to complete the TB treatment; while the control u_2 governs the fraction of persistent latent individuals L_2 under treatment with anti-TB drugs. An optimal control problem was formulated and solved theoretically using the Pontryagin maximum principle.

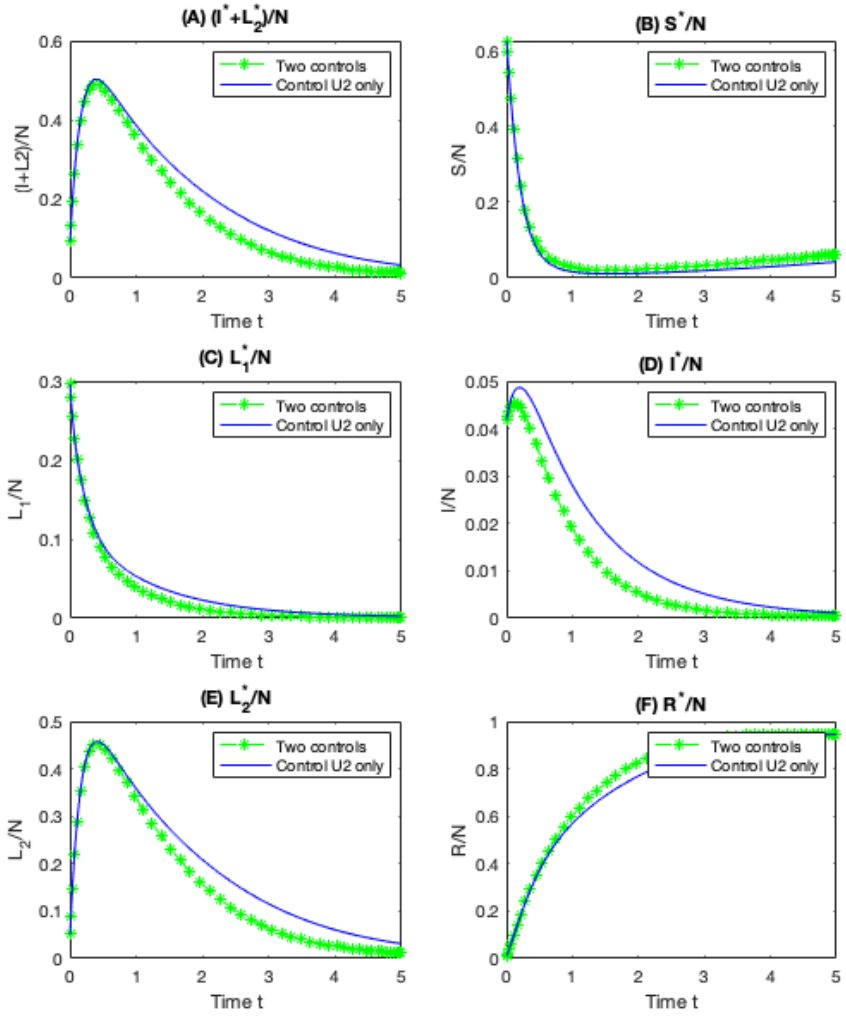

Figure 3. Optimal states for Strategy 2 and Strategy 3 in a time scale in units of years

The solution to the problem was then illustrated by numerical simulations using available data from Angola. From the numerical results, one may conclude that considering only control u_1 or only control u_2 does not lead to the best results in terms of the number of active infected

and persistent latent individuals. A combined strategy that involves both controls is preferable.

Figure 4 shows the simulation of the system for the uncontrolled case, when $u_1 = 0$ and $u_2 = 0$, compared with the strategies here proposed. Results justify the need for intervention in tuberculosis treatment. The values of Table 2 put in evidence that the uncontrolled situation is the worst: does not only result in more infected and persistent latent individuals but also gives a higher value to the cost functional (2).

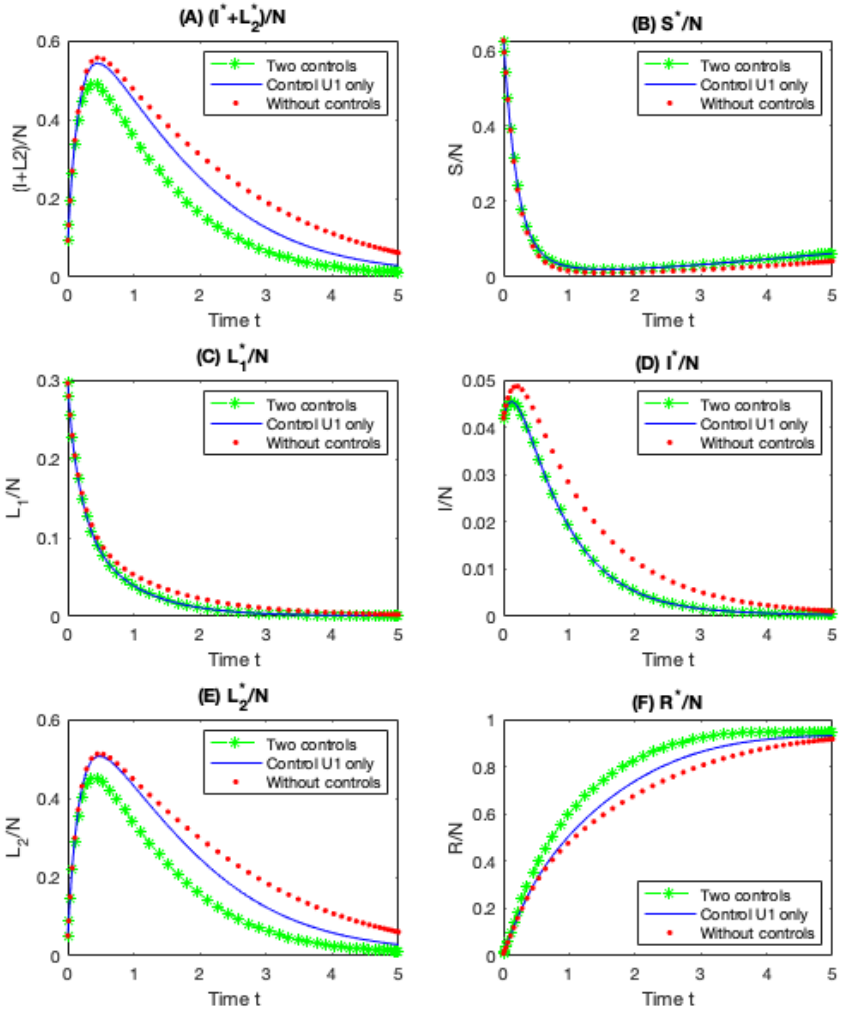

Figure 4. State variables with and without controls in a time scale in units of years

	Strategy 1	Strategy 2	Strategy 3	Without controls
$I(5) + L_2(5)$	≃ 751	≃ 831	≃ 334	≃ 1, 584
Cost: functional	≃ 32, 511.2	≃ 28, 585.9	≃ 24, 133.1	≃ 37, 760.3

Table 2. Comparison of Strategies 1, 2, 3 with the uncontrolled case

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