EXISTENCE, CHARACTERIZATION, AND SIMULATION OF OPTIMAL POLICIES IN A FAMILY OF EPIDEMIC MODELS

CONTROSAUL DÍAZ-INFANTE, FRANCISCO PEÑÚÑURI, AND DAVID GONZÁLEZ-SÁNCHEZ

Abstract. We survey some some theoretical results about a family of optimal control problems that arise in epidemiology. We also implement the so-called forward-backward-sweep method in Python to find approximate optimal control policies via the Maximum principle. In addition, four specific models are described and simulated.

1. Introduction

By the end of the Middle Ages, smallpox cut down the population in centers of Europe and Asia—three of each ten dies by smallpox—perhaps that gives its alias, "speckled monster". Although experts understand the mechanism of transmission of this "monster" until the early 20 century, it represents the first documented disease [3, 6, 13] against which a specific control intervention was available: the inoculation. This process relies on putting material from smallpox sores to healthy people, usually scratching material over the armor or inhaling it through the nose. People develop the symptoms associated with smallpox—fever and a rash. However, the death rate due to inoculation is considerably lower than natural smallpox.

Then Bernoulli naturally sets a question like this: What happens if everybody were inoculated? Here, we address the question: How to inoculate in an optimal way? Throughout the following lines, we try to answer and illustrate the implications of this question.

Optimal control theory is a way to deal with the above question. In the fifties, Pontryagin and Bellman propose generalizations of the calculus of variations of broader applicability: the Maximum Principle and the method of Dynamic Programming, respectively. Now, these results sustain application in the biological sciences and, in particular, to the optimal control of infectious diseases, see [9, 20, 24, 42] for recent literature.

Our approach in this work relies on Pontryagin's Maximum Principle [29] and follows the same methodology of Lenhart and Workman [25]. Lenhart's work makes an accessible optimal control device to describe common epidemic interventions like vaccination, treatment, quarantine, isolation among others. Our intention in this work is illustrating the mentioned strategies throughout recent literature and state results for existence and characterization of optimal controls for a particular family of epidemic models. Likewise we present some goals and issues that appear within the theory and numerical approximations.

The paper is organized as follows. We start in Section 2 by introducing a rather simple but seminal dynamical system from which most of the epidemic models are derived. In Section 3 we describe four epidemic models as well as some control policies. In Section 4 we provide the main theoretical results for a family of optimal control problems (OCPs); such a family includes the models in Section 3. Our proofs are based on well known results—stated, for completeness, in the Appendix of Section 8—from optimal control theory. Some numerical methods to solve OCPs are given in Section 5, in particular, we provide the python implementation code of the forward-backward-sweep method in repository [11]. The reader is free to comment, use, improve or whatever he wants about this repository. In Section 6 we run several numerical experiments, based on [11], for the models described in Section 3. We conclude with some remarks in Section 7.

2. The uncontrolled SIR model

Infectious diseases have struck civilizations in different periods of human history. HIV/AIDS, Spanish influenza, and Black Death are the most devastating pandemics, they have killed more

(S. Díaz-Infante, D. González-Sánchez) Departamento de Matemáticas, CONACYT-Universidad de Sonora, Hermosillo, Sonora.

(F. Peñúñuri) Departamento de Ingeniería Física, Universidad Autónoma de Yucatán, Mérida Yucatán

E-mail addresses: sdinfante@conacyt.mx, francisco.pa@correo.uady.mx, dgonzalezsa@conacyt.mx.

than 100 million people. Therefore, understanding the mechanism of spread and control of diseases of this kind is essential. In this line, the SIR structure is a convenient option to model its spreading.

The SIR model is a compartmental structure. Primarily, the model consists of three compartments: susceptible S, infected I, and recovered R, and transitions functions between compartments.

Practically, all the existing epidemic models are variants of this structure. The variants emerge to describe particular characteristics of a disease, mechanism of transmission, population dynamics, among others. To fix ideas, consider the classic model of Kermack and Mckendrick [22]

$$\begin{aligned} \frac{dS}{dt} &= -\kappa SI \\ \frac{dI}{dt} &= \kappa SI - \lambda I \\ \frac{dR}{dt} &= \lambda I, \end{aligned} \tag{1}$$

here the transition from the susceptible S to the infected class I occur with constant rate κ, and from the infected class I to the recovered happens with rate λ.

In next sections, we provide the main ideas to modify this basic structure with control policies.

3. Control policies in epidemics

Here we present several control models that we consider as good examples. Before talking about this good examples, we give the core of optimal policy modeling, see for example the survey of Wickwire [39], for more details.

First, we require a model to describe the spreading of an uncontrolled disease, and whose transitions generate a cost. Then, we add a continuous control action to modify the changes from one state to another but in such way that the mentioned cost is optimized. A rule that prescribes which control operation to use at each time, is a control policy. A control policy which applies only information from the current state of the controlled system to prescribe control actions is a *closed-loop* or *feedback* control. If the current state is not observable, or the control function only depends on the time we have an *open-loop* policy: the sort of policies that we consider in this work.

Here, we consider control policies that affect the bounded rates at which population moves from one class (e.g., infected) to another (e.g., recovered). In all these problems, the control function appears linearly in the relevant dynamic. Next, we specify a cost functional which assigns the total cost of the control policy implementation. Then the problem is to determine a policy that optimizes the regarding cost strategy.

Now we present the mentioned good examples. In what follows X denotes a vector with all concerning populations, for example, according to SIR model (1), $X = (S, I, R)^\top$.

3.1. Culling.

Pathogens that are transmitted between wildlife, livestock, and humans present major challenges for the protection of human and animal health: the economic sustainability of agriculture and the conservation of wildlife. Mycobacterium bovis, the aetiological agent of bovine tuberculosis (TB), is one such pathogen. For example, according with Donnelly et al. [12] the incidence of TB in cattle has increased substantially in parts of Great Britain in the past two decades, adversely affecting the livelihoods of cattle farmers and potentially increasing the risks of human exposure. The control of bovine TB in Great Britain is complicated by the involvement of wildlife, particularly badgers which appear to sustain endemic infection and can transmit TB to cattle. Between 1975 and 1997 over 20 000 badgers were culled as part of British TB control policy, generating conflict between conservation and farming interest groups.

Badger bovine tuberculosis. Bolzoni et al. [4] reports a controlled model to describe a outbreak of badger bovine tuberculosis. The regarding model reads

$$\min_{u(t)\in\mathcal{U}} \int_0^T I(t) + P[u(t)]^\theta, \quad \theta \in \{1, 2\}, \quad P = B/A$$

subject to:

$$\begin{aligned} \frac{dS}{dt} &= rS\left(1 - \frac{S+I}{K}\right) - \beta SI - u(t)S \\ \frac{dI}{dt} &= \beta SI - (\alpha + \mu + u(t))I. \end{aligned} \tag{2}$$

Parameter	Description
ν	Natural fertility rate
μ	Natural mortality rate
K	Carrying capacity
α	Disease-induced mortality rate
R_0	Basic reproductive number
β	Transmission coefficient
P	Relative cost per unit culling effort over the cost of a single infection

TABLE 1. Parameter description of the control model (2).

Here the susceptible class follows a logistic dynamics with net grow rate $r = \nu - \mu$ and carrying capacity K, see Table 1 for more details. According with the approach, of van den Driessche [36], the basic reproductive number results

$$R_0 = \frac{\beta K}{\alpha + \mu}.$$

Our intention with this model is to illustrate the difference between the optimal policies for linear and quadratic costs, though the corresponding infected populations are quite similar. Then, as we can see in Section 6.1 below, the resulting controlled paths depend on the form of the functional cost and the basic reproductive number.

3.2. **Vaccination.** Usually, public health organizations consider vaccination as a primarily preventive action against infectious diseases but it incurs a cost.Due to the limited resources associated with vaccination programs, it is imperative to optimize the use of available resources. Using optimal control theory, we formulate a vaccination schedule. The goal is to minimize the number of infected persons and the cost of vaccine during a fixed time, for this example, we optimize the functional

$$\int_0^T AI(t) + u^2(t).$$

Here u is the vaccination control and denotes the fraction of susceptible individuals to vaccinate per unit of time. Since managing infected population imply resource consumption, A represents the cost per individual. We also need a spread dynamics. So, let $S(t)$, $E(t)$, $I(t)$, $R(t)$ respectively be the number of susceptible, exposed, infectious, and recovered (immune) individuals at time t. Since vaccination of the entire susceptible population is impractical, the model considers $0 \leq u(t) \leq 0.9$. Then the whole population N is given by $N(t) = S(t) + E(t) + I(t) + R(t)$, and obeys $\dot{N}(t) = (b-d)N(t) - aI(t)$. Since b is the recruitment rate and d natural death, the term $b - d$ denotes the growth of the entire population. Then, the optimal control problem reads

$$\begin{aligned}
&\min_u \int_0^T AI(t) + u^2(t)dt, \\
&\text{subject to} \\
&\dot{S}(t) = bN(t) - dS(t) - cS(t)I(t) - u(t)S(t), \quad S(0) = S_0 \geq 0, \\
&\dot{E}(t) = cS(t)I(t) - (e+d)E(t), \quad E(0) = E_0 \geq 0, \\
&\dot{I}(t) = eE(t) - (g+a+d)I(t), \quad I(0) = I_0 \geq 0, \\
&\dot{R}(t) = gI(t) - dR(t) + u(t)S(t), \quad R(0) = R_0 \geq 0, \\
&\dot{N}(t) = (b-d)N(t) - aI(t), \quad N(0) = S_0 + E_0 + I_0 + R_0,
\end{aligned} \tag{3}$$

see Table 2 for a description of the parameters.

	Parameter Description
b	Recruitment rate
a, d	Disease and natural death rates
c	Incidence of disease
e	Rate at which the exposed individuals become infectious
g	Recovering rate
A	Vaccination cost
T	Final time

TABLE 2. Parameters and simulation values of the epidemic model (3).

3.3. **Case finding and case control.**

Two-strains Tuberculosis. Seeking to reduce the latent and infectious groups with the resistant-strain tuberculosis, in [26] the authors use control theory to describe optimal strategies in a tuberculosis model which considers the effect of treatment in two kinds of strains. The controlled version reads:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S\frac{I_1}{N} - \beta_3 S\frac{I_2}{N}\mu S,\\
\frac{L_1}{dt} &= \beta_1 S\frac{I_1}{N} - (\mu+k_1)L_1 - u_1(t)r_1L_1 + (1-u_2(t))pr_2I_1 + \beta_2 T\frac{I_1}{N} - \beta_3 L_1\frac{I_2}{N},\\
\frac{I_1}{dt} &= k_1L_1 - (\mu+d_1)I_1 - r_2I_1,\\
\frac{L_2}{dt} &= (1-u_2(t))qr_2I_1 - (\mu+k_2)L_2 + \beta_3(S+L_1+T)\frac{I_2}{N},\\
\frac{I_2}{dt} &= k_2L_2 - (\mu+d_2)I_2,\\
\frac{dT}{dt} &= u_1(t)r_1L_1 + (1-(1-u_2(t))(p+q))r_2I_1 - \beta T\frac{I_1}{N} - \beta_3 T\frac{I_2}{N} - \mu T.
\end{aligned}
\tag{4}
$$

Lenhart, Jung, and Feng [26] consider time dependent optimal control strategies associated with *case holding* and *case finding*. They incorporate the case finding control by adding a term which identifies and cure a fraction of latent individuals. Case finding consequently reduces the rate of disease development by latent individuals. The authors include case holding by adding a term which may decrease the treatment failure rate of individuals with sensitive TB, so, this control reduce the incidence of drug resistant TB. In model (4), u_1 denotes the fraction of typical TB latent individuals that are identified and put under treatment —case finding control—and $1-u_2$ represents the effort that prevents the failure treatment in typical TB infectious individuals.

The controls u_1 ,u_2 reduce the latent and infected groups with resistant TB. However, the case holding and the case finding strategies produce a cost modeled as

$$
\int_0^{t_f}\left[L_2(t) + I_2(t) + \frac{B_1}{2}[u_1(t)]^2 + \frac{B_2}{2}[u_2(t)]^2\right]dt. \tag{5}
$$

3.4. **Isolation and quarantine.**

SARS. If an emergent disease lacks of a rapid diagnostic test, therapy or vaccine, then isolation and quarantine of individuals exposed to the disease seems an obvious control policy. For example Gumel et al. [16] model strategies of this kind for the severe acute respiratory syndrome (SARS). SARS was a highly contagious and viral disease emerged in China late in 2002 and quickly spread to 32 countries and regions causing more than 774 deaths and 8098 infections worldwide.

Based in the work of Gumel et al. [16], Yan and Zou report in [40] a control epidemic model for SARS. They use quarantine and isolation as mitigation controls. The authors also propose sub-optimal control policies and perform numerical simulations with genetic algorithms. The controlled

Parameter Description			
β_1	Probability that a susceptible individual becomes infected.	r_1	Treatment recover rate of individuals with latent TB.
β_2	Probability that a recovered individual become infected	r_2	Treatment rate recover of individuals with infectious TB.
β_3	Probability that a uninfected individual become infected by resistant-TB	p, q	Proportion of infectious individuals that not complete the treatment for TB or MDR-TB respectively.
μ	Natural per-capita death rate.	N	Total population size.
d_1	Per-capita death rate by TB.	Λ	Recruitment rate.
d_2	Per-capita death rate by MDR-TB.	t_f	Final time.
k_1	Rate at which an latent TB individual becomes infectious.	B_1	Systematic cost of the case finding control.
k_2	Rate at which an latent individual with MDR-TB becomes infectious.	B_2	Cost of the case holding strategy

TABLE 3. Parameters description for the control problem (4).

version used in the mentioned reference reads:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{S\left(\beta I + \mathcal{E}_E \beta E + \mathcal{E}_Q \beta Q + \mathcal{E}_J \beta J\right)}{N} - \mu S,\\
\frac{dE}{dt} &= p + \frac{\beta S\left(\beta I + \mathcal{E}_E \beta E + \mathcal{E}_Q \beta Q + \mathcal{E}_J \beta J\right)}{N} - (u_1(t) + k_1 + \mu)E,\\
\frac{dQ}{dt} &= u_1(t)E - (k_2 + \mu)Q,\\
\frac{dI}{dt} &= k_1 E - (u_2(t) + d_1 + \sigma_1 + \mu)I,\\
\frac{dJ}{dt} &= u_2(t)I + k_2 Q - (d_2 + \sigma_2 + \mu)J,\\
\frac{dR}{dt} &= \sigma_1 I + \sigma_2 J - \mu R.
\end{aligned} \tag{6}
$$

The control variable u_1 denotes the proportion of people in quarantine who had contact with an infected person inside of a quarantine program or educational campaigns. Control u_2 models the proportion of symptomatic population which is in an isolation program. The authors consider the following epidemiological classes. We enclose a description of the model parameters in Table 4.

S: Susceptible individuals
E: Asymptomatic individuals who have been exposed to the virus but have not yet developed clinical symptoms of SARS
Q: Quarantine individuals
I: Symptomatic
J: Isolated
R: Recovered
$N = S + E + Q + I + J + R.$

So, giving the disease dynamics in (6), the problem is to minimize the functional cost

$$
\int_0^{t_f} \left[B_1 E(t) + B_2 Q(t) + B_3 I(t) + B_4 J(t) + \frac{C_1}{2} u_1^2(t) + \frac{C_2}{2} u_2^2(t) \right] dt. \tag{7}
$$

Here, parameter B_i denotes the linear cost of the infected class and C_1, C_2 are the costs for isolation and quarantine controls, respectively. Table 4 displays a description of the regarding parameters.

	Parameter Description
β	Transmission coefficient
ε_E, ε_Q, ε_J	Modification parameter for exposed, quarantine and isolation classes
μ	Natural death rate.
Λ	Constant recruitment rate
p	Net inflow of asymptomatic individuals
k_1	Transfer rate from class of asymptomatic to symptomatic
k_2	Transfer rate from the quarantine class to isolation
d_1, d_2	Per-capita disease induced death rates for the symptomatic individuals and isolated individuals.
σ_1, σ_2	Per-capita recovery rates for the symptomatic individuals and isolated individuals
t_f	Final time
B_1, B_2, B_3, B_4	Respectively cost for E,Q,I,J classes
C_1, C_2	Costs for Isolation and Quarantine policies.

TABLE 4. Parameter description for the SARS model (6).

A common practice to deal with the above control problems follows the next steps:

(i) Prove that there exists an optimal policy.
(ii) Find necessary conditions for the optimality of a policy.
(iii) From the necessary conditions, determine qualitative properties of the optimal policies and the corresponding state paths.

Usually this kind of problems are non linear, then finding a solution is extremely difficult. Therefore, choosing a convenient numerical scheme is very important. In this work we implement the forward-backward-sweep method [25]. Next sections provide a technique to transform a given optimization problem into solve a ordinary differential equation with boundary values coupled with an optimization problem.

4. Existence and characterization of optimal policies

Notation. Each element x in $\mathbb{R}^n$ is written as a column vector and $x^\top$ denotes the transpose. We write the gradient of $g : \mathbb{R}^n \to \mathbb{R}$ as a row vector

$$g_x = (\partial g/\partial x_1, \dots, \partial g/\partial x_n).$$

If $\lambda : \mathbb{R} \to \mathbb{R}^n$ is differentiable, the derivative is denoted $\dot{\lambda} = (d\lambda^1/dt, \dots, d\lambda^n/dt)^\top$. The Jacobian matrix of $f = (f^1, \dots, f^n)^\top : \mathbb{R}^n \to \mathbb{R}^n$ is

$$f_x = \begin{bmatrix} f^1_x \\ f^2_x \\ \vdots \\ f^n_x \end{bmatrix}.$$

Given a matrix A, the j-th row of A is denoted $r_j(A)$.

The non controlled epidemic models described above are of the form

$$\begin{aligned}\dot{X} &= AX + \begin{bmatrix} X^\top B^{(1)} \\ \vdots \\ X^\top B^{(n)} \end{bmatrix} X + k \\ &= \left(A + [X^\top \cdots X^\top] \begin{bmatrix} B^{(1)} \\ \vdots \\ B^{(n)} \end{bmatrix} \right) X + k\end{aligned}$$

where the matrix A represents the linear part of the system, each matrix $B^{(j)}$, $j = 1, \ldots, n$, gives the *interaction* part as a quadratic form, and k is a constant vector.

Thus the j-th row of the above system takes the form

$$\dot{X}_j = r_j(A)X + X^\top B^{(j)} X + k_j.$$

In this section we consider control policies in both the linear and the interaction parts of the latter system. This family of control systems with a corresponding cost functional include the above epidemic models.

For such a family of optimal control problems we state and prove three main results. First, given any control policy, we establish the existence and uniqueness of the associated state path. Second, the existence of an optimal control policy is proved. Finally, by means of the Maximum Principle, sufficient conditions on a control policy and the corresponding state path are also given. Our proofs are based on general and well-known results in optimal control theory which, for completeness, are stated in the Appendix at the end of the paper.

4.1. **A family of control systems.** Let $\mathbf{X} \subseteq \mathbb{R}^n$ and $\mathbf{U} \subseteq \mathbb{R}^m$ be nonempty and compact sets. The sets $\mathbf{X}$ and $\mathbf{U}$ are respectively called the *state space* and the *control space*. The vectors in X have non-negative entries, in particular we assume that $0 \in X$. The control set $\mathbf{U}$ is convex. We consider the following control system, for $j = 1, \ldots, n$,

$$\dot{X}_j = [r_j(A) + u^\top C^{(j)}]X + X^\top \begin{bmatrix} r_1(B^{(j)}) + u^\top D^{(j1)} \\ \vdots \\ r_n(B^{(j)}) + u^\top D^{(jn)} \end{bmatrix} X + k_j \tag{8}$$

where $A \in \mathbb{R}^{n\times n}$, $B^{(j)} \in \mathbb{R}^{n\times n}$, $C^{(j)} \in \mathbb{R}^{m\times n}$, and $D^{(jl)} \in \mathbb{R}^{m\times n}$ for $l = 1, \ldots, n$.

The proof of the following theorem slightly differs from that given in Yong [41, Sect. 2.1] since we consider a weighted norm. This improvement allows us to give a global solution instead of a local one.

For each measurable function $u : [0, T] \to \mathbf{U}$ and each initial condition $x_0 \in X$, there exists a unique absolutely continuous function $X_u : [0, T] \to \mathbb{R}^n$ that satisfies the the system (8) almost everywhere.

Proof. Let $u : [0, T] \to U$ be a measurable function. The control system (8) can be written as

$$\dot{X}(t) = f(X(t), u(t)), \quad X(0) = x_0, \quad 0 \le t \le T,$$

where $f : \mathbf{X} \times \mathbf{U} \to \mathbb{R}^n$. Since f is of class $\mathcal{C}^1$ on the compact set $\mathbf{X} \times \mathbf{U}$, there exists a constant $L > 0$ such that

$$\|f(x, u) - f(x_1, u)\| \le L\|x - x_1\| \tag{9}$$

$$\|f(0, u)\| \le L \tag{10}$$

for every $x, x_1 \in \mathbf{X}$ and $u \in \mathbf{U}$.

Consider the linear space

$$\mathbb{X} = \{X : [0, T] \to \mathbb{R}^n \mid X \text{ is continuous}\}$$

with the norm

$$\|X\|_w := \sup_{t\in[0,T]} \frac{\|X(t)\|}{w(t)},$$

where $w(t) := e^{Lt}$ for each $t \in [0, T]$. It can be shown, with slight modifications in [35, Section 2.1], that the pair $(\mathbb{X}, \|\cdot\|_w)$ is a Banach space. Define the operator $K : \mathbb{X} \to \mathbb{X}$ by

$$K[X](t) := x_0 + \int_0^t f(X(s), u(s))ds.$$

By (9) and (10), any (x,u) satisfies

$$\|f(x,u)\| \leq L(1+\|x\|), \tag{11}$$

thus $f(X(\cdot),u(\cdot))$ is Lebesgue integrable and $K[X]$ is absolutely continuous. We claim that K is a contraction with contraction constant $1-e^{-LT}$. Indeed,

$$\begin{aligned}
\|K[X]-K[Y]\|_w &= \sup_{t\in[0,T]} \frac{|\int_0^t [f(X(s),u(s))-f(Y(s),u(s))]ds|}{w(t)} \\
&\leq \sup_{t\in[0,T]} \frac{L\int_0^t w(s)[w(s)]^{-1}|X(s)-Y(s)|ds}{w(t)} \\
&\leq L\|X-Y\|_w \sup_{t\in[0,T]} \frac{\int_0^t w(s)ds}{w(t)} \\
&= L\|X-Y\|_w \sup_{t\in[0,T]} \frac{[e^{Lt}-1]/L}{e^{Lt}} \\
&= (1-e^{-LT})\|X-Y\|_w.
\end{aligned}$$

Then by Banach's fixed point theorem [35, Theorem 2.1], there exists a unique $X\in\mathbb{X}$ satisfying

$$X(t) = x_0 + \int_0^t f(X(s),u(s))ds.$$

Therefore (8) holds almost everywhere [27, Corollary 5.4.1]. □

4.2. **Existence of optimal policies.** Consider the *cost functional* of an admissible control u, given the initial state x_0,

$$V(u,x_0) := \int_0^T g(X(t),u(t))\ ,dt, \tag{12}$$

where $g:\mathbf{X}\times\mathbf{U}\to\mathbb{R}$ is continuous. The *optimal control problem* (OCP) consists of finding an admissible control u^* such that

$$V(u^*,x_0) = \inf\{V(u,x_0)\mid u\in\mathbb{U}_B\}.$$

If there exists such a control u^*, then it is called an *optimal policy* or *optimal control*. The pair (u^*,X^*), where X^* is given by Theorem **??**, is called an *optimal pair*.

Theorem 1. *Suppose the function g is continuous, and, for each x, the function $g(x,\cdot)$ is convex, i.e.,*

$$\alpha g(x,u_1)+(1-\alpha)g(x,u_2)\geq g(x,\alpha u_1+(1-\alpha)u_2)\quad \forall u_1,u_2\in\mathbf{U},\ \alpha\in[0,1].$$

Then there exists an optimal pair that minimizes (12) subject to (8).

Proof. Let us write the control system (8) as $\dot{X}=f(X,u)$. By Filippov's Theorem 3, it is enough to show that each set

$$\{(z,y)\in\mathbb{R}\times\mathbb{R}^n\mid z\geq g(x,u),\ y=f(x,u),\ u\in\mathbf{U}\},\qquad x\in X,$$

is convex. Fix $x\in X$. Let $z_1,z_2\in\mathbb{R}$ and $y_1,y_2\in\mathbb{R}^n$ such that

$$z_j\geq g(x,u_j),\quad j=1,2, \tag{13}$$

and

$$y_j = f(x,u_j),\quad j=1,2, \tag{14}$$

for some $u_1,u_2\in U$. We need to show that, for any $\alpha\in[0,1]$, there exists $u'\in U$ such that

$$\alpha z_1+(1-\alpha)z_2\geq g(x,u') \tag{15}$$

and

$$\alpha y_1+(1-\alpha)y_2 = f(x,u'). \tag{16}$$

Let $u':=\alpha u_1+(1-\alpha)u_2$. Then (15) follows from (13) and the convexity of $g(x,\cdot)$. On the other hand, (16) holds because $f(x,\cdot)$ is affine, i.e.,

$$f(x,\alpha u_1+(1-\alpha)u_2) = \alpha f(x,u_1)+(1-\alpha)f(x,u_2).$$

□

4.3. **Sufficient conditions for optimality.** Consider the Hamiltonian $\mathcal{H} : \mathbf{X} \times \mathbf{U} \times \mathbb{R}^n \to \mathbb{R}$, defined as

$$\mathcal{H}(x, u, \lambda) := g(x, u) + \lambda^\top f(x, u),$$

and

$$\mathcal{H}^*(x, \lambda) := \inf_{u \in \mathbf{U}} \mathcal{H}(x, u, \lambda),$$

where g determines the cost functional (12) and f is given by the right-hand side of the control system (8). The function $\lambda : [0, T] \to \mathbb{R}^n$ and the admissible pair (u, X) are said to satisfy the necessary conditions of the *Maximum Principle* (MP) if they satisfy the *adjoint equation*

$$\dot{\lambda}(t) = -\mathcal{H}_x(X(t), u(t), \lambda(t))^\top, \quad \lambda(T) = 0, \tag{17}$$

and the *optimality condition*

$$\mathcal{H}^*(X(t), \lambda(t)) = \mathcal{H}(X(t), u(t), \lambda(t)). \tag{18}$$

Definition 1. The function w from $[0, T]$ to some Euclidean space is *piecewise continuous* if

(a) w is continuous on $[0, T]$ except at a finite number of points, and
(b) if w is discontinuous at t, then

$$\lim_{s \to t^-} w(s) \text{ and } \lim_{s \to t^+} w(s)$$

are finite.

Theorem 2. *Let $\lambda : [0, T] \to \mathbb{R}^n$ be a continuous function and let (u^*, X^*) be an admissible pair such that*

(a) *u^* is piecewise continuous,*
(b) *$\dot{X}^*$ exists and is piecewise continuous,*
(c) *(λ, u^*, X^*) satisfies the optimality condition (18), and,*
(d) *except at the points of discontinuity of u^*, the adjoint equation (17) holds.*

If, for each t, the function $\mathcal{H}^*(\cdot, \lambda(t))$ is convex on $\mathbf{X}$, then (u^*, X^*) is an optimal pair.

Proof. The conclusion follows from Theorem 5, whenever Assumptions 3 and 4 hold. If u^* is piecewise continuous, then X^* is absolutely continuous, by Theorem **??**, and so continuous. Thus Assumption 4 holds. Assumption 3 also holds since $\mathcal{H}$ and $\mathcal{H}_x$ are clearly continuous. This completes the proof. □

Remark 1. *In general, the convexity of $H^*(\cdot, \lambda(t))$ does not hold for the whole family (8) even if g is convex. However, the models above meet this assumption.*

5. Numerical analysis

5.1. **Direct and indirect methods.** Since we can transform the problem of optimal control into a two-point boundary ODE problem, the methods designed for this sort of problem are applicable see [1, 21, 33] for classic references. In this line [8, 40] use multiple shooting methods to solve the resulting extended two-value boundary ODE.

Multiple shooting method Consider the controlled dynamics and corresponding adjoint equations given by

$$\begin{aligned} \dot{x}(t) &= f(x(t), u(t)), \qquad x(0) = x_0 \\ \dot{\lambda}(t) &= -\mathcal{H}_x(x(t), u(t), \lambda(t))^\top, \quad \lambda(T) = 0. \end{aligned} \tag{19}$$

Roughly speaking, the multiple shooting method follows the next algorithm. Given a partition of the interval $[0, T]$ with uniform step h,

$$\tau_h^n := \{t_k = kh,\ k = 0, \dots n\},$$

the multi shooting method is described in Algorithm 1.

However, the *forward-backward-sweep method* is the most popular method in works on optimal control epidemic models, perhaps for its simple implementation and acceptable convergence. All simulations presented in this work runs with this scheme. Hackbusch [17] propose this numerical scheme to solve a class of optimal problems that encloses the models of Section 3. Lenhart and Workman [25] provides MATLAB code for many of its regarding work in biological models.

Algorithm 1 Multi shooting method

Input: $t_0, T, x_0, h, \text{tol}, \lambda_f, n_{max}$
Output: x^*, u^*, λ

procedure MULTI_SHOOTING($g, \lambda_{\text{function}}, u, x_0, \lambda_f, h, n_{max}$)
  while $\epsilon >$ tol **do**
    Choose $y_i := [x(t_i), \lambda(t_i)], \quad i = 1, \ldots, n.$

    Integrate (19) for each sub-interval $[t_i, t_{i+1})$ using y_i as the initial conditions and obtain $y(t_{i-1}) = [x(t_{i-1}), \lambda(t_{i-1})]$, $i = 2, \ldots, n$.

    $\mathcal{Y} \leftarrow [y_i - y(t_i)]$, $i = 0, \ldots, n$
    Actualize initial condition y_i for next iteration using for a example a Newton's method.
    $\epsilon \leftarrow |\mathcal{Y}|$
  end while
end procedure

Algorithm 2 Forward Backward Sweep

Input: $t_0, t_f, x_0, h, \text{tol}, \lambda_f$
Output: x^*, u^*, λ

procedure FORWARD_BACKWARD_SWEEP($g, \lambda_{\text{function}}, u, x_0, \lambda_f, h, n_{max}$)
  while $\epsilon >$ tol **do**
    $u_{\text{old}} \leftarrow u$
    $x_{\text{old}} \leftarrow x$
    $x \leftarrow$ RUNGE_KUTTA_FORWARD(g, u, x_0, h)
    $\lambda_{\text{old}} \leftarrow \lambda$
    $\lambda \leftarrow$ RUNGE_KUTTA_BACKWARD($\lambda_{\text{function}}, x, \lambda_f, h$)
    $u_1 \leftarrow$ OPTIMALITY_CONDITION(u, x, λ)
    $u \leftarrow \alpha u_1 + (1-\alpha) u_{old}, \qquad \alpha \in [0,1]$ ▷ convex combination
    $\epsilon_u \leftarrow \dfrac{||u - u_{\text{old}}||}{||u||}$
    $\epsilon_x \leftarrow \dfrac{||x - x_{\text{old}}||}{||x||}$ ▷ relative error
    $\epsilon_\lambda \leftarrow \dfrac{||\lambda - \lambda_{\text{old}}||}{||\lambda||}$
    $\epsilon \leftarrow \max\{\epsilon_u, \epsilon_x, \epsilon_\lambda\}$
  end while
  return x^*, u^*, λ ▷ Optimal pair
end procedure

5.2. **Evolutionary algorithms.** Evolutionary algorithms are a kind of heuristic algorithms well suited for global optimization. Such algorithms emulate natural evolution introducing operators for mutation (**M**), crossover (**C**) and selection (**S**). One of the earliest works on evolutionary methods was developed by George E. P. Box [5]. Nevertheless, it can be said that the first evolutionary algorithm at least as they are known today, was the so called Genetic Algorithm (GA) introduced by Holland [19]. Many variations of evolutionary algorithms have been developed being Differential Evolution (DE), introduced by Storn and Price [34], one of the simplest yet efficient and effective optimization algorithms.

Algorithm 3 shows the general form of Evolutionary Algorithms for optimizing the objective function fob. There, an initial population Y of size N_p, generated in the search space $\mathcal{V}$ by the operator $\mathbf{Y}_0$, is subject to the evolutionary process until certain stopping criterion is met. Then the best individual ($\mathbf{y}_{best}$), i.e., the individual who optimizes fob, is selected by introducing the operator **Best**. In Algorithm 3 the variable M stores a mutated population, the variable C stores the results of the crossover operator. The selection operator selects from C and Y the individuals which will conform the new generation of individuals of Y. This selection is based in some criteria

usually dictated by the objective function. For instance, if $\mathbf{y}$ is an element of Y and $\mathbf{c}$ an element of C, a common criterion for minimization is to select $\mathbf{y}$ if $fob(\mathbf{y}) < fob(\mathbf{c})$.

A detailed explanation for constructing the main operators $\mathbf{M}$, $\mathbf{C}$ and $\mathbf{S}$, can be found in [2] for GA and in [30] for the DE algorithm.

Algorithm 3 Evolutionary Algorithms

$Y \leftarrow \mathbf{Y}_0(Np, \mathcal{V})$
while (the stopping criterion has not been met) **do**
  $M \leftarrow \mathbf{M}(Y)$
  $C \leftarrow \mathbf{C}(Y, C)$
  $Y \leftarrow \mathbf{S}(Y, C, fob)$
end while
$\mathbf{y}_{best} \leftarrow \mathbf{Best}(Y, fob)$

Regarding the optimal control policies problem, authors frequently apply the evolutionary method by using piecewise constant functions for the controllers u_k, $k = 1, 2, \ldots, n$. For instance, the optimization of a quantity of the form

$$V(u, x_0) = \int_0^T g(X(t), u(t))dt, \tag{20}$$

can be conducted by discretizing the interval $I = [0, T]$ in disjoint subintervals I_j and choosing

$$u_k(t) = \begin{cases} u_k^j & \text{if } t \in I_j \\ 0 & \text{otherwise.} \end{cases} \tag{21}$$

Usually the function $X(t)$ under the sign of integral in Equation (20) obeys a specific dynamical model which needs to be solved but in such a way that V is optimized. Now, the numbers u_k^j will be part of an individual who will be subject to the evolutionary process. Junyoung et al. [20], Yan and Zou [40] follows this approach respectively for the GA and the DE algorithms.

5.3. **Optimal Control Software.** In addition to the implementation of the schemes discussed above, here we provide a list with useful software and some of its references. Here we follow the list reported by Rodrigues, Monteiro, and Torres in the preprint [31], see this reference for code examples and more details.

OC-ODE. The `OC-ODE` [15], Optimal Control of Ordinary-Differential Equations, by Matthias Gerdts, is a collection of Fortran 77 routines for optimal control problems subject to ordinary differential equations. It uses an automatic direct discretization method for the transformation of the OC problem into a finite-dimensional non linear problem, OC-ODE includes procedures for numerical adjoint estimation and sensitivity analysis.

DOTcvp. Hirmajer et al. [18], provide the MATLAB Toolbox `DOTcvp`. Giving a piecewise solution for the control, the toolbox uses the control vector parametrization approach for the calculation of the optimal control profiles.

Muscod-II. `MUSCOD-II` is a robust and efficient optimization tool that allows to quickly implement and solve very general optimal control problems in differential-algebraic equations (DAE). This package relies on the Multiple Shooting method for the solution of mixed integer nonlinear ODE or DAE. The authorsprovide the code and a reference manual [23].

Ipopt. Wächter and Biegler [37] provide the software package Ipopt (Interior Point OPTimizer). Ipopt implements a primal-dual interior point method and uses a line search strategy based on filter method and is written in `Fortran` and `C`.

Knitro. Byrd, Nocedal, and Waltz reports in [7] `Knitro 5.0`, a C-package for nonlinear optimization that combines complementary approaches to nonlinear optimization to achieve robust performance over a wide range of application requirements. The package is designed for solving large-scale, smooth nonlinear programming problems, and it is also effective for the following special cases: unconstrained optimization, nonlinear systems of equations, least squares, and linear and quadratic programming. Various algorithmic options are available, including two interior methods and an active-set method.

6. Numerical experiments

6.1. **Culling in badger bovine tuberculosis.** In this numerical experiment we go back to the culling control model (2). Our main objective is to contrast two kinds of controls that produce quite similar paths for the infected population under different cost schemes. All simulation runs with the forward-backward-method and with the parameters enclosed in Table 5.

Parameters values		**Initial Conditions**
ν	0.6	
μ	0.4	$S(0) = K$, $I(0) = 1$
K	0.4	
α	0.05	
R_0	6.0, 3.5	**Control bound**
β	$\dfrac{R_0(\alpha+\mu)}{K}$	$u_{max} = 0.1$
P	70.0, 110.0	

Table 5. Parameters values of model (2) to reproduce Figures 1 to 3.

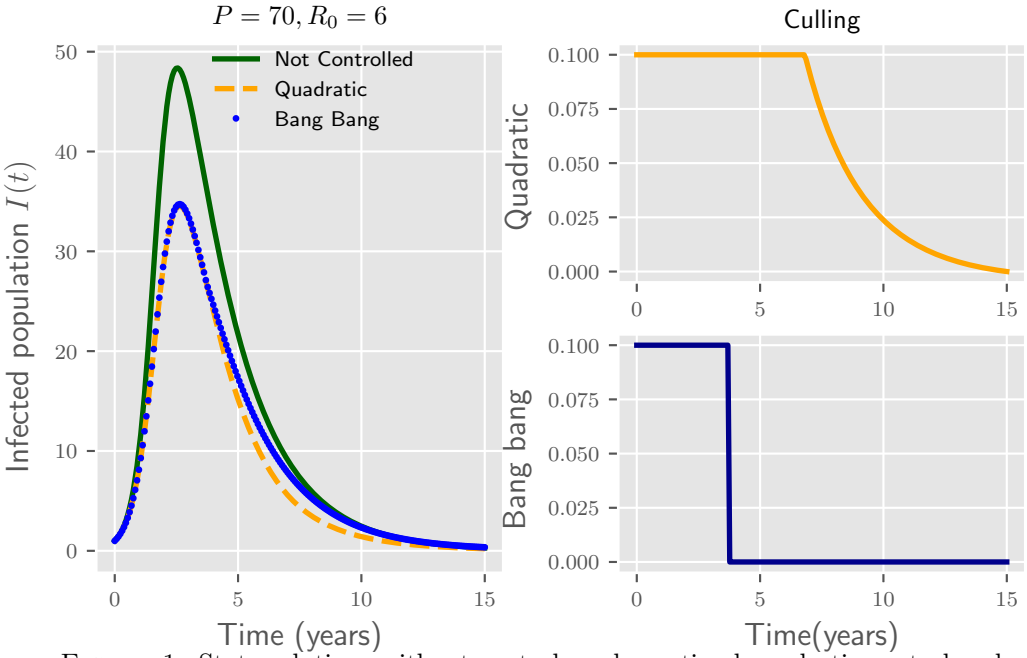

Figure 1. State solutions without control, under optimal quadratic control and with linear (bang-bang) control.

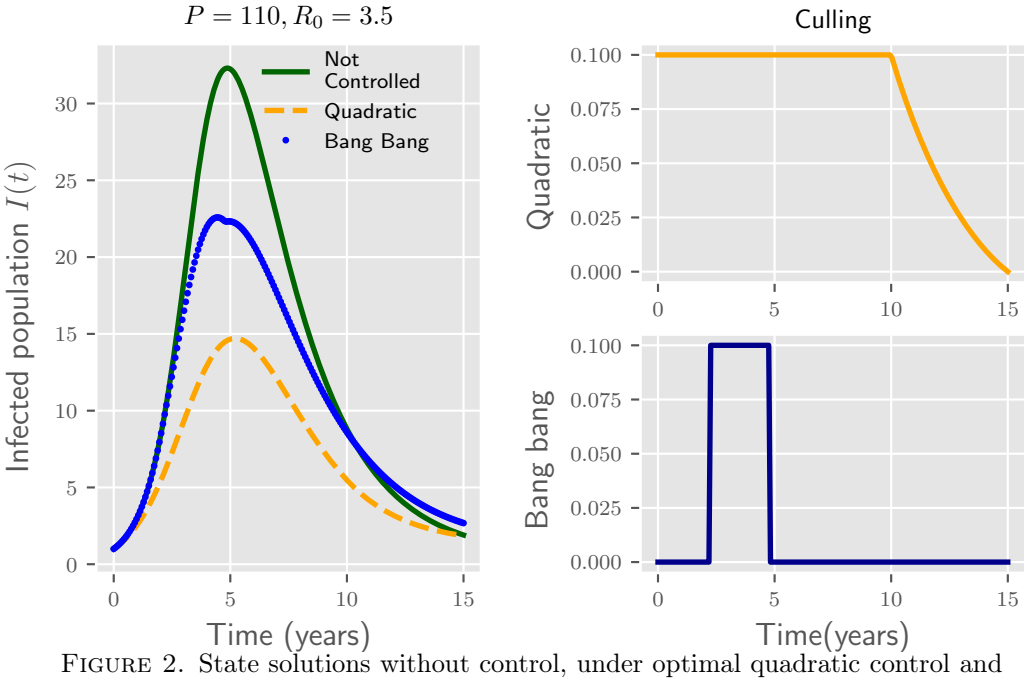

FIGURE 2. State solutions without control, under optimal quadratic control and with linear (bang-bang) control.

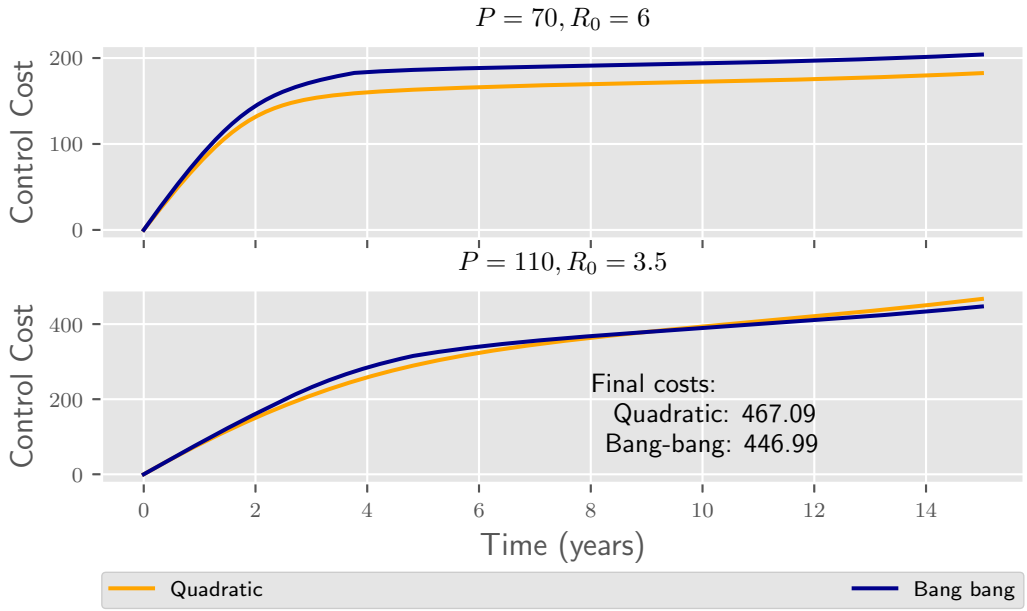

FIGURE 3. Cost for the linear and quadratic controls under two scenarios. Upper $P = 70$, $R_0 = 6$, bottom, $P = 110$, $R_0 = 3.5$, and the rest of parameters as in Table 5.

6.2. **Vaccination.** Now, we come back to the vaccination control presented in model (3). According to Table 6, in Figure 4 we illustrate the effect of vaccination control. The simulation shows that the optimal-vaccination policy diminish almost to zero the infected population. In green we plot the state solution without control to stress the impact of the optimal policy.

Parameters values		Initial conditions
b	0.525	$S(0) = 1000$, $E(0) = 100$
a, d	0.2, 0.5	$I(0) = 50$, $R(0) = 15$
c	0.0001	
e	0.5	
g	0.1	
A	0.1	
T	20.0	

TABLE 6. Parameters and simulation values of the epidemic model (3).

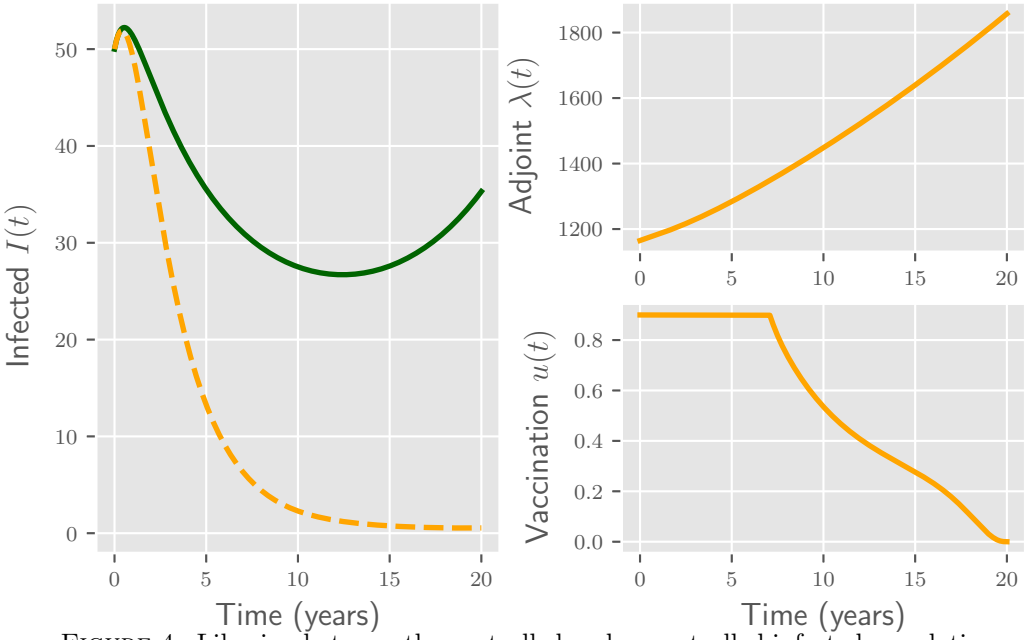

FIGURE 4. Likening between the controlled and uncontrolled infected population. On the left, we show the optimal infected state against the dynamics without control. On the right, we present the corresponding adjoint function λ and the optimal control.

Parameter values				Initial Conditions
β_1	13.0	β_2	13.0	$S(0) = (76/120)N$
β_3	0.0131, 0.0217, 0.029, 0.0436			$L_1(0) = (36/120)N$ $L_2(0) = (2/120)N$ $I_1(0) = (4/120)N$
μ	0.0143			$I_2(0) = (1/120)N$
d_1	0.0	d_2	0.0	$T(0) = (1/120)N$
k_1	0.5	k_2	1.0	
r_1	2.0	r_2	1.0	
p	0.4	q	0.1	
N	6000, 12 000, 30 000	Λ	μN	
				Control Bounds
				Lower 0.05 Upper 0.95
t_f	5.0 years			
B_1	50.0	B_2	500.0	

TABLE 7. Simulation values for the control problem (4).

6.3. **Case finding and case control in a two strain tuberculosis model.** Figure 5 shows the effect of case finding and case holding controls. The combination of these strategies diminish the multi-drug resistant population. Table 7 compiles the parameters and its values used to produce this figure with $N = 30\,000$, $\beta_3 = 0.29$. To minimize the resistant TB population, L2 + I2, the simulation suggest that the case holding strategy u_2 would be at the upper bound during almost 4.3 years and then decreasing to the lower bound. Meanwhile, case finding is applied over most of the simulated time, 5 years. The total number of infected resistant TB $L2 + I2$ at the final time $t_f = 5$ years results 1123. This same number, but without control, sums 4176. So this policy prevents 3053 cases of resistant TB.

According to Table 7 and taking different values for the parameter β_3, in Figure 6 we display the effect of parameter β_3 over controls. At the top, both controls experiment small variations at the beginning and reach almost the same level after 5 years. The simulation suggests that lower values of β_3 just delay the control profile for few months. At bottom we enclose a zoom frame to emphasize the small difference for case holding. Summarizing, the simulation shows that parameters β_3 modifies the case finding control in a wider way.

Figure 7 illustrates case finding and case holding strategies under population of different sizes. The simulation suggests that under relative small population, is more important to hold case finding at the top. While for relatively bigger population the case holding is the more important strategy.

All figures runs with the forward-backward-sweep method, see [11] to check a Python implementation code.

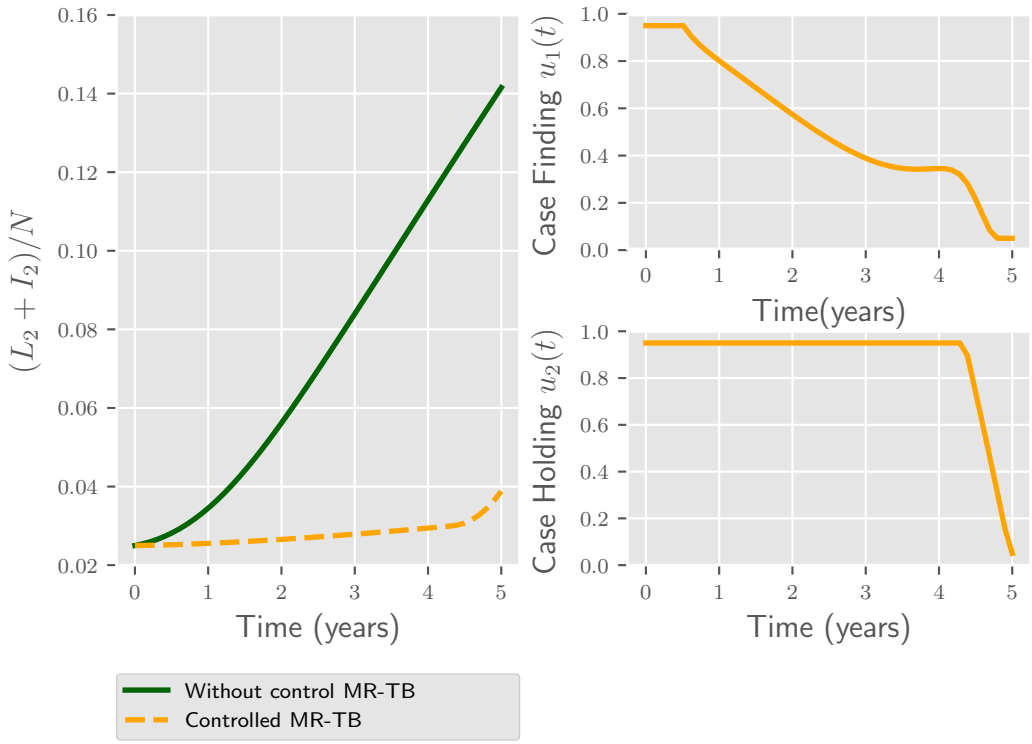

FIGURE 5. Normalized infected population according to parameters of Table 7. Here the green line represents the infected population without control. As we see, combining case finding $u_1(t)$ and case holding $u_2(t)$, dramatically diminish the density of infected with resistant TB.

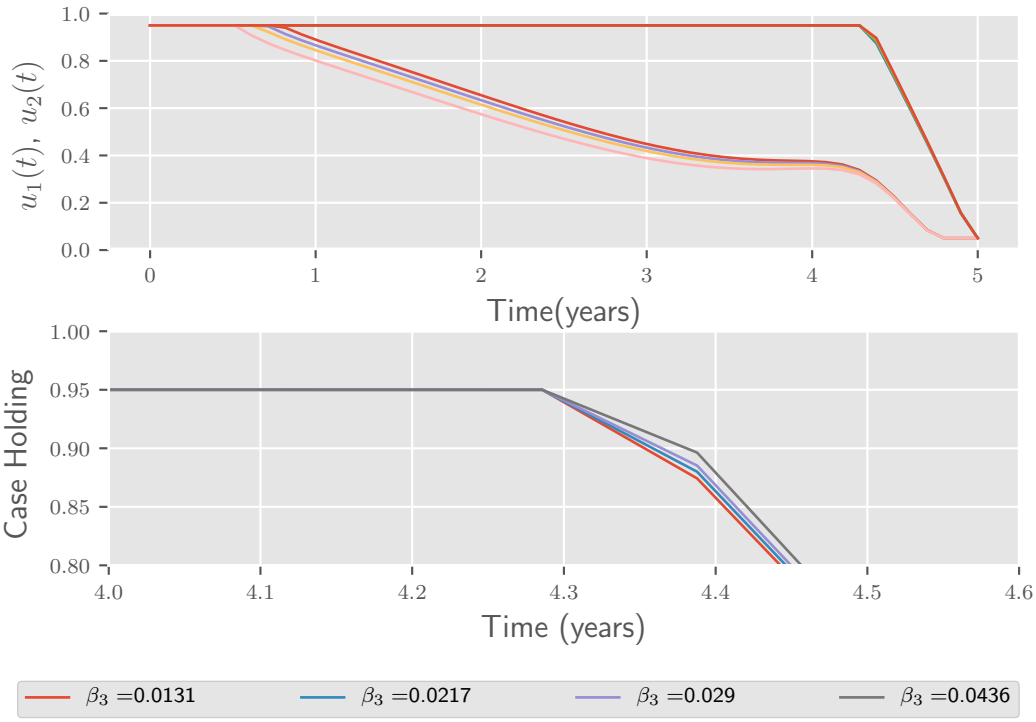

FIGURE 6. At top, case finding and case holding controls under parameters encased in Table 7 and different values of parameter β_3. At bottom, we capture a smaller region to illustrate the variations regarding to case holding. Simulation suggests that case holding remains almost with the same profile, while case finding delays same period for only for a few months.

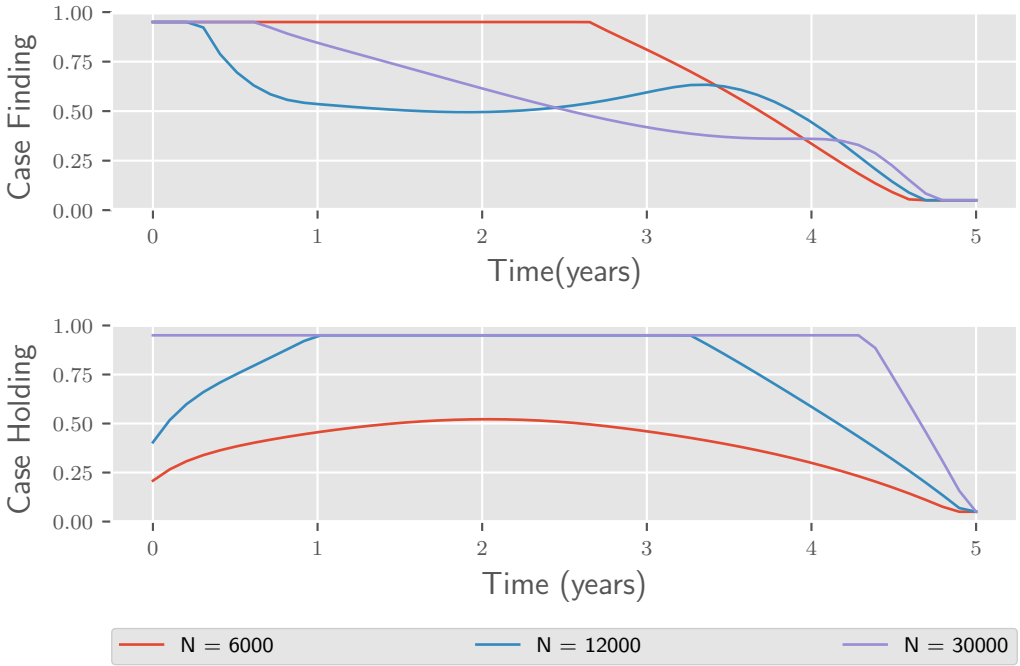

FIGURE 7. The effect of different sizes of population. For relatively small population, the case finding strategy is more important than case finding, meanwhile for bigger populations, the case holding plays a more important role. The rest of parameters as in Table 7.

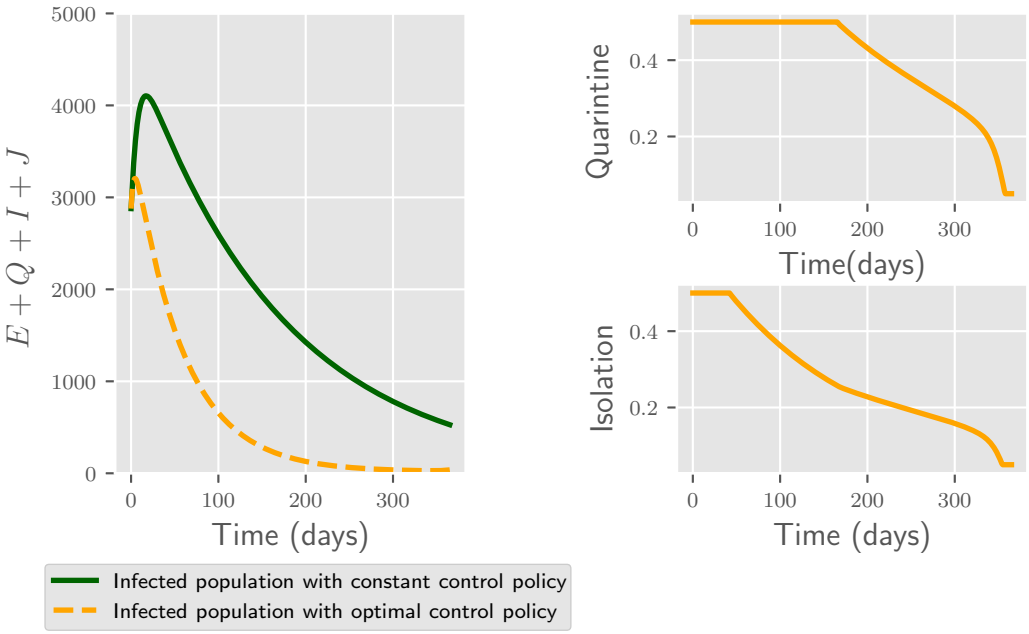

FIGURE 8. On the left, a likening of the whole infected population without constant control and under the optimal control policy.

6.4. **Isolation and quarantine for SARS.** Since SARS lacks of valid medicines or vaccines, measures to control the spread of SARS had to take two major forms: isolation of symptomatic individuals and quarantining and close observation of asymptomatic individuals [38]. We return to model (6) and obtain via the forward-backward-sweep method the optimal policies. We use the value parameters listed in Table 8.

Figure 8 displays on the left a likening between the controlled total infected population $E+Q+I+J$. Here we contrast the resulting dynamics using a constant policy (solid green), $\widehat{u}_1 = 0.2$, $\widehat{u}_2 = 0.2$ with the optimal quarantine and isolation control (dash orange) policies u_1, and u_2. At left, we see that in order to minimize the total infected individuals, optimal control quarantine u_1 is at its upper bound during more than 150 days, then u_1 is steadily decreased to the lower bound. Optimal control isolation u_2 stays at its upper bound about 70 days and then steadily decreases to the lower bound over the rest simulated time.

Parameters values			
β	0.2	d_1, d_2	0.0079, 0.0337
ε_E, ε_Q, ε_J	0.3, 0.0, 0.1	k_1, k_2	0.1, 0.125
μ	0.000 034		
Λ	μN		
p	0.0		
σ_1, σ_2	0.0337, 0.0386	**Initial conditions**	
		$S(0) = 12 \times 10^6$, $E(0) = 1565$,	
t_f	1.0 year	$Q(0) = 292$, $I(0) = 695$,	
Step size	$dt = 1.0$ day	$J(0) = 326$, $R(0) = 20$	
u_i bounds	0.05, 0.5		
B_1, B_2, B_3, B_4	1.0, 1.0, 1.0, 1.0		
C_1, C_2	300, 600		

TABLE 8. Parameter description for the SARS model (6).

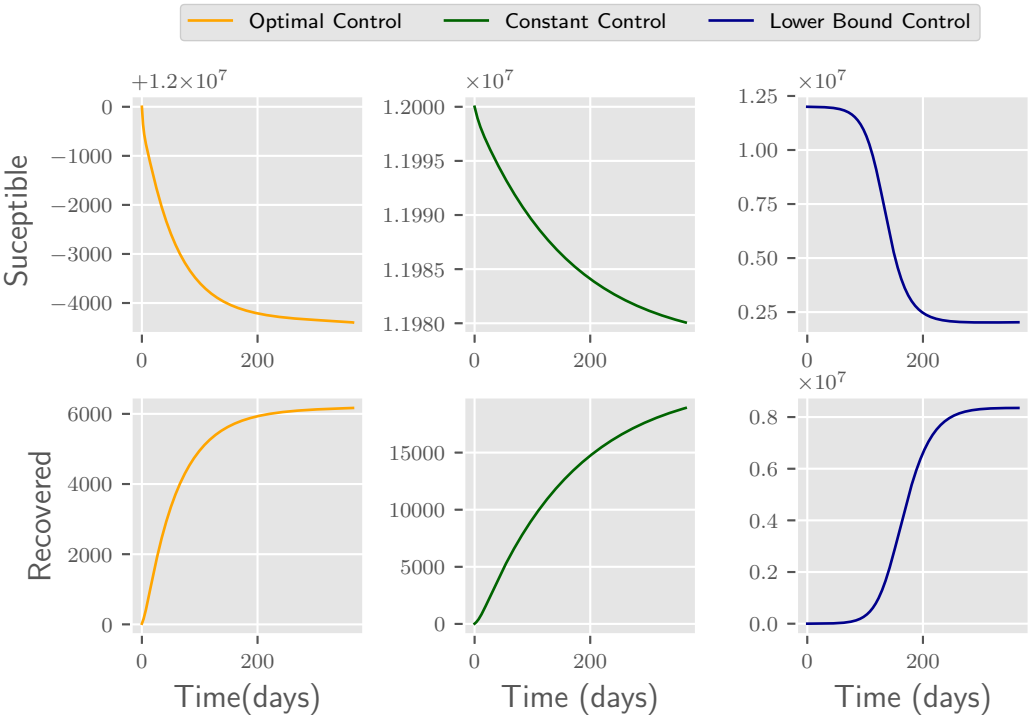

FIGURE 9. Susceptible and recover populations under optimal, constant and lower bound control policies.

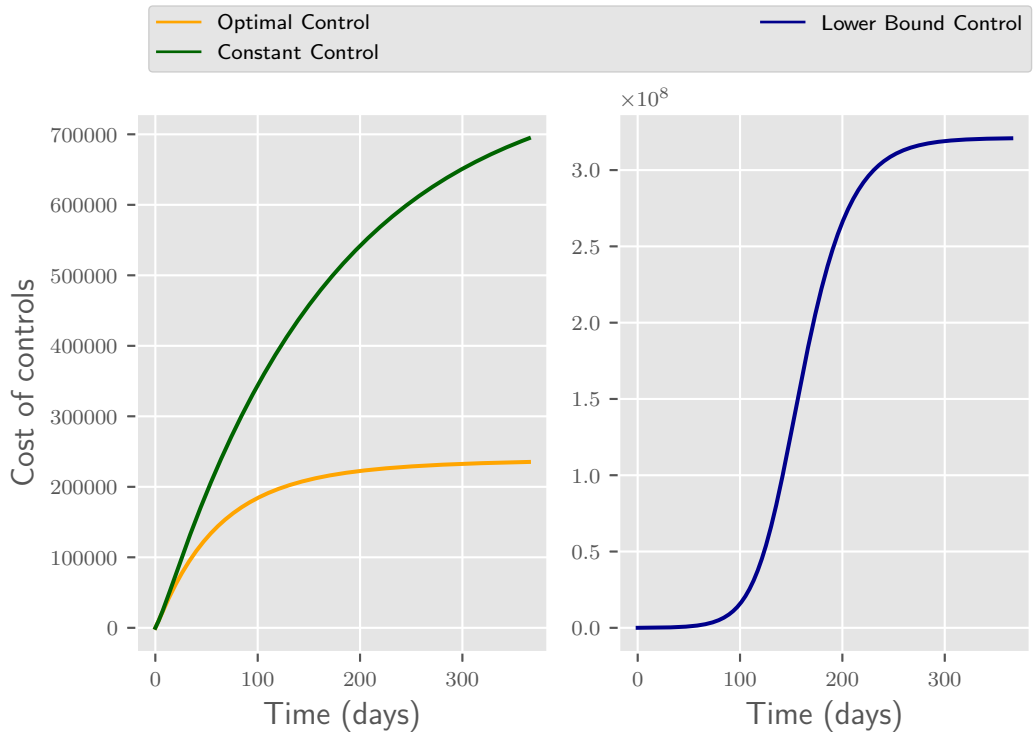

FIGURE 10. Cost of control-disease for the optimal, constant and lower bound policies, see Equation (7).

Figure 9 contrasts the evolution of the dynamics controlled with the optimal policy, a constant policy $\widehat{u}_1 = \widehat{u}_2 = 0.2$ and the lower bound policy, $\bar{u_1} = \bar{u_2} = 0.05$.

7. Concluding remarks

We end by mentioning some points that should be kept in mind when dealing with OCPs in epidemics.

Uniqueness of optimal policy. The proof of the uniqueness of the state path X_u, given a policy u, is fairly standard (Theorem **??**). However, the uniqueness of an *optimal policy* is not trivial and it can be established on some small enough interval; see, for instance, [14] and the references therein.

Numerical Issues. According with the forward-backward-sweep and multi shooting methods, both schemes needs a ODE solver one of its steps. However some times this solver generates spurious solutions as resulting of numeric instability. We see an opportunity to apply nonstandard numerical schemes which are consistent with the underlying conservations laws, see for example the work of Mickens [28].

Regarding to the application of genetic algorithms, it would be interesting to address the problem of considering the control functions as general functions and not only restricted to piecewise constant functions in the interval I. As far as we know, there is no work addressing the optimal control policies problem in this manner, and thus this paragraph intends to motivate further research in this direction.

Maximum principle vs. Dynamic programming. The same approach is followed in almost all the related literature on optimal control of epidemics/diseases. As an alternative, the so-called Dynamic programming approach can be used to analyze this kind of problems. With the Maximum principle we need to solve a system of ordinary differential equations (ODEs) whereas in Dynamic programming a partial differential equation (PDE) arises. In addition, both approaches involve an optimization problem. The Maximum principle is mostly used because there are plenty of methods to numerically solve ODEs.

By following the DP approach, the optimal policies are obtained in *feedback* (or *Markov*) form, i.e., the control policy is a function of the state of the system. Thus DP is a natural approach to solve stochastic models.

8. Appendix: Deterministic OCPs in continuous time

Consider the following *control system*

$$\dot{X}(t) = f(t, X(t), u(t)), \quad X(0) = x_0, \quad 0 \le t \le T, \tag{22}$$

where $f : [0,T] \times \mathbf{X} \times \mathbf{U} \to \mathbb{R}^n$ and $u : [0,T] \to U$. For each u, it is assumed that there exists a unique solution X_u to (22) (ensured, for instance, by Theorem **??**). In some applications the terminal state $X_u(T)$ is constrained to belong to a given set $\mathbf{B}$, then the set of *admissible controls* is defined

$$\mathbb{U}_{\mathbf{B}} := \{u : [0,T] \to \mathbf{U} \mid u \text{ is measurable and } X_u(T) \in \mathbf{B}\} \tag{23}$$

and $\mathbb{U}_{\mathbf{B}}$ is also assumed nonempty. A pair (u, X_u), where $u \in \mathbb{U}_{\mathbf{B}}$, is called an *admissible pair*. To ease notation, we simply write (u, X).

The following performance index is said to be in the *Bolza form*

$$V(u, x_0) := \int_0^T g(t, X(t), u(t))dt + h(X(T)), \tag{24}$$

where $g : [0,T] \times \mathbf{X} \times \mathbf{U} \to R$ and $h : \mathbf{X} \to \mathbb{R}$ are measurable. When $g = 0$ and $h \neq 0$, it is said to be in the *Mayer form*. Another form occurs when $h = 0$ and $g \neq 0$; in such a case, (24) is said to be in the *Lagrange form*. These three forms are equivalent; see, for instance, Cesari [10, Sect. 1.9].

In Section X.X we considered minimization problems, in contrast, in this appendix we consider maximization problems. The reason is due to the name *Maximum principle* which appears in (28). Then the OCP consists of finding an admissible control u^* such that

$$V(u, x_0) = \sup\{V(u, x_0) \mid u \in \mathbb{U}_{\mathbf{B}}\}$$

The elements of the OCP can be given in the following seven-tuple

$$(\mathbf{X}, \mathbf{U}, \mathbf{B}, f, g, h, T). \tag{25}$$

Assumption 1. The sets $\mathbf{X}$, $\mathbf{U}$, and $\mathbf{B}$ are compact. The functions f, g, and h are continuous.

A proof of the following theorem can be found, for instance, in Cesari [10, Sect. 9.3.] or Yong [41, Theorem 2.2.1].

Theorem 3 (Filippov). *Assume the OCP (25) satisfies Assumptions 1. If, for almost every t in $[0,T]$, each set*

$$F(t,x) := \{(\alpha, y) \in \mathbb{R} \times \mathbb{R}^n \mid \alpha \leq g(t,x,u),\ y = f(t,x,u),\ u \in \mathbf{U}\}, \qquad x \in X, \tag{26}$$

is convex, then there exists an optimal pair (u^*, X^*).

Define the *Hamiltonian*, for each $(t,x,u,\lambda_0,\lambda)$ in $[0,T] \times \mathbf{X} \times \mathbf{U} \times \mathbb{R} \times \mathbb{R}^n$,

$$H(t,x,u,\lambda_0,\lambda) := \lambda_0 g(t,x,u) + \lambda^\top f(t,x,u).$$

Assumption 2. (a) The function h is of class $\mathcal{C}^1$.
(b) For every (t,u,λ_0,λ), the function $H(t,\cdot,u,\lambda_0,\lambda)$ is of class $\mathcal{C}^1$.
(c) For every (t,x,λ_0,λ), the functions

$$H(t,x,\cdot,\lambda_0,\lambda) \text{ and } H_x(t,x,\cdot,\lambda_0,\lambda)$$

are continuous.

The following theorem is proved in Yong [41, Theorem 2.3.1].

Theorem 4 (Maximum Principle). *Suppose the OCP (25) satisfies Assumptions 1 and 2 hold and the set $\mathbf{B}$ is convex. Let (u^*, X^*) be an optimal pair. Then there exists a constant $\lambda_0 \geq 0$ and an absolutely continuous function $\lambda : [0,T] \to \mathbb{R}^n$, with*

$$(\lambda_0)^2 + \|\lambda(T) - \lambda_0 h_x(X^*(T))^\top\|^2 = 1, \tag{27}$$

that satisfy

(a) *the maximum condition, for almost every $t \in [0,T]$,*

$$\mathcal{H}(t, X^*(t), u^*(t), \lambda_0, \lambda(t)) \geq \mathcal{H}(t, X^*(t), u, \lambda_0, \lambda(t)) \quad \forall u \in \mathbf{U}, \tag{28}$$

(b) *the adjoint equation, for almost every $t \in [0,T]$,*

$$\dot{\lambda}(t) = -H_x(t, X^*(t), u^*(t), \lambda_0, \lambda(t))^\top, \tag{29}$$

(c) *and the transversality condition*

$$[\lambda(T)^\top - \lambda_0 h_x(X^*(T))][y - X^*(T)] \geq 0 \quad \forall y \in \mathbf{B}. \tag{30}$$

Remark 2. *As pointed out by Yong [41, p. 43], if $\mathbf{B} = \mathbb{R}^n$, then (30) implies*

$$\lambda(T) - \lambda_0 h_x(X^*(T))^\top = 0$$

and so $\lambda_0 = 1$ by (27). In such a case, the Hamiltonian takes the form

$$\mathcal{H}(t,x,u,\lambda) := g(t,x,u) + \lambda^\top f(t,x,u) = H(t,x,u,1,\lambda).$$

Then the form of the Hamiltonian used in Section XX is justified. Further, when $h = 0$, the adjoint equation (29) and the transversality condition (30) become

$$\dot{\lambda}(t) = -g_x(t, X^*(t), u^*(t))^\top - [f_x(t, X^*(t), u^*(t))]^\top \lambda(t), \quad \lambda(T) = 0$$

as in (17).

Consider the OCP (25) with $\mathbf{B} = \mathbb{R}^n$ and $h \equiv 0$. Define

$$\begin{aligned} \mathcal{H}^*(t,x,\lambda) &:= \sup_{u \in \mathbf{U}} \mathcal{H}(t,x,u,\lambda) \\ &= \sup_{u \in \mathbf{U}} \{g(t,x,u) + \lambda^\top f(t,x,u)\}. \end{aligned}$$

Assumption 3. The functions $\mathcal{H}$ and $\mathcal{H}_x$ are continuous.

Assumption 4. The functions $u^* : [0,T] \to \mathbf{U}$ and $X^* : [0,T] \to \mathbf{X}$ satisfy the following:
(a) u^* is piecewise continuous on $[0,T]$,
(b) X^* is continuous on $[0,T]$,
(c) $\dot{X}^*$ exists and it is piecewise continuous on $[0,T]$.

The following theorem is proved in Seierstad and Sydsæter [32, Theorem 3].

Theorem 5. *Suppose that Assumption 3 holds. Let (u^*, X^*) be an admissible pair that satisfies Assumption 4. Suppose that there exists a continuous function $\lambda : [0, T] \to \mathbb{R}^n$ such that*

$$\mathcal{H}(t, X^*(t), u^*(t), \lambda(t)) \geq \mathcal{H}(t, X^*(t), u, \lambda(t)) \quad \forall u \in \mathbf{U}, \tag{31}$$

and, except at the points of discontinuity of u^*,

$$\dot{\lambda}(t) = -\mathcal{H}_x(t, X^*(t), u^*(t), \lambda_0, \lambda(t))^\top, \quad \lambda(T) = 0. \tag{32}$$

If the set $\mathbf{X}$ is convex and, for each t, the function $\mathcal{H}^*(t, \cdot, \lambda(t))$ is concave on $\mathbf{X}$, then (u^*, X^*) is an optimal pair.

References

[1] U. Ascher, R. Mattheij, and R. Russell. *Numerical Solution of Boundary Value Problems for Ordinary Differential Equations*. Society for Industrial and Applied Mathematics, 1995. doi: 10.1137/1.9781611971231. URL https://epubs.siam.org/doi/abs/10.1137/1.9781611971231.

[2] Tapan P. Bagchi. *Multiobjective Scheduling by Genetic Algorithms*. Springer US, New York, 1999.

[3] Daniel Bernoulli. Essai d'une nouvelle analyse de la mortalité causée par la petite vérole, et des avantages de l'inoculation pour la prévenir. *Histoire de l'Acad., Roy. Sci.(Paris) avec Mem*, pages 1–45, 1760.

[4] Luca Bolzoni, Valentina Tessoni, Maria Groppi, and Giulio A. De Leo. React or wait: which optimal culling strategy to control infectious diseases in wildlife. *Journal of Mathematical Biology*, 69(4):1001–1025, oct 2014. ISSN 0303-6812. doi: 10.1007/s00285-013-0726-y. URL http://link.springer.com/10.1007/s00285-013-0726-y.

[5] George E. P. Box. Evolutionary operation: A method for increasing industrial productivity. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*, 6(2):81–101, 1957.

[6] Leslie Bradley, Daniel Bernoulli, and Jean Le Rond d'Alembert. *Smallpox inoculation: an eighteenth century mathematical controversy*. Continuing Education Press, 1971. ISBN 0902031236.

[7] Richard H. Byrd, Jorge Nocedal, and Richard A. Waltz. *Knitro: An Integrated Package for Nonlinear Optimization*, pages 35–59. Springer US, Boston, MA, 2006. ISBN 978-0-387-30065-8. doi: 10.1007/0-387-30065-1_4. URL https://doi.org/10.1007/0-387-30065-1_4.

[8] Marco Antonio Leonel Caetano and Takashi Yoneyama. Optimal and sub-optimal control in Dengue epidemics. *Optimal Control Applications and Methods*, 22(2):63–73, 2001. ISSN 01432087. doi: 10.1002/oca.683.

[9] Liming Cai, Xuezhi Li, Necibe Tuncer, Maia Martcheva, and Abid Ali Lashari. Optimal control of a malaria model with asymptomatic class and superinfection. *Mathematical Biosciences*, 288:94 – 108, 2017. ISSN 0025-5564. doi: https://doi.org/10.1016/j.mbs.2017.03.003. URL http://www.sciencedirect.com/science/article/pii/S0025556417301244.

[10] Lamberto Cesari. *Optimization—theory and applications*, volume 17 of *Applications of Mathematics (New York)*. Springer-Verlag, New York, 1983. ISBN 0-387-90676-2. doi: 10.1007/978-1-4613-8165-5. URL https://doi.org/10.1007/978-1-4613-8165-5. Problems with ordinary differential equations.

[11] Saúl Díaz-Infante, Francisco Peñuñuri, and David González-Sánchez. Python implementation of the forward-backward-sweep method for epidemic models. https://github.com/SaulDiazInfante/PythonLenhartCode, 2018. Accessed: Aug-15-2018.

[12] Christl A Donnelly, Rosie Woodroffe, DR Cox, John Bourne, George Gettinby, Andrea M Le Fevre, John P McInerney, and W Ivan Morrison. Impact of localized badger culling on tuberculosis incidence in british cattle. *Nature*, 426(6968):834, 2003.

[13] Ivo M. Foppa. *A Historical Introduction to Mathematical Modeling of Infectious Diseases. Seminal Papers in Epidemiology*. Academic Press, 1 edition, 2016. ISBN 0128022604,978-0-12-802260-3. URL http://gen.lib.rus.ec/book/index.php?md5=1fc878c650bd401495051a43f657e7ee.

[14] Holly Gaff and Elsa Schaefer. Optimal control applied to vaccination and treatment strategies for various epidemiological models. *Math. Biosci. Eng.*, 6(3):469–492, 2009. ISSN 1547-1063. doi: 10.3934/mbe.2009.6.469. URL https://doi.org/10.3934/mbe.2009.6.469.

[15] M Gerdts. User's guide oc-ode (version 1.4). Technical report, Technical report, Universität Würzburg, 2009.

[16] A. B. Gumel, S. Ruan, T. Day, J. Watmough, F. Brauer, P. van den Driessche, D. Gabrielson, C. Bowman, M. E. Alexander, S. Ardal, J. Wu, and B. M. Sahai. Modelling strategies for controlling sars outbreaks. *Proceedings of the Royal Society of London B: Biological Sciences*, 271(1554):2223–2232, 2004. ISSN 0962-8452. doi: 10.1098/rspb.2004.2800. URL http://rspb.royalsocietypublishing.org/content/271/1554/2223.

[17] Wolfgang Hackbusch. A numerical method for solving parabolic equations with opposite orientations. *Computing*, 20(3):229–240, 1978.

[18] Tomáš Hirmajer, Eva Balsa-Canto, and Julio R. Banga. Dotcvpsb, a software toolbox for dynamic optimization in systems biology. *BMC Bioinformatics*, 10(1):199, Jun 2009. ISSN 1471-2105. doi: 10.1186/1471-2105-10-199. URL https://doi.org/10.1186/1471-2105-10-199.

[19] John H. Holland. *Adaptation in Natural and Artificial Systems: An Introductory Analysis with Applications to Biology, Control, and Artificial Intelligence*. MIT Press, Cambridge, MA, 1975.

[20] Jang Junyoung, Jang Kihoon, Kwon Hee-Dae, and Lee Jeehyun. Feedback control of an hbv model based on ensemble kalman filter and differential evolution. *Mathematical Biosciences and Engineering*, 15(3):667–691, June 2018. ISSN 1551-0018. doi: 10.3934/mbe.2018030. URL http://aimsciences.org//article/id/76857b34-ec22-484d-9c83-07039dad313e.

[21] H. Keller. *Numerical Solution of Two Point Boundary Value Problems*. Society for Industrial and Applied Mathematics, 1976. doi: 10.1137/1.9781611970449. URL https://epubs.siam.org/doi/abs/10.1137/1.9781611970449.

[22] WO Kermack and AG Mckendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, 115(772):700–721, 1927. ISSN 0950-1207. doi: 10.1098/rspa.1927.0118. URL http://rspa.royalsocietypublishing.org/content/115/772/700.

[23] Peter Kühl, Joachim Ferreau, Jan Albersmeyer, Christian Kirches, Leonard Wirsching, Sebastian Sager, Andreas Potschka, Gerrit Schulz, Moritz Diehl, Daniel B Leineweber, et al. *MUSCOD-II Users Manual*. University of Heidelberg, 2007.

[24] A. Lahrouz, H. El Mahjour, A. Settati, and A. Bernoussi. Dynamics and optimal control of a non-linear epidemic model with relapse and cure. *Physica A: Statistical Mechanics and its Applications*, 496:299 – 317, 2018. ISSN 0378-4371. doi: https://doi.org/10.1016/j.physa.2018.01.007. URL http://www.sciencedirect.com/science/article/pii/S0378437118300074.

[25] Suzanne Lenhart and John T. Workman. *Optimal control applied to biological models*. Chapman & Hall/CRC Mathematical and Computational Biology Series. Chapman & Hall/CRC, Boca Raton, FL, 2007. ISBN 978-1-58488-640-2; 1-58488-640-4.

[26] Suzanne Lenhart, E. Jung, and Z. Feng. Optimal control of treatments in a two-strain tuberculosis model. *Discrete and Continuous Dynamical Systems - Series B*, 2(4):473–482, aug 2002. ISSN 1531-3492. doi: 10.3934/dcdsb.2002.2.473. URL http://www.aimsciences.org/journals/displayArticles.jsp?paperID=482.

[27] Peter A. Loeb. *Real analysis*. Birkhäuser/Springer, 2016. ISBN 978-3-319-30742-8; 978-3-319-30744-2. doi: 10.1007/978-3-319-30744-2. URL https://doi.org/10.1007/978-3-319-30744-2.

[28] Ronald E. Mickens. Numerical integration of population models satisfying conservation laws: Nsfd methods. *Journal of Biological Dynamics*, 1(4):427–436, 2007. doi: 10.1080/17513750701605598. URL https://doi.org/10.1080/17513750701605598. PMID: 22876826.

[29] L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelidze, and E. F. Mishchenko. *The mathematical theory of optimal processes*. Translated from the Russian by K. N. Trirogoff; edited by L. W. Neustadt. Interscience Publishers John Wiley & Sons, Inc. New York-London, 1962.

[30] Kenneth V. Price, Rainer M. Storn, and Jouni A. Lampinen. *Differential Evolution: A Practical Approach to Global Optimization*. Springer-Verlag, Berlin, 2005.

[31] Helena Sofia Rodrigues, M Teresa T Monteiro, and Delfim FM Torres. Optimal control and numerical software: an overview. *arXiv preprint arXiv:1401.7279*, 2014.

[32] Atle Seierstad and Knut Sydsaeter. Sufficient conditions in optimal control theory. *Internat. Econom. Rev.*, 18(2):367–391, 1977. ISSN 0020-6598. doi: 10.2307/2525753. URL https://doi.org/10.2307/2525753.

[33] J. Stoer, R. Bartels, W. Gautschi, R. Bulirsch, and C. Witzgall. *Introduction to Numerical Analysis*. Texts in Applied Mathematics. Springer New York, 2013. ISBN 9781475722727. doi: 10.1007/978-1-4757-2272-7.

[34] Rainer Storn and Kenneth Price. Differential evolution – a simple and efficient heuristic for global optimization over continuous spaces. *Journal of Global Optimization*, 11(4):341–352, 1997.

[35] Gerald Teschl. *Ordinary differential equations and dynamical systems*, volume 140 of *Graduate Studies in Mathematics*. American Mathematical Society, Providence, RI, 2012. ISBN 978-0-8218-8328-0. doi: 10.1090/gsm/140. URL https://doi.org/10.1090/gsm/140.

[36] Pauline van den Driessche. Reproduction numbers of infectious disease models. *Infectious Disease Modelling*, 2(3):288 – 303, 2017. ISSN 2468-0427. doi: https://doi.org/10.1016/j.idm.2017.06.002. URL http://www.sciencedirect.com/science/article/pii/S2468042717300209.

[37] Andreas Wächter and Lorenz T. Biegler. On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming. *Mathematical Programming*, 106 (1):25–57, Mar 2006. ISSN 1436-4646. doi: 10.1007/s10107-004-0559-y. URL https://doi.org/10.1007/s10107-004-0559-y.

[38] World Health Organization WHO. Consensus document on the epidemiology of severe acute respiratory syndrome (sars). http://www.who.int/csr/sars/en/WHOconsensus.pdf, May 2003. Accessed: Aug-15-2018.

[39] K. Wickwire. Mathematical models for the control of pests and infectious diseases: A survey. *Theoretical Population Biology*, 11(2):182 – 238, 1977. ISSN 0040-5809. doi: https://doi.org/10.1016/0040-5809(77)90025-9. URL http://www.sciencedirect.com/science/article/pii/0040580977900259.

[40] Xiefei Yan and Yun Zou. Optimal and sub-optimal quarantine and isolation control in sars epidemics. *Mathematical and Computer Modelling*, 47(1):235 – 245, 2008. ISSN 0895-7177. doi: https://doi.org/10.1016/j.mcm.2007.04.003. URL http://www.sciencedirect.com/science/article/pii/S0895717707001628.

[41] Jiongmin Yong. *Differential games: a concise introduction*. World Scientific, 2015.

[42] Tianhu Yu, Dengqing Cao, and Shengqiang Liu. Epidemic model with group mixing: Stability and optimal control based on limited vaccination resources. *Communications in Nonlinear Science and Numerical Simulation*, 61:54 – 70, 2018. ISSN 1007-5704. doi: https://doi.org/10.1016/j.cnsns.2018.01.011. URL http://www.sciencedirect.com/science/article/pii/S1007570418300170.