



OPTIMAL CONTROL OF EPIDEMIOLOGICAL SEIR MODELS WITH L^1 -OBJECTIVES AND CONTROL-STATE CONSTRAINTS

Helmut Maurer^{*} and Maria do Rosario de Pinho[†]

Abstract: Optimal control is an important tool to determine vaccination policies for infectious diseases. SEIR compartment models have been developed to describe the spread of a disease transmitted horizontally. Most of the literature on SEIR models deals with cost functions that are quadratic with respect to the control variable, the rate of vaccination. In this paper, we consider L^1 -type objectives that are linear with respect to the control variable. Various control, mixed control-state and pure state constraints are imposed. For each type of constraint, we discuss the necessary optimality conditions of the Maximum Principle and compute optimal control strategies that satisfy the necessary optimality conditions with high accuracy. Since the control variable appears linearly in the Hamiltonian, the optimal control is a concatenation of bang-bang arcs, singular arcs or boundary arcs. For bang-bang controls, we are able to check second-order sufficient conditions.

Key words: SEIR models, L^1 -objectives, optimal control, mixed control-state constraints, state constraints.

Mathematics Subject Classification: 49J15; 37N25, 37N40.

1 Introduction

The annual WHO report on infectious diseases points to the fact that infectious diseases continue to be one of the most important health problems worldwide. Mathematical models have become an important tool in describing the dynamics of the spread of a disease and the effect of vaccination and treatment [20]. A survey of epidemic models may be found in Hethcote [16, 17]. Based on such dynamic models, various vaccination and treatment policies have been studied using optimal control techniques [12,21,35]. Most of these papers assume a control-quadratic objective to measure the cost of vaccination or treatment. It has been argued in [34] that such L^2 -type objectives are rarely appropriate in biological and biomedical application.

In this paper, we study optimal vaccination policies in epidemiological SEIR models with L^1 -type objectives which are linear in the control variable (vaccination). SEIR models comprise four compartments, where S, E, I and R denote the number of individuals in the susceptible, exposed, infectious and and recovered compartment, respectively. The control

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variable is the rate of vaccination applied in the susceptible compartment. We shall consider various control, mixed control-state and pure state constraints. Our L^1 objective is the integral over the weighted sum of the number of infectious individuals and the (linear) cost of vaccines. We discuss the necessary optimality conditions of the Maximum Principle for all classes of control and state constraints and present numerical solutions that satisfy the necessary optimality conditions with high accuracy. In some cases, we are able to check sufficient optimality conditions.

In Section 2, several optimal control problems for SEIR models are discussed with different types of control and state constraints. In the following sections, we compare numerical solutions for two different weights in the control cost. Section 3 gives a brief account of numerical methods that we use in our computations. We focus on discretization and nonlinear programming methods for which efficient implementations have been developed in the last three decades. In Section 4, we consider the basic SEIR control problem with a simple control constraint. Since the control variable appears linearly in the Hamiltonian, the Maximum Principle leads to either bang-bang or singular controls. We derive an expression of the singular control in terms of the state and adjoint variable. The numerical solution furnishes an optimal control with a bang-singular-bang structure. The solution exhibits a rather high total number W of vaccines. For that reason, in Section 5 we consider a terminal constraint for the total number W(T) at the terminal time T. For a small weight in the control cost, the control has a bang-singular-bang structure, whereas for a larger weight the control is bang-bang with only one switch. Section 6 considers a mixed control-state constraint which was introduced by Biswas et al. [1]. The constraint is motivated by the observation that it is a more realistic scenario to consider a limited supply of vaccines at each instant of time than to merely limit the total amount of vaccines. Finally, in Section 7 we study the basic control problem with a pure state constraint, where an upper bound is imposed on the number of susceptible individuals.

2 Optimal Control Problems for SEIR Models with L¹–Objectives

In SEIR models, the population is divided into four compartments. An individual is in the S compartment if susceptible (vulnerable) to the disease. Those infected, but not able to transmit the disease, are in the E compartment of exposed individuals. Infected individuals capable of spreading the disease are in the I compartment and those who are immune are in the R compartment. In SEIR models, everyone is assumed to be susceptible to the disease by birth and the disease is transmitted to the individual by horizontal incidence, i.e., a susceptible individual becomes exposed when in contact with infectious individuals. Let S(t), E(t), I(t), and R(t) denote the number of individuals in the susceptible, exposed, infectious and recovered compartments at time t respectively. The total population is

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

The disease transmission in a certain population is described by the parameters e, the rate at which the exposed individuals become infectious, g, the rate at which infectious individuals recover, and a, the death rate due to the disease. Also b is the natural birth rate and d denotes the natural death rate. Let c be the incidence coefficient of horizontal transmission. Then the rate of transmission of the disease is cS(t)I(t). For simplicity, the parameters are assumed as constants although they may vary in reality if the time horizon is large. Recall that the control u(t) represents the *rate of vaccination per unit time*. It is assumed that all vaccinated susceptible individuals become immune.

In the following, we consider the dynamical system of a SEIR model which is similar to that in Neilan, Lenhart [29] and takes into account the variable population size N(t); cf. the SIR model in Ledzewicz, Schättler [20]:

$$\dot{S}(t) = bN(t) - dS(t) - cS(t)I(t)/N(t) - u(t)S(t), \qquad S(0) = S_0, \qquad (2.1)$$

$$\dot{E}(t) = cS(t)I(t)/N(t) - (e+d)E(t),$$
 $E(0) = E_0,$ (2.2)

$$I(t) = eE(t) - (g + a + d)I(t),$$
 $I(0) = I_0,$ (2.3)

$$\dot{N}(t) = (b-d)N(t) - aI(t),$$
 $N(0) = N_0$ (2.4)

Since u(t) represents the rate of vaccination per unit time, it is reasonable to impose a bound on the control which is chosen as

$$0 \le u(t) \le 1$$
 for $x t \in [0, T]$. (2.5)

The recovered population is related to the total population by

$$R(t) = N(t) - S(t) - E(t) - I(t),$$

which gives the differential equation

$$\dot{R}(t) = gI(t) - dR(t) + u(t)S(t), \quad R(0) = R_0.$$
 (2.6)

To keep track of the number of vaccinated individuals we introduce an extra variable W that satisfies the equation

$$\dot{W}(t) = u(t)S(t), \quad W(0) = 0.$$
 (2.7)

The papers by Biswas et al. [1], Neilan and Lenhart [29], Gaff and Schaefer [12] consider control quadratic cost functionals of L^2 -type. Schättler et al. [34] point out that a control quadratic cost is rarely appropriate for problems with a biological or biomedical background. Therefore, we consider a L^1 -cost functional that is linear with respect to the control variable u (cf. also [34]):

$$J(x,u) = \int_0^T (I(t) + Bu(t)) dt \quad (B > 0).$$
(2.8)

Our basic optimal control problem then consists of determining a piecewise continuous control function $u: [0,T] \to \mathbb{R}$ that minimizes the L^1 -type functional (2.8) subject to the dynamic constraints (2.1)–(2.4) and control constraint (2.5). We shall consider several extensions of the basic control problem. Firstly, as in Neilan and Lenhart [29] we impose the terminal constraint

$$W(T) \le W_T \quad \text{with} \quad W_T > 0. \tag{2.9}$$

Biswas et al. [1] argue that it is more realistic to limit the supply of vaccines at each time t rather than limiting the total number of vaccines as in the boundary condition (2.9). This leads to a *mixed control-state constraint* of the form:

$$u(t)S(t) \le V_0 \quad \text{for } x \ t \in [0, T],$$
(2.10)

where $V_0 > 0$ is an upper bound on vaccines available at each instant t. The inequality (2.10) is also known in the literature as state dependent control constraint. The constraint (2.9) will be satisfied only at the terminal time T, whereas the mixed constraint (2.10) should

hold at all times during the whole vaccination program. Furthermore, we shall consider the following pure state inequality constraint

$$S(t) \le S_{max} \quad \forall \ t \in [0, T].$$

Since the control u appears linearly in the system dynamics and the objective, the necessary optimality condition of Pontryagin's Maximum Principle show that any optimal control is a concatenation of arcs that are either of bang-bang or singular type. The notion "bang-bang arc" or "singular arc" even refers to the mixed constraint (2.10) itself which will be explained in section 6.

Table 1 presents the values of the initial conditions, parameters and constants which we use in our computations. Apart from the weight parameter B in the cost functional and the incidence coefficient c they coincide with those in [29]. The higher value c = 1.3 results from the fact that the value c = 0.001 in [29] has to be multiplied by an average value of the population size N to account for the variable population size N in the denominator of equations (2.1) and (2.2). In the following computations we shall keep the rather high birth

Table 1: Parameters with their clinically approved values and constants as in [1, 29].

Parameter	Description	Value
b	natural birth rate	0.525
d	natural death rate	0.5
c	incidence coefficient	1.3
e	exposed to infectious rate	0.5
g	recovery rate	0.1
a	disease induced death rate	0.2
B	weight parameter	$\in [2, 10]$
T	number of years	20
S_0	initial susceptible population	1000
E_0	initial exposed population	100
I_0	initial infected population	50
R_0	initial recovered population	15
N_0	initial population	1165
W_0	initial vaccinated population	0

rate b = 0.525 and death rate d = 0.5. However, using smaller values of birth and death rate we obtained the same optimal control structure, i.e., the same sequence of bang-bang and singular arcs.

3 Numerical Methods: Verification of Necessary and Sufficient Conditions

We obtain numerical solutions of the SEIR control problems by applying direct optimization methods, i.e., we discretize the control problem and use nonlinear programming methods. The discretized optimal control problem can be conveniently formulated as a nonlinear pogramming problem (NLP) with the help of the Applied Modeling Programming Language AMPL created by Fourer et al. [11]. AMPL can be interfaced to the Interior-Point optimization solver IPOPT, which was developed by Wächter and Biegler [36] to solve

large scale optimization problems. The task of formulating and solving the discretized control problem can be facilitated by employing the Imperial College London Optimal Control Software ICLOCS [10]. This is an optimal control interface, implemented in Matlab, that also calls the solver IPOPT. For a study of different optimal control solvers see [31].

In our computations, we mostly choose N = 10000 or N = 20000 grid points and the Implicit Euler Scheme or the Trapezoidal Rule to compute the solution with an error tolerance less than 10^{-8} . Alternatively, we use he control package NUDOCCCS developed by C. Büskens [3] (cf. also [4]) which provides another approach to solving discretized control problems using nonlinear programming methods. Since high-order adaptive integration methods are implemented in NUDOCCCS, one needs less than N = 1000 grid points to obtain highly accurate solutions.

Although we do not show in all cases that the numerical solution is indeed a (local) optimum, we do however validate our findings. Using the Lagrange multipliers provided by the optimization solver IPOPT or by NUDOCCCS, we can validate our numerical solution by showing that it satisfies the necessary condition of optimality with high accuracy. In the special case that the control is bang-bang, we can do better by showing that second-order sufficient conditions (SSC) are satisfied. Here, we solve the so-called *Induced Optimization Problem*, where switching times are directly optimized, and show that SSC are satisfied for the Induced Optimization Problem and that the strict bang-bang property holds; cf. Maurer, Büskens, Kim, Kaya [25] and Osmolovskii, Maurer [30]. The test of SSC can be conveniently carried out by implementing the *arc-parametrization method* [25] in the control package NUDOCCCS. This approach also allows to perform a sensitivity analysis of the optimal solution with respect to changes in the parameters.

4 Solution of the Basic Optimal Control Problem

4.1 Necessary Optimality Conditions: Maximum Principle

The basic optimal control problem is written in a compact form as

$$(OCP) \begin{cases} \text{Minimize} \quad J(x,u) = \int_0^T (I(t) + Bu(t)) \ dt \\ \text{subject to} \\ \dot{S}(t) &= bN(t) - dS(t) - cS(t)I(t)/N(t) - u(t)S(t), \quad S(0) = S_0, \\ \dot{E}(t) &= cS(t)I(t)/N(t) - (e+d)E(t), \qquad E(0) = E_0, \\ \dot{I}(t) &= eE(t) - (g+a+d)I(t), \qquad I(0) = I_0, \\ \dot{N}(t) &= (b-d)N(t) - aI(t), \qquad N(0) = N_0, \\ u(t) &\in [0,1] \text{ for } x \ t \in [0,T], \end{cases} \end{cases}$$

The state vector is given by x = (S, E, I, N). Since the control variable appears linearly in the dynamics, the right hand side of the ODEs has the form

$$\dot{x} = f(x) + g(x)u, \quad f(x) = \begin{pmatrix} bN - dS - cSI/N \\ cSI/N - (e+d)E \\ eE - (g+a+d)I \\ (b-d)N - aI \end{pmatrix}, \quad g(x) = \begin{pmatrix} -S \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$
(4.1)

The integrand of the objective is denoted by L(x, u) = I + Bu.

In the following, we shall evaluate the necessary optimality condition of the Maximum Principle for problem (OCP). Since we are maximizing -J(x, u), the standard Hamiltonian

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function is given by

$$H(x, p, u) = -\lambda L(x, u) + \langle p, f(x) + g(x)u \rangle, \quad \lambda \in \mathbb{R},$$

$$(4.2)$$

where $p = (p_S, p_E, p_I, p_N) \in \mathbb{R}^4$ denotes the adjoint variable.

Let $(x_*, u_*) \in W^{1,\infty}([0,T], \mathbb{R}^4) \times L^{\infty}([0,T], \mathbb{R})$ be an optimal state and control pair. Then the Maximum Principle (cf. [7,15,32]) asserts the existence of a scalar $\lambda \geq 0$, an absolutely continuous function $p: [0,T] \to \mathbb{R}^4$ such that the following conditions are satisfied almost everywhere, where the time argument [t] denotes the evaluation along the optimal solution:

- (i) $\max\{|p(t)| : t \in [0,T]\} + \lambda > 0$,
- (ii) (adjoint equation and transversality condition)

$$\dot{p}(t) = -H_x[t] = \lambda L_x[t] - \langle p(t), f_x[t] + g_x[t]u_*(t) \rangle, p(T) = (0, 0, 0, 0),$$

(iii) (maximum condition for Hamiltonian H)

$$H(x_*(t), p(t), u_*(t)) = \max_{u} \{ H(x_*(t), p(t), u) \mid 0 \le u \le 1 \}$$

The adjoint equations in (ii) for the adjoint variable $p = (p_S, p_E, p_I, p_N)$ are explicitly given by

$$\dot{p}_S(t) = p_S(t)(d + cI_*(t)/N_*(t) + u_*(t)) - p_E(t) c I_*(t)/N_*(t), \qquad (4.3)$$

$$\dot{p}_E(t) = p_E(t)(e+d) - p_I(t) e,$$
(4.4)

$$\dot{p}_I(t) = 1 + (p_S(t) - p_E(t)) c S_*(t) / N_*(t) + p_I(t)(g + a + d) + p_N(t) a, \qquad (4.5)$$

$$\dot{p}_N(t) = -p_S(t) b + (p_E(t) - p_S(t))c S_*(t) I_*(t) / N_*(t)^2 - p_N(t)(b-d).$$
(4.6)

To evaluate the maximum condition (iii) for the Hamiltonian H, we consider the *switching* function

$$\phi(x,p) = H_u(x,u,p) = -B - p_S S, \quad \phi(t) = \phi(x(t),p(t)).$$
(4.7)

Then the condition (iii) is equivalent to the maximum condition

$$\phi(t)u_*(t) = \max_u \{ \phi(t)u \mid 0 \le u \le 1 \}, \tag{4.8}$$

which gives the control law

$$u_*(t) = \left\{ \begin{array}{cccc} 1 & , & \text{if} & \phi(t) > 0 \\ 0 & , & \text{if} & \phi(t) < 0 \\ \text{singular} & , & \text{if} & \phi(t) = 0 \ \forall \ t \in [t_1, t_2] \subset [0, T] \end{array} \right\}.$$
(4.9)

Any isolated zero of the switching function $\phi(t)$ yields a switch of the control from 1 to 0 or vice versa. The control u is called *bang-bang* on an interval $[t_1, t_2] \subset [0, T]$, if the switching function $\phi(t)$ has only isolated zeros on $[t_1, t_2]$. The control u is called *singular* on an interval $[t_1, t_2] \subset [0, T]$, if the switching function $\phi(t)$ vanishes identically on $[t_1, t_2]$. The optimal control is a concatenation of arcs that are either bang-bang and singular.

Our computations in the next section show indeed that singular control arcs may occur. Hence, the singular case needs further analysis. To compute an expression for the singular

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control, we differentiate the relation $\phi(t) = -B - p_S(t)S(t) = 0$ holding on a time interval $[t_1, t_2] \subset [0, T]$. The derivatives can be computed using Lie-brackets; cf. Schättler, Ledzewicz [33]. Here, we compute the derivatives directly using the state and adjoint equations. For the first derivative we get omitting the time argument:

$$\dot{\phi} = p_E \, c \, I \, S/N - p_S \, b \, N = 0. \tag{4.10}$$

In agreement with the theory, the control variable u does not appear in the first derivative. From $\phi = -B - p_s S = 0$ we get $p_S = -B/S$. Substituting this expression into $\dot{\phi} = 0$ and multiplying with S, we obtain the relation

$$\dot{\phi} \cdot S = B \, b \, N + p_E \, c \, I \, S^2 / N = 0.$$
 (4.11)

The total time derivative of this equation yields $0 = \frac{d(\dot{\phi}S)}{dt} = \ddot{\phi}S$, since $\dot{\phi}(t) = 0$ holds. Using the state and adjoint equations again, we get an expression for the second derivative $\ddot{\phi}$ which contains the control variable u explicitly. Hence, the singular arc has order one. Setting $\ddot{\phi} = 0$ we can solve for the control variable u which yields the singular control

$$u_{sing}(x,p) = B b N((b-d)N - a I)/(p_E c I S^2) + e E/(2I) - (g + a - e)/2 + b N/S - d - c I/N.$$
(4.12)

The elimination of u from $\ddot{\phi} = 0$ is possible, since the *strict Generalized Legendre-Clebsch Condition* (GLC) holds:

$$\frac{\partial \ddot{\phi}}{\partial u} = -p_E \, 2 \, c \, I \, S/N > 0 \,. \tag{4.13}$$

This inequality follows from (4.11) in view of $p_E cIS/N = -BbN/S < 0$, N(t) > 0 and S(t) > 0.

4.2 Comparison of Solutions for B = 2 and B = 10

For both weights B = 2 and B = 10, AMPL/IPOPT and NUDOCCCS furnish the control structure

$$u(t) = \left\{ \begin{array}{ccc} 1 & \text{for} & 0 \le t < t_1 \\ u_{sing}(x(t), p(t)) & \text{for} & t_1 \le t \le t_2 \\ 0 & \text{for} & t_2 < t \le T \end{array} \right\}.$$
 (4.14)

The optimal state and control variables are shown in Figure 1. We do not exhibit the corresponding adjoint variables $p = (p_S, p_E, p_I, p_N)$ but only list the computed initial values p(0).

Numerical results for B = 2:

$$J = 211.498, t_1 = 6.67, t_2 = 10.98, S(T) = 1854.44, E(T) = 0.533561, I(T) = 0.375550, N(T) = 1861.07, R(T) = 5.72302, W(T) = 4379.26, (4.15) p_S(0) = -0.031835, p_E(0) = -0.92789, p_I(0) = -1.9944, p_N(0) = 0.025736.$$



Figure 1: State and control variables for basic control problem with control constraint $0 \le u(t) \le 1$: comparison for weights B = 2 and B = 10. Top row: (left) susceptible population S, (right) total population N. Row 2: (left) exposed population E, (right) infectious population I. Row 3 (left) recovered population R, (right) vaccinated individuals W. Bottom row: (left) B = 2. control u and (scaled) switching function ϕ satisfying the control law (4.9), (right) B = 10: control u and (scaled) switching function ϕ satisfying the control law (4.9).

Numerical results for B = 10:

$$J = 262.395, t_1 = 2.80, t_2 = 8.25, S(T) = 1852.57, E(T) = 1.60151, I(T) = 1.12569, N(T) = 1856.71, R(T) = 1.40908, W(T) = 2815.38, p_S(0) = -0.036259, p_E(0) = -1.0277, p_I(0) = -2.1343, p_N(0) = 0.028828.$$

$$(4.16)$$

The bottom row of Figure 1 clearly exhibits a significant difference of the controls for B = 2and B = 10, since the bang-bang arc with u(t) = 1 for B = 10 is much smaller than that for B = 2. Note, however, that the infectious population I(t) is nearly the same for both weights and, hence, the total population N is nearly identical in view of equation (2.4). We are not aware in the literature on epidemiological models that singular controls have actually been computed, though a theoretical analysis of singular controls in SIR models may be found in Ledzewicz, Schättler [20].

Note that the correctness of the formula (4.12) for the singular control can be checked in the following way: evaluate the singular control $u_{sing}(x(t), p(t))$ by inserting the computed state and adjoint variables (x(t), p(t)) into the formula (4.12) and then check whether the obtained values are in complete agreement with the values of the directly computed control u(t). In our problem, this is indeed the case.

For practical reasons it is convenient to approximate the bang-singular-bang by the following simpler control protocol, where the singular arc is replaced by a constant control u_c :

$$u(t) = \left\{ \begin{array}{ccc} 1 & \text{for} & 0 \le t < t_1 \\ u_c & \text{for} & t_1 \le t \le t_2 \\ 0 & \text{for} & t_2 < t \le T \end{array} \right\}.$$
 (4.17)



Figure 2: Weight B = 10: Comparison of basic and approximate control problem for control constraint $0 \le u(t) \le 1$. Top row: (left) control u in (4.14), (right) susceptible population S. Bottom row: (left) approximate control u in (4.17), (right) susceptible population S for approximate control u.

To optimize the constant control u_c and the switching times t_1 and t_2 we use the arcparametrization method [25] and implement the code NUDOCCCS with a Runge-Kutta method of 7th order.

Numerical results for the approximating control with B = 10:

$$J = 262.590, \quad u_c = 0.414934,$$

$$t_1 = 3.54707, \quad t_2 = 7.16272,$$

$$S(T) = 1852.70, \quad E(T) = 1.62707, \quad I(T) = 1.14359,$$

$$N(T) = 1856.73, \quad R(T) = 1.25718, \quad W(T) = 2782.16.$$
(4.18)

It is remarkable that the optimal value J = 262.590 of the approximate control problem is very close to the optimal value J = 262.395 in (4.16). Also it is noteworthy that secondorder sufficient conditions are satisfied for the induced optimization problem with respect to the optimization variables t_1, t_2, u_c . In Figure 2, the optimal and approximate control and susceptible population S are compared for B = 10.

5 Solution with Terminal Constraints $W(T) = W_T$

For the basic optimal control problem (OCP) we obtained the terminal value W(T) = 4379.26 for B = 2 and W(T) = 2815.38 for B = 10. In order to reduce the total number of vaccinated individuals, we prescribe as in [29] the much smaller terminal value W(T) = 2500. Then the necessary optimality conditions slightly change, since we have to take into account the equation (2.7) for W,

$$\dot{W}(t) = u(t) S(t), \quad W(0) = 0.$$

Now the state vector is $x = (S, E, I, N, W) \in \mathbb{R}^5$, while the adjoint variable is $p = (p_S, p_E, p_I, p_N, p_W) \in \mathbb{R}^5$. The adjoint equations $\dot{p}(t) = -H_x[t]$ are explicitly:

$$\dot{p}_{S}(t) = p_{S}(t)(d + cI_{*}(t)/N_{*}(t) + u_{*}(t)) - p_{E}(t) c I_{*}(t)/N_{*}(t) - p_{W}(t)u_{*}(t),
\dot{p}_{E}(t) = p_{E}(t)(e + d) - p_{I}(t) e,
\dot{p}_{I}(t) = 1 + (p_{S}(t) - p_{E}(t)) c S_{*}(t)/N_{*}(t) + p_{I}(t)(g + a + d) + p_{N}(t) a,
\dot{p}_{N}(t) = -p_{S}(t) b + (p_{E}(t) - p_{S}(t)) c S_{*}(t) I_{*}(t)/N_{*}(t)^{2} - p_{N}(t)(b - d),
\dot{p}_{W}(t) = 0.$$
(5.1)

The transversality condition is $(p_S, p_E, p_I, p_N)(T) = (0, 0, 0, 0)$, whereas no terminal condition is prescribed for the (constant) adjoint variable p_W . The modified *switching function* ϕ becomes

$$\phi(x,p) = H_u(x,u,p) = -B - p_S S + p_W S, \quad \phi(t) = \phi(x(t), p(t)).$$
(5.2)

Then the maximization of the Hamiltonian with respect to the control u gives the control law

$$u_*(t) = \left\{ \begin{array}{cccc} 1 & , & \text{if} & \phi(t) > 0 \\ 0 & , & \text{if} & \phi(t) < 0 \\ \text{singular} & , & \text{if} & \phi(t) = 0 \ \forall \ t \in [t_1, t_2] \subset [0, T] \end{array} \right\}.$$
 (5.3)

For B = 10 we get the bang-singular-bang control

$$u(t) = \left\{ \begin{array}{ll} 1 & \text{for} & 0 \le t < t_1 \\ u_{sing}(x(t), p(t)) & \text{for} & t_1 \le t \le t_2 \\ 0 & \text{for} & t_2 < t \le T \end{array} \right\}.$$
 (5.4)

Numerical results for B = 10:



Figure 3: State and control variables for the basic control problem with control constraint $0 \le u(t) \le 1$ and terminal constraint W(T) = 2500: comparison for weights B = 2 and B = 10. Top row: (left) susceptible population S, (right) total population N. Row 2: (left) exposed population E, (right) infectious population I. Row 3 (left) recovered population R, (right) vaccinated individuals W. Bottom row: (left) B = 2: control u and (scaled) switching function ϕ satisfying the control law (5.3), (right) B = 10: control u and (scaled) switching function ϕ satisfying the control law (5.3).

However, for B = 2 the control does not possess a singular arc and is bang-bang with one switch:

$$u(t) = \left\{ \begin{array}{ccc} 1 & \text{for} & 0 \le t < t_1 \\ 0 & \text{for} & t_1 < t \le T \end{array} \right\}.$$
 (5.6)

Thus, the Induced Optimization Problem has only one optimization variable t_1 .

Numerical results for B = 2 using the arc-parametrization method [25] :

J	=	223.682,	t_1	=	5.11953,				
S(T)	=	1852.48,	E(T)	=	1.89232,	I(T)	=	1.32995,	
N(T)	=	1856.51,	R(T)	=	0.810966,	W(T)	=	2500.0,	(5.7)
$p_S(0)$	=	-0.049169,	$p_E(0)$	=	-1.0282,	$p_I(0)$	=	-2.1236,	
$p_N(0)$	=	-0.0042893,	$p_W(t)$	\equiv	-0.019887.				

A comparison of optimal state and control variables is presented in Figure 3.

6 Solution for Mixed Control-State Constraint $uS \le 125$

In this section, we consider the pointwise mixed control-state constraint (2.10),

$$u(t)S(t) \le V_0 \quad \text{for } x t \in [0, T], \tag{6.1}$$

instead of the terminal condition $W(T) = W_T = 2500$. Since the time horizon is T = 20, a convenient choice of the bound is $V_0 = W_T/20 = 125$. We write the mixed control-state constraint in the form

$$m(x, u) = u S - V_0 \le 0. \tag{6.2}$$

On every boundary arc of the mixed constraint with m(x(t), u(t)) = 0, the following regularity condition holds:

$$m_u(x(t), u(t)) = S(t) \neq 0.$$
 (6.3)

6.1 Evaluation of the Maximum Principle

Let the pair (x_*, u_*) be a local minimum. We shall evaluate the necessary optimality condition of the *Maximum Principle* as given in [7] (cf. also [15,27]). We use again the standard Hamiltonian function (4.2) defined by

$$H(x, p, u) = -\lambda L(x, u) + \langle p, f(x) + g(x)u \rangle, \quad \lambda \in \mathbb{R}, \ p \in \mathbb{R}^4,$$

where $p = (p_S, p_E, p_I, p_N) \in \mathbb{R}^4$ denotes the adjoint variable. Then the *augmented* Hamiltonian is obtained by adjoining the mixed constraint by a multiplier $q \in \mathbb{R}$ to the Hamiltonian:

$$\mathcal{H}(x, p, q, u) = H(x, p, u) - q m(x, u).$$

Here, the minus sign is due to the fact that the Maximum Principle assumes that the controlstate constraint is written in the form $-m(x, u) = V_0 - u S \ge 0$. In view of the regularity condition (6.3), Theorem 7.1 in [7] (cf. also [15,27]) asserts the existence of a scalar $\lambda \ge 0$, an absolutely continuous function $p: [0,T] \to \mathbb{R}^4$ and an integrable function $q: [0,T] \to \mathbb{R}$ such that the following conditions are satisfied almost everywhere:

(i) $\max\{|p(t)|: t \in [0,T]\} + \lambda > 0$,

(ii) (adjoint equation and transversality condition)

$$\dot{p}(t) = -\mathcal{H}_x[t] = \lambda L_x[t] - \langle p(t), f_x[t] + g_x[t]u_*(t) \rangle + q(t) m_x[t],$$

$$p(T) = (0, 0, 0, 0),$$

(iii) (maximum condition for Hamiltonian H)

$$H(x_*(t), p(t), u_*(t)) = \max_{u} \{ H(x_*(t), p(t), u) \mid 0 \le u \le 1, \ m(x_*(t), u) \le 0 \},\$$

(iv) (local maximum condition for augmented Hamiltonian \mathcal{H})

$$\mu(t) = \mathcal{H}_u[t] = -L_u[t] + \langle p(t), g[t] \rangle - q(t) \, m_u[t] \in N_{[0,1]}(u_*(t)),$$

(v) (complementarity condition)

$$q(t) m(x_*(t), u_*(t)) = q(t) (u_*(t)S_*(t) - V_0) = 0$$
 and $q(t) \ge 0$.

In (iv), $N_{[0,1]}(u_*(t))$ stands for the normal cone from convex analysis to [0,1] at the optimal control $u_*(t)$ (see e.g. [5]) and it reduces to $\{0\}$ when $u^*(t) \in]0,1[$. Since the terminal state x(T) is free, it is easy to prove that the above necessary conditions hold with $\lambda = 1$; for a complete discussion see [1]. Hence, our problem is *normal*. We can further prove the existence of a constant K_q^1 such that

$$|q(t)| \le K_q^1 |p(t)| \tag{6.4}$$

for almost every $t \in [0, T]$ (see [7]).

Now we want to extract information from the conclusions (i)–(v) with $\lambda = 1$ which will be used later to validate our numerical solution. The adjoint equations in (ii) for the adjoint variable $p = (p_S, p_E, p_I, p_N)$ read explicitly:

$$\dot{p}_S(t) = p_S(t)(d + cI_*(t)/N_*(t) + u_*(t)) - p_E(t) c I_*(t)/N_*(t) + q(t)u_*(t), \quad (6.5)$$

$$\dot{p}_E(t) = p_E(t)(e+d) - p_I(t) e, \tag{6.6}$$

$$\dot{p}_I(t) = 1 + (p_S(t) - p_E(t)) c S_*(t) / N_*(t) + p_I(t)(g + a + d) + p_N(t) a,$$
(6.7)

$$\dot{p}_N(t) = -p_S(t) b + (p_E(t) - p_S(t))c S_*(t) I_*(t) / N_*(t)^2 - p_N(t)(b-d).$$
(6.8)

Next, we evaluate the maximum condition (iii) for the Hamiltonian H. As in (4.7) the switching function ϕ is given by

$$\phi(x,p) = H_u(x,u,p) = -B - p_S S, \quad \phi(t) = \phi(x(t),p(t)).$$
(6.9)

Then the condition (iii) is equivalent to the maximum condition

$$\phi(t)u_*(t) = \max_u \{ \phi(t)u \mid 0 \le u \le 1, \, u \, S_*(t) \le V_0 \}, \tag{6.10}$$

which yields the control law

$$u_*(t) = \left\{ \begin{array}{ccc} \min\left\{1, \frac{V_0}{S_*(t)}\right\} &, & \text{if } \phi(t) > 0\\ 0 &, & \text{if } \phi(t) < 0. \end{array} \right\}.$$
(6.11)

Any isolated zero of the switching function $\phi(t)$ yields a switch of the control from $\min\{1, V_0/S_*(t)\}$ to 0 or vice versa. If $\phi(t) = 0$ holds on an interval $[t_1, t_2] \subset [0, T]$, then we have a *singular control*. However, due to the small bound V_0 we did not obtain singular controls. Moreover, we always have $0 < u_*(t) < 1$ on a boundary arc of the mixed

constraint $uS \leq V_0$, i.e., whenever $u_*(t) = V_0/S_*(t)$ holds. Hence, the control is determined by

$$u_*(t) = \left\{ \begin{array}{ccc} V_0/S_*(t) &, & \text{if } \phi(t) > 0\\ 0 &, & \text{if } \phi(t) < 0. \end{array} \right\}.$$
(6.12)

Due to $0 < u_*(t) < 1$ the multiplier $\mu(t)$ in (iv) vanishes, which yields the relation

 $0 = \mu(t) = \mathcal{H}_u[t] = -B - p_S(t)S_*(t) - q(t)S_*(t).$

This allows us to compute the multiplier q(t) for which we get in view of the complementarity condition (v):

$$q(t) = \left\{ \begin{array}{ccc} -\frac{B}{S_*(t)} - p_s(t) = \phi(t)/S_*(t) &, & \text{if} \quad u_*(t) = V_0/S_*(t) \\ 0 &, & \text{if} \quad u_*(t) < V_0/S_*(t) \end{array} \right\}.$$
 (6.13)

6.2 Comparison of Optimal Solutions for Weights B = 2 and B = 10

For both weights B = 2 and B = 10 we find the following control structure with one boundary arc $u(t)S(t) = V_0$ in $[0, t_1]$:

$$u_*(t)S_*(t) = \left\{ \begin{array}{ccc} V_0 & , & \text{for } 0 \le t \le t_1 \\ 0 & , & \text{for } t_1 < t \le T \end{array} \right\}.$$
 (6.14)

Thus the new control variable v defined by v = uS is a bang-bang control with a single switch at t_1 . This transformation of control variables has been studied in Maurer, Osmolovskii [26]. Hence, the Induced Optimization Problem for the bang-bang control problem (cf. [25, 30]) has the single optimization variable t_1 and the cost functional becomes a function $J = J(t_1)$. The arc-parametrization method in [25] and the code NUDOCCCS provide the following results for B = 2,

$$J = 342.909, t_1 = 16.8862, \\ S(T) = 1763.12, E(T) = 3.21607, I(T) = 2.31859, \\ N(T) = 1821.98, R(T) = 53.3217, W(T) = 2110.77 \\ p_S(0) = -0.13858, p_E(0) = -1.5728, p_I(0) = -3.1689, \\ p_N(0) = 0.026592, (6.15)$$

and for B = 10,

$$J = 356.793, t_1 = 13.3784, S(T) = 1805.01, E(T) = 3.95907, I(T) = 2.79733, N(T) = 1821.60, R(T) = 9.82591, W(T) = 1672.31, p_S(0) = -0.13797, p_E(0) = -1.5855, p_I(0) = -3.1919, p_N(0) = 0.038863.$$
(6.16)

The optimal state variables for B = 2 and B = 10 are shown in Figure 4. Figure 5 displays the controls u and switching functions ϕ as well as the constraint functions u(t)S(t) in relation to the multiplier q in (6.13). It can be seen from Figure 5 that the following strict bang-bang property (cf. the definition in [25,30]) holds for B = 2 and B = 10:

$$\phi(t) > 0$$
 for $0 \le t < t_1$, $\phi(t_1) < 0$, $\phi(t) < 0$ for $t_1 < t \le T$



Figure 4: State variables for basic control problem with mixed control-state constraint $u(t)S(t) \leq 125$: comparison for weights B = 2 and B = 10. Top row: (left) susceptible population S, (right) total population N. Middle row: (left) exposed population E, (right) infectious population I. Bottom row: (left) recovered population R, (right) vaccinated individuals W.

Recall that the objective $J = J(t_1)$ is a function of the single optimization variable t_1 . The second derivative of $J(t_1)$ is computed as:

$$B = 10$$
: $J''(t_1) = 0.3530 > 0$; $B = 2$: $J''(t_1) = 0.1787 > 0$.

Hence, it follows from [30], Chapter 7, and [25] that the solutions shown in Figures 4 and 5 provide a strict strong minimum.

<u>7</u> Optimal Solution for State Constraint $S(t) \leq S_{max} = 1300$ and Terminal Constraint $W(T) \leq W_T$

We infer from Figure 1 that the susceptible population S(t) assumes rather large values, when only control constraints $u(t) \in [0, 1]$ are present. Imposing a smaller terminal value S(T) does not prevent the solution from reaching large intermediate values S(t). For that reason we require the point-wise state constraint (2.11),

$$S(t) \le S_{max} \quad \forall \ t \in [0, T], \tag{7.1}$$

with an appropriate value S_{max} that will be specified below. Let use first write the state constraint in the form

$$s(x) = S - S_{max} \le 0.$$
 (7.2)



Figure 5: State and control variables for basic control problem with mixed control-state constraint $u(t)S(t) \leq 125$: comparison for weights B = 2 and B = 10. Top row: Weight B = 2: (left) control u and (scaled) switching function ϕ , (right) function uS and multiplier q in (6.13). Bottom row: Weight B = 10: (left) control u and (scaled) switching function ϕ , (right) function uS and multiplier q in (6.13).

This is a state constraint of *order one*, since the control variable u appears in the first total time derivative of s(x), cf. [14,24]:

$$s^{(1)}(x,u) = \frac{d}{dt}s(x) = \dot{S} = bN - dS - cSI/N - uS.$$

The state constraint satisfies the regularity condition

$$\frac{\partial}{\partial u} s^{(1)}(x(t), u(t)) = S(t) \neq 0$$
(7.3)

on every boundary arc $[t_1, t_2] \subset [0, T]$ with $S(t) = S_{max}$. Then the boundary control $u = u_b(x)$ is determined by the equation $s^{(1)}(x, u) = 0$ as the feedback control

$$u = u_b(x) = bN/S - d - cI/N.$$
 (7.4)

When we choose small values for the upper bound $S_{max} \ge S(0)$, the terminal value W(T) can attain rather large values. For that reason we impose, as in Section 5, the constraint (2.9),

$$W(T) \le W_T \,,$$

and take into account the equation

$$\dot{W}(t) = u(t)S(t), \quad W(0) = 0.$$

7.1 Evaluation of the Maximum Principle

Now we shall evaluate the necessary optimality condition of the *Maximum Principle* as given in [14,24]. In view of the regularity condition (7.3), the multiplier associated with the state

constraint has a density q which is a differentiable function on the boundary arc [24]. The Hamiltonian function is given by

$$H(x, p, u) = -\lambda L(x, u) + \langle p, f(x) + g(x)u \rangle, \quad \lambda \in \mathbb{R}, \ p = (p_S, p_E, p_I, p_N, p_W) \in \mathbb{R}^5.$$

The *augmented* Hamiltonian is defined by adjoining the state constraint

$$-s(x) = S_{max} - S \ge 0$$

to the Hamiltonian H by a multiplier q, cf. [14]:

$$\mathcal{H}(x, p, q, u) = H(x, p, u) - q s(x) = H(x, p, u) - q(S - S_{\max}).$$

Let the pair (x_*, u_*) be a local minimum. In view of the regularity condition (7.3), the Maximum Principle in [14,24] asserts the existence of a scalar $\lambda \geq 0$, an absolutely continuous function $p : [0,T] \to \mathbb{R}^5$, an absolutely continuous function $q : [0,T] \to \mathbb{R}$, and jump parameters γ_s at any junction or contact time t_s with the state boundary, such that the following conditions are satisfied almost everywhere:

- (i) $\max\{|p(t)|: t \in [0,T]\} + \lambda > 0$,
- (ii) (adjoint equation, jump conditions and transversality condition)

$$\begin{split} \dot{p}(t) &= -\mathcal{H}_x[t] = \lambda L_x[t] - \langle p(t), f_x[t] + g_x[t]u_*(t) \rangle + q(t) \, s_x[t], \\ p(t_s+) &= p(t_s-) - \gamma_s \, s_x(x(t_s)), \quad \gamma_s \geq 0, \\ p(T) &= (0, 0, 0, 0, p_W(T)) \quad \text{if} \quad S_*(T) < S_{max}, \\ p(T) &= (p_S(T), 0, 0, 0, p_W(T)) \quad \text{if} \quad S_*(T) = S_{max}. \end{split}$$

(iii) (maximum condition for Hamiltonian H)

$$H(x_*(t), p(t), u_*(t)) = \max_{0 \le u \le 1} H(x_*(t), p(t), u).$$

(iv) (complementarity condition)

$$q(t) s(x_*(t)) = q(t) (S_*(t) - S_{max}) = 0$$
 and $q(t) \ge 0$.

We assume that the problem is normal so that we can put $\lambda = 1$ in the necessary conditions. This assumption will be verified by the numerical results. The adjoint equations in (ii) for the adjoint variable $p = (p_S, p_E, p_I, p_N, p_W)$ read explicitly:

$$\dot{p}_{S}(t) = p_{S}(t)(d + cI_{*}(t)/N_{*}(t) + u_{*}(t)) - p_{E}(t) c I_{*}(t)/N_{*}(t) + p_{W}(t)u_{*}(t) + q(t), \dot{p}_{E}(t) = p_{E}(t)(e + d) - p_{I}(t) e, \dot{p}_{I}(t) = 1 + (p_{S}(t) - p_{E}(t)) c S_{*}(t)/N_{*}(t) + p_{I}(t)(g + a + d) + p_{N}(t) a, \dot{p}_{N}(t) = -p_{S}(t) b + (p_{E}(t) - p_{S}(t))c S_{*}(t) I_{*}(t)/N_{*}(t)^{2} - p_{N}(t)(b - d). \dot{p}_{W}(t) = 0.$$

$$(7.5)$$

To evaluate the maximum condition (iii) for the Hamiltonian H, we need the *switching* function

$$\phi(x,p) = H_u(x,u,p) = -B - p_S S + p_W S, \quad \phi(t) = \phi(x(t), p(t)), \tag{7.6}$$

which agrees with the switching function (5.2). Then the maximum condition (iii) gives

$$u_{*}(t) = \begin{cases} 1 & , & \text{if } \phi(t) > 0, \\ 0 & , & \text{if } \phi(t) < 0, \\ \text{singular or boundary control} & , & \text{if } \phi(t) = 0 & \text{on } [t_{1}, t_{2}] \subset [0, T]. \end{cases}$$
(7.7)

A formula of a singular control $u_{sing}(x, p)$ on interior arcs with $S(t) < S_{max}$ was derived in (4.12) in Section 4.1. Recall that the boundary control (7.4) is given by $u_b(x) = bN/S - d - cI/N$. Computations show that $0 < u_b(x(t)) < 1$ holds along a boundary arc. This implies that $\phi(t) = 0$ holds on a boundary arc $[t_1, t_2]$. Hence, in view of (4.9) the boundary control behaves formally like a singular control; cf. Maurer [23]. Differentiating the relation $\phi = -B - p_S S + p_W S = 0$, using the modified adjoint equations (7.5) and noting that $p_W(t)S(t)$ is constant on a boundary arc, we get

$$\dot{\phi} = -p_S b N + p_E c I S/N - q S = 0.$$

This equation gives the multiplier for the state constraint as a function of the state and adjoint variables:

$$q = q(x, p) = -p_S b N / S + p_E c I / N.$$
(7.8)

7.2 Optimal Solution
$$S_{max} = 1300$$
, $W(T) = 3000$ and Weight $B = 10$.

We choose the upper bound $S_{max} = 1300$ in (7.1) and the terminal constraint $W(T) \leq W_T = 3000$. For both weights B = 2 and B = 10, the solutions are nearly identical. Therefore, we show only the solution for B = 10. The optimal control has two bang-bang arcs followed by a terminal boundary arc:

$$u_*(t) = \left\{ \begin{array}{ccc} 1 & \text{for} & 0 \le t < t_1 \\ 0 & \text{for} & t_1 \le t < t_2 \\ u_b(x(t)) & \text{for} & t_2 \le t \le T \end{array} \right\}.$$
 (7.9)

The boundary control $u_b(x)$ is given by the expression (7.4). Using this structure the Induced Optimization Problem consists of determining the two switching times t_1 and t_2 such that the conditions $S(t_2) = S_{max} = 1300$ and W(T) = 3000 are satisfied. The arc-parametrization method [25] and the control package NUDOCCCS yield the following numerical results:

$$J = 332.624, t_1 = 1.32399, t_2 = 7.68000, \\ S(T) = 1300.0, E(T) = 2.42694, I(T) = 2.04866, \\ N(T) = 1832.97, R(T) = 528.498, W(T) = 3000.0, \\ p_S(0) = -0.096943, p_E(0) = -2.3534, p_I(0) = -1.2543, \\ p_N(0) = -0.77412, p_S(T) = -0.076920.$$
 (7.10)

Figure 6, top row, left, shows that the control is *discontinuous* at the junction t_2 of the singular arc with the boundary arc. Then it follows from the junction theorems in Maurer [23] that the adjoint variable $p_S(\cdot)$ does not have a jump at t_2 , i.e., $\gamma_2 = 0$ holds in (ii). Hence, the adjoint variable $p_S(\cdot)$ is *continuous* on [0, T]; cf. Figure 6, bottom row, left.

We can check that the solution shown in Figure 6 satisfies second-order sufficient conditions (SSC) by applying the test of SSC in Maurer, Vossen [28]. The Jacobian of the equality constraints $S(t_1) = S_{max}$ and W(T) = 3000 with respect to the optimization variables t_1, t_2 is a regular 2 × 2-matrix. Moreover, the switching function $\phi(t)$ satisfies the following strict bang-bang property in relation to the boundary arc, where we have $\phi(t) = 0$ for all $t \in [t_2, T]$:

$$\phi(t) > 0 \quad \forall \ 0 \le t < t_1, \quad \phi(t_1) < 0; \quad \phi(t) < 0 \quad \forall \ t_1 < t < t_2, \quad \phi(t_2 -) > 0.$$



Figure 6: Weight B = 10: state variables for basic control problem with state constraint $S(t) \leq S_{max} = 1300$ and terminal constraint $W(T) \leq 3000$. Top row: (left) control u, (right) control u and (scaled) switching function ϕ in (7.6). Middle row: (left) susceptible population S and total population N, (right) exposed population E and infectious population I. Bottom row: (left) continuous adjoint variable p_S , (right) vaccinated individuals W.

8 Conclusion

We have studied the optimal control of an epidemiological SEIR model under various control and state constraints. In contrast to control-quadratic L^2 -type objectives, which are often used in the literature, we have assumed more realistic L^1 -type objectives with control appearing linearly. For each type of constraint, we have evaluated the necessary conditions of optimality of Pontryagin's Maximum Principle and derived explicit formulas of the multipliers associated with the mixed control-state constraint and pure state constraint. Since the control variable appears linearly in the Hamiltonian, the optimal control is a combination of bang-bang or singular arcs and boundary arcs of the constraints. By applying discretization and NLP methods we computed optimal control solutions that perfectly match the necessary conditions, in particular, the switching conditions and the sign of the multipliers on boundary arcs. For mixed control-state constraints, a simple control transformation allows us to convert the original control into a bang-bang control for which we could check the second order sufficient conditions in [26, 30]. The control and state trajectories were compared for two weight parameters in the L^1 objective.

In the future, we shall study SEIR models with vaccination and treatment stratgeis; cf. the SIR model in [20]. Also, we are planning a more systematic study of optimal control problems with L^1 -type objectives in the modeling of diseases, e.g., a study of the tuberculosis

model in Silva, Torres [35]. To make such models more realistic, we shall introduce delays in the state variables; cf. the survey [9] on dynamic epidemiological models with delays and also [8,18].

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References

- M.H.A. Biswas, L.T. Paiva and M.d.R. de Pinho, A SEIR model for control of infectious diseases with constraints, *Mathematical Biosciences and Engineering* 11 (2014) 761– 784.
- [2] F. Brauer and C. Castillo-Chavez, Mathematical Models in Population Biology and Epidemiology, Springer-Verlag. New York, 2001.
- [3] C. Büskens, Optimierungsmethoden und Sensitivitätsanalyse für optimale Steuerprozesse mit Steuer- und Zustands-Beschränkungen, Dissertation, Institut für Numerische Mathematik, Universität Münster, Germany, 1998.
- [4] C. Büskens and H. Maurer, SQP-methods for solving optimal control problems with control and state constraints: Adjoint variables, sensitivity analysis and real-time control, Journal of Computational and Applied Mathematics 120 (2000) 85–108.
- [5] F. Clarke, Optimization and Nonsmooth Analysis, John Wiley, New York, 1983.
- [6] F. Clarke, Functional Analysis, Calculus of Variations and Optimal Control, Springer-Verlag, London, 2013.
- [7] F. Clarke and MdR de Pinho, Optimal control problems with mixed constraints, SIAM J. Control Optim. 48 (2010) 4500–4524.
- [8] S. Eikenberry, S. Hews, J.D. Nagy and Y. Kuang, The dynamics of a delay model of Hepatitis B virus infection with logistic hepatocyte growth, *Mathematical Biosciences* 6 (2009) 283–299.
- [9] P. van den Driessche, Some epidemiological models with delays, Report DMS-679-IR, (1994), Dept. of Mathematics and Statistics, University of Victoria, Canada.
- [10] P. Falugi, E. Kerrigan and E. van Wyk, Imperial College London Optimal Control Software User Guide (ICLOCS), Department of Electrical and Electronic Engineering, Imperial College London, London, England, UK, 2010.
- [11] R. Fourer, D.M. Gay and B.W. Kernighan, AMPL: A Modeling Language for Mathematical Programming, Duxbury Press, Brooks-Cole Publishing Company, 1993.
- [12] H. Gaff and E. Schaefer, Optimal control applied to vaccination and treatment strategies for various epidemiological models, *Mathematical Biosciences and Engineering* 6 (2009) 469–492.

- [13] G.N. Galbraith and R.B. Vinter, Lipschits continuity of optimal controls for state constrained problems, SIAM J. Control Optimization 42 (2003) 1727–1744.
- [14] R.F. Hartl, S.P. Sethi and R.G. Vickson A survey of the maximum principles for optimal control problems with state constraints, SIAM Review 37 (1995) 181–218.
- [15] M.R. Hestenes, Calculus of Variations and Optimal Control Theory, 2nd Edition (405 pages), John Wiley, New York, 1980.
- [16] H.W. Hethcote, The Mathematics of Infectious Diseases, SIAM Review 42 (2000) 599–653.
- [17] H.W. Hethcote, The basic epidemiology models: models, expressions for R₀, parameter estimation, and applications. in *Mathematical Understanding of Infectious Disease Dynamics*, S. Ma and Y. Xia (eds.), Vol. **16**. Chap. 1, World Scientific Publishing Co. Pte. Ltd., Singapore, 2008, pp. 1–61.
- [18] A. Kaddar, A. Abta and H. T. Alaoui, A comparison of delayed SIR and SEIR epidemic models, Nonlinear Analysis: Modelling and Control 16 (2011) 181–190.
- [19] D. Kirschner, S. Lenhart and S. Serbin, Optimal control of the chemotherapy of HIV, J. Mathematical Biology 35 (1996) 775–792.
- [20] U. Ledzewicz and H. Schättler, On optimal singular control for a general SIR-model with vaccination and treatment, in *Discrete and Continuous Dynamical Systems*, Supplement 2011, pp. 981–990.
- [21] S. Lenhart and J.T. Workman, Optimal Control Applied to Biological Models, Chapman and Hall, 2007.
- [22] R. Martin and K.L. Teo, Optimal Control of Drug Administration in Cancer Chemotherapy, World Scientific, Singapore, 1994.
- [23] H. Maurer, On optimal control problems with bounded state variables and control appearing linearly, SIAM J. Control and Optimization 15 (1977) 345–362.
- [24] H. Maurer, On the Minimum Principle for optimal control problems with state constraints, Schriftenreihe des Rechenzentrums, Report no. 41, Universität Münster, Germany, 1979.
- [25] H. Maurer, C. Büskens, J.-H.R. Kim and Y. Kaya, Optimization methods for the verification of second-order sufficient conditions for bang-bang controls, *Optimal Control Methods and Applications* 26 (2005) 129–156.
- [26] H. Maurer and N.P. Osmolovskii, Second-order conditions for optimal control problems with mixed control-state constraints and control appearing linearly, in *Proceedings of* the 52nd IEEE Conference on Control and Design (CDC 2013), Firenze, 2013, pp. 514–519.
- [27] H. Maurer and S. Pickenhain, Second order sufficient conditions for optimal control problems with mixed control-state constraints, J. Optimization Theory and Applications 86 (1995), 649–667.

- [28] H. Maurer and G. Vossen, Sufficient conditions and sensitivity analysis for bang-bang control problems with state constraints, in *Proceedings of the 23rd IFIP Conference* on System Modeling and Optimization, Cracow, Poland, A. Korytowski, M. Szymkat (eds.), Springer Verlag, Berlin, 2009, pp. 82–99.
- [29] R.M. Neilan and S. Lenhart, An Introduction to Optimal Control with an Application in Disease Modeling, DIMACS Series in Discrete Mathematics 75 (2010) 67–81.
- [30] N.P. Osmolovskii and H. Maurer, Applications to Regular and Bang-Bang Control: Second-Order Necessary and Sufficient Optimality Conditions in Calculus of Variations and Optimal Control, SIAM Advances in Design and Control, 24, SIAM Publications, Philadelphia, 2013.
- [31] L.T. Paiva, Optimal Control in Constrained and Hybrid Nonlinear Systems, Project Report (2013), http://paginas.fe.up.pt/~faf/ProjectFCT2009/report.pdf.
- [32] L.S. Pontryagin, V.G. Boltyanski, R.V. Gramkrelidze and E.F. Miscenko, *The Mathe-matical Theory of Optimal Processes* (in Russian), Fitzmatgiz, Moscow; English translation: Pergamon Press, New York, 1964.
- [33] H. Schättler and U. Ledzewicz, Geometric Optimal Control. Theory, Methods and Examples, Springer, New York, 2012.
- [34] H. Schättler, U. Ledzewicz and H. Maurer Sufficient conditions for strong local optimality in optimal control problems with L²-type objectives and control constraints, *Discrete and Continuous Dynamical Systems*, Series B, 19 (2014) 2657–2679.
- [35] C.J. Silva and D.F.M. Torres, Optimal control strategies for tubercolosis treatment: A case study in Angola, *Numerical Algebra, Control and Optimization* 2 (2010) 601–617.
- [36] A. Wächter and L.T. Biegler, On the implementation of an interior-point filter linesearch algorithm for large-scale nonlinear programming, *Mathematical Programming* 106 (2006) 25–57.

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HELMUT MAURER Westflische Wilhelms-Universität Münster Institut für Numerische und Angewandte Mathematik Einsteinstr. 62 48149 Münster, Germany E-mail address: maurer@math.uni-muenster.de

MARIA DO ROSARIO DE PINHO University of Porto, Faculdade de Engenharia, ISR, Porto, Portugal E-mail address: mrpinho@fe.up.pt