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ON APPLICATION OF OPTIMAL CONTROL TO SEIR NORMALIZED MODELS: PROS AND CONS

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ABSTRACT. In this work we normalize a SEIR model that incorporates exponential natural birth and death, as well as disease-caused death. We use optimal control to control by vaccination the spread of a generic infectious disease described by a normalized model with L^1 cost. We discuss the pros and cons of SEIR normalized models when compared with classical models when optimal control with L^1 costs are considered. Our discussion highlights the role of the cost. Additionally, we partially validate our numerical solutions for our optimal control problem with normalized models using the Maximum Principle.

1. Introduction. Since the publication of the seminal paper [11] mathematical compartmental models are widely used to describe infectious diseases dymanics in large populations (see, for example [9], [4], [2] and [8]). It is well accepted that once an infected individual comes into contact with an unaffected population, the disease will spread by contact with the infectious individuals. Compartmental models divide the population into compartments characterizing the spread of the diseases and letters are used to denote the number of individuals in each compartment. Usually, the size of the population to be studied is N, S is the number of susceptible individuals and the number of infectious individuals is I. The letter R is also used to denote the number of those who *recover* from the disease or, as in [11], those who are *removed* from the disease by death or by recovery. The nature of the disease as well the reason why the models are studied may dictate the need for different compartments to be included. For example, SEIR models are used for diseases where infected individuals do not become immediately *infectious*; they are considered to be *exposed* to the disease and placed in compartment E, being moved to the *I* compartment only after some latent period of time.

The basic reproduction number, R_0 , measures the transmission potential of a disease (see, for example, [10]). It is defined as "the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population". From the mathematical point of view, it is an important concept when dealing with the dynamic systems defined by the compartmental models (SIR model, SEIR

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models, etc) because of its relevance to the stability of the equilibrium points. Indeed, there is a vast literature devoted to the stability analysis of such models; in this respect we refer the reader to [4] [2] and [8] (to name but a few!) and references within. Recently one has witnessed an increasing interest on applications of optimal control to such models (see [17], [13], [18], [1], [12], [6] and [16]). This comes as no surprise since optimal control theory has been a successful tool in the design of different control strategies for dynamic systems in general ([20]).

Many papers on optimal control applied to epidemiology propose L^2 costs (see, for example, [17] and [1]). One reason for this is that a closed form of the optimal control may be obtained, a form that facilitates the numerical verification of the solution (although, by itself, it does not guarantees that the solution is the optimal one since it usually depends on the multipliers). On the other hand, it has been argued that L^1 costs are appropriated to biological systems while those with L^2 costs are not ([13]). This reasoning may explain the attention optimal control problems with L^1 costs have recently gained; see, for example, [13], [12] and [16].

In this paper we focus on optimal control problems to control, via vaccination, the spread of a disease described by a SEIR model. We follow closely the approach in [16]: we consider L^1 costs, we solve the problems numerically applying the *direct method*, we use known software packages, and we present numerical solutions that satisfy necessary optimality conditions with high accuracy. Notably, and differing from [16], we work with a **normalized** SEIR model.

The normalized SEIR model differs from the usual SEIR model since the variables are *fractions* of the whole population instead of the number of individuals in each compartment. The theoretical and numerical treatment involving the latter model is usually done as if the variables are continuous and not integers; treating such variables as integers would demand the use of integer programming what is known to be very heavy computationally. When we turn to normalized models the variables are, by nature, continuous. In the literature, normalized models are common when the total population is assumed to remain constant during the time frame under study. This is not our case; here we normalize a SEIR model that incorporates exponential natural birth and death, as well as disease-caused death (similarly to what is done in [14]). As far as optimal control is concerned, normalizing such model brings out some new issues related to the choice of costs and the introduction of non standard constraints, questions we discuss here when comparing optimal control for normalized and not normalized SEIR models.

Herein, we refer to the SEIR model, where the variables S, E, I and R denote the number of individuals in each compartment, as the *classical SEIR model* as opposed to the *normalized SEIR model*.

We emphasize that we do not concentrate on any particular disease. Rather, our aim is to illustrate how previously proposed optimal control formulations can be handled by this new model, when different scenarios are considered. Taking into account that the set of parameters for the population in [16], based on [17], are not to be found in today's world, we use different population's parameters closed related to some European countries.

Like other models in epidemiology, SEIR models represent only a rough approximation of reality. However, they provide new insights into the spreading of diseases and, when optimal control is applied, new insight on different vaccination policies.

This paper is organized in the following way. In Section 2 we introduce an optimal control problem with L^1 cost involving the classical SEIR model and its

"normalized" counterpart. A brief description of our numerical methods as well as the tables with the set of parameters used in our simulation are presented in Section 3. Numerical methods give a helping hand for the discussion on the pros and cons of optimal control problems with classical and normalized models presented in Section 4. This discussion highlights the need for a criterious choice of cost. In Sections 5 and 6, we solve our optimal control problem numerically partially validating our solution using the maximum principle and the computed multipliers. Conclusions follow in the last section of this paper.

2. Optimal control problems for SEIR models with L^1 cost. The SEIR model is a compartmental model well accepted as modelling some infectious diseases. At each instant t, S(t), E(t), I(t), and R(t) denote the number of individuals in the susceptible, exposed, infectious and recovered compartments. The total population is N(t) = S(t) + E(t) + I(t) + R(t). We assume that our population has exponential natural birth rate b and death rate d and that that all newborns are susceptible to the diseases. The disease transmission is described by the parameters f, denoting the rate at which the exposed individuals become infectious, g, denoting the rate at which infectious individuals recover, a, denoting the death rate due to the disease and c, denoting the disease incidence coefficient of horizontal transmission (vertical transmission is not considered). The rate of transmission of the disease is $c \frac{I(t)}{N(t)}$. For simplicity the parameters a, b, c, d and f are assumed to be constants. For more information about such model we refer the reader to [2], [10], [17] and references within.

Optimal control techniques for SEIR models allow the study of different vaccines policies; different policies are confronted in [17] and [1] where the minimizing cost is L^2 , and in [16], covering the case of L^1 cost. As in the aforementioned works we assume that only susceptible people is vaccinated (implying that it is possible to distinguish between exposed and susceptible individuals) and that the vaccine is effective so that all vaccinated susceptible individuals become immune. Let u(t)represent the percentage of the susceptible individuals being vaccinated per unit of time. Taking all the above considerations into account we are led to the following dynamical system (see [17]):

$$\dot{S}(t) = bN(t) - dS(t) - c\frac{S(t)I(t)}{N(t)} - u(t)S(t), \qquad S(0) = S_0, \qquad (1)$$

$$\dot{E}(t) = c \frac{S(t)I(t)}{N(t)} - (f+d)E(t), \qquad E(0) = E_0, \qquad (2)$$

$$I(t) = fE(t) - (g + a + d)I(t), I(0) = I_0, (3)$$

$$\dot{N}(t) = (b-d)N(t) - aI(t),$$
 $N(0) = N_0,$ (4)

where S_0 , E_0 , I_0 and N_0 are nonnegative initial conditions.

For some $\bar{u} \ge 0$, we impose the following control constraint to u:

$$0 \le u(t) \le \bar{u} \quad a.e. \ t \in [0, T],\tag{5}$$

where T represents the period of time under consideration. The recovered population is related to the total population by N(t) = S(t) + E(t) + I(t) + R(t). Hence, R(t) = N(t) - S(t) - E(t) - I(t) which gives the differential equation

$$\dot{R}(t) = gI(t) - dR(t) + u(t)S(t), \quad R(0) = R_0.$$
 (6)

Here, the aim of applying optimal control to SEIR models is to control the spreading of the disease with some minimum financial cost. The cost should then be a weighted sum of the society financial costs of having, at each time, I(t) infected individuals and the cost of the vaccination effort what is mathematical translated as (7). This leads to the L^1 cost as in [16]:

$$J_C(X, u) = \int_0^T (AI(t) + Bu(t)) \, dt,$$
(7)

where X = (S, E, I, N) and A > 0, B > 0 are weight parameters related with financial costs.

Throughout this paper we refer to the optimal control problem of minimizing $J_1(X, u)$ over all $X \in W^{1,1}([0,T] : \mathbb{R}^4)$ and all piecewise continuous functions $u : [0,T] \to \mathbb{R}$ satisfying (1)-(6) and (5) as the *classical and basic* optimal control problem:

$$(P) \begin{cases} \text{Minimize} & \int_{0}^{T} (AI(t) + Bu(t)) \ dt \\ \text{subject to} \\ \dot{S}(t) &= bN(t) - dS(t) - c\frac{S(t)I(t)}{N(t)} - u(t)S(t), \qquad S(0) = S_{0}, \\ \dot{E}(t) &= c\frac{S(t)I(t)}{N(t)} - (f + d)E(t), \qquad E(0) = E_{0}, \\ \dot{I}(t) &= fE(t) - (g + a + d)I(t), \qquad I(0) = I_{0}, \\ \dot{N}(t) &= (b - d)N(t) - aI(t), \qquad N(0) = N_{0}, \\ u(t) \in & [0, \bar{u}] \quad \text{for a. e.} \quad t \in [0, T], \text{ with } \bar{u} \in]0, 1]. \end{cases}$$

Next, we associate (P) with a normalized optimal control problem. Normalizing models are obtained considering the percentage of the total population to be 1 at each instant t. Then, defining

$$s(t) = \frac{S(t)}{N(t)}, \quad e(t) = \frac{E(t)}{N(t)}, \quad i(t) = \frac{I(t)}{N(t)}, \quad r(t) = \frac{R(t)}{N(t)}, \tag{8}$$

we have

$$s(t) + e(t) + i(t) + r(t) = 1$$
 for all t. (9)

Notice that s(t) is the percentage of the population in compartment S(t), e(t) is the percentage of the population in compartment E(t), i(t) is the percentage of the population in compartment I(t) and r(t) be the percentage of the population in compartment R(t). The normalized counterpart of (1)-(6) is then:

$$\dot{s}(t) = b - cs(t)i(t) - bs(t) + ai(t)s(t) - u(t)s(t),$$
(10)

$$\dot{e}(t) = cs(t)i(t) - (f+b)e(t) + ai(t)e(t), \tag{11}$$

$$\dot{i}(t) = fe(t) - (g + a + b)i(t) + ai^{2}(t), \qquad (12)$$

$$\dot{r}(t) = gi(t) - rb(t) + ai(t)r(t) + u(t)s(t).$$
(13)

Remarkably, the dead rate parameters do not appear in this model (a feature we discuss in Remark 1 below). It is a simple matter to see that due to (9) we can discard equation (13), allowing us to reduce the number of differential equations from the normalized SEIR model (10)-(13).

Now we are faced with the choice of the cost for the normalized model. Taking into account that the main aim is to control or to eliminate the disease from the

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population under study, different costs is may be considered, reflecting different concerns.

The choice of the cost for (P) is based on the need to define vaccine policies to minimize some social and financial burden of the disease into the population. The cost J_C for (P) captures two easily recognized social and financial costs that the infectious disease imposes on a society; the burden of having people infected among the population, translated in J_C as AI(t), and the burden of vaccination to combat the spreading of the diseases, translated in J_C as Bu(t). Noteworthy, the weights A and B can be easily changed to reflect different scenarios.

An almost straightforward translation of this reasoning to our normalized model yields $J_n(x, u) = \int_0^T (\rho i(t) + u(t)) dt$, where x = (s, e, i) is now the state variable and ρ a parameter reflecting different weights on i and u. Numerically speaking, this cost is clearly different to J_C since its two terms are now both *percentages* while J_C has a weighted sum of two distinctive amounts. Not surprising, some simple tuning of ρ may lead to similar results specially in situations where the total population N does not vary much and, in particular, when the total population remains constant. However, J_n demands that the cost of infected people should be calculated in terms of the *percentage* of people infected instead of using the *number* of infected people as in J_C , something that depends on the economic practices.

We postpone this discussion of the introduction of different costs to future research and we proceed now with the cost J_n above for our normalized model. Putting all together we are led to the *normalized basic optimal control problem*:

$$(P_n) \begin{cases} \text{Minimize} & \int_0^T (\rho i(t) + u(t)) \ dt \\ \text{subject to} \\ \dot{s}(t) = & b - cs(t)i(t) - bs(t) + ai(t)s(t) - u(t)s(t), \quad s(0) = s_0, \\ \dot{e}(t) = & cs(t)i(t) - (f + b)e(t) + ai(t)e(t), \qquad e(0) = e_0, \\ \dot{i}(t) = & fe(t) - (g + a + b)i(t) + ai^2(t), \qquad i(0) = i_0, \\ u(t) \in & [0, \bar{u}] \quad \text{for a. e.} \quad t \in [0, T], \text{ with } \bar{u} \in]0, 1]. \end{cases}$$

Note that the dynamics is of the form $\dot{x}(t) = f(x(t)) + g(x(t))u$, with x = (s, e, i)and appropriate functions f(x) and g(x).

Remark 1. A word of caution regarding the way the system (10)-(13) is viewed. We cannot interpret the dynamics between these new compartments in the same way as with the classical model. Indeed, in equation (10) the term +ai(t)s(t) does not mean that those who died of the disease become susceptible as if reborn in a different compartment. Instead, this dynamical model can be better understood using fluid analogies in the following way. Consider a system with four tanks with the same amount of water circulating between them. At each instant t the total amount of water in the system is constant but the level of water in each tank varies. This analogy is presented in Figure 1 assuming that u(t) = 0. As mentioned before, (P_n) does not depend on the parameter d. This happens because the normal dead rate is equal for any compartment and thus it does not affect the distribution of population into compartments. On the other hand, the birth rate works as if feeding the susceptible compartment.



FIGURE 1. Fluid Analogy of the Normalized SEIR compartmental model.

We will discuss pros and cons of (P) and (P_n) using numerical solutions. Before that, however, we need to briefly present some remarks on the numerical tools and to describe the set of parameters used in our simulations.

3. Numerical methods and data for simulations. Optimal control problems can be solved numerically by direct or indirect methods. Here, we opt to use the direct method (for a description these two methods see, for example, [19]): first the problem is discretized and the subsequent optimization problem is then solved using software packages with large scale nonlinear continuous optimization solvers. In this work all the simulations were made with the Applied Modelling Programming Language (AMPL), developed by [7], and interfaced to the Interior-Point optimization solver IPOPT, developed by [21]. Alternatively, the optimization solver WORHP (see [3]) can also be interfaced with AMPL. We refer the reader to [16] and references within for more information on software for optimal control problems.

The application of the Maximum Principle to problems in the form of (P) (the control appearing linearly in the dynamics and the cost and with box control constraints) yields that the solution is a concatenation of bang-bang arcs and/or singular arcs. That is the case of (P_n) and (P). When the optimal control is bang-bang, sufficient second order optimality conditions (SSC) can be checked numerically; SSC as described in [15] and [19] can be checked with high accuracy using the control package NUDOCCCS. Alternatively they can also be tested with AMPL interfaced with IPOPTS or with WORHP.

In all the computations we consider the time horizon to be 20 years: thus T = 20. The parameters characterizing the population and the disease are in table 1. These

Parameter	Description	Value
b	Natural birth rate	0.01
d	Death rate	0.0099
с	Incidence coefficient	1.1
f	Exposed to infectious rate	0.5
g	Recovery rate	0.1
a	Disease induced death rate	0.2
Т	Number of years	20

TABLE 1. Parameters for SEIR models

parameters do not correspond to any specific population or diseases. In fact, f, a

and g are equal to those in [17], while c is adapted from the corresponding values in [17]. As for b and d, these are closely related to birth rates and death rate in European countries. The disease parameters correspond to a devastating disease as one can see either by calculating the reproduction number, which is higher than 1 (see [10]) or by solving the classical SEIR system ((1)-(6)) with u(t) = 0. In the next section, and when convenient, we use different parameters but this will be clearly stated. The values of the initial conditions follow those in [17]: for classical SEIR models they are presented at table 2 together with the parameters A and B of the objective functional. The initial conditions for the normalized problem (P_n) are presented at table 3.

Parameter	Description	Value
А	weight parameter	1
В	weight parameter	2
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

TABLE 2. Initial Conditions and cost parameters for problems with classical SEIR model

TABLE 3. Initial Conditions and cost parameters for problems with classical SEIR model normalized model.

Parameter	Description	Value
s_0	Percentage of initial susceptible population	0.858
e_0	Percentage of initial exposed population	0.086
i_0	Percentage of initial infected population	0.043

4. Comparison (P) with (P_n) . The problem (P) is sensitive to the dimension of the population. For example, the solution changes when we merely perturb the dead rate parameter, d, or when the initial values S_0 , E_0 , I_0 and R_0 are multiplied by a given positive constant. The first situation is illustrated in the left graph of figure 2, where the optimal control for a problem (P) with d = 0.0009 is shown together with the optimal control for a problems with d = 0.0005; although the profile of the optimal control is the same, the switching times do change. Sensitivity of (P)to different initial values is illustrated in the right graph of figure 2. For a smaller population the optimal control is of the bang-singular-bang type whereas, for a larger population it is bang-bang. In both cases, the percentages of susceptible, exposed and infected initial individuals is the same. Clearly, the cost is in the core of sensitivity of (P) with respect to the size of the initial population and also with respect to different death rates.

Although the two problem (P) and (P_n) are different, we can get (P_n) to produce approximately the same solutions of (P) as mentioned above. To do so, we need to



FIGURE 2. Optimal control for (P): parameters in tables 1 and 2. Left: Optimal control different dead rates: in red for d = 0.0099 and in blue for d = 0.0005. Right: Optimal control with different initial values. In red for S_0 , E_0 , I_0 and R_0 as in the table 2, in blue for initial conditions $S_0 \times 100$, $E_0 \times 100$, $I_0 \times 100$ and $R_0 \times 100$.

choose the parameter ρ in J_n to be $\rho = \frac{A \times \pi}{B}$, where A and B are the weights of I(t) and u(t) and π is an average of the total population during T. An example is shown in 3. Observe that if the total population remains almost constant, we can choose $\pi = N_0$.



FIGURE 3. Optimal control for (P_n) with $\rho = 500$ in blue. Optimal control calculated for (P) in blue. The parameters are described in Tables 1, 3, and 2.

Clearly, the reason why (P) and the (P_n) , with parameters associated to (P), differ resides on the cost. As mentioned before, the cost of J_n , introduced in section 2 as an adaptation of J_C , requires a fresh approach. Indeed, (P_n) demands that the "financial" cost be expressed in terms of percentages and not numbers of individuals.

When considering problem (P_n) , we are mainly concerned on how the total population is distributed into compartments. Because of the nature of the percentages we use, both the total number of the population as well as the dead rate are simply not there. The problem (P_n) may be useful to simulate the same disease acting on different sized populations but with similar birth rates. Observe also, that if needed, when solving (P_n) numerically we can keep track of the changes of the total the population by adding the differential equation $\dot{N}(t) = (b-d)N(t) - ai(t)N(t)$ to our code. This does not cause any change on the optimal control since the solution does

not depend on N. While (P_n) has the advantage of covering different populations in one go, it does not always subsumes or replaces (P). For example, the situation when one seeks vaccination policies when the total number of vaccines available are bounded (as in [17]) is tailored for the classical model (P). Mixed constraints like those introduced in [1], i.e., of the form

$$u(t)S(t) \le V_0,\tag{14}$$

can be mathematically translated to normalized models but they loose their meaning. However, this drawback may be overcome by considering $u(t) \in [0, \bar{u}]$, for a suitable contant $\bar{u} < 1$. This technique was also used in [16], for (P), as numerical simulations shows that the results obtained by using this strategy are similar to the solutions obtained by using the restriction described in (14).

5. Solution of (P_n) . We now focus on the *Maximum Principle* for the problem (P_n) . The Hamiltonian given by

$$H(x, p, u) = pf(x) + pg(x)u - \lambda(\rho i + u),$$

for appropriated f and g, x = (s, e, i) and where $p(t) = (p_s(t), p_e(t), p_i(t)) \in \mathbb{R}^3$ denotes the adjoint variable. Let $(x^*, u^*) \in W^{1,\infty} \times L^{\infty}$ be an optimal solution to (P_n) . Then the maximum principle [5] asserts the existence of a scalar $\lambda \geq 0$ and an absolutely continuous function p such that the following conditions are satisfied almost everywhere:

- (i) $\max\{|p(t)|: t \in [0,T]\} + \lambda > 0$ (nontriviality condition)
- (ii) $\dot{p}(t) = -H_x[t] = \langle p(t), f_x[t] + g_x[t]u^*(t) \rangle \lambda(0, 0, \rho)$ (adjoint condition),
- (iii) $H(x^*(t), p(t), u^*(t)) = \max_u \{H(x^*(t), p(t), u(t)) : 0 \le u \le \overline{u}\}$ (maximization of the Hamiltonian),
- (iv) p(T) = 0 (transversality condition).

Since (P_n) does not have final time constraints on the states, it is well known that the above conditions hold with $\lambda = 1$. Set $\phi(t) = H_u[t] = \langle p(t), g[t] \rangle - 1$. This is called the switching function and it is of help to deduce a characterization of the optimal control u^* from (i)–(iv) which we proceed to do next.

It is a simple matter to see that condition (iii) is equivalent to

$$\phi(t)u^*(t) = \max_{u} \{\phi(t)u(t) : 0 \le u \le \bar{u}\}.$$
(15)

It follows that u^* is bang-bang in an interval $I \subset [0, T]$, if the switching function ϕ has a finite number of isolated zeros at which the control switches between 0 and \bar{u} . If ϕ is zero on an interval, then u^* is singular, i.e.,

$$u^{*}(t) = \begin{cases} \bar{u} & , & \text{if } \phi(t) > 0, \\ 0 & , & \text{if } \phi(t) < 0, \\ \text{singular } , & \text{if } \phi(t) = 0. \end{cases}$$
(16)

In terms of the data of (P_n) the adjoint condition (ii) reads

$$-\dot{p}_s(t) = (ai(t) - ci(t) - b - u(t))p_s(t) + ci(t)p_e(t),$$
(17)

$$-\dot{p}_e(t) = (ai(t) - b - f)p_e(t) + fp_i(t),$$
(18)

$$-\dot{p}_{i}(t) = (as(t) - cs(t))p_{s}(t) + (cs(t) + ae(t))p_{e}(t) + (2ai(t) - a - b - g)p_{i}(t) - \rho.$$
(19)

Also, we have

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$$\phi(t) = -1 - p_s(t)s(t).$$
(20)

Since our computations show that a singular arc appear, let us assume that $\phi(t) = 0$ for t in an interval $I \subset [0, T]$ and check if we can obtain formulas for the singular controls. We work in the region¹

$$\mathcal{R} := \left\{ (s, e, i) \in \mathbb{R}^3 : s \ge 0, \ e \ge 0, \ i \ge 0 \right\}$$

and so we deduce that

$$\phi(t) = 0$$
 implies that $p_s(t) = -\frac{1}{s(t)} < 0.$

In the interior of the singular interval we have $\frac{d\phi}{dt} = 0$ and $\frac{d^2\phi}{dt} = 0$. Now

$$\frac{d\phi}{dt} = cs(t)i(t)p_e(t) - bp_s(t) = 0$$

implies that that $p_e = \frac{-b}{cs^2(t)i(t)} \leq 0$. Since

$$\frac{d^2\phi}{dt} = aci(t)^2 p_e(t)s(t) - aci(t)p_e(t)s(t) - bci(t)p_e(t)s(t)
+ cfe(t)p_e(t)s(t) - cgi(t)p_e(t)s(t) - c^2i(t)^2 p_e(t)s(t) - ci(t)p_e(t)s(t)u(t)
+ 2bci(t)p_e(t) + cfi(t)p_e(t)s(t) - cfi(t)s(t)p_i(t) + abi(t)p_s(t)
- bci(t)p_s(t) - b^2 p_s(t) - bp_s(t)u(t),$$
(21)

depends on the control variable u, we say that the singular control (if it exists) is of order one. Moreover, since $p_s(t) \leq 0$ and $p_e(t) \leq 0$, we have

$$\frac{d}{du}\left(\frac{d^2\phi}{dt}\right) = -ci(t)p_e(t)s(t) - bp_s(t) > 0.$$

Thus the strict Generalized Legendre- Clebsch Condition (GLC) holds and we can solve $\frac{d^2\phi}{dt} = 0$ with respect to the control variable to get

$$u_{sing}(x,p) = \frac{c(-c+a)s(t)i(t)^2 p_e(t)}{ci(t)p_e(t)s(t) + bp_s(t)} + \frac{cefs(t)p_e(t) - b^2 p_s(t)}{ci(t)p_e(t)s(t) + bp_s(t)} + \frac{((((-a-b+f-g)s(t)+2b)p_e(t) - fs(t)p_i(t) - bp_s(t))c + abp_s(t))i(t)}{ci(t)p_e(t)s(t) + bp_s(t)}$$
(22)

It is important to observe that the above expression for singular controls depends on the multipliers. Since we do not establish that the multipliers are unique, we can only expect to use (22) to validate numerical findings but not to prove to optimality. In fact, to prove optimality of computed solution we need to check numerically sufficient conditions. Unfortunately, there are no numerically verifiable sufficient conditions for problems with singular arcs.

¹Since the initial condition belong to the interior of \mathcal{R} and $\bar{u} \in]0,1]$, this statement is easily verified numerically.

6. Numerical solutions for (P_n) . We now present and discuss the results of our simulations for (P_n) . Recall that we use the data in table 1 and 3. We treat three different cases:

- Case 1: $\bar{u} = 1$ and $\rho = 500$,
- Case 2: $\bar{u} = 1$ and $\rho = 10$,
- Case 3: $\bar{u} = 0.2$ and $\rho = 500$.

In the first two cases the computed optimal control exhibits a bang-singular-bang structure while in the last one the optimal control is bang-bang. For all the three cases we present graphs with the computed controls and trajectories. As in [16] and to keep the exposition short, we do not present the graphs of the multipliers but we give their computed initial values, and we also present the final states, the costs and the switching times

Case 1. Taking \bar{u} to be 1 depicts the situation when all the susceptible population can be vaccinated. The results of the simulations are shown in figures 4 and 5. In Fig. 4 we show that the numeric optimal control and switching function, ϕ , satisfy (16) while the computed singular control (22) coincides with the computed optimal control u^* . The optimal trajectories are presented in Fig. 5.



FIGURE 4. Case 1: Computed optimal control u^* plotted together with the singular control computed according to (22) and with the switching function ϕ . During the first five years $\phi(t) > 1$ and during the last eight years $\phi(t) < 0$.



FIGURE 5. Case 1: optimal trajectories (including r).

Numerical results for	Case 1: $J = 327.15$,	$t_1 = 6.4, t_2 = 12.07,$
s(T) = 0.095341,	e(T) = 0.00051104,	i(T) = 0.0020380,
$p_s(0) = -126.5,$	$p_e(0) = -2253,$	$p_i(0) = -3219.$

Case 2. The results of the simulations are shown in figures 6 and 7. In figure 6 the optimal control, u^* , and the switching function, ϕ , are presented. As expected, $u^* = 1$ and $u^* = 0$ when, respectively, $\phi(t) > 0$ and $\phi < 0$. The optimal trajectories for the state are presented in figure 7.



FIGURE 6. Case 2: Computed optimal control u^* plotted together with the scaled switching function ϕ . During the last seventeen years $\phi(t) < 0$.



FIGURE 7. Case 2: optimal trajectories.

Numerical results for	case 2: $J = 10.181$,	$t_1 = 2.71,$	
s(T) = 0.16598,	e(T) = 0.0033060,	i(T) = 0.0079433,	
$p_s(0) = -377.0,$	$p_e(0) = -5137,$	$p_i(0) = -7081.$	

When we go from case 1 to case 2, the optimal control goes from singular to bang-bang. This is because when we decrease the value of ρ , the weight of the control in the cost increases.

Case 3. While keeping $\rho = 500$, we now consider that only 20% of the susceptible people are eligible to be vaccinated, i.e., $\bar{u} = 0.2$. Results of the simulations are illustrated in figures 8 and 9. In Fig. 8 the optimal vaccinate rate, u^* , and the switching function, ϕ , are presented. As expected, $u^*(t) = \bar{u} = 0.2$ and $u^* = 0$ when, respectively, $\phi > 0$ and $\phi < 0$. The trajectories for the state are presented in

Fig. 9. The profile of the optimal control is *bang-bang*. The control becomes equal to zero at instant $t_1 = 16.67$.



FIGURE 8. Case 3: Computed optimal control u^* plotted together with the scaled switching function ϕ . During the first sixteen years $\phi(t) > 0$ and during the last three years $\phi(t) < 0$.



FIGURE 9. Case 3: Optimal trajectories.

Numerical results for	case 3: $J = 806.12$,	$t_1 = 16.67,$
s(T) = 0.071623,	e(T) = 0.0031999,	i(T) = 0.015275,
$p_s(0) = -1025,$	$p_e(0) = -4692,$	$p_i(0) = -6872.$

6.1. Approximation for optimal control. If the control is bang-bang as in case 2 and 3 second order sufficient conditions may be checked numerically as described in [15] and [16]. Here we refrain from engaging in such discussion to keep the exposition short. Here we compute numerically the switching times using the so called *induced optimization problem* as in [15]. Recall that the switching times are the points t_{s1} at which the optimal control changes from one bound to another.

Implementing the *induced optimization problem* with AMPL for case 2, with $\rho = 10$ and $\bar{u} = 1$ and denoting by t_{s1} and J_s the computed switching time and cost, we get $t_{s1} = t_1 = 2.71$ and $J_s = 10.183$ which in contrast with J = 10.181 is a good approximation.

For case 3, with $\rho = 500$ and $\bar{u} = 0.2$, we have $t_{s1} = 16.63 < t_1 = 16 - 67$ while we get get a match for the cost $J_s = J = 806.12$.

We now turn to case 1 where the computed control u^* is of the form of *Bang-Singular-Bang*. As discussed in [16], singular controls may be hard to implemented in practice. To remedy this, [16] proposes to approximate the singular control by a constant value \tilde{u} . Here we do as in [16] to calculate the switching times defining the singular interval t_{s1} and t_{s2} , the value $0 \leq \tilde{u} \leq 1$ and the corresponding cost for case 1 where $\rho = 500$ and $\bar{u} = 1$. Using the arc parametrization method described in [15], now implemented in AMPL code, we obtain $t_{s1} = 7$, $t_{s2} = 11.5$, $\tilde{u} = 0.55$ with cost $J_s = 326.12$ a value very close to the previous J = 327.15. Figure 10 a comparison between u^* and u_{apr} is shown.



FIGURE 10. Optimal vaccinated rate, u^* , in red. Approximate control u_{apr} , in blue dash. $\rho = 500$ and $u \in [0, 1]$.

7. Conclusion. We studied the optimal control of an epidemiological normalized SEIR model using a L^1 -type objectives. We extracted information about the optimal solution from the Maximum Principle. In particular, we determined a closed form for the singular controls. Numerical NP solvers were applied to the discretized problem enabling us to compute optimal control solutions that match the necessary conditions, in particular, the switching conditions and forms for the singular controls.

Moreover, we confronted this problem with the one previously studied in [16] where the so called *classical* SEIR model is used. The normalized model may cover in one single problem populations of different size and it is defined with what may be seen as a more realistic cost. Because of the use of normalized model, the solution of (P_n) is dictated by the distribution of the population into the three different compartments and the disease characteristics. On the other hand, the normalized model has the disadvantage of not allowing the analysis of certain real situations that cannot be translated by percentages, such as when there is a limited stock of vaccine at a non-constant population. Our discussion of these two problems highlights their differences and the need for a criterion choice of cost, a challenging and relevant subject in optimal control for biomathematics problems.

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REFERENCES

- M. Biswas, L. Paiva and M. 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. Buskens and D. Wassel, The ESA NLP solver WORHP, Modeling and optimization in space engineering, *Springer Optim. Appl.*, Springer, New York, **73** (2013), 85–110.
- [4] V. Capasso, Mathematical Structures of Epidemic Systems, Springer-Verlag, Berlin Heidelberg, 2008.
- [5] F. Clarke, Optimization and Nonsmooth Analysis, John Wiley & Sons, New York, 1983.
- [6] M. de Pinho, I. Kornienko and H. Maurer, Optimal control of a SEIR model with mixed constraints and L¹ cost, Springer International Publishing, Switzerland, Lecture Notes in Electrical Engineering, **312** (2015), 135–145.
- [7] R. Fourer, D. Gay and B. Kernighan, AMPL: A Modeling Language for Mathematical Programming, Duxbury Press, Brooks-Cole Publishing Company, USA, 1993.
- [8] A. Friedman and C. Kao, Mathematical Modeling of Biological Processes, Springer, Switzerland, 2014.
- [9] H. Hethcote, The mathematics of infectious diseases, SIAM Review, 42 (2000), 599-653.
- [10] H. Hethcote, The basic epidemiology models: Models, expressions for r_0 , parameter estimation, and applications, Mathematical Understanding of Infectious Disease Dynamics (S. Ma and Y. Xia, Eds.), World Scientific Publishing Co. Pte. Ltd., Singapore, **16** (2009), 1–61.
- [11] W. O. Kermack and A. G. McKendrick, Contributions to the mathematical theory of epidemics, Proceedings of the Royal Society of London. Series A Containing papers of a Mathematical and Physical Nature, 115.
- [12] A. Korobeinikov, E. V. Grigorieva and E. N. Khailov, Optimal control for an epidemic in a population of varying size, *Discrete Contin. Dyn. Syst.*, (2015), 549–561.
- [13] U. Ledzewicz and H. Schaettler, On optimal singular controls for a general sir-model with vaccination and treatment supplement, *Discrete and Continuous Dynamical Systems, Series* B, 2 (2011), 981–990.
- [14] M. Y. Li, J. R. Graef, L. Wang and J. Karsai, Global dynamics of a SEIR model with varying total population size, *Mathematical Biosciences*, 160 (1999), 191–213.
- [15] H. Maurer, C. Buskens, J.-H. R. Kim and C. Y. Kaya, Optimization methods for the verification of second order sufficient conditions for bang-bang controls, *Optimal Control Applications* and Methods, 26 (2015), 129–156.
- [16] H. Maurer and M. R. de Pinho, Optimal control of seir models in epidemiology with l¹ objectives, https://hal.inria.fr/hal-01101291/file/Maurer-dePinho-SEIR.pdf (Accepted).
- [17] 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.
- [18] K. Okosun, O. Rachid and N. Marcus, Optimal control strategies and cost-effectiveness analysis of a malaria model, *Biosystems*, **111** (2013), 83–101.
- [19] N. P. Osmolovskii and H. Maurer, Applications to Regular and Bang-Bang Control: Secondorder Necessary and Sufficient Optimality Conditions in Calculus of Variations and Optimal Control, SIAM Advances in Design and Control, 24, SIAM Publications, Philadelphia, 2012.
- [20] H. Schaettler and U. Ledzewicz, Geometric Optimal Control. Theory, Methods and Examples, Springer, New York, 2012.

[21] A. Wächter and L. T. Biegler, On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming, *Mathematical Programming*, **106** (2006), 25–57.

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