

OPTIMAL CONTROL OF AN EPIDEMIC THROUGH EDUCATIONAL CAMPAIGNS

CÉSAR CASTILHO

ABSTRACT. In this work we study the best strategy for educational campaigns during the outbreak of an epidemic. Assuming that the epidemic is described by the simplified SIR model and that the total time of the campaign is limited due to budget, we consider two possible scenarios. In the first scenario we have a campaign oriented to decrease the infection rate by stimulating susceptibles to have a protective behavior. In the second scenario we have a campaign oriented to increase the removal rate by stimulating the infected to remove themselves from the infected class. The optimality is taken to be to minimize the total number of infected by the end of the epidemic outbreak. The technical tool used to determine the optimal strategy is the Pontryagin Maximum Principle.

1. INTRODUCTION

In this work we study the best strategy for educational campaigns during the outbreak of an epidemic. We assume that the epidemic is described by the simplified SIR model [16] and also assume that the total time of the campaign is budget limited. Optimality is measured minimizing the total number of infected at the end of the optimal outbreak. If we cannot make a campaign during all the epidemic time, what is the optimal way of using the time we have? How many campaigns should we make? What should be their intensities? When should they start? The difficult point is, of course, how to model the effect of the campaign on the spread of the epidemic. Here we face two problems: first, the model must be intuitively plausible and second, it must be mathematically tractable.

With respect to the first requirement we will model the campaign effects by reducing the rate at which the disease is contracted from an average individual *during* the campaign (called shortly infection rate). We justify this with an example: suppose during a flu outbreak one starts a campaign orienting susceptibles to avoid contracting the virus (assuming some protective behavior, e.g., washing hands, avoiding close environments, etc.). The effect of the campaign will be that the probability of a susceptible contracting the virus will decrease. The same reasoning applied to a campaign oriented to the infected (e.g. stimulating quarantine) will be modelled increasing the rate at which an average individual leaves the infective rate

2000 *Mathematics Subject Classification.* 92D30, 93C15, 34H05.

Key words and phrases. Epidemic; optimal control; educational campaign.

©2006 Texas State University - San Marcos.

Submitted September 21, 2005. Published October 11, 2006.

(called shortly removal rate). With respect to the second requirement we assume, for mathematical simplicity, that this reduction (increase) is bounded below (above) and the campaigns cost are linear on the controls. With those hypotheses the problem renders itself to analytical treatment and we can prove the main facts about the optimal campaign. The theorems of section 4 reduce the dimension of the optimal problem allowing a complete numerical study of the problem.

Application of control theory to epidemics is a very large field. A comprehensive survey of control theory applied to epidemiology was performed by Wickwire [17]. Many different models with different objective functions have been proposed (see [8, 9, 12] and more recently [3, 18]). A major difficulty in applying control theoretic methods to practical epidemiology problems is the commonly made assumption that one has total knowledge of the state of the epidemics [7].

2. STATEMENT OF THE PROBLEM

We denote by $S(t)$, $I(t)$, $R(t)$ the number of susceptible, infectives and removed in a closed population of size N at time t . We assume the controlled dynamics

$$\begin{aligned}\dot{S} &= -u_1SI, \\ \dot{I} &= u_1SI - u_2I, \\ \dot{R} &= u_2I,\end{aligned}\tag{2.1}$$

The above models assume a mass-action type interaction (for more realistic interactions see [4]). We let positive constants β and γ denote the infection and removal rates respectively without the influence of an education campaign. Our controls are $u_1(t), u_2(t)$ with $u_1(t) \in [\beta_m, \beta]$ and $u_2(t) \in [\gamma, \gamma_M]$ with $0 < \beta_m$. Observe that $u_1(t)$ and $u_2(t)$ regulate the goals and efforts of two types of campaigns. For example, if $u_2(t) = \gamma$ for all t we are controlling only the infection rate. In this case $u_1(t) = \beta$ will correspond to not having a campaign affecting the susceptibles and $u_1(t) = \beta_m$ will correspond to the maximum effort that can be made. The reciprocal case will be if $u_1(t) = \beta$ for all t . In this scenario we will be controlling only the removal rate γ . The above considerations motivate the introduction of the following cost constraints.

$$J_1 = \int_0^{t^*} [(\beta - u_1(t)) + (u_2(t) - \gamma)]I(t) dt,\tag{2.2}$$

$$J_2 = \int_0^{t^*} (\beta - u_1(t)) + (u_2(t) - \gamma) dt,\tag{2.3}$$

In both cases the cost is linear in the controls u_1 and u_2 . In the first case the cost of the campaign is supposed to be proportional to the number of infected (if one assumes that the number of infected is proportional to the number of regions where the disease occurs and therefore, to the number of regions to be covered by the campaign, higher the number of infected, higher the costs) . The second case assumes that the cost is independent of the number of infected.

Our goal will be to find the optimal control strategies that minimize the total number of infected over the course of the epidemic outbreak (equivalently, that maximize the total number of susceptibles). In this work, the end of the epidemic outbreak will be defined as a (very large) time instant t^* for which $I(t^*) < 1$ (see remark (2.1) about the existence of t^*). In other words, t^* is the first time such that

$I(t^*) < 1$. This is a technicality in order to avoid dealing with a infinite horizon control problem. Since in the simplified SIR model the only way to enter in the removed class is from the infected class, the total number of infected at the end of the epidemics is given by $\lim_{t \rightarrow \infty} R(t)$. However,

$$\dot{R} = \gamma I,$$

and since we always assume $R(0) = 0$, we obtain that the total number of infected is given by

$$\lim_{t \rightarrow \infty} R(t) = \int_0^{\infty} \gamma I(t) dt.$$

Remark 2.1. We make some remarks that are important for what follows.

- (1) Since $S(t) + I(t) + R(t) = N$ we will ignore the last equation of (2.1).
- (2) The set $M = \{I \geq 0, S \geq 0, S + I \leq N\}$ is an invariant set for system (2.1).
- (3) In the simplified SIR model we always have that $\lim_{t \rightarrow \infty} I(t) = 0$ (see e.g. [6]).

Since we are working only on M and the controls u_1 and u_2 are bounded and positive, we will always have that $\lim_{t \rightarrow \infty} I(t) = 0$ for any control. This establishes the existence of t^* .

The constant cost constraints J_1 and J_2 can be imposed introducing a new variable w to our system. We obtain the two control systems

$$\begin{aligned} \dot{S} &= -u_1 S I, \\ \dot{I} &= u_1 S I - u_2 I, \quad Y_1 = \int_0^{t^*} I(t) dt \\ \dot{w} &= \left((\beta - u_1(t)) + (u_2(t) - \gamma) \right) I(t), \quad w(0) = 0, \quad w(t^*) = C. \end{aligned} \quad (2.4)$$

with cost J_1 , and the system

$$\begin{aligned} \dot{S} &= -u_1 S I, \\ \dot{I} &= u_1 S I - u_2 I, \quad Y_2 = \int_0^{t^*} u_2(t) I(t) dt \\ \dot{w} &= (\beta - u_1(t)) + (u_2(t) - \gamma), \quad w(0) = 0, \quad w(t^*) = C. \end{aligned} \quad (2.5)$$

with cost J_2 . In both systems we are imposing $J_1 = J_2 = C$, where C is a constant.

Remark 2.2. The constant C is the value of the total amount of campaign effort. We will assume henceforth that C is such that the controls can not be at the maximum effort level during the whole time period.

The problems will be referred as problem C1 and C2 respectively. The goal is to find the optimal controls to (2.4) that minimize Y_1 and the optimal controls to (2.5) that minimize Y_2 . We will refer to the first problem as problem C1 and to the second problem as problem C2. As it will turn out, problem C1 is trivial. We will assume that the admissible controls u_1 and u_2 are measurable locally bounded functions. Since u_1 and u_2 appear linearly in our control problems, an optimal control will in general be a combination of bang-bang controls and singular controls (see [14, 11]).

3. OPTIMALITY PROBLEM C1

Problem C1 is such that all the differential equations involved are multiplied by the positive function $I(t)$. This motivates the introduction of a new parameter s defined by

$$s(t) = \int_0^t I(t)dt.$$

Observing that $\frac{d}{dt} = I \frac{d}{ds}$ we obtain for the objective functional that

$$Y_1 = \int_0^{t^*} I dt = \int_0^{s^*} ds = s^*,$$

where $s^* = \int_0^{t^*} I(t)dt$. Therefore, problem C1 write as the minimum time problem

$$\begin{aligned} S' &= -u_1 S, \\ I' &= u_1 S - u_2 \\ w' &= (\beta - u_1) + (u_2 - \gamma), \quad w(0) = 0, w(s^*) = C, \end{aligned} \tag{3.1}$$

where $' = \frac{d}{ds}$, and $s^* = \int_0^{t^*} I(t)dt$. Now we see that in order for the variable $w(s)$ achieve the value C in the smallest possible time s , it suffices that the derivative w' be the largest possible, therefore it suffices that $u_1(s) = \beta_m$ and $u_2(s) = \gamma_M$.

4. OPTIMALITY PROBLEM C2

Our main tool for the study of the optimality of system (2.5) will be the Pontryagin Maximum Principle (PMP) [1, 14]. Let p_S , p_I and p_w denote the adjoint variables to S , I , and w respectively. The Hamiltonian for problem C2 is

$$H = p_S(-u_1 SI) + p_I(u_1 SI - u_2 I) + p_w[(\beta - u_1(t)) + (u_2(t) - \gamma)] - u_2(t)I.$$

That we write as

$$H = g + u_1 \phi_1 + u_2 \phi_2, \tag{4.1}$$

where

$$g \equiv p_w(\beta - \gamma), \phi_1 \equiv SI(p_I - p_S) - p_w, \phi_2 \equiv -I(p_I + 1) + p_w.$$

The adjoint variables satisfy Hamilton's equations

$$\dot{p}_S = -\frac{\partial \mathcal{H}}{\partial S}, \quad \dot{p}_I = -\frac{\partial \mathcal{H}}{\partial I}, \quad \dot{p}_w = -\frac{\partial \mathcal{H}}{\partial w}, \tag{4.2}$$

that are given by

$$\begin{aligned} \dot{p}_S &= u_1 I(p_S - p_I), \\ \dot{p}_I &= u_1 S(p_S - p_I) + u_2(p_I + 1), \\ \dot{p}_w &= 0. \end{aligned} \tag{4.3}$$

By the PMP, the optimal controls $u_1(t)$, $u_2(t)$ are the ones that maximize \mathcal{H} (we are ignoring abnormal controls see [1]). PMP implies that at optimal trajectories the following transversality conditions will hold [14]

$$p_S(0) = p_I(0) = 0 \quad \text{and} \quad p_S(t^*) = p_I(t^*) = 0. \tag{4.4}$$

This is implied by the boundary conditions to be satisfied by w . The derivatives of the functions ϕ_1 and ϕ_2 along the flow of hamiltonian dynamical system induced by (4.1) can be computed using (2.5) and (4.3). We obtain

$$\dot{\phi}_1 = u_2 IS(p_S + 1), \quad (4.5)$$

$$\dot{\phi}_2 = -u_1 IS(p_S + 1). \quad (4.6)$$

From where it follows that

$$u_1 \dot{\phi}_1 + u_2 \dot{\phi}_2 = 0.$$

Remark 4.1. The existence of the optimal control for problem C_2 is given by an application of Filipov's theorem [1, 15]: We observe that the vector field X defined by (2.5) is bounded in M and complete (M is compact). Also the controls are bounded and for each fixed allowed pair (u_1, u_2) the set

$$\bar{X}(u_1, u_2) = \left\{ SI \begin{pmatrix} u_1 \\ -u_1 \\ 0 \end{pmatrix} + I \begin{pmatrix} 0 \\ u_2 \\ 0 \end{pmatrix}, \text{ for } S, I \in M \right\}$$

is convex, which implies that the set $X(u_1, u_2) = \{X \text{ for } S, I \in M\}$ is convex. To apply directly Filipov's theorem it remains to establish the compact support of the vector fields. But this is not necessary by the boundness and completeness of the vector fields (see discussion in [1] and [5]).

4.1. Controlling the infection parameter. In this subsection we will control only the infection parameter; i.e., we will assume $u_2(t) = \gamma$ for all $t \geq 0$. The pre-hamiltonian (4.1) is given by

$$H = \beta p_w - \gamma I(p_I + 1) + u_1(t)\phi_1. \quad (4.7)$$

We observe that the derivative of the switching function $\dot{\phi}_1 = \gamma SI(p_S + 1)$ is a continuous function and its number of zeros is determined only by the behavior of p_S since $-\gamma IS \neq 0$.

Lemma 4.2. *If $u_2(t) = \gamma$ in the control problem (2.5) then there is no open interval where $\phi_1(t) = \dot{\phi}_1(t) = 0$.*

Proof. Assume there exists an open interval \mathcal{D} , where $\phi_1(t) = \dot{\phi}_1(t) = 0$ for $t \in \mathcal{D}$. The derivative of ϕ_1 being zero implies that $p_S = -1$ in \mathcal{D} what implies that $\dot{p}_S = 0$ and by the first equation of (4.3) we have that $p_I = p_S = -1$ in \mathcal{D} ; but equations (4.3) imply that $p_I = p_S = -1$ for all future t ($p_I = p_S = -1$ is an equilibrium point for the vector field (4.3)) what contradicts the transversality condition (4.4). \square

Theorem 4.3. *If $u_2(t) = \gamma$ in the control problem (2.5), the optimal control $u_1^*(t)$ has at most two switches.*

Proof. First we observe that when $\phi_1 = 0$ we have by (4.7) that

$$H - \beta p_w = -\gamma I(p_I + 1).$$

For latter use we multiply this equation by $-\frac{S}{\gamma}$ obtaining the equality

$$SI(p_I + 1) = -\frac{S}{\gamma}(H - \beta p_w). \quad (4.8)$$

When $\phi_1 = 0$ we have that $SI(p_I - p_S) = p_w$. Solving for p_S and substituting back in $\dot{\phi}_1$, we obtain

$$\dot{\phi}_1 = \gamma SI(p_S + 1) = \gamma(SI(p_I + 1) - p_w).$$

Using (4.8), we obtain that at the zeros of ϕ_1 ,

$$\dot{\phi}_1 = (\beta p_w - H)S - p_w. \quad (4.9)$$

From equation (4.9) we define the function

$$h = (\beta p_w - H)S - p_w.$$

By the first equation of (2.1) we see that S is a strictly monotone function. Therefore since p_w and H are constant along the flow we have that h is a monotonic function. (4.9) shows that at the zeros of ϕ_1 , $\dot{\phi}_1 = h$. Therefore, we have that at the zeros of the C^1 function ϕ_1 , the values of its derivative $\dot{\phi}_1$ is a monotonic function. Therefore $\dot{\phi}_1$ can switch signs at most one time. What implies that ϕ_1 can have at most two switches of sign (and at most three zeros). \square

4.2. Controlling the removal parameter. In this section we will assume that $u_1 = \beta$ for all times. The pre-hamiltonian is

$$H = -p_w\gamma + \beta SI(p_I - p_S) + u_2\phi_2. \quad (4.10)$$

We observe that $\dot{\phi}_2 = -\beta SI(p_S + 1)$ is a continuous function.

Lemma 4.4. *If $u_1(t) = \gamma$ in the control problem (2.5) then there is no singular optimal control $u_2(t)$.*

The proof of the above lemma is similar to the proof of lemma (4.2). Therefore, it is omitted.

Theorem 4.5. *If $u_1(t) = \beta$ in the control problem (2.5), the optimal control $u_2(t)$ has at most two switches.*

Proof. When $\phi_2 = 0$ we have that $p_I - 1 = p_w/I$. Since at the zeros of ϕ_2 we have

$$H + \gamma p_w = \beta SI(p_I - p_S)$$

it follows that

$$\dot{\phi}_2 = H + p_w(\gamma - \beta S). \quad (4.11)$$

The argument here is the same as the in proof of theorem (4.3). The left hand side of (4.11) is a monotonic function. Therefore we have that at the zeros of the C^1 function ϕ_2 , $\dot{\phi}_2$ can switch signs at most one time. Therefore ϕ_2 can have at most two switches of sign (and at most three zeros). \square

4.3. Controlling the infection and the removal parameters. In this case we are working in a more complex case. We recall that $\dot{\phi}_1 = u_2 IS(p_S + 1)$ and $\dot{\phi}_2 = -u_2 IS(p_S + 1)$. The functions $\dot{\phi}_1$ and $\dot{\phi}_2$ depend on the controls and are not necessarily continuous (we are assuming that $u_1(t)$ and $u_2(t)$ are measurable locally bounded functions). Therefore ϕ_1 and ϕ_2 are not C^1 functions and the previous reasoning does not apply in this case.

Theorem 4.6. *Along the optimal solution there is no time instant \bar{t} for which $\phi_1(\bar{t}) = \phi_2(\bar{t}) = 0$.*

Proof. At \bar{t} we would have that $p_S = p_I = -1$ what contradicts the boundary conditions for w at $t = t^*$. \square

A corollary of this fact is that $H - g \neq 0$. As in lemma 4.2, we can prove the following result.

Theorem 4.7. *There is no time interval for which $\phi_1(t) = \dot{\phi}_1(t) = 0$ and for which $\phi_2(t) = \dot{\phi}_2(t) = 0$.*

Theorem 4.8. *The two types of campaign, that is, the campaign for reducing β and the campaign for increasing γ are either time disjoint or time nested.*

The theorem says, for example, that if you start a reducing infection rate campaign (RIRC), when there is no campaign being made, then there are only two possibilities: either you start and finish a increasing removal rate campaign (IRRC) before you finish the RIRC or you wait until the RIRC is over to start the IRRC.

Proof. We recall that

$$H = g + u_1\phi_1 + u_2\phi_2.$$

Since g is constant and H is a first integral for the control system it follows that the two functions $f_1 \equiv u_1\phi_1$ and $f_2 \equiv u_2\phi_2$ add to a constant. The proof is a direct consequence of this fact. A campaign will start or end at a switch time, i.e. at a time where some of the functions ϕ_1 or ϕ_2 changes sign. Now let $\alpha \equiv H - g$. Therefore if $f_1(t_1)$ is zero we have that $f_2 = \alpha$ and vice-versa. Assume, by way of contradiction, that campaigns are neither disjoint neither nested. We have two cases to consider a) The number of total switches is two or b) The number of total switches is greater than two. (the case of only one switch satisfies the theorem). If we are in case a) the only situation that does not satisfy the theorem is the one where each function has one switch and one of the campaigns (say campaign 2) starts when the other campaign (say campaign 1) is still on. In this case, since there is only one switch left, it follows that only one of the two will be turned off. As a net result we will have at least one campaign being made during all epidemic time what is ruled out by the main hypothesis of the paper: one can not make campaign for all times (see remark 2.2). In case b) We have at least three zeros. Now assume, by way of contradiction, that there are two campaigns that are neither disjoint or nested. Then there is at least one switching time \bar{t} for say f_2 that is inside the f_1 campaign interval $I = [t_1, t_2]$. Assume without loss of generality that \bar{t} is a start and that there is no other switch of f_2 in the interval $\bar{I} = [\bar{t}, t_2]$ (intersection hypothesis) Now at t_1 we have $f_1(t_1) = 0$ and $f_2(t_1) = \alpha$. At t_2 we also have that $f_1(t_2) = 0$ and $f_2(t_2) = \alpha$. But this impossible, since f_2 switches signs at \bar{t} and does not switch signs in the interval \bar{I} . \square

5. CONTROLLING AN EPIDEMIC

In this section we study an example numerically. We will be controlling only the infection parameter. We assume that the campaign cost is independent of the number of infected, i.e. We will be considering the problem C2. Since the optimal campaign has at most two switches it will consist of only one campaign with maximal effort. Therefore, to determine the optimal campaign, one must only to determine the time instant when it starts. We call it the optimal start. The strategy to determine the optimal control numerically is as follows: For a fixed campaign time C we fix the susceptible and infective initial values. A grid of N starting campaign times t_i , $i = 1, \dots, N$ is then specified. The equations for $S(t)$ and $I(t)$ (the adjoints are not used) are then integrated N times, one for each campaign starting time t_i . The total number of infected T_i by the end of the epidemic outbreak is then computed. The optimal start is the t_i that results in the smaller of all T_i .

Our goal is to understand how the optimal start depends on the campaign total time C (we will present only the results for reducing β since the results for increasing γ are equal in nature). The model case is a severe flu epidemic described in the 4th March 1978 issue of the British Medical Journal. The parameters for the epidemic were determined by a best fit numerical technique in [13]. The values for the influenza epidemic are $N = 763$, $S(0) = 762$, $I(0) = 1$, $\gamma = 2.18 \times 10^{-3}$ and $\beta = 0.44036$. Time is measured in days. We plot the epidemic dynamics in figure 1. The maximum number of infected occurs at $t = 6.49$. This instant is called (according Bailey [2]) the central epoch.

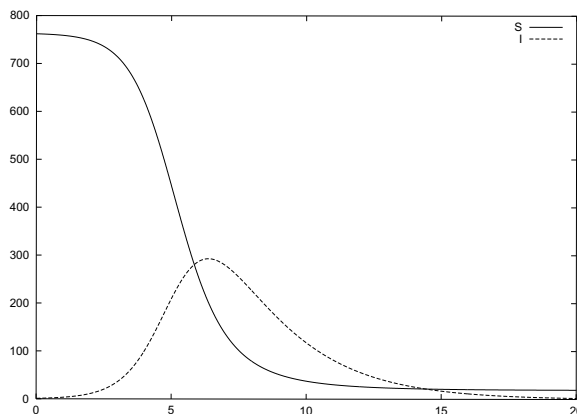


FIGURE 1. Epidemic dynamics: The number of infected I and the number of susceptibles S . Time is measured in days.

We used a Runge-Kutta Fehlberg 7-8 to integrate the system of equations with tolerance 10^{-8} and step size $h = 0.01$. We will take $\beta_m \equiv 1.08 \times 10^{-3}$ what gives a reduction of 50% of the infection rate. The results obtained are valid for all ranges of reduction studied. The optimal start can be determined numerically by a simple search procedure. We partition the time interval in intervals of length 0.1. Then we do the campaign (reducing the infection parameter by 50%) during time C for all starting times. In figure 2 we show the number of infected at the end of the epidemic as a function of the starting time. Each curve represents different campaign times.

In figure 3 we show the optimal starting time as a function of the campaign time. We observe that as the campaign time increases the starting time decreases until eventually becomes zero.

Figure 4 shows that the optimal campaigns always include the central epoch. In other words, limited cost campaigns are optimal around the central epoch for non-controlled epidemics. In the figure we show in the horizontal axis the campaign duration. The two solid curves represent the time when the campaign starts (lower) and the time when the campaign finishes (upper). The dashed curve shows the central epoch. It is always inside the campaign duration even for very small times.

Conclusions. In this paper we studied optimal strategies for a limited cost educational campaign during the outbreak of an epidemic. Optimality was measured by the minimality of the total number of infected at the end of the outbreak. Assuming that the effect of the campaign was to decrease (or increase) infection (removal)

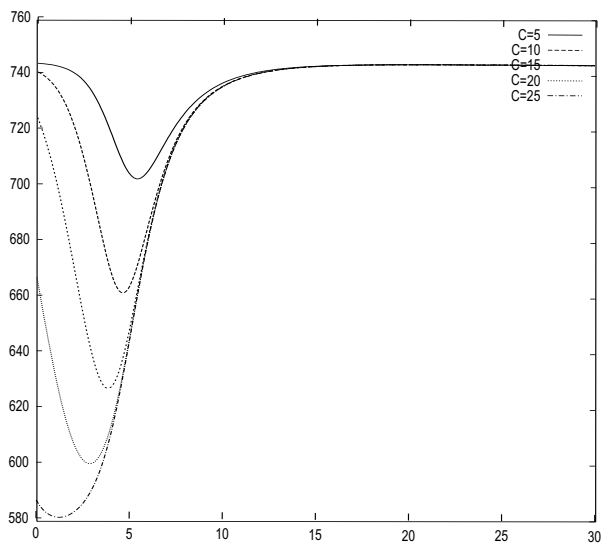


FIGURE 2. Number of total infected at the end of epidemics as a function of the campaign starting time. Different curves represent different campaign times C .

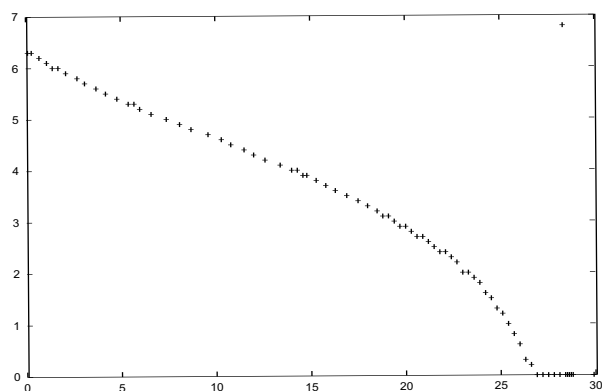


FIGURE 3. Optimal starting time for different values of campaign values C .

rate we were able to show, using the Pontryagin Maximum Principle, that the optimal campaign must consist of only one maximum effort. Numerical simulations, concerning a particular epidemic, gave us additional information about the optimal

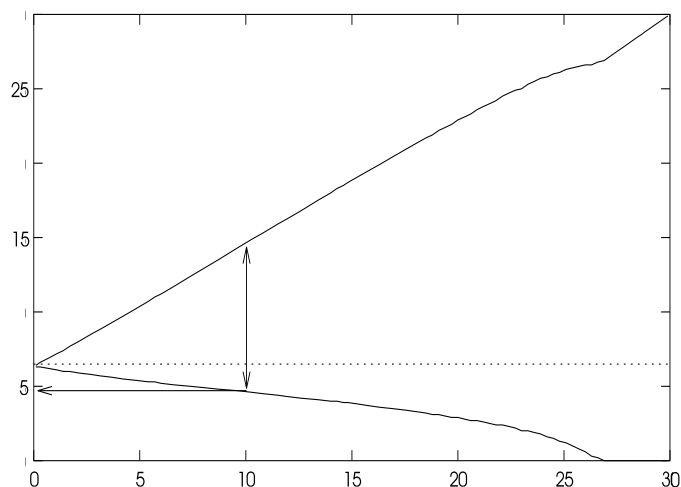


FIGURE 4. Relative position of the central epoch (dashed line) with respect to the optimal campaign interval.

start, i.e. the time to start this maximum effort, in order to minimize our objective functional. Calling \tilde{t} the central epoch we summarize our results in the following: If the campaign cost is proportional to the number of infected than both campaigns, to decrease infection rate and to increase removal rate must be done with maximum intensity at the start of the epidemic. If the campaign cost is independent of the number of infected and only one scenario is chosen, then 1) only one maximum effort campaign should be made, 2) all campaigns should include \tilde{t} . If the goals of the campaign is both to decrease infection rate *and* to increase removal rate then campaign for different scenarios must be nested or disjoint. They should never start or end at the same time.

Acknowledgments. It is a great pleasure to thank A. Agrachev for help during the preparation of this work. Also I would like to thank P. D. N. Siriniwasu for many discussions and S. Lenhart for useful remarks.

REFERENCES

- [1] Agrachev A. and Sachkov Y. L.; *Control Theory from the geometric viewpoint* Mathematical Control Theory, ed. A. Agrachev, ICTP Lecture Notes Vol 8, Trieste, 2002.
- [2] Bailey N. T. J.; *The mathematical theory of infectious diseases and its applications*, Giffin, High Wycombe 1975.
- [3] Behncke H.; *Optimal control of deterministic epidemics*. Optimal Contr. Appl. Meth. 21 6:269-285 (2000).
- [4] Brauer, F. and Castillo-Chavez, C.; *Mathematical models in population biology and epidemiology*. Springer-Verlag, New-York 2001.
- [5] Cesari, L.; *Optimization - theory and applications, problems with ordinary differential equations*. Springer-Verlag, New York 1983.
- [6] Daley, D. J.; *Epidemic modelling*, Cambridge studies in mathematical biology, Cambridge University Press, Cambridge 1999.
- [7] Dietz, K. and Schenzle D.; *Mathematical models for infectious disease statistics*, in A celebration of Statistics, **ISI** Centenary Volume (A.C. Atkinson and S. E. Fienberg, Eds.) Springer, New York, 1985 pp 167-204.
- [8] Gupta N. K. and Rink, R. E.; *Optimum control of epidemics*. Math. Biosci. 18:383-396 (1973).

- [9] Hethcote H. W. and Waltman P.; *Optimal vaccination schedules in a deterministic epidemic model*. Math. Biosci. 18:365-381 (1973).
- [10] Jurdjevic V.; *Geometric control theory* Cambridge Studies in Advanced Mathematics 52, Cambridge University Press, Cambridge 1997.
- [11] Ledzewicz U. and Schattler H.; *Optimal bang-bang controls for a two-compartment model in cancer chemotherapy* J. Optim. Theory and Appl. 114:609-637 2002.
- [12] Morton, R. and Wickwire K. H.; *On the optimal control of a deterministic epidemic*. J. Appl. Probab. 6:622-635 (1974).
- [13] Murray D. J.; *Mathematical Biology*, Biomathematics V.19 Springer-Verlag, Berlin 1993.
- [14] Pontryagin L. S. et al.; *The mathematical theory of optimal processes* Interscience, New York 1962
- [15] Soueres, P. and Boissourat J. D.; *Optimal trajectories for nonholonomic mobile robots* in J. P. Laumond, editor, Robot Motion Planning and Control, pages 93-169, Springer-Verlag, Berlin, 1998.
- [16] Thieme, H. R.; *Mathematics in population biology* Princeton series in theoretical and computational biology. Princeton university press, New Jersey 2003.
- [17] Wickwire K. H.; *Mathematical models for the control of pests and infectious diseases, A survey*. Theor. Population Biol. 11 : 182-238, 1977.
- [18] Zaric G. S. and Brandeau M. L.; *Resource allocation for epidemic control over short time horizons*. Math. Biosci. 171:33-58 (2001).

DEPARTAMENTO DE MATEMÁTICA, UNIVERSIDADE FEDERAL DE PERNAMBUCO, RECIFE, PE CEP 50740-540 BRAZIL

AND THE ABDUS SALAM ICTP, STRADA COSTIERA 11 TRIESTE 34100 ITALY

E-mail address: castilho@dmate.ufpe.br