OPTIMAL CONTROL METHODS APPLIED TO DISEASE MODELS

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ABSTRACT. In this paper, we treat two examples to illustrate the idea of optimal control in two types of disease models. In the first example, we consider an epidemic model with two different incidence forms. A percentage of the population are vaccinated in the model to achieve control of the disease. In the second example, we illustrate a drug treatment strategy in an immunology model. We show the effects of varying the form of the objective functional.

1. INTRODUCTION

The theoretical foundation of optimal control of models with underlying dynamics given by ordinary differential equations was developed by Pontryagin and his co-workers in Moscow about 1950 [25]. The theory, the application areas, and corresponding numerical algorithms have steadily progressed. Using Pontryagin's Maximum Principle [25], its extensions and appropriate numerical methods, one can adjust the control in a model to achieve a goal. The controls are usually functions of time which are coefficients or source terms in the model. The controls may also be initial conditions or other parameters that are to be optimized. See the recent work by Kang, Lenhart and Protopopescu [17] for optimizing over parameters and control functions.

Optimal control theory has been used successfully to make decisions involving biological or medical models. The desired outcome, goal, and performance of the control actions depend on the particular situation. In Joshi's work [14], two control functions as coefficients in a system of differential equations represented treatment effects in a two-drug regime in an HIV immunology model. The goal was to maximize the concentration of T cells while minimizing the toxic effects of the drugs. The analytic and numerical results showed the levels of the two drugs to be given over the chosen time interval. Such a balancing effect between two competing goals can be handled using optimal control theory. See [5, 18] for other such HIV models using optimal control to design treatment strategies. For deciding how to divide the efforts between two treatment strategies (case-holding and case-finding), see the work by Jung, Lenhart and Feng [15] on an epidemic model involving standard and resistant strains of tuberculosis.

Analytic results for optimal control applied to a simple SIR epidemic model including vaccination, quarantine and health promotion campaign were obtained by Behncke [1]. Greenhalgh considers control of an epidemic spreading in a homogeneously mixing population, which is controlled by both immunizing susceptibles

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and isolating infecteds [9]. For epidemics in heterogeneous populations in which the optimal vaccinnation policy is linked to the changing growth rate, see the work by Cairns [2]. For deterministic and stochastic models with discrete time describing an epidemic in an university setting, see the work by Martin et al. [23]. Clancy treated optimal intervention policies for general stochastic epidemic models [3]. See a recent paper by Francis [8] which gives an economic viewpoint for a vaccination model in a flu season. See the works by Sethi, Morton and Wickwire for some survey and fundamental work on control of epidemics [22, 28, 30].

Optimal control techniques involve appending adjoint functions to the problem to characterize the optimal control. The optimality system, which characterizes the optimal control(s), consists of the differential equations of the original model (state equations) together with the adjoint differential equations. Pontryagin's Maximum Principle gives the format of the adjoint differential equations and the corresponding terminal boundary conditions. If the original model has three differential equations, then the adjoint system has three differential equations also. Adjoint functions have a similar purpose as "Lagrange Multipliers" in multivariable calculus (appending constraints to the function of several variables to be maximized or minimized). The adjoint variables bring the state differential equations into the maximization or minimization of the objective functional (goal). See [7, 16] for details of a derivation of the necessary conditions for the adjoint and optimal controls.

To formulate an appropriate optimal control problem, the system of differential equations must be a reasonable representation of the scenario to be considered. Deciding how the results of possible vaccination strategies or drug treatments enter the equations as coefficients is crucial. Designing an appropriate objective functional is equally important. The form of the optimal control results depend strongly on the system of equations, how the controls enter that system, and the objective functional. The exact occurrence of the controls in the equations and in the objective functional can be linear or nonlinear. In this paper, we take a simple quadratic dependence on the control in the objective functional to illustrate our ideas. Problems which are linear in control in both the differential equations and the objective functional, can lead to "bang-bang" or "singular" optimal control cases, which can be more difficult to handle. Bang-bang means that the optimal control only takes on values at the upper and lower bounds of the control set, and finding the times at which the switching from lower bound to upper bound (or vice versa) occurs is more difficult than the quadratic case treated. See the works by Sethi, Fister and Panetta [6, 28] for bang-bang control cases. Singular control happens when the coefficients of the control vanish for some time interval and the choice of the optimal control value must be found by other methods. The choice of the format of the objective functional must depend on the particular application and goal to be treated.

The technical questions of whether an optimal control exists and is unique and whether the solution of the optimality system is unique can be handled in a standard way using Lipschitz (a type of continuity) properties of the solutions of the differential equations [7]. For example, see the paper by Fister, Lenhart and McNally for such results [5]. Having established such existence and uniqueness results mathematically, we can feel confident that solving our optimality system numerically will give the desired optimal control.

In this paper, we treat two examples to illustrate the idea of optimal control in two types of disease models. In the first example, we consider an epidemic model with two different incidence forms. A percentage of the population are vaccinated in the model to achieve control of the disease. This percentage as a function of time will be the control. We illustrate how optimal control theory can be applied to find a vaccination strategy to minimize the size of infectious population and the cost as well. We also illustrate how the form of the interaction between susceptible and infectious populations can affect the form of the optimal control. In the second example, we illustrate a drug treatment strategy in an immunology model [19]. Given an objective functional, one can choose the drug delivery strategy that maximizes that functional. We vary the form of the objective functional and see the effect on the optimal control. Section 2 gives some background on optimal control, while sections 3 and 4 treat the two examples.

2. Background of a Simple Optimal Control Problem with a Bounded Control

To state the optimal control problem, we first make the following notational conventions. Let a, b, $T > 0$ be given and define the control set:

$$\mathbf{U} = \{u(t) \,:\, a \le u(t) \le b,\ 0 \le t \le T,\ u(t) \ \text{ is Lebesgue measurable}\}.$$

We assume that the evolution of the state $x(t) \in \mathbb{R}^n$, under a given control $u \in \mathbf{U}$, is determined by a system of ordinary differential equations:

$$\begin{cases} x'(t) = g(t, x, u), \\ x(0) = x_0, \end{cases} \tag{2.1}$$

where $g : \mathbb{R} \times \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ is continuous and has continuous first partial derivatives with respect to x and u. Because $u(t)$ is only assumed measurable and bounded, the right side of the system $x'(t) = g(t, x, u(t))$ is continuous in x but only measurable in t for fixed x. Therefore, solutions to (2.1) are understood to be absolutely continuous functions that satisfy (2.1) almost everywhere. Under these assumptions, the existence of solutions to (2.1) is guaranteed by results in [20, 24]. The solution of (2.1) for a given $u(t)$ will be called *the state response* to $u(t)$, denoted by $x(t, u)$. The basic optimal control problem involves a cost functional or performance criterion, say $J[u]$, which is of the form

$$J[u] = \int_0^T f(t, x, u)dt + \phi(x(T)),$$

where f is a given real-valued function and ϕ is a continuously differentiable real-valued function. The ϕ term represents "salvage" term, representing the value of the state at the final time. The goal is to find a control $u^* \in \mathbf{U}$ such that

$$J[u^*] = \min_{u \in \mathbf{U}} J[u]. \tag{2.2}$$

In optimal control theory, after formulating a model and corresponding objective functional appropriate to the scenario, there are several basic problems (see [21, 29]):

(a) to prove the existence of an optimal control,
(b) to characterize the optimal control,
(c) to prove the uniqueness of the optimal control,
(d) to compute the optimal control numerically,

(e) to investigate how the optimal control depends on various parameters in the model.

The following theorem (see [7, 21]) is an example of sufficient conditions for the existence of an optimal control in the case with no salvage term.

Theorem 2.1. *Consider the optimal control problem* (2.1) *and* (2.2) *on a fixed interval* $[0,T]$. *Assume that*

(1) *There exists an* $M > 0$, *such that* $||x(t,u)|| \leq M$ *for all* $u \in \mathbf{U}$ *and* $0 \leq t \leq T$;
(2) f *is lower semicontinuous;*
(3) $\mathbf{D}^+ = \{(y^0, y) : \exists v \in \mathbf{U},\ y = g(t,x,v),\ y^0 \geq f(t,x,v)\}$ *is convex for* $(t,x) \in [0,T] \times \{|x| \leq M\}$.

Then there exists an optimal control $u^* \in \mathbf{U}$.

Necessary conditions for an optimal control are obtained using Pontryagin's Maximum Principle with a salvage term [16, 25].

Theorem 2.2. (Necessary Conditions) *Let* $u^* \in \mathbf{U}$ *be an optimal control. Then there exists an adjoint function* $\lambda : \mathbb{R} \to \mathbb{R}^n$ *such that* $x(t,u^*), u^*, \lambda$ *satisfy the state system*

$$\begin{cases} x'(t) = g(t,x,u^*), \\ x(0) = x_0, \end{cases} \tag{2.3}$$

and the adjoint system

$$\begin{cases} \lambda'(t) = -\frac{\partial H}{\partial x} = -(f_x(t,x,u^*) + \lambda^\tau \cdot g_x(t,x,u^*)), \\ \lambda(T) = \phi'(x(T)), \quad \textit{transversality condition} \end{cases} \tag{2.4}$$

where the Hamiltonian H *is given by:*

$$H(t,x,u) = f(t,x,u) + \lambda^\tau \cdot g(t,x,u), \tag{2.5}$$

where τ *denotes transpose.*

To show the uniqueness of the optimal control we show the uniqueness of solutions of the optimality system. The optimality system consists of the state system coupled with the adjoint system with the initial and transversality conditions together with the characterization of the optimal control. We formulate a system with the properties of the optimality system.

Consider the following two-point boundary value problem

$$\begin{cases} x' = p(t,x,y), \\ y' = q(t,x,y), \\ x(0) = x_0,\ y(T) = y_T, \end{cases} \tag{2.6}$$

where $x \in \mathbb{R}^m$, $y \in \mathbb{R}^n$, and $p : \mathbb{R} \times \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}^m$ and $q : \mathbb{R} \times \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}^n$ are continuous.

Theorem 2.3. *Assume that* p *and* q *are bounded and satisfy a Lipschitz condition relative to* x *and* y *with constant* $C > 0$. *Then solutions of system* (2.6) *are unique if* T *is sufficiently small.*

Proof. Suppose (2.6) has two solutions $(x_1(t), y_1(t))$ and $(x_2(t), y_2(t))$. The Lipschitz condition on p implies

$$\|x_1(t) - x_2(t)\| \leq \int_0^t C\left(\|(x_1(s) - x_2(s)\| + \|y_1(s) - y_2(s)\|\right) ds. \tag{2.7}$$

A similar inequality is true for y_1 and y_2,

$$\|y_1(t) - y_2(t)\| \leq \int_t^T C(\|(x_1(s) - x_2(s)\| + \|y_1(s) - y_2(s)\|)ds. \tag{2.8}$$

Adding (2.7) and (2.8) together yields

$$\|x_1(t) - x_2(t)\| + \|y_1(t) - y_2(t)\| \leq \int_0^T C(\|(x_1(s) - x_2(s)\| + \|y_1(s) - y_2(s)\|)ds.$$

Then the Mean Value Theorem for Integrals can be applied to conclude that, there exists a $\xi,\ 0 \leq \xi \leq T$, such that

$$\|x_1(t) - x_2(t)\| + \|y_1(t) - y_2(t)\| \leq TC(\|x_1(\xi) - x_2(\xi)\| + \|y_1(\xi) - y_2(\xi)\|)$$

for all $t \in [0, T]$. If T is so small that $TC < 1$, we arrive at a contradiction, completing the proof. □

Note that the small-time condition in this theorem is due to having initial conditions on some ODEs of the system and final time conditions on the other ODEs; this condition can occur in systems of this type, not just in optimality systems from optimal control problems.

3. SEIR Example

Vaccination is an important disease control and prevention measure in the area of public heath. Optimal vaccination strategy for an SIR model has been studied using dynamic programming technique in [13, 26]. In this section, we study the effects of a vaccination campaign on an infectious disease modeled by an SEIR model. We first suppose that all those who are susceptible are vaccinated at a constant per capita rate v, so that a fraction vS of susceptible individuals are moved from the S class directly to the R class. Consequently, the following system of differential equations with constant vaccination is obtained.

$$\begin{cases} S' = bN - dS - \dfrac{\lambda(N)IS}{N} - vS, \\ E' = \dfrac{\lambda(N)IS}{N} - (\epsilon + d)E, \\ I' = \epsilon E - (\gamma + \alpha + d)I, \\ R' = \gamma I - dR + vS, \\ N' = (b - d)N - \alpha I, \end{cases} \tag{3.1}$$

where $S(t), E(t), I(t)$ and $R(t)$ denote the population size that are susceptible, exposed (not yet infectious), infectious, and recovered individuals at time t, respectively, and $N = S + E + I + R$ is the total population size. The natural birth rate and the death rate are assumed to be b and d. The disease transmission is assumed to occur through direct contact of hosts and the incidence is described by $\lambda(N)IS/N$, where $\lambda(N)$ is the average number of adequate contacts of a person per unit time. We are particularly interested in two special cases when $\lambda(N) = \beta$, a constant, and $\lambda(N) = \lambda N$, a linear function. The resulting incidence terms are the standard incidence $\beta IS/N$ and the bilinear incidence λIS, respectively. Heuristically, model (3.1) with incidence $\beta IS/N$ describes the dynamics of an infectious disease in a rural area, where as the total population increases the density remains

constant and so does the contact rate. Model (3.1) with incidence λIS describes the dynamics of an infectious disease in a urban area where the density and hence the contact rate increases as the population size increases. For more information about these two forms of incidence, see [12] and the references therein. The parameter $\epsilon > 0$ is the rate at which exposed individuals become infectious, $\gamma > 0$ is the rate that infectious individuals become recovered, and α is the death rate caused by the disease. The immunity is assumed to be permanent, so once recovered, an individual will not become susceptible again.

We know that, in order to prevent the disease from becoming endemic, it is necessary to vaccinate a large fraction of susceptible hosts, i.e., let v be large. For instance, the eradication of smallpox was actually achieved after an intensive campaign for vaccination worldwide and a very high vaccination rate [11]. However, for some infectious diseases such as measles or TB, despite the wide usage of vaccines, the diseases still persist somewhere since the vaccines are less effective or sometimes even completely ineffective [27], and vaccination campaigns are never able to reach everyone. Different vaccination policies have been adopted in different parts of the world. In practice, the application of a vaccination policy is limited by many factors including the cost. Cost may be increased by bringing more equipment, personnel and suppliers to a locale. With limited resources, there is a need to balance the vaccination rates and the cost. In this section, an optimal vaccination strategy is designed to minimize an objective functional that takes into account both the number of infectious individuals and the cost. The existence of the optimal control holds from verifying the conditions of Theorem 2.1. Necessary conditions on optimal control and the optimality system are derived using Pontryagin's Maximum Principle [25]. An optimal vaccination function is found numerically.

Consider system (3.1) with incidence $\beta IS/N$. We only give a detailed analysis for this case. The case with incidence form λIS can be done similarly. We now let the vaccination rate be given as a function of time by $u(t)$. Thus, $u(t)$ is the fraction of susceptible individuals being vaccinated per unit time at t. Notice that R does not appear in the other equations in system (3.1). Therefore the state system of differential equations becomes

$$\begin{cases} S' = bN - dS - \dfrac{\beta IS}{N} - u(t)S, \\ E' = \dfrac{\beta IS}{N} - (\epsilon + d)E, \\ I' = \epsilon E - (\gamma + \alpha + d)I, \\ N' = (b-d)N - \alpha I, \end{cases} \tag{3.2}$$

with appropriate initial conditions. The control set $\mathbf{U}$ is

$$\mathbf{U} = \{u(t) : 0 \le u(t) \le 1,\ 0 \le t \le T,\ u(t) \text{ is Lebesgue measurable}\}.$$

The model (3.2) with $u(t) \equiv 0$ predicts the outcome of the disease without vaccination program. If the predicted outcome is unacceptable, the course of infection could be altered by introducing a vaccination program. The objective functional is defined as

$$J[u] = \int_0^T \left(I(t) + \frac{1}{2} W u^2(t) \right) dt \tag{3.3}$$

where W represents the "weight" on the cost. The goal is to characterize an optimal control $u^* \in \mathbf{U}$ satisfying

$$J[u^*] = \min_{u \in \mathbf{U}} J[u]. \tag{3.4}$$

Other forms of the objective functional could make sense depending on the goal of the vaccination. One could use a quadratic term, like $u^2 + ku$, instead of the u^2 term and the results would be similar if k was small. As we stated in the introduction, we are not choosing to illustrate the "bang-bang' case arising from problems which are linear in the control, but that case could also be appropriate here.

To show the existence of an optimal control for problem (3.2) and (3.4), we use Theorem 2.1, since L^∞ bounds hold for this system and integrand of the objective functional is convex.

The necessary conditions on an optimal control are derived using Theorem 2.2. Assume u^* is an optimal control and S, E, I, and N are state responses to u^*. The Hamiltonian is given by

$$\begin{aligned} H = I + \frac{1}{2}Wu^2 + \lambda_1\left(bN - dS - \frac{\beta IS}{N} - uS\right) + \lambda_2\left(\frac{\beta IS}{N} - \epsilon E - dE\right) \\ + \lambda_3(\epsilon E - \gamma I - \alpha I - dI) + \lambda_4(bN - dN - \alpha I). \end{aligned} \tag{3.5}$$

Then there exist adjoint variables λ_i, $i = 1, 2, 3, 4$, satisfying

$$\begin{cases} \lambda_1' &= \left(\dfrac{\beta I}{N} + d + u^*\right)\lambda_1 - \dfrac{\beta I}{N}\lambda_2, \\ \lambda_2' &= (\epsilon + d)\,\lambda_2 - \epsilon\lambda_3, \\ \lambda_3' &= -1 + \dfrac{\beta S}{N}\lambda_1 - \dfrac{\beta S}{N}\lambda_2 + (\gamma + \alpha + d)\lambda_3 + \alpha\lambda_4, \\ \lambda_4' &= -\left(b + \dfrac{\beta IS}{N^2}\right)\lambda_1 + \dfrac{\beta IS}{N^2}\lambda_2 - (b - d)\lambda_4, \\ \lambda_1(T) &= \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = 0. \end{cases} \tag{3.6}$$

where we used $\lambda_1' = -\frac{\partial H}{\partial S}$, $\lambda_2' = -\frac{\partial H}{\partial E}$, etc.

On the set $\{t : 0 < u^*(t) < 1\}$, $\frac{\partial H}{\partial u} = 0$ at u^*, and we obtain

$$u^* = \frac{\lambda_1(t)S(t)}{W}.$$

Using upper and lower bounds on control u^*, it can be seen that the optimal control u^* can be characterized as:

$$u^* = \min\left\{1, \left(\frac{\lambda_1 S}{W}\right)^+\right\}, \tag{3.7}$$

where $\kappa^+ = \kappa$ if $\kappa \geq 0$, $\kappa^+ = 0$ if $\kappa < 0$.

The following system which characterizes the optimal control is called the *optimality system.*

$$
\left\{
\begin{aligned}
S' &= b\,N \;-\; d\,S \;-\; \frac{\beta\, I S}{N} - \min\left\{1, \left(\frac{\lambda_1 S}{W}\right)^+\right\} S,\\
E' &= \frac{\beta\, I S}{N} \;-\; (\epsilon \;+\; b)\, E,\\
I' &= \epsilon\, E \;-\; (\gamma \;+\; \alpha \;+\; d)\, I,\\
N' &= (b-d)N - \alpha I,\\
S(0) &= S_0,\; E(0) = E_0,\; I(0) = I_0, N(0) = N_0,\\
\lambda_1' &= \left(\frac{\beta I}{N} + d + \min\left\{1, \left(\frac{\lambda_1 S}{W}\right)^+\right\}\right)\lambda_1 - \frac{\beta I}{N}\lambda_2,\\
\lambda_2' &= (\epsilon + d)\,\lambda_2 - \epsilon\lambda_3,\\
\lambda_3' &= -1 + \frac{\beta S}{N}\lambda_1 - \frac{\beta S}{N}\lambda_2 + (\gamma+\alpha+d)\lambda_3 + \alpha\lambda_4,\\
\lambda_4' &= -\left(b + \frac{\beta I S}{N^2}\right)\lambda_1 + \frac{\beta I S}{N^2}\lambda_2 - (b-d)\lambda_4,\\
\lambda_1(T) &= \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = 0.
\end{aligned}
\right. \tag{3.8}
$$

From Theorem 2.3, we know that the optimality system (3.8) has a unique solution when T is sufficiently small.

Similarly, we can derive the optimality system for model (3.1) with bilinear incidence λIS as follows

$$
\left\{
\begin{aligned}
S' &= b\,N \;-\; d\,S \;-\; \lambda\, I S - \min\left\{1, \left(\frac{\lambda_1 S}{W}\right)^+\right\} S,\\
E' &= \lambda\, I S \;-\; (\epsilon \;+\; b)\, E,\\
I' &= \epsilon\, E \;-\; (\gamma \;+\; \alpha \;+\; d)\, I,\\
N' &= (b-d)N - \alpha I,\\
S(0) &= S_0,\; E(0) = E_0,\; I(0) = I_0, N(0) = N_0,\\
\lambda_1' &= \left(\lambda\, I + d + \min\left\{1, \left(\frac{\lambda_1 S}{W}\right)^+\right\}\right)\lambda_1 - \lambda I\lambda_2,\\
\lambda_2' &= (\epsilon + d)\,\lambda_2 - \epsilon\lambda_3,\\
\lambda_3' &= -1 + \lambda S\lambda_1 - \lambda S\lambda_2 + (\gamma+\alpha+d)\lambda_3 + \alpha\lambda_4,\\
\lambda_4' &= -b\lambda_1 - (b-d)\lambda_4,\\
\lambda_1(T) &= \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = 0.
\end{aligned}
\right. \tag{3.9}
$$

Numerical solutions to the optimality systems (3.8) and (3.9) are carried out using Mathematica [31] and using the following parameter values and initial conditions:
$b = 0.008,\ d = 0.005,\ \alpha = 0.03,\ \lambda = 0.004,\ \beta = 0.4,\ \epsilon = 0.05,\ \gamma = 0.04,\ W = 0.2,$
$S(0) = 500, E(0) = 10, I(0) = 150, R(0) = 140, N(0) = 800.$
The algorithm is the forward-backward scheme; starting with an initial guess for the optimal control u, the state system is solved forward in time. Then those state

variables and the initial guess u are used to solve the adjoint system backward in time. A new u is defined by (3.7), and is used to solve the state and then the adjoint system. The iteration continues until convergence. See [10] for background on such iterative algorithms.

In Figure 1, we show the outcome of model (3.1) when no vaccination policy is applied. Figure 1(a) shows the outcome with the standard incidence, while 1(b) shows the outcome with the bilinear incidence. In both cases, the disease incidence remains positive for all time. Note that the time scale is in months.

In Figure 2, outcomes of numerical simulations on model (3.1) with the standard incidences are shown. In Figure 2(d), the profile of the control function $u(t)$ is shown. These figures show that by vaccinating at a high percentage in the earlier stage of the epidemics, we can drastically reduce the number of both exposed and infectious individuals with a much lower rate of vaccination at later stage of the epidemic.

In Figure 3, we show the outcome of a similar numerical simulation for model (3.1) with the bilinear incidence. We can see that, while the epidemic is controlled, the outcome is not as ideal as shown in Figure 2, and at a much higher cost; based on the profile of $u(t)$ as shown in Figure 3(d), we need to vaccinate at the very high percentage for a much longer time. Note that for the time period shown, the number of infectious individuals near the final time is not as low as in the standard incidence case

The contrast between the outcomes in Figures 2 and 3 suggests that the incidence form seems to have a substantial influence on the optimal control strategies. We interpret the standard incidence as representing a population in a rural environment, and the bilinear incidence representing a population in a big urban center. Our numerical findings seem to suggest that different optimal control strategies need to be considered for these two different environments. Note that the optimal control function in Figure 2(d) is much smaller than in Figure 3(d). But the biological situation should guide the choice of the incidence function; choices besides the two choices treated here might be appropriate for certain epidemics. Then as we note here, the choice of the incidence function will influence the form of the optimal control.

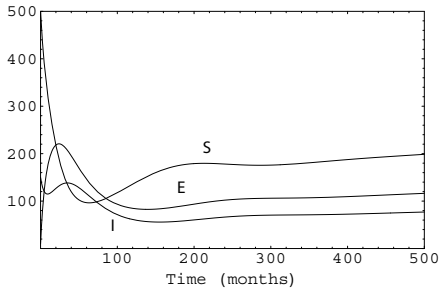

Figure 1 (a). Outcome of the epidemic without vaccination: the standard incidence.

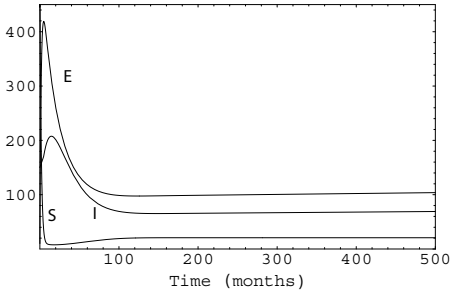

Figure 1 (b). Outcome of the epidemic without vaccination: the bilinear incidence.

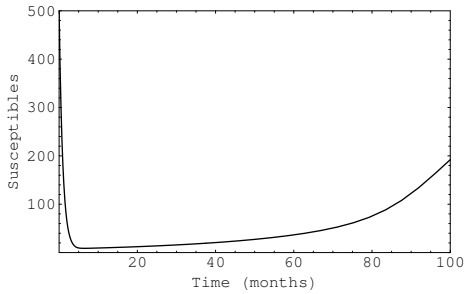

Figure 2 (a). Plot of the number of susceptible individuals: optimal control with the standard incidence.

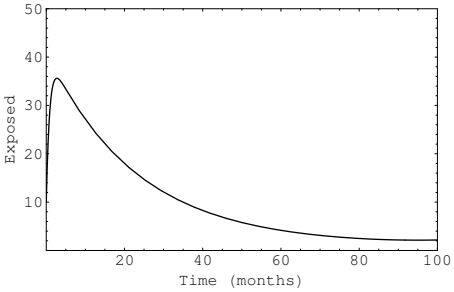

Figure 2 (b). Plot of the number of exposed individuals: optimal control with the standard incidence.

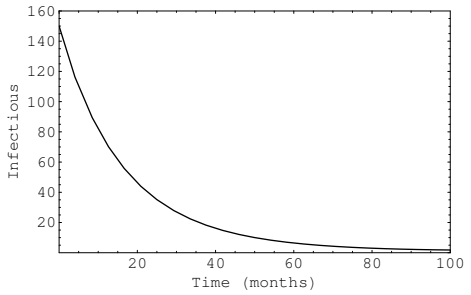

Figure 2 (c). Plot of the number of infectious individuals: optimal control with the standard incidence.

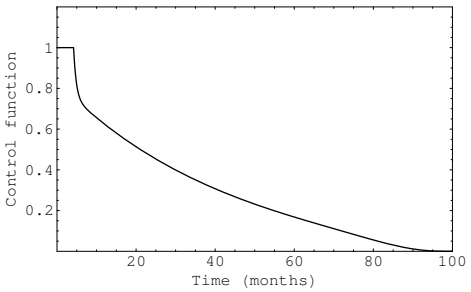

Figure 2 (d). Profile of the control function $u(t)$: optimal control with the standard incidence.

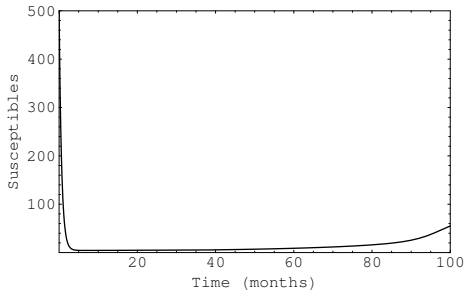

Figure 3 (a). Plot of the number of susceptible individuals: optimal control with the bilinear incidence.

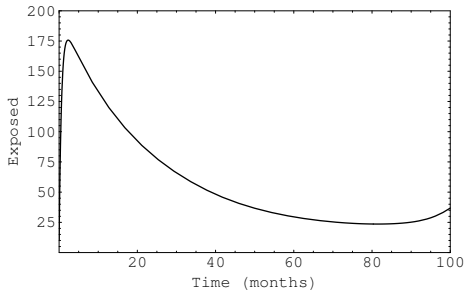

Figure 3 (b). Plot of the number of exposed individuals: optimal control with the bilinear incidence.

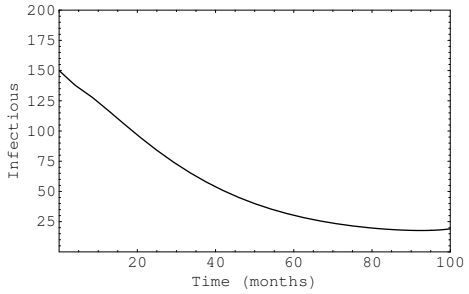

Figure 3 (c). Plot of the number of infectious individuals: optimal control with the bilinear incidence.

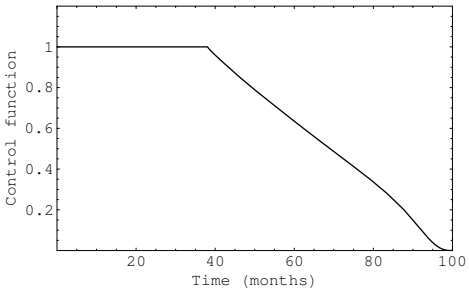

Figure 3 (d). Profile of the control function $u(t)$: optimal control with the bilinear incidence.

4. Immunology Model

We consider optimal control of an ordinary differential equation model, taken from Komorova et al., [19], which describes the interaction of virus population y,

and a population of immune cells, z

$$\begin{cases} y' = (1-u)ry\left(1-\dfrac{y}{k}\right) - ay - pyz, \\ z' = \dfrac{cyz}{1+\epsilon y} - qyz - bz, \end{cases} \tag{4.1}$$

with $y(0) = y_0$ and $z(0) = z_0$. The control function u represents a drug treatment to reduce the growth of the virus. The control set $\mathbf{U}$ is

$$\mathbf{U} = \{u(t) \,:\, 0 \le a \le u(t) \le B < 1,\ 0 \le t \le T,\ u(t) \text{ is Lebesgue measurable}\}.$$

In our state system (4.1), the virus population grows at a density dependent rate $ry\left(1-\frac{y}{k}\right)$. The control coefficient $1-u$ reduces the virus growth; when $u = B$, then the growth rate is reduced the most. The parameter r represents the rate of viral replication, whereas the parameter k represents the "carrying capacity" (target cell limitation). The virus population dies at a rate ay and becomes inhibited by the immune response at a rate pyz. The immune response expands at a rate $\frac{cyz}{1+\epsilon y}$ Thus, expansion is a saturating function of the amount of virus present. The virus population also inhibits the immune response at a rate qyz. In the absence of antigenic stimulation, the immune response declines at a rate bz [19].

Our goal is to find a control $u(t)$ and associated state variables $y(t), z(t)$ to minimize the following objective functional:

$$J[u] = A_1 y(T) + \int_0^T \left(A_2 y + Au^2\right) dt$$

where u^2 represents the systemic cost due to side effects. By choosing appropriate positive balancing constants A_1, A_2, A, our goal could be to minimize virus population only at the final time ($A_2 = 0$ case), or minimize virus population and cost over entire time interval ($A_1 = 0$ case) or combination of both. Note that we have a salvage term in this example, $\phi(y(T)) = A_1 y(T)$.

Theorem 2.1 gives the existence of an optimal control. By using Pontryagin's Maximum Principle [25] we derive necessary conditions for our optimal control and corresponding states. The Hamiltonian is:

$$\begin{aligned} H = {} & \left(A_2 y + Au^2\right) + \lambda_1 \left[(1-u)ry\left(1-\frac{y}{k}\right) - ay - pyz\right] \\ & + \lambda_2 \left[\frac{cyz}{1+\epsilon y} - qyz - bz\right]. \end{aligned}$$

Given optimal control u^*, there exist λ_1, λ_2 such that:

$$\begin{cases} \lambda_1' = -A_2 + \lambda_1 \left[\left(\dfrac{2ry}{k} - r\right)(1-u) + a + pz\right], \\ \qquad\quad - \lambda_2 \left[\dfrac{cz}{(1+\epsilon y)^2} - qz\right] \\ \lambda_2' = \lambda_1 py - \lambda_2 \left[\dfrac{cy}{(1+\epsilon y)} - qy - b\right], \end{cases} \tag{4.2}$$

where $\lambda_1(T) = A_1$ and $\lambda_2(T) = 0$ are the transversality conditions.

By using necessary conditions on the set $\{t : a < u^*(t) < B\}$, we have

$$u^* = \frac{1}{2A}\left[\lambda_1 ry\left(1-\frac{y}{k}\right)\right].$$

As our control is bounded below by a and bounded above by B, thus we have:

$$u^* = \begin{cases} a & \frac{1}{2A}\left[\lambda_1 r y\left(1-\frac{y}{k}\right)\right] \le a \\ \frac{1}{2A}\left[\lambda_1 r y\left(1-\frac{y}{k}\right)\right] & a < \frac{1}{2A}\left[\lambda_1 r y\left(1-\frac{y}{k}\right)\right] < B \\ B & \frac{1}{2A}\left[\lambda_1 r y\left(1-\frac{y}{k}\right)\right] \ge B. \end{cases} \tag{4.3}$$

Existence and uniqueness of solutions of the optimality system follows from Theorems 2.1 and 2.3. See [14] for for similar results. We are only considering the short term behavior of this system; for further analysis of this model and possible long term behavior, see [19].

Using different combinations of weight factors (A_1, A_2, A) and upper bound (B) for controls, one can generate several treatment schedules for various time periods. Here we illustrate a case for $A_1 = 1, A_2 = 0$, and $A_1 = 0, A_2 = 1$ with other parameters $b = 0.30, B = 0.14$, $A = 70$, $\epsilon = 5$, $c = 12$, $k = 10$, and $r = 3.5$. We used initial conditions $y(0) = 1.5$ and $z(0) = .05$. We want to illustrate the importance of the format of the objective functional. One can see the effect on the optimal control of the change from minimizing the integral y over the interval in figure 6 as contrasted with y at the final time in figure 9.

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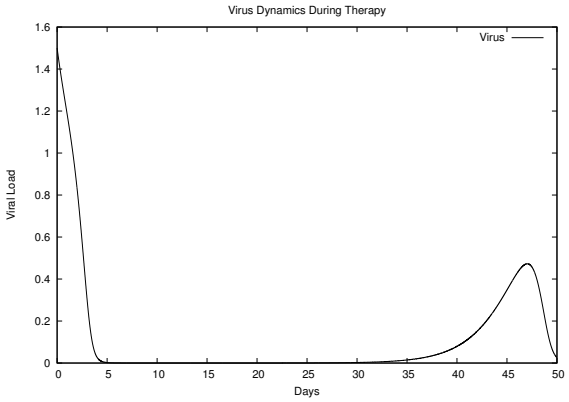

FIGURE 4. *Virus Population for* $A_1 = 1, A_2 = 0, A = 70$

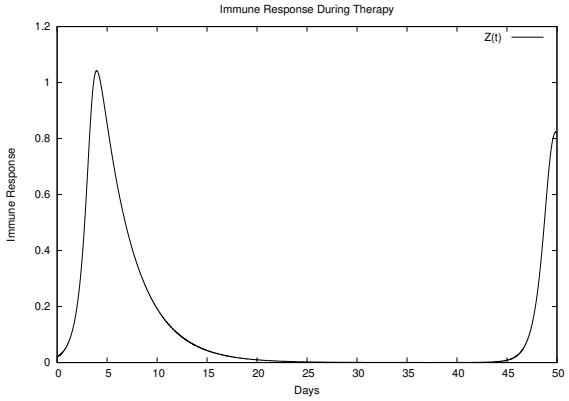

FIGURE 5. *Immune Response for* $A_1 = 1, A_2 = 0, A = 70$

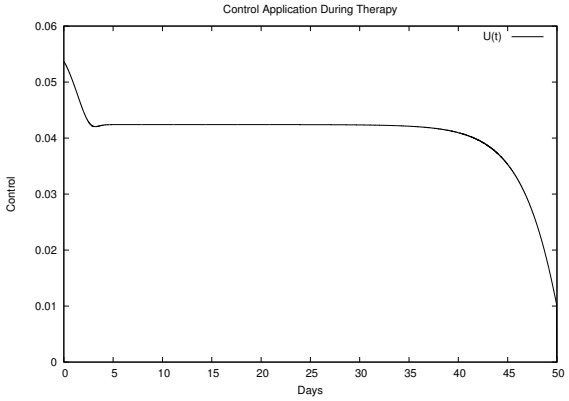

FIGURE 6. *Control for* $A_1 = 1, A_2 = 0, A = 70$

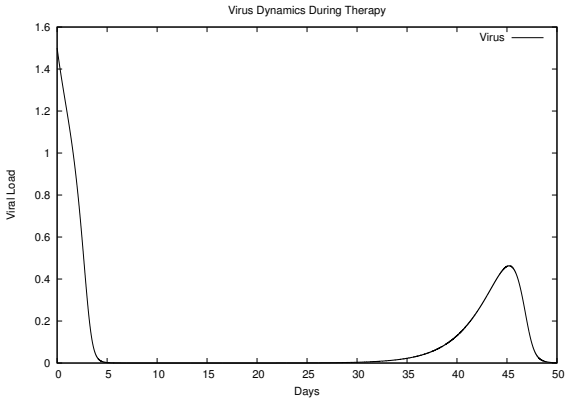

FIGURE 7. *Virus Population for* $A_1 = 0, A_2 = 1, A = 70$

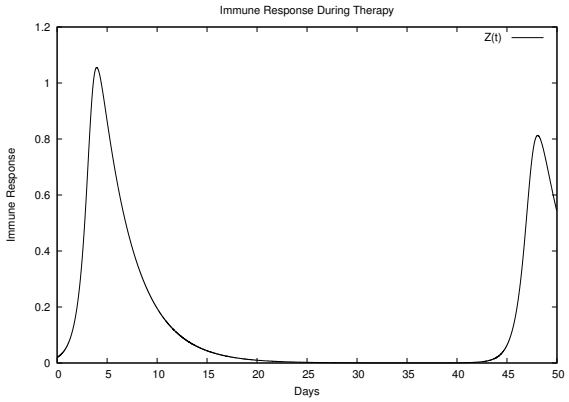

FIGURE 8. *Immune Response for* $A_1 = 0, A_2 = 1, A = 70$

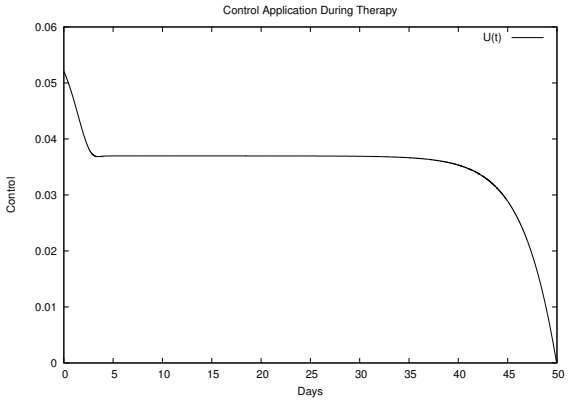

FIGURE 9. *Control for* $A_1 = 0, A_2 = 1, A = 70$

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