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An Introduction to Optimal Control Applied to Immunology Problems

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1. Introduction

We present the motivating idea of optimal control theory in an example of an ordinary differential equation model, taken from Komarova et.al. [**16**], which describes the interaction of virus population y, and a population of immune cells z,

$$\begin{aligned} y'(t) &= \big(1-u(t)\big)ry(t)\left(1-\frac{y(t)}{k}\right)-ay(t)-py(t)z(t),\ y(0)=y_0,\\ z'(t) &= \frac{cy(t)z(t)}{1+\epsilon y(t)}-qy(t)z(t)-bz(t),\ z(0)=z_0. \end{aligned} \tag{1.1}$$

The control function u represents a drug treatment to reduce the growth of the virus. In the system (1.1), the virus population grows at a density dependent rate $ry(1-\frac{y}{k})$. 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 with the term $\frac{cyz}{1+\epsilon y}$, which 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 [**16**].

Our goal is to find a control u, in appropriately chosen class, and associated variables y, z to minimize the following objective functional

$$J(u)=\int_0^T \left(A_2y(t)+Au(t)^2\right)dt,$$

where u^2 represents the systemic cost due to side effects. We are minimizing a combination the virus population and the cost.

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We would say that this problem has two states y, z and one control u. Analyzing such a problem with a variety of parameter values can give interesting conclusions [**12**]. We will discuss the tools to solve such problems.

The goal of this paper is to give a brief introduction to optimal control theory as applied to biological models, concentrating on immunology models. Our focus here is ordinary differential equations with time as the underlying variable. For other types of systems, see [**1, 2, 8, 20, 21, 28**].

Optimal control theory can be used to make decisions involving biological or medical models. For example, what percentage of the population should be vaccinated in a given epidemic model? The desired outcome, goal, or performance of the control actions taken depends on the particular situation. Sometimes this goal will include tradeoffs between two competing factors. Perhaps two quantities need to be balanced, such as minimizing a certain harmful virus population while keeping the level of the toxic drug administered low. In such a case, the level of the drug can be a function of time and appears in the system of ordinary differential equations as a coefficient of certain terms.

The behavior of the underlying dynamical system is described by a *state* variable(s). We assume that there is a way to steer the state by acting upon it with a suitable control(s), which enters the system of ordinary differential equation and affects the dynamics of the state. The goal is to adjust the control in order to maximize a given objective functional, which balances judiciously the desired goal with the required *cost* to reach it. The *cost* may not always represent money but may include side effects or damages caused by the control. In general, the objective functional depends on the state and the control. For some examples of optimal control in epidemic models, see [**3, 9, 13, 24**]. For examples specifically related to immunology models, see [**6, 15, 26**].

We will only consider examples in which the control enters the problem in a simple nonlinear way, mostly quadratic. The underlying idea is that finding the maximum or minimum of a quadratic function is easy, while in the linear case, the control may switch several times between bounds or to other values. The case with the control switching between upper and lower bounds is called "bang-bang." See the papers by Ledzewicz and Schattler [**17**] and Fister and Panetta [**7**] for such examples.

In the next section, we present a sketch of the derivation of the necessary conditions for a basic optimal control problem. The third section illustrates the techniques with two simple examples and the last two sections treat immunology examples, including some numerical results.

2. Necessary Conditions for an Optimal Control

Here, we focus on the simple case of one control and one state. The main idea is the introduction of the "adjoint function" to attach the differential equation onto the objective functional; this is similar to Lagrange multipliers attaching a constraint to a multivariable optimization problem.

We use $u(t)$ for the control and $x(t)$ for the state. The basic optimal control problem consists of finding a continuous control $u(t)$ and the associated continuously differentiable state variable $x(t)$ to maximize the given objective functional, i.e.,

$$\begin{aligned} &\max_u \ \phi(x(T)) + \int_0^T f(t, x(t), u(t))\, dt \\ &\text{subject to} \quad x'(t) = g(t, x(t), u(t)), \\ &\qquad\qquad\ \ x(0) = x_0 \text{ and } x(T) \text{ free.} \end{aligned} \tag{2.1}$$

For our purposes, f and g will always be continuously differentiable functions in all three arguments, and ϕ will be a continuously differentiable *salvage* term. The principal technique for such an optimal control problem is to solve a set of "necessary conditions" that an optimal control and corresponding state must satisfy. Express our objective functional in terms of the control

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

where x is state corresponding to the control u.

Assume a continuous optimal control exists, and that u^* is such a control, with x^* the corresponding state. Let $h(t)$ be a continuous variation function and $\epsilon \in \mathbb{R}$ a constant. Then $u^\epsilon(t) = u^*(t) + \epsilon h(t)$ is another continuous control.

Let x^ϵ be the state corresponding to the control $u^* + \epsilon h$, namely,

$$\frac{dx^\epsilon}{dt}(t) = g(t, x^\epsilon(t), (u^* + \epsilon h)(t)).$$

Since all trajectories start at same position, $x^\epsilon(0) = x_0$. Note that by the differentiability assumption on the dynamics of g,

$$x^\epsilon(t) \to x^*(t) \text{ for each } t \text{ as } \epsilon \to 0.$$

The objective functional depending on ϵ becomes

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

We introduce a continuously differentiable adjoint function $\lambda(t)$ to be determined shortly. By the Fundamental Theorem of Calculus,

$$\int_0^T \frac{d}{dt}[\lambda(t)x^\epsilon(t)]\, dt = \lambda(T)x^\epsilon(T) - \lambda(0)x_0,$$

which implies

$$\int_0^T \frac{d}{dt}[\lambda(t)x^\epsilon(t)]\, dt + \lambda(0)x_0 - \lambda(T)x^\epsilon(T) = 0.$$

Adding this 0 expression to our $J(u^\epsilon)$ gives

$$\begin{aligned} J(u^\epsilon) &= \int_0^T \left[f(t, x^\epsilon(t), u^\epsilon(t)) + \frac{d}{dt}(\lambda(t)x^\epsilon(t)) \right] dt \\ &\quad + \lambda(0)x_0 - \lambda(T)x^\epsilon(T) + \phi(x^\epsilon(T)), \\ &= \int_0^T \left[f(t, x^\epsilon(t), u^\epsilon(t)) + \lambda'(t)x^\epsilon(t) + \lambda(t)g(t, x^\epsilon, u^* + \epsilon h) \right] dt \\ &\quad + \lambda(0)x_0 - \lambda(T)x^\epsilon(T) + \phi(x^\epsilon(T)), \end{aligned}$$

where we used the product rule of differentiation and the fact that $g(t, x^\epsilon, u^\epsilon) = \frac{d}{dt}x^\epsilon(t)$. Since the maximum of J with respect to the control u occurs at u^*,

$$0 = \lim_{\epsilon \to 0} \frac{J(u^\epsilon) - J(u^*)}{\epsilon}.$$

This gives a limit of an integral expression. A version of the Lebesgue Dominated Convergence Theorem allows us to move the limit (and thus the derivative) inside the integral. This is due to the compact interval of integration and the differentiability of the integrand. Therefore,

$$\begin{aligned} 0 = \int_0^T \left[f_x \frac{\partial x^\epsilon}{\partial \epsilon} + f_u \frac{\partial u^\epsilon}{\partial \epsilon} + \lambda'(t) \frac{\partial x^\epsilon}{\partial \epsilon} + \lambda(t) \Big(g_x \frac{\partial x^\epsilon}{\partial \epsilon} + g_u \frac{\partial u^\epsilon}{\partial \epsilon} \Big) \right] \Bigg|_{\epsilon=0} dt \\ + (\phi'(x^*(T)) - \lambda(T)) \frac{\partial}{\partial \epsilon} x^\epsilon(T) \Bigg|_{\epsilon=0}, \end{aligned} \tag{2.2}$$

where the arguments of the f_x, f_u, g_x, and g_u terms are $(t, x^*(t), u^*(t))$. Note that

$$\frac{\partial u^\epsilon}{\partial \epsilon} = \frac{\partial}{\partial \epsilon}(u^* + \epsilon h) = h.$$

Rearranging the terms in (2.2) gives

$$\begin{aligned} 0 = \int_0^T \left[(f_x + \lambda g_x + \lambda') \frac{\partial x^\epsilon}{\partial \epsilon} \Bigg|_{\epsilon=0} + (f_u + \lambda g_u) h \right] dt \\ + \Big(\phi'(x^*(T)) - \lambda(T) \Big) \frac{\partial x^\epsilon}{\partial \epsilon}(T) \Bigg|_{\epsilon=0}. \end{aligned} \tag{2.3}$$

Choose the adjoint function $\lambda(t)$ to satisfy

$$\lambda'(t) = -[f_x(t, x^*, u^*) + \lambda(t) g_x(t, x^*, u^*)] \quad (\textit{adjoint equation}),$$

and

$$\lambda(T) = \phi'(x^*(T)) \quad (\textit{transversality condition}).$$

Now, (2.3) reduces to

$$0 = \int_0^T (f_u + \lambda g_u)\, h \, dt.$$

As h is an arbitrary continuous function, this implies the "optimality condition"

$$f_u(t, x^*, u^*) + \lambda(t) g_u(t, x^*, u^*) = 0 \quad \text{for all } 0 \le t \le T.$$

We can generate the above necessary conditions from the Hamiltonian H, which is defined as follows,

$$\begin{aligned} H(t, x, u, \lambda) &= f(t, x, u) + \lambda(t) g(t, x, u) \\ &= \text{integrand } + \text{adjoint} * \text{RHS of DE}. \end{aligned}$$

We are maximizing H with respect to u at u^*, and from above

$$\frac{\partial H}{\partial u} = 0 \Rightarrow f_u + \lambda g_u = 0 \text{ at } u^* \quad (\textit{optimality equation}),$$
$$\lambda' = -\frac{\partial H}{\partial x} \Rightarrow \lambda' = -(f_x + \lambda g_x) \quad (\textit{adjoint equation}),$$
$$\lambda(T) = \phi'(x^*(T)) \quad (\textit{transversality condition}).$$

These conclusions can be extended to a simple case of Pontryagin's Maximum Principle [**27**].

THEOREM 1. If $u^*(t)$ and $x^*(t)$ are optimal for problem (2.1), then there exists an adjoint variable $\lambda(t)$ such that

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))$$

for all controls u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda(t) g(t, x(t), u(t))$$

and

$$\lambda'(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},$$
$$\lambda(T) = \phi'(x^*(T)).$$

We have converted the problem of finding the control to maximize the objective functional subject to the differential equation and initial condition, to using the Hamiltonian pointwise. We can also derive concavity conditions to distinguish between controls that maximize and those that minimize the objective functional [**8**]. If one has

$$\frac{\partial^2 H}{\partial u^2} < 0 \quad \text{at } u^*,$$

then it is a maximization problem. Similarly, the problem is necessarily minimization if

$$\frac{\partial^2 H}{\partial u^2} > 0 \quad \text{at } u^*.$$

We can view our problem as having two unknowns, u^* and x^*, at the start. We have introduced an adjoint variable λ, which is similar to a Lagrange multiplier. The adjoint variable attached the differential equation information onto the objective functional. Then, there are three unknowns, u^*, x^* and λ. We try to eliminate u^* by using the optimality equation $H_u = 0$ and solve for u^* in terms of x^* and λ. If the Hamiltonian is linear in the control variable u, it can be difficult to solve for u^* from the optimality equation; instead, maximization of the Hamiltonian with respect to the control is used. We do not treat this case here, but see [**7, 17**]. If we can solve for u^* from the optimality equation, we are then left with two unknowns x^* and λ satisfying two differential equations with two boundary conditions. We solve that system of differential equations for the optimal state and adjoint and then obtain the optimal control.

3. Simple Examples

We treat two simple examples that can be worked explicitly to illustrate the solution techniques.

EXAMPLE 1. (from [**14**])

$$\min_u \frac{1}{2}\int_0^1 u^2(t)\,dt$$
$$\text{subject to} \quad x'(t) = x(t) + u(t),\ x(0) = 1.$$

Form the Hamiltonian and generate the necessary conditions.

$$H = \frac{1}{2}u^2 + \lambda(x+u),$$
$$\frac{\partial H}{\partial u} = u + \lambda = 0 \ \Rightarrow\ u^* = -\lambda,$$
$$\frac{\partial^2 H}{\partial u^2} = 1 > 0, \quad \text{which indicates minimization,}$$
$$\lambda' = -\frac{\partial H}{\partial x} = -\lambda \quad \text{and} \quad \lambda(1) = 0 \ \Rightarrow$$
$$\lambda(t) \equiv 0.$$

Hence, the optimal solutions are

$$\lambda \equiv 0, \quad u^* \equiv 0, \quad x^*(t) = e^t.$$

EXAMPLE 2.

$$\min_u \frac{1}{2}\int_0^1 3x^2(t) + u^2(t)\,dt$$
$$\text{subject to} \quad x'(t) = x(t) + u(t),\ x(0) = 1.$$

We first form the Hamiltonian of the problem

$$H = \frac{3}{2}x^2 + \frac{1}{2}u^2 + x\lambda + u\lambda.$$

The optimality condition gives us

$$0 = \frac{\partial H}{\partial u} = u + \lambda \text{ at } u^* \ \Rightarrow\ u^* = -\lambda.$$

The problem is a minimization problem as

$$\frac{\partial^2 H}{\partial u^2} = 1 > 0.$$

We use the Hamiltonian to find the differential equation of the adjoint λ,

$$\lambda' = -\frac{\partial H}{\partial x} = -3x - \lambda,\ \lambda(1) = 0.$$

Substituting the derived characterization for the control variable u in the equation for x', we arrive at the differential "optimality" system

$$\begin{pmatrix} x \\ \lambda \end{pmatrix}' = \begin{pmatrix} 1 & -1 \\ -3 & -1 \end{pmatrix} \begin{pmatrix} x \\ \lambda \end{pmatrix}.$$

The eigenvalues of the coefficient matrix are 2 and -2. Using $x(0) = 1$ and $\lambda(1) = 0$, we find that the optimal solutions are

$$u^*(t) = \frac{3e^{-4}}{3e^{-4}+1}e^{2t} - \frac{3}{3e^{-4}+1}e^{-2t},$$
$$x^*(t) = \frac{3e^{-4}}{3e^{-4}+1}e^{2t} + \frac{1}{3e^{-4}+1}e^{-2t}.$$

Before going to the more realistic examples, we briefly discuss a numerical method which can be used to solve the optimality system, that is, the state and adjoint equations (and boundary conditions) and the characterization of the optimal control.

We make a few observations about the optimality system. First, we are given an initial condition for the state but a final time condition for the adjoint. Second, the state ODE system is a function of time, the state, and the control only. Values for the adjoint are not needed to solve the state system using a standard ODE solver. Taking this into account, the method we present here is very intuitive. It is generally referred to as the Forward-Backward Sweep method. Information about convergence and stability of this method can be found in [**10**]. A rough outline of the algorithm is given below.

Step 1. Make an initial guess for u over the interval. Store the initial guess as u.
Step 2. Using the initial conditions and the stored values for u, solve the state ODE forward in time.
Step 3. Using the transversality condition and the stored values for u and the state, solve the adjoint ODE backward in time according to the differential equation in the optimality system.
Step 4. Update the control by entering the new state and adjoint values into the characterization of u.
Step 5. Check convergence. If values of the variables in this iteration and the last iteration are close, output the current values as solutions. If values are not close, return to Step 2.

4. Virus Example

Reconsider the model (1.1) presented in the introduction. In this model, there are two states and one control. The earlier necessary conditions are easily extended to this case, by introducing two adjoints. Further, we wish to consider bounds on the control; then, the optimality condition is satisfied when the control is away from the bounds. Finally, the results of Section 2 can be extended to controls which are only measurable.

Consider the control set

$$U = \Big\{ u(t) \,:\, a \le u(t) \le B \text{ for } 0 \le t \le T,\ u(t) \text{ is Lebesgue measurable} \Big\},$$

where $0 \le a < B < 1$. Our goal is to find a control $u \in U$ and associated state variables y, z to minimize the objective functional

$$J(u) = A_1 y(T) + \int_0^T \left(A_2 y(t) + A u(t)^2\right) dt,$$

which is slightly more general than the original objective functional. By choosing appropriate positive balancing constants A, A_1, A_2, 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 a combination of both. Note, $\phi(y(T)) = A_1 y(T)$ and $\phi' = A_1$, so that A_1 appears in the transversality condition of the first adjoint variable.

Using Pontryagin's Maximum Principle [**27**], we derive necessary conditions for our optimal control and corresponding states, including constraints on the controls. Since we have 2 state variables y, z, we will have two corresponding adjoint variables, where λ_1 corresponds to y and λ_2 corresponds to z.

The Hamiltonian is

$$H = \left(A_2 y + A u^2\right) + \lambda_1 \left[(1-u) r y \left(1 - \frac{y}{k}\right) - a y - p y z\right] + \lambda_2 \left[\frac{c y z}{1+\epsilon y} - q y z - b z\right].$$

The adjoint equations are

$$\lambda_1' = -\frac{\partial H}{\partial y} = -A_2 + \lambda_1 \left[\left(\frac{2ry}{k} - r\right)(1-u) + a + pz\right] - \lambda_2 \left[\frac{cz}{(1+\epsilon y)^2} - qz\right]$$
$$\lambda_2' = -\frac{\partial H}{\partial z} = \lambda_1 p y - \lambda_2 \left[\frac{cy}{(1+\epsilon y)} - qy - b\right],$$

where $\lambda_1(T) = A_1$ and $\lambda_2(T) = 0$.

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

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

As our control is bounded below by a and bounded above by B, we must constrain the values of the control and obtain the characterization

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

Existence of the optimal control follows from standard results [**8, 14, 23, 27, 28**]. Uniqueness is only guaranteed for small time; see [**6**] for a technique to obtain such a result.

Using different combinations of weight factors (A, A_1, A_2) and upper bounds (B) for controls, one can generate several treatment schedules for various time periods [**12**]. Here we illustrate the cases $A_1 = 1, A_2 = 0$ and $A_1 = 0, A_2 = 1$, with other parameters $b = 0.3$, $B = 0.14$, $A = 70$, $\epsilon = 5$, $c = 12$, $k = 100$, and $r = 3.5$. We want to illustrate the importance of the format of the objective functional. Note in Figures 1-6 the difference in the optimal solutions when minimizing the integral of y versus only y at the final time.

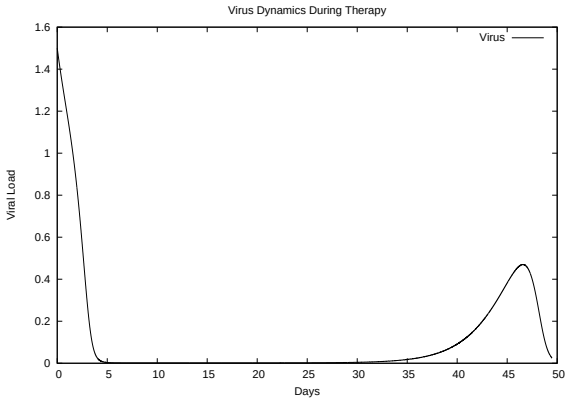

FIGURE 1. Virus Population for $A_1 = 1$, $A_2 = 0$, $A = 70$

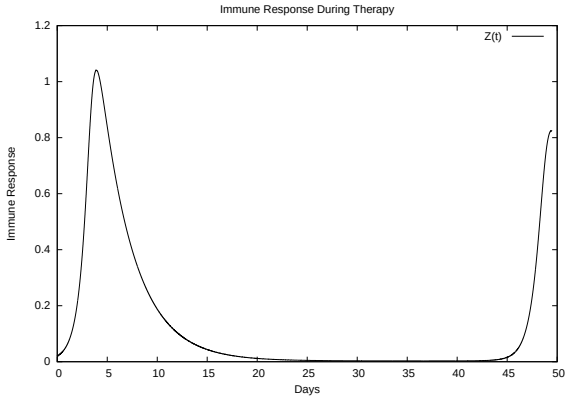

FIGURE 2. Immune Response for $A_1 = 1$, $A_2 = 0$, $A = 70$

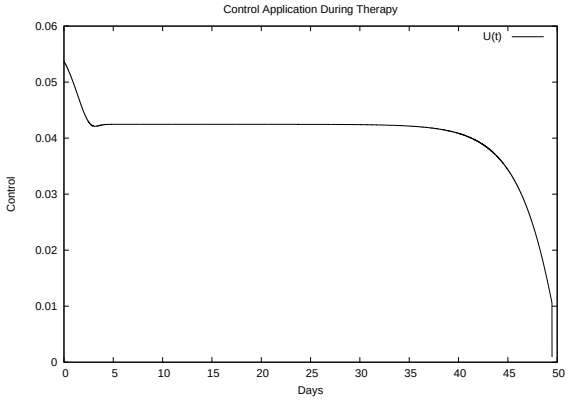

FIGURE 3. Control for $A_1 = 1$, $A_2 = 0$, $A = 70$

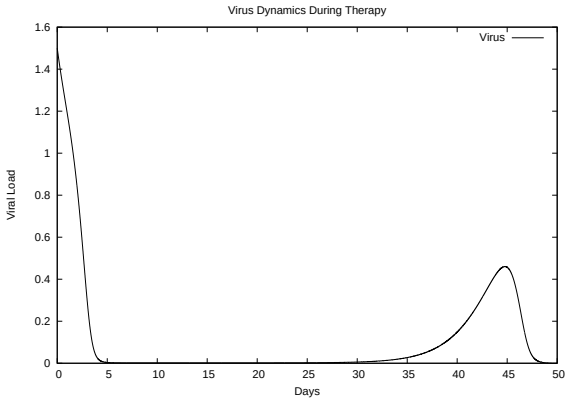

FIGURE 4. Virus Population for $A_1 = 0$, $A_2 = 1$, $A = 70$

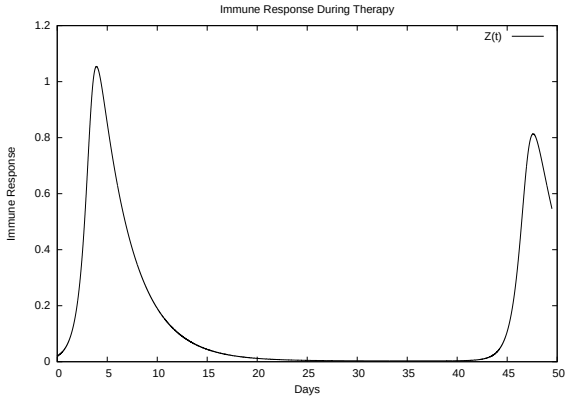

FIGURE 5. Immune Response for $A_1 = 0$, $A_2 = 1$, $A = 70$

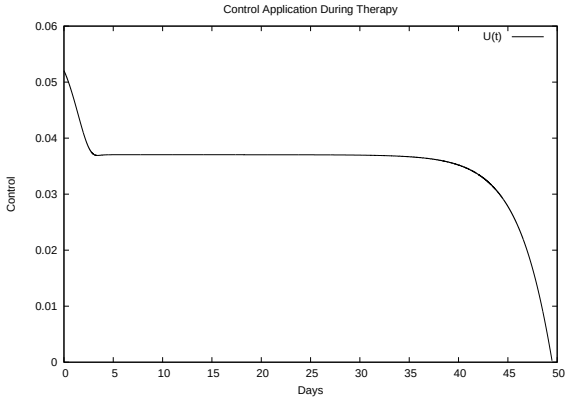

FIGURE 6. Control for $A_1 = 0$, $A_2 = 1$, $A = 70$

5. Leukemia Example

This example, taken from the work of Nanda, Moore, and Lenhart [**26**], is a model of drug therapy for chronic mylegenous leukemia (CML). See [**25, 26**] for background on this model. Let $C(t)$ denote the cancer cell population, $T_n(t)$ the naive T cell population, and $T_e(t)$ the effector T cell population at time t. We assume that the effector T cells are specific to CML, activated by the presence of CML antigen. The state system for our model is given by

$$\begin{aligned}
T_n'(t) &= s_n - u_2(t)d_nT_n(t) - k_nT_n(t)\left(\frac{C(t)}{C(t)+\eta}\right),\\
T_e'(t) &= \alpha_n k_n T_n(t)\left(\frac{C(t)}{C(t)+\eta}\right) + \alpha_e T_e(t)\left(\frac{C(t)}{C(t)+\eta}\right)\\
&\quad - u_2(t)d_eT_e(t) - \gamma_e C(t)T_e(t),\\
C'(t) &= \big(1-u_1(t)\big)r_cC(t)\ln\left(\frac{C_{\max}}{C(t)}\right) - u_2(t)d_cC(t) - \gamma_cC(t)T_e(t),
\end{aligned}$$

where $T_n(0)$, $T_e(0)$ and $C(0)$ are known. Time dependent drug efficacies are incorporated using $u_1(t)$ and $u_2(t)$.

The last term in the first equation represents the decline in T_n cells due to encounters with CML antigen in the lymph nodes. As the population of T_n cells is very small in comparison to the CML cells, this term takes into account the saturation effect of CML cells in the lymph nodes. Since some of these lost T_n cells reappear as effector T cells (T_e), a Michaelis-Menten factor appears in the first term in T_n equation.

The model assumes Gompertz growth for CML cells. The encounters in the blood between T_e cells and C cells are modelled by the law of mass action, i.e., the effect of these cells on each other is based on the sizes of the two cell populations, and there is no saturating effect in the blood circulation system.

The effect of the targeted drug is represented by the control function $u_1(t)$, which slows the production of cancer cells. We assume this drug (like Gleevec) affects only cancer cells and not the other cells, so $u_1(t)$ appears only in C equation. The $u_2(t)$ control is used to incorporate treatment by a broad chemotherapy, such as cytarabine, hydroxyurea, or a combination of such drugs, which is cytotoxic to all three cell populations. The control u_2 appears in all three state equations as a coefficient in the natural attrition terms. Values of $u_2 > 1$ correspond to treatment with a cytotoxic drug.

We define the objective functional (to be minimized over all $(u_1, u_2) \in U$) as

$$J(u_1,u_2) = \int_0^T \left[C(t) + \frac{B_1}{2}u_1(t)^2 + \frac{B_2}{2}u_2(t)^2\right]dt + B_3\,C(T) - B_4\,T_n(T)$$

where

$$U = \Big\{(u_1(t),u_2(t)) \,:\, m_i \le u_i(t) \le M_i,\ u_i \text{ Lebesgue measurable},\ i=1,2\Big\}.$$

In the objective functional, we minimize the total cancer cell population over the time interval through the first term in the integrand, and at the final time through a salvage term $B_3C(T)$. We also minimize the systemic costs to the body of the

two drugs u_1 and u_2. The coefficients B_1 and B_2 are weight constants on the controls. The salvage term $B_3C(T)$ is included to counter the effect of using a fixed treatment time. We include the salvage term $-B_4T_n(T)$ to penalize for low values of T_n, since this affects the patient's ability to fight off other diseases. The coefficients B_3 and B_4 allow the salvage terms to be weighted differently from each other and the integral terms.

The lower bounds for u_1 and u_2 correspond to no therapy. For u_1, this lower bound is $m_1 = 0$, and for u_2 the lower bound is $m_2 = 1$. We restrict $M_1 < 1$, as $M_1 = 1$ would correspond to no new cancer cells. The upper bound M_2 is greater than 1 and is determined by $\min\{1/d_n, 1/d_e, 1/d_c\}$.

We next characterize the optimal control pair $({u_1}^*, {u_2}^*)$, which gives the optimal drug dosage for patient recovery, and corresponding states $({T_n}^*, {T_e}^*, C^*)$. The existence of an optimal control pair is guaranteed by the compactness of the control and state spaces and the convexity in the problem; see such results in [**8**].

If $({u_1}^*, {u_2}^*)$ is an optimal control pair with corresponding states ${T_n}^*, {T_e}^*$, and C^*, then there exist adjoint variables λ_1, λ_2, and λ_3, which satisfy

$$\begin{aligned}
\lambda_1' &= \lambda_1 \left(u_2 d_n + k_n \frac{C}{C+\eta} \right) - \lambda_2 \alpha_n k_n \frac{C}{C+\eta}, \\
\lambda_2' &= \lambda_3 \gamma_c C - \lambda_2 \left(\alpha_e \frac{C}{C+\eta} - u_2 d_e - \gamma_e C \right), \\
\lambda_3' &= -1 + \lambda_1 k_n T_n \frac{\eta}{(C+\eta)^2} - \lambda_2 \left(\alpha_n k_n T_n \frac{\eta}{(C+\eta)^2} + \alpha_e T_e \frac{\eta}{(C+\eta)^2} - \gamma_e T_e \right) \\
&\quad - \lambda_3 \left((1-u_1) r_c \left(\ln \left(\frac{C_{\max}}{C} \right) - 1 \right) - u_2 d_c - \gamma_c T_e \right),
\end{aligned}$$

and transversality conditions

$$\lambda_1(T) = -B_4, \ \lambda_2(T) = 0, \ \lambda_3(T) = B_3.$$

Since we have two controls, we will obtain the characterization of each control separately. On the interior of the control set, we solve for the optimal controls by

$$\begin{aligned}
\frac{\partial H}{\partial u_1} &= 0 \text{ at } u_1^*, u_2^*, \\
\frac{\partial H}{\partial u_2} &= 0 \text{ at } u_1^*, u_2^*.
\end{aligned}$$

This gives

$$\begin{aligned}
u_1^* &= \min \left\{ \max \left\{ m_1, \frac{\lambda_3 r_c C \ln(\frac{C_{\max}}{C})}{B_1} \right\}, M_1 \right\}, \\
u_2^* &= \min \left\{ \max \left\{ m_2, \frac{\lambda_1 d_n T_n + \lambda_2 d_e T_e + \lambda_3 d_c C}{B_2} \right\}, M_2 \right\}.
\end{aligned}$$

In [**26**], approximate optimal controls were computed using the forward-backward sweep method as discussed above. Simulations for two different sets of parameters representing two different patients were run to illustrate different therapy regimes. Also, single drug treatment was compared with the two drug treatment case, and

the idea of treatment interruptions was considered. Below, we show the effects of varying two parameters in the model [**26**].

We performed sensitivity analysis by individually varying the parameters in the state equations and observing the changes on the controls. We concluded that among all the parameters, the controls are most sensitive to d_c and r_c, the death rate and growth rate of cancer cells, respectively. We found that both controls are negatively correlated with d_c and positively correlated with r_c. See Fig. 7 for examples of these effects in a sample patient. These findings are consistent with that of [**25**] for the underlying model.

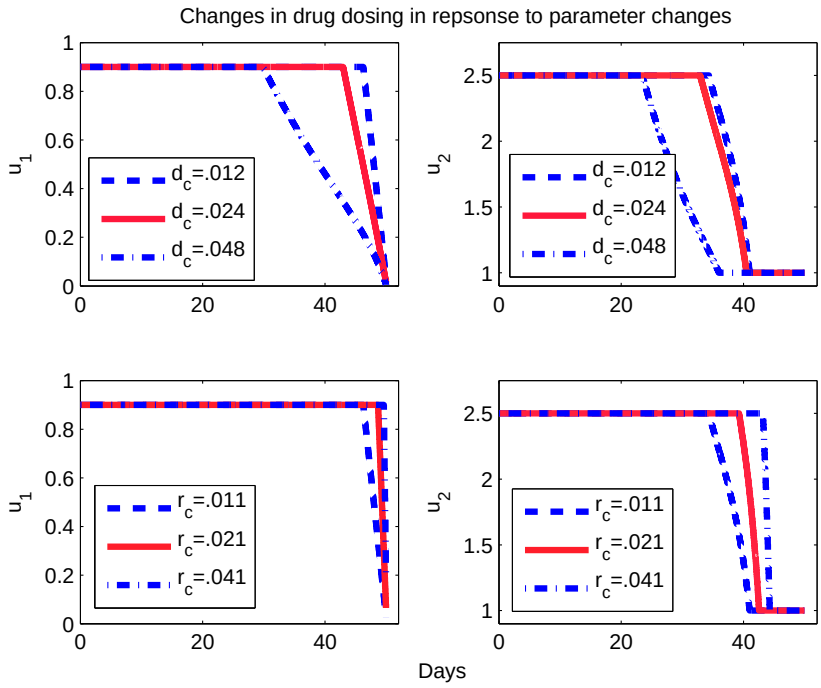

FIGURE 7. The top two graphs show the impact of varying d_c values on optimal drug regimen for u_1 and u_2. The lower two graphs show the impact of varying r_c values on optimal drug regimen for both drugs for some hypothetical patient.

6. Concluding Remarks

In this paper, we have only presented one model with more than one control. Using multiple controls is important for treatments with more than one drug. See [**11**] for another such example. Using quadratic costs in the objective functionals is not always realistic; see [**7, 17**] for immunology models which are linear in the control.

In both examples presented here, the control(s) represent drug treatments. However, for certain treatments, a drug may have its own dynamics while interacting with the other factors in the system. In this case, the drug would need to

be represented by its own differential equation. The control would simply be the input of the drug and appear as a source term in the drug equation. An illustrative example can be found in [**5**]. See [**18**] for such an example using pharmacokinetics.

For more details about the ideas introduced here and some computer lab illustrations, see the book by the authors [**19**].

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