Lab 1

We begin with a simple minimization problem to illustrate the effect of certain parameters. Our goal is to minimize the objective functional below.

$$\min_u \ \frac{1}{2}\int_0^1 Ax^2(t) + Bu^2(t)\,dt$$

$$\text{subject to,} \qquad x'(t) = x(t) + u(t)$$

$$x(0) = x_0 \text{ fixed}, \quad x(1) \text{ free}$$

Let us now derive the necessary conditions for this problem. Write the adjoint equation in the space below.

Write the optimality equation and solve for the optimal control in terms of the adjoint and state variables.

To begin, open MATLAB. At the prompt, type "lab1" and press enter. This will begin the program. A quick note on MATLAB: if at any point you would like to stop the program you are running, simply press Crtl-c. This will terminate the current application and return the prompt.

You will now be asked to enter a value for the variable A. Type the number you would like to use and press enter. It will then ask you for a B value and x_0 value. We require $A \geq 0$ and $B > 0$, or no optimal control would exist. It may take MATLAB a few seconds to calculate the solution. Once it has, it will ask you which variable(s) you would like to plot. Finally, the program will ask if you would like to vary any parameters. If you decide to do so, you will be able to enter a second value for the parameter of your choosing. Then, solutions for a second problem, with identical parameter values except for the parameter which you chose to vary, will be generated and plotted on the same graph as the solutions to the first problem. This will allow you to see exactly how each variable affects the optimal control, state, and/or adjoint. If you choose not to vary any parameters, MATLAB will plot the solutions to the problem specified by your original entries. Run the program several times to get a feel for how it works.

Now, we will use the program to ascertain how each parameter affects the solution. Enter the following values: $A = 1$, $B = 1$, $x_0 = 1$. Enter plot option 4 and that you would like to vary a parameter. Choose to vary A. Specifically, try $A = 3$ as your second value. Look at the resulting graphs. In the second system, $A > B$, so minimizing $x(t)$ is more important than minimizing $u(t)$. We see this is exactly what happens on the graphs. $u(t)$ is forced more negative so that $x(t)$ can be minimized appropriately.

Enter the same values as before, this time varying B, say $B = 3$. In this case, minimizing $u(t)$ is more important, as $B > A$. We see on the graph, $u(t)$ is pulled closer to zero, even though this causes $x(t)$ to increase more rapidly.

Now try varying x_0. You will notice the system with the greater x_0 value has a lower control. As the state begins much higher, the control is forced lower to compensate.

Enter $x_0 = 0$. This will cause the trivial solution of $u(t) \equiv 0$, regardless of A, B values. To see this, consider our goal. We are trying to minimize both $x^2(t)$ and $u^2(t)$, but $x^2(t)$ begins at 0. So, it is already minimized, and we would not choose to move it, i.e., $u(t) = 0$. However, if both the state and control are everywhere zero, then the objective function is zero, thus minizmized.

Finally, let $A = 0$. What is the result? Why does this happen?

Lab 2

In this lab, we compare the two different optimal control problems below.

Problem 1.

$$\min_u \int_0^1 u^2(t)\,dt$$

$$\begin{aligned} \text{subject to,} \quad & x'(t) = x(t) + u(t) \\ & x(0) = x_0, \;\; x(1) = x_1 \text{ fixed} \end{aligned}$$

Problem 2.

$$\min_u \int_0^1 u^4(t)\,dt$$

$$\begin{aligned} \text{subject to,} \quad & x'(t) = x(t) + u(t) \\ & x(0) = x_0, \;\; x(1) = x_1 \text{ fixed} \end{aligned}$$

We see the only difference between problem 1 and 2 is the exponent on the control in the objective functional. Consequently, you may think the optimal control would be the same for both. However, as you will see, the exponent affects the problem more than one might think. First, consider the necessary conditions for both.

Write out the necessary conditions for Problem 1. How are they different from the necessary conditions in Lab 1?

Write the necessary conditions for problem 2.

First, note the similarity between problem 1 and the problem in Lab 1, with $A = 0$ and $B = 2$. The only difference is the $x(1)$ being fixed or free. As such, the necessary conditions are almost identical, with the only difference being whether $\lambda(1)$ is fixed or free.

Also, the adjoint equations in problem 1 and problem 2 are the same. However, the optimal controls are different. This is entirely the effect of the exponent in the functional.

To begin, type "lab2" at the prompt. The program will ask for a x_0 value and then a x_1 value. After the solutions have been calculated, you will be asked which variables you would like to plot. Try the problem with several different values. We can see the exponent greatly affects the optimal control.

As a final note, both of these problems had optimal controls regardless of initial and final state position. However, this is generally not the case. In most problems, only certain initial and final positions will be compatible. These problems are more flexible because the state on the optimal trajectory is the sum of two exponentials, which can be forced to fit any initial and final conditions.

Lab 3

In this lab, we study a fish harvesting model. Let the state $x(t)$ be the number of fish in a lake at time t. We assume x grows exponentially, namely $x'(t) = 4x(t)$, when there is no harvesting. The rate at which fish are caught during harvesting is $2\sqrt{x(t)u(t)}$, where $u(t)$, our control, is the harvesting intensity. We wish to maximize profit over the harvesting period $[0, T]$, when the unit price per crop is twice the price for one unit of harvesting.

$$\max_u \int_0^T 4\sqrt{x(t)u(t)} - u(t)\,dt$$

$$\text{subject to,} \qquad x'(t) = 4x(t) - 2\sqrt{x(t)u(t)}, \;\; x(0) = x_0$$

To begin, type "lab3" at the prompt. The program will ask for x_0 and T values. As usual, you will then be asked which variables you would like to plot and if you would like to vary any parameters.

The first thing you will notice is the sinusoidal nature of the state and control. The fish population increases to its maximum, which causes harvesting intensity to increase. Fish population decreases accordingly, causing harvesting intensity to lower. This pattern is cyclic. Notice that the harvesting rate reaches its minimum twice for each cycle, allowing the fish population to increase to a certain level before intense harvesting recommences.

After running the program several times, vary the initial fish population. Notice how the greater initial condition causes the population to maximize at a much higher level. Further, the higher fish population allows for a greater harvesting rate.

Now, vary T. The optimal control and states are very different. This is a good illustration of an important concept in optimization theory. One might think that by extending the time period, the optimal control would simply be an extension of the original optimal control. However, this is rarely the case. We can see this in our problem. Also, the shorter time period forces a more intense harvesting rate, but over shorter intervals.

Reference:

M. Eisen, *Mathematical Methods and Models in the Biological Sciences: Nonlinear and Mulitidimensional Theory*, Prentice Hall, Engelwood Cliffs, New Jersey, 1988, p. 267-8.

Lab 4

In this lab, we examine a maximization problem with bounded control.

$$\max_u \int_0^2 Ax(t) + Bu(t) + Cu^2(t)\,dt$$

$$\text{subject to,} \qquad x'(t) = x(t) + u(t)$$

$$x(0) = x_0, \;\; 0 \le u(t) \le M$$

To begin, type "lab4" at the prompt. Enter the following values for the constants: $A = 2$, $B = -3$, $C = -1$, $x_0 = 5$, and $M = 2$. For now, don't vary any parameters. Looking at the control, we see the effect of the bounds. u begins at 2, moves down, and ends at 0.

Now, enter the same values, but vary M. Try $M = 4$. Then, try $M = 6$. Watch as the control changes with these bounds, and how this affects the state. You will also notice that the adjoint does not change. It seems the adjoint is not a function of M. In fact, by varying the other constants, you will see the only parameter which affects the adjoint is A.

Try a negative A value. Specifically, use $A = -1$, $B = 3$, $C = -1$, $x_0 = 4$, and $M = 1$. Notice that the negative A causes the control to start at 0 and move up to $M = 1$. Also, the adjoint is now an increasing function.

To finish, run the program several more times with different values. Try to get a feel for the specific effect of each parameter. Construct a problem with an optimal control that touches neither bound.

Lab 5

Optimal control techniques are of great use in developing optimal strategies for chemotherapy. We assume a Gompertzian growth, and Skipper's log-kill hypothesis is used. Thus, if $N(t)$ is the normalized density of the tumor at time t, we have the model $N'(t) = rNln(\frac{1}{N}) - u(t)\delta N$, where r is the growth rate of the tumor, δ is the magnitude of the dose, and $u(t)$ describes the time dependent pharmacokinetics of the drug, i.e., $u(t) = 0$ implies no drug effect and $u(t) > 0$ is the strength of the drug effect. Our goal is to find $u(t)$ that will drive tumor density to desired level N_d and minimize side-effects of the drug. So, our problem is

$$\min_u \int_0^T a(N(t) - N_d)^2 + bu^2(t)\, dt$$

$$\text{subject to,} \qquad N'(t) = rNln(\tfrac{1}{N}) - u(t)\delta N$$

$$N(0) = N_0, \;\; 0 \leq u(t)$$

To begin, type "lab5" at the prompt. First, try these values: $r = 0.1$, $a = 3$, $b = 1$, $\delta = 0.45$, $N_d = 0$, $N_0 = 0.975$, and $T = 20$. We see the tumor density is not actually forced to $N_d = 0$, but minimized over the interval.

Now, enter the same values, varying b this time to a much lower value, say $b = 0.01$. Do not enter $b = 0$, the program must have a non-zero b to calculate the solution. Notice we are able to push the tumor density to a much lower level when minimizing side-effects is of little importance. However, you will also notice the strength of the drug is much higher, particularly at the beginning of the treatment period.

Run the program with the same parameters, this time varying a to $a = 1$. We have two systems, one where minimizing tumor density is three times as important as minimizing drug side-effects, and the second where they are of equal importance. The results are as we would expect.

The previous simulations were run with initial tumor density near carrying capacity. Try varying N_0 now to something smaller, say $N_0 = 0.5$. Notice how the two tumor densities and drug strengths converge. It seems initial tumor density only affects the early stages of treatment.

Try varying the other parameters to see the effect they have on the optimal control. Is it what you expected?

Reference:

K. R. Fister and J. C. Panetta, *Optimal Control Applied to Competing Chemotherapeutic Cell-Kill Strategies*, 2003.

Lab 6

A good produced at a rate $x(t)$ can either be reinvested to expand productive capacity or sold. Productive capacity grows at the reinvestment rate. We wish to find the fraction $u(t)$ of output that should be reinvested to maximize total sales over the period $[0, T]$, given an initial capacity $c > 0$.

$$\max_u \int_0^T x(t)[1 - u(t)]\, dt$$

$$\text{subject to,} \quad x'(t) = u(t)x(t)$$

$$x(0) = c, \;\; 0 \leq u(t) \leq 1$$

To begin, type "lab6" at the prompt. As usual, enter the requested values, select variables to plot, and vary parameters if you choose. First, try $c = 100$ and $T = 5$. If you look at the control, you will notice an abrupt shift at $t = 4$. In fact, the graph should not be continuous. MATLAB creates the graph by connecting a series of points, making it continuous. The control in this problem is known as "bang-bang," i.e., it switches between the lower bound and upper bound. Specifically, $u(t) = 1$ for $0 \leq t \leq 4$ and $u(t) = 0$ for $4 < t \leq 5$. Also, $x(t)$ is exponential for $0 \leq t \leq 4$ and constant for $4 < t \leq 5$, as expected.

Try varying c. The adjoint and control are unchanged. The state with higher initial condition increases faster, but both switch at the same point.

Now, vary T. We see the switching time of the control, and consequently the state, are determined entirely by our choice of T. Try $T \leq 1$. The control is now $u = 0$ for all t.

Reference:

M. I. Kamien and N. L. Schwartz, *Dynamic Optimization: The Calculus of Variations and Optimal Control in Economics and Manangement*, North-Hollan Press, New York, 1991, p. 205-7.

Lab 7

Many times, we wish to move a state (or states) from an initial position to a specified final position in minimum time. We can construct this problem as an optimal control problem by minimizing the integral $\int_0^T 1\,dt$ subject to the state equations. To illustrate this concept, along with an example of a system and bounded control, we examine the following simple example. The goal is to move a point in the xy-plane, starting at (x_0, y_0), to the origin in minimum time, where the movement of the point is dictated by the equations $y'(t) = x(t)$ and $x'(t) = u(t)$. Thus, our problem is

$$\min_{u,T} \int_0^T 1\,dt$$

$$\begin{aligned} \text{subject to,} \qquad & y'(t) = x(t), \;\; y(0) = y_0, \;\; y(T) = 0 \\ & x'(t) = u(t), \;\; x(0) = x_0, \;\; x(T) = 0 \\ & -1 \le u(t) \le 1, \;\; T \text{ free} \end{aligned}$$

Write out the necessary conditions for this problem.

To begin, type "lab7" at the prompt. Enter the initial coordinate and graph choice. The graphs will be plotted and the transition time will be displayed on the home screen. First, try the intial position $(1, 1)$. That's $x_0 = 1$ and $y_0 = 1$. Choose plot option number 5, all graphs. We see the optimal control here is bang-bang, switching from -1 to 1. The bottom graph is the optimal trajectory of the point in the xy-plane.

Now, try $(-2, 1)$. The control is bang-bang, starting at 1 switching to -1.

What is the control if $(x_0, y_0) = (-2, 2)$? $(2, -2)$?

These are the four possibilities for the optimal control, with the switching point varying. Try several more initial positions to find the regions which produce these controls.

Reference:

S. K. Agrawal and B. C. Fabien, *Optimization of Dynamic Systems*, Kluwer Academic Publishers, Boston, 1999, p. 85-7.

Lab 8

Often in applications, we are concerned with the values of more than one variable. Specifically, we would have a system of multiple state variables and equations depending on a control or controls , whether directly or indirectly. The following lab studies a model of an infectious disease taking into account the number of susceptible, exposed, and infectious persons.

Let $x_1(t)$, $x_2(t)$, and $x_3(t)$ be the percentage of the population at time t which is susceptible, exposed, and infectious, respectively. Let $u(t)$, our control, be the percentage of susceptible individuals being vaccinated per unit of time. Let b be the natural birth rate of the population, and d the rate of death caused by the disease. The parameter e is the rate at which the exposed individuals become infectious, and g is the rate at which infectious individuals recover. Therefore, $\frac{1}{e}$ is the mean latent period and $\frac{1}{g}$ the mean infectious period. We assume a permanent immunity. Finally, cx_1x_3 describes the incidence of the disease. We wish to minimize the percentage of infectious individuals and the cost of the vaccinations.

$$\min_u \int_0^T x_3(t) + \frac{1}{2}Wu^2(t)\,dt$$

$$\begin{aligned}
\text{subject to,} \qquad & x_1'(t) = b - bx_1(t) + (d-c)x_1(t)x_3(t) - u(t)x_1(t) \\
& x_2'(t) = cx_1(t)x_3(t) - (e+b)x_2(t) + dx_2(t)x_3(t) \\
& x_3'(t) = ex_2(t) - (g+d+b)x_3(t) + dx_3^2(t) \\
& x_1(0) = x_{10},\ x_2(0) = x_{20},\ x_3(0) = x_{30},\ 0 \le u(t) \le 1
\end{aligned}$$

To begin, type "lab8" at the prompt. Start with the following values: $d = 6$, $b = 0.5$, $c = 5$, $e = 4$, $g = 1.5$, $x_{10} = 0.3$, $x_{20} = 0.3$, $x_{30} = 0.3$, $W = 0.2$, and $T = 20$. This is a simulation of a disease with a fairly low incidence measure. As such, the number of people who are exposed during this period is very low. Thus, the exposed and infectious populations quickly disappear (through death and recovery). The susceptible population rapidly grows, as very few people are catching the disease, and the vaccination rate is subsequently low. Now, try $c = 20$. This is a much higher, and more realistic, incidence level. Here, the vaccination rate is higher and more varied. We are still able to drive the infectious population to a very low level.

Now, enter the above values, with $c = 20$, and vary W, say $W = 0.2$ and $W = 0.7$. We have looked at the effect of cost parameters before. When the cost is lower, we are able to vaccinate at a higher rate and drive the percentage of infectious people much lower.

Try varying the death rate, $d = 1$ and $d = 5$. Notice the difference. The simulation with the lower rate has a lower susceptible percentage and vaccination rate, but higher exposed and infectious percentages. Why should this be?

Vary g, using $g = 1.5$ and $g = 5$. The second system represents a disease with a very short recovery time. How does this affect the optimal vaccination rate?

Try varying each parameter several times to decifer its effect on the system. Does it have the effect you expected?

Reference:

L. Wang, *Mathematical Analysis of Global Dynamics of SEIR Type Epidemiological Models*, 2000.

Lab 9

In the following lab, optimal control is used to find an optimal chemotherapy strategy in the treatment of the HIV virus. Unlike the last lab, where the dynamics of a population affected by an epidemic were considered, this problem studies the immune system of an individual. We consider the chemotherapy of reverse transcription inhibitors, such as AZT, which interupt keys stages of the infection process during the life cycle of HIV within a host cell. It is assumed the treatment acts to reduce the "infectivity" of the virus for a finite time, until drug resistance occurs.

We are interested in the retention and/or increase of the $CD4^+T$ cell count. Let $T(t)$ and $T_i(t)$ be the concentration of uninfected and infected $CD4^+T$ cells, respectively, and $V(t)$ be the concentration of free virus particles. By concentration, we mean population number per unit volume. Let $\frac{s}{1+V(t)}$ be source term from the thymus, representing the rate of generation of new $CD4^+T$ cells. Let r be the growth rate of T cells per day. This growth is assumed to be logistic, with maximum level of T_{max}. Let $kV(t)T(t)$ be the rate free virus cells infect T cells. Let m_1, m_2, m_3 be the natural death rates of uninfected T cells, infected T cells, and free virus particles, respectively. Once infection of a T cell occurs, replication of the virus is initiated and an average of N viruses are produced before the host cell dies.

Our control, $u(t)$, is the strength of the chemotherapy, where $u(t) = 0$ is maximum therapy and $u(t) = 1$ is no therapy. We wish to maximize the number of uninfected T cells while simultaniously minimizing the "cost" of the chemotherapy to the body. Letting $B > 0$ be our cost parameter, our problem is

$$\max_u \int_0^{t_{final}} T(t) - \frac{B}{2}(1-u(t))^2 \, dt$$

subject to,

$$T'(t) = \frac{s}{1+V(t)} - m_1T(t) + rT(t)\left[1 - \frac{T(t)+T_i(t)}{T_{max}}\right] - u(t)kV(t)T(t)$$

$$T_i'(t) = u(t)kV(t)T(t) - m_2T_i(t)$$

$$V'(t) = Nm_2T_i(t) - m_3V(t)$$

$$T(0) = T_0,\ T_i(0) = T_{i0},\ V(0) = V_0,\ 0 \le u(t) \le 1$$

To begin, type "lab9" at the prompt. Begin with the values $s = 10$, $m_1 = 0.02$, $m_2 = 0.5$, $m_3 = 4.4$, $r = 0.03$, $T_{max} = 1500$, $k = 0.000024$, $N = 300$, $T_0 = 800$, $T_{i0} = 0.04$, $V_0 = 1.5$, $B = 40$, and $t_{final} = 20$. Choose plot option 5 and do not vary any parameters. We see the optimal chemotherapy therapy is a dynamic one, beginning with the strongest dose and followed by a decreasing of treatment. This has the effect of increasing the T cell count initially and then balacing it off, even though treatment is not 100% effective 100% of the time. This behavior is seen in drugs such as AZT and DDT. Also, infected T cell count and viral concentration initially decrease and then increase as treatment lessens, but not to original levels.

Let us begin with an evaluation of the cost variable. Enter the same values as before, varying B, say $B = 80$ as our second value. As expected, the problem with lower cost variable has a control where maximum treatment is continued longer. Subsequently, the T cell count is driven higher, and infected T cell count and viral concentration are pushed lower.

Enter the original values again, this time varying the number of virus produced by infected cells, say $N = 100$ as the second value. Notice the dramatic difference. In the second problem, we are able to drive the T cell count higher, but with a much less strenuous treatment regimen. Further, with $N = 100$, the virus actually dies out because it is not reproducing enough to sustain itself.

Now, enter the same values, varying T cell growth rate to $r = 0.1$. In this run, we are able to drive the T cell count much higher with virtually the same chemotherapy treatment, because of the higher natural growth rate. By the same token, however, the infected T cell count and viral concentration are also higher, as there are more T cells to act as hosts.

Vary the infection rate, using the original $k = 0.000024$ and $k = 0.00003$. Notice the effect only a slight change in k has. We are forced to continue maximum treatment longer for a less desired result. Also, the infected cell count and viral concentration grow much higher despite the stronger treatment.

Try varying the three death rates, m_1, m_2, and m_3, one by one. Are the effects as you expected? Which death rate seems to have the greatest impact?

To finish, vary each of the remaining parameters. What effect does each have?

References:

S. Butler, D. Kirschner, and S. Lenhart, "Optimal control of chemotherapy affecting the infectivity of HIV," *Advances in Mathematical Population Dynamics - Molecules, Cells, and Man*, O. Arino, D. Axelrod, and M. Kimmel (Eds.), 1995.

Lab 10

In earlier labs, you may have encountered solutions which were unrealistic or received error messages when you supplied your own parameter values. Mathematical models are designed for specific situations and are sometimes very sensative to constant values. In this final lab, we examine an ill-conditioned problem wtih this type of behavior.

In a study by Ackerman et al, a simplified, but highly accurate, model of the blood regulartory system was developed to improve the ability of the GTT (glucose tolerance test) to detect prediabetics and mild diabetics. The model considers the concertration of blood glucose (g) and net hormonal concentration (h). It was shown that $g'(t) = c_1 g(t) + c_2 h(t)$ and $h'(t) = c_3 g(t) + c_4 h(t)$. The constants c_i, for $i = 1, 2, 3, 4$, are the values of unknown functions at specified levels. However, using properties of the blood glucose regulatory system, they determined that c_1, c_2, $c_3 \leq 0$ and $c_4 \geq 0$.

We are interested in the control of blood glucose for diabetics. We will use the above model, letting $x_1 = g$, $x_2 = h$. The above study also showed that for diabetics, $c_4 = 0$ is a reasonable assumption. Thus, we wish to find the insulin injection level, $u(t)$, which will minimize the difference between x_1 and the desired glucose level, l, taking cost into account.

$$\min_u \int_0^T (x_1(t) - l)^2 + \beta u^2(t)\, dt$$

subject to,

$$x_1'(t) = -a x_1(t) - b x_2(t), \quad x_1(0) = x_{10}$$

$$x_2'(t) = -c x_2(t) + u(t), \quad x_2(0) = 0$$

where a, b, c, $\beta > 0$

Write out the necessary conditions for this problem.

To begin, type "lab10" at the prompt. Enter the following values: $a = b = c = 1$, $x_{10} = 0.75$, $\beta = 1$, $l = 0.5$, and $T = 20$. We see the glucose concentration and insulin levels become negative. This is clearly impossible. Also, notice that instead of moving towards and staying close to $l = 0.5$, the glucose level continues to decrease.

Now, try $a = b = c = 1$, $x_{10} = 0.25$, $\beta = 0.1$, $l = 0.5$, and $T = 20$. This seems to be worse. The glucose, hormonal, and insulin levels all fly out of control towards the end of the time period. All three also go negative. What is wrong with this problem?

One problem could be the lack of control restrictions. The insulin level became negative in both runs. Why not just require $u(t) \geq 0$? While this might help somewhat, the problem is deeper. As we said earlier, the ODE model used in this optimal control problem was created for more accurate GTTs. While the model has proven very accurate for this purpose, in this problem we have asked much more. A GTT requires the monitoring of glucose for only three to five hours. Our problem requires the accurate prediction of glucose levels for weeks or even months. We have pushed the model well beyond its boundaries of reliability. In the second run of this program, we saw the solutions became unstable after 15 days. Before finishing, run several more values. Try running the simulation for more than 20 days. When do you encounter error messages?

References:

E. Ackerman, L. Gatewood, J. Rosevar, and G. Molnar, "Blood glucose regulation and diabetes," *Concepts and Models of Biomathematics*, F. Heinmets (Ed.), Marcel Dekker, New York, 1969.

M. Eisen, *Mathematical Methods and Models in the Biological Sciences*, Prentice Hall, Englewood Cliffs, New Jersey, 1988, p. 71-5, 301-4.