MATH 228: Project 2

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(Link to Google Sheet, see details below)

1 Introduction

This project focuses on how eigenvalues can be used to design an artificial pancreas that regulates glucose levels. Using the methods we've developed for analyzing linear systems, your job is to design a control policy for the artificial pancreas.

2 Background

In this section, we first describe a model of the artificial pancreas. We then make four assumptions that simplify the model so that it can be written as a linear system.

Model

In this section, we describe a model that predicts how glucose and insulin levels change throughout the day. This model was first described by Bergman, Phillips, and Cobelli [1]. However, we will use a version of the model that appears in Roy and Parker [2]. The model contains three variables:

$I(t)$ blood insulin level $\quad$ $X(t)$ intercellular insulin level $\quad$ $G(t)$ blood glucose level

$I(t)$ is the concentration of insulin in the bloodstream. Insulin in the bloodstream diffuses into the interstitial fluid within cells, and $X(t)$ is the concentration of the intercellular insulin. This intercellular insulin is responsible for clearing glucose from the bloodstream. $G(t)$ is the concentration of glucose in the bloodstream.

The variables $I(t)$, $X(t)$, and $G(t)$ are functions of time. Our goal is to have the pancreas release insulin so that $I(t)$ remains close to a desired value I_b, $X(t)$ remains close to 0, and $G(t)$ remains close to a desired value G_b. Values and units for the constant parameters I_b, G_b, and all other parameters are given in Appendix A of this document.

The way in which $I(t)$, $X(t)$, and $G(t)$ change throughout the day is described by a system of nonlinear differential equations,

$$\begin{aligned} I'(t) &= -nI(t) + p_4 v_1(t) \\ X'(t) &= -p_2 X(t) + p_3(I(t) - I_b) \\ G'(t) &= -X(t)G(t) - p_1(G(t) - G_b) + \frac{1}{V} v_2(t). \end{aligned} \tag{1}$$

Values and units for the constant parameters n, p_1, p_2, p_3, p_4, and V are given in Appendix A.

In Equation (1), the variable $v_1(t)$ specifies the rate at which insulin is infused into the bloodstream by the artificial pancreas, and $v_2(t)$ specifies the rate at which glucose is added to the bloodstream (for example, from eating meals). The insulin infusion rate $v_1(t)$ is bounded from below by 0 (since the artificial pancreas cannot remove insulin from the bloodstream) and is bounded from above by the constant $v_{1,max}$. The insulin infusion rate must satisfy $0 \leq v_1(t) \leq v_{1,max}$ at all times t. Our goal is to choose the function $v_1(t)$ so that the variables $(I(t), X(t), G(t))$ remain near $(I_b, 0, G_b)$. The way in which we choose $v_1(t)$ is called our control policy.

Model Simplifications

Before deciding how to choose $v_1(t)$, we will make three assumptions that will simplify the model in Equation (1). These assumptions will be used to design a control policy in the following section. The assumptions that we will make are:

1. We will ignore the bounds placed on $v_1(t)$.
2. We will ignore $v_2(t)$, the glucose that is being added to the bloodstream.
3. We will approximate the nonlinear system in Equation (1) with a linear system.

Assumptions 1 and 2 are easy to implement. For assumption 1, we simply ignore the bounds $0 \leq v_1(t) \leq v_{1,max}$ on $v_1(t)$. For assumption 2, we can set $v_2(t) = 0$ in Equation (1). The method for applying assumption 3 is described in Appendix B. The variables in the approximate linear system are

$$x_1(t) = I(t) - I_b \qquad x_2(t) = X(t) \qquad x_3(t) = G(t) - G_b \qquad u(t) = v_1(t) - v_b, \tag{2}$$

where $v_b = \frac{n}{p_4} I_b$ is the constant insulin infusion rate needed to maintain an insulin level of I_b. In the approximate linear system, the variables $x_1(t)$, $x_2(t)$, and $x_3(t)$ satisfy the differential equations

$$x_1'(t) = -n x_1(t) + p_4 u(t) \qquad x_2'(t) = p_3 x_1(t) - p_2 x_2(t) \qquad x_3'(t) = -G_b x_2(t) - p_1 x_3(t),$$

which we can rewrite in matrix form as

$$\frac{d}{dt}\begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} = \begin{bmatrix} -n & 0 & 0 \\ p_3 & -p_2 & 0 \\ 0 & -G_b & -p_1 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} + \begin{bmatrix} p_4 \\ 0 \\ 0 \end{bmatrix} u(t). \tag{3}$$

After defining

$$x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} \qquad A = \begin{bmatrix} -n & 0 & 0 \\ p_3 & -p_2 & 0 \\ 0 & -G_b & -p_1 \end{bmatrix} \qquad B = \begin{bmatrix} p_4 \\ 0 \\ 0 \end{bmatrix},$$

the system in Equation (3) can be expressed as

$$x'(t) = Ax(t) + Bu(t). \tag{4}$$

We have seen equations of this form previously in Problem 4 of Homework 6. In the following section, we will design a control policy for the linear system in Equation (4).

3 Problem

This section describes the problem that you are asked to solve.

Feedback Control

Remember that we want the variables $(I(t), X(t), G(t))$ to remain close to $(I_b, 0, G_b)$. Looking back at how $x_1(t)$, $x_2(t)$, and $x_3(t)$ were defined in Equation (2), $(I(t), X(t), G(t))$ remains close to $(I_b, 0, G_b)$ when $x(t)$ remains close to the zero vector. We know that $x(t)$ changes according to Equation (4). How can we choose $u(t)$ so that $x(t)$ remains close to the zero vector?

We will do this using the idea of feedback control. (See Problem 4 in Homework 6 for more details on feedback). In particular, we will let $u(t)$ be a linear function of $x_1(t)$, $x_2(t)$, and $x_3(t)$, so that

$$\begin{aligned} u(t) &= -k_1 x_1(t) - k_2 x_2(t) - k_3 x_3(t) \\ &= -\begin{bmatrix} k_1 & k_2 & k_3 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} \\ &= -Kx(t), \end{aligned} \tag{5}$$

where $K = \begin{bmatrix} k_1 & k_2 & k_3 \end{bmatrix}$ and the constants k_1, k_2, and k_3, which are called gains, are yet to be determined. Plugging this choice of $u(t)$ into Equation (4) gives

$$\begin{aligned} x'(t) &= Ax(t) + Bu(t) \\ &= Ax(t) + B(-Kx(t)) \\ &= (A - BK)x(t). \end{aligned}$$

Our system has now become $x'(t) = (A - BK)x(t)$. As we have shown in class, the behavior of $x(t)$ as $t \to \infty$ is governed by the eigenvalues of the matrix $A - BK$. In particular, $x(t)$ decays to the zero vector if all the eigenvalues of $A - BK$ have negative real parts. For a given set of eigenvalues, we can solve for the constants k_1, k_2, and k_3 so that $A - BK$ has the desired eigenvalues.

Simulation

The Google Sheet located at this link allows you to simulate the artificial pancreas model in Equation (1) along with the control policy in Equation (5) over the course of one day (6 AM to midnight). Note that we are attempting to control the original model in Equation (1) by using the control policy designed for the simplified model in Equation (4).

The Google Sheet at the link above is read only. To edit the spreadsheet, you will need to make a copy to your Google account. To do this, click on "File" in the menu bar and select "Make a copy." You will then have a copy of the spreadsheet in your account that you can edit.

In the simulation, you will choose the gains k_1, k_2, and k_3 corresponding to desired eigenvalues. (You were asked to do similar computations for a simpler system in Problem 4 of Homework 6.) The simulation also allows you to run multiple trials. There is some randomness in each trial, as described below. Finally, the simulation allows you to turn the artificial pancreas on or off.

You are required to input three things into the simulation:

- Place the values of the gains k_1, k_2, and k_3 in the three boxes next to "Place your desired gains k_1, k_2, and k_3 in these three boxes:"

- Place the number of trials you want to run in the box next to "Place the number of trials to run in this box:"

- Place an x in the box next to "On/Off switch" if you want the artificial pancreas to release insulin. If the box is blank, no insulin will be released.

After supplying these inputs, click the button "Click to run simulation."

The simulation provides three outputs. The number next to "Number of simulations run" records how many times you have clicked the "Click to run simulation" button. The number next to "Average score per trial" provides a score, averaged over all trials, defined by

$$\text{score} = \int_{6\text{ AM}}^{\text{Midnight}} \left(0.1 \frac{|I(t) - I_b|}{I_b} + \frac{|G(t) - G_b|}{G_b} \right) \, dt.$$

This score measures how close the variables $I(t)$ and $G(t)$ are to their desired values of I_b and G_b throughout the day. The constant 0.1 is included so that the glucose error term is given a larger weight in the score than the insulin term. A lower score equates to a better performing control policy. Finally, the number next to "Success rate" tells you the percentage of trials in which the glucose levels did not exceed safety bounds. See Appendix A for the values of these safety bounds.

The simulation also produces plots of the blood glucose level $G(t)$ and the insulin infusion rate $v_1(t)$ throughout the day. In the blood glucose level plot, the dashed black lines show the safety bounds. Also shown are red boxes that correspond to meals. In the red regions, glucose is being absorbed into the bloodstream, so $v_2(t) > 0$. Outside of the red regions, no glucose is being absorbed into the bloodstream, so $v_2(t) = 0$. The times, durations, and sizes of each meal are random for each trial. See Appendix A for more details.

In the insulin infusion rate plot, the dashed black lines show the bounds placed on $v_1(t)$. The control policy is not allowed to exceed these bounds.

Finally, the second spreadsheet titled "parameters" allows you to adjust some of the parameters in the system. This spreadsheet includes the parameter descriptions, symbols, and nominal values. If you place a number in the "Parameter value" column, that value will be used in the simulations. If the entry in the "Parameter value" column is left blank, then the nominal value will be used in the simulations.

4 Requirements

In your project report, you should address the following topics/questions:

a. Model Description:

- Provide a short summary of the variables in the model, including $I(t)$, $X(t)$, $G(t)$, $v_1(t)$, $v_2(t)$, $x(t)$, and $u(t)$.
- Provide a short summary of the use of feedback control in the model.

b. Analysis:

- If our desired eigenvalues are λ_1, λ_2, and λ_3, find expressions for the gains k_1, k_2, and k_3 so that the matrix $A - BK$ has the desired eigenvalues.

c. Simulation:

- Choose a goal that you would like your system to achieve (for example, 95% success rate, average score per trial below 10, etc.)
- Run 100 trials in which the artificial pancreas releases no insulin. Was your goal met in this case? (Remember that you can run multiple trials at once by changing the number next to "Place the number of trials to run in this box:")

- Choose four sets of desired eigenvalues, and then compute the corresponding gains k_1, k_2, and k_3 for each set of eigenvalues.
- For each set of gains, run 100 trials.
- Summarize your findings (for example, which sets of eigenvalues met your goals, which did not, did you observe any patterns?)
- For your favorite set of eigenvalues, include a plot from one of your trials showing the blood glucose levels and insulin infusion rate throughout the day.

d. Finally, you should address at least one of the following questions, which involve adjusting the parameters on the "parameters" spreadsheet:

- How do the initial values of blood insulin, remote insulin, and blood glucose at 6 AM affect the average score and success rate?
- How do the bounds on blood glucose and insulin infusion rate affect the average score and success rate?
- How do the meal times, meal durations, and meal sizes affect the average score and success rate?

You are welcome to explore other questions that build upon the questions listed above. Furthermore, you are welcome to explore the Javascript code that is used in the simulations. To access the code, click on "Extensions" in the menu bar and select "Apps Script." The file Code.gs contains the Javascript code that is used to run the simulations. **Word of caution:** If you make changes to the code and the simulation stops running correctly, simply get a fresh copy at the link above rather than trying to fix the code.

5 Project Report

The report is due by 1:30PM on November 30, and it must address items (a)-(d) above. The report should be typed (but handwritten equations are ok), and it should highlight your approach to the questions descried above, your results, and your conclusions. Longer computations, if needed, can be placed in an appendix of the report. The report should not be written in the style of a homework assignment (e.g., it should not have section headings of "part a," "part b," etc.), but instead in the style of a short lab or research report. You will submit the report as a pdf on Moodle.

6 Evaluation

Your report will be evaluated based on the following rubric:

- (20%) The report has the correct format, as described above
- (20% each) Items (a)-(d)
  - (15%) Content: Complete and thoughtful responses are given to all questions, and claims are supported with evidence such as computations, plots, or simulations.
  - (5%) Presentation: The submission is organized into a cohesive report, and the writing is both clear and concise.

A System Parameters

Table 1 shows the units and values for the variables that appear in the model, which were obtained from [2].

Variable	Units	Value
$I(0)$	μU/ml	Random number between 5 and 15
$X(0)$	μU/ml	0
$G(0)$	mg/dl	Random number between 60 and 100
I_b	μU/ml	10
G_b	mg/dl	80
n	1/hour	8.52
p_1	1/hour	2.1
p_2	1/hour	3
p_3	ml/μU$\cdot$hour^2	0.1008
p_4	1/ml	0.098
V	dl	117
h	hour	0.1
$u_{1,min}$	μU/hour	0
$u_{1,max}$	μU/hour	10,000
G_{min}	mg/dl	40
G_{max}	mg/dl	400
Time of meal 1	hours after midnight	Random number between 6.75 and 7.25
Time of meal 2	hours after midnight	Random number between 11.75 and 12.25
Time of meal 3	hours after midnight	Random number between 17.75 and 18.25
Duration of meal 1	hours	Random number between 0.75 and 1.25
Duration of meal 2	hours	Random number between 0.75 and 1.25
Duration of meal 3	hours	Random number between 0.75 and 1.25
Size of meal 1	grams of glucose	Random number between 90 and 110
Size of meal 2	grams of glucose	Random number between 90 and 110
Size of meal 3	grams of glucose	Random number between 90 and 110

Table 1: System Parameters

B Linear system approximation

In this appendix, we describe the process for approximating the nonlinear system in Equation (1) with a linear system. First, recall that we want the variables $I(t)$, $X(t)$, and $G(t)$ to remain close to I_b, 0, and G_b, respectively. In Equation (2), we defined $x_1(t)$, $x_2(t)$, and $x_3(t)$ to be the differences between the current and desired values of $I(t)$, $X(t)$, and $G(t)$, and we defined $u(t)$ to be the difference between the current and desired value of $v_1(t)$.

We will use $f_1(I, X, G, v_1)$, $f_2(I, X, G, v_1)$, and $f_3(I, X, G, v_1)$ to denote the right hand sides in the nonlinear system in Equation (1), i.e.,

$$\begin{aligned}
f_1(I(t), X(t), G(t), v_1(t)) &= -nI(t) + p_4 v_1(t) \\
f_2(I(t), X(t), G(t), v_1(t)) &= -p_2 X(t) + p_3(I(t) - I_b) \\
f_3(I(t), X(t), G(t), v_1(t)) &= -X(t)G(t) - p_1(G(t) - G_b),
\end{aligned}$$

where the glucose infusion term $v_2(t)$ has been set to 0. Next, taking the derivatives of $x_1(t)$, $x_2(t)$, and $x_3(t)$ gives

$$\begin{aligned}
x_1'(t) &= I'(t) = f_1(I(t), X(t), G(t), v_1(t)) = f_1(I_b + x_1(t), x_2(t), G_b + x_3(t), v_b + u(t)) \\
x_2'(t) &= X'(t) = f_2(I(t), X(t), G(t), v_1(t)) = f_2(I_b + x_1(t), x_2(t), G_b + x_3(t), v_b + u(t)) \\
x_3'(t) &= G'(t) = f_3(I(t), X(t), G(t), v_1(t)) = f_3(I_b + x_1(t), x_2(t), G_b + x_3(t), v_b + u(t))
\end{aligned}$$

Now, if we assume that the errors $x_1(t)$, $x_2(t)$, $x_3(t)$, and $u(t)$ are small, we can approximate the right hand sides in each of the above equations with a Taylor series. For $x_1(t)$, this gives

$$\begin{aligned}
x_1'(t) &= f_1(I_b + x_1(t), x_2(t), G_b + x_3(t), v_b + u(t)) \\
&\approx f_1(I_b, 0, G_b, v_b) + \left(\left.\frac{\partial f_1}{\partial I}\right|_{(I_b,0,G_b,v_b)}\right) x_1(t) + \left(\left.\frac{\partial f_1}{\partial X}\right|_{(I_b,0,G_b,v_b)}\right) x_2(t) + \ldots \\
&\quad \left(\left.\frac{\partial f_1}{\partial G}\right|_{(I_b,0,G_b,v_b)}\right) x_3(t) + \left(\left.\frac{\partial f_1}{\partial v_1}\right|_{(I_b,0,G_b,v_b)}\right) u(t) \\
&= 0 + (-n)x_1(t) + (0)x_2(t) + (0)x_3(t) + (p_4)u(t) \\
&= -nx_1(t) + p_4 u(t).
\end{aligned}$$

Similarly, for $x_2(t)$ and $x_3(t)$ we have

$$\begin{aligned}
x_2'(t) &= f_2(I_b + x_1(t), x_2(t), G_b + x_3(t), v_b + u(t)) \\
&\approx f_2(I_b, 0, G_b, v_b) + \left(\left.\frac{\partial f_2}{\partial I}\right|_{(I_b,0,G_b,v_b)}\right) x_1(t) + \left(\left.\frac{\partial f_2}{\partial X}\right|_{(I_b,0,G_b,v_b)}\right) x_2(t) + \ldots \\
&\quad \left(\left.\frac{\partial f_2}{\partial G}\right|_{(I_b,0,G_b,v_b)}\right) x_3(t) + \left(\left.\frac{\partial f_2}{\partial v_1}\right|_{(I_b,0,G_b,v_b)}\right) u(t) \\
&= 0 + (p_3)x_1(t) + (-p_2)x_2(t) + (0)x_3(t) + (0)u(t) \\
&= p_3 x_1(t) - p_2 x_2(t).
\end{aligned}$$

$$\begin{aligned}
x_1'(t) &= f_3(I_b + x_1(t), x_2(t), G_b + x_3(t), v_b + u(t)) \\
&\approx f_3(I_b, 0, G_b, v_b) + \left(\left.\frac{\partial f_3}{\partial I}\right|_{(I_b,0,G_b,v_b)}\right) x_1(t) + \left(\left.\frac{\partial f_3}{\partial X}\right|_{(I_b,0,G_b,v_b)}\right) x_2(t) + \ldots \\
&\quad \left(\left.\frac{\partial f_3}{\partial G}\right|_{(I_b,0,G_b,v_b)}\right) x_3(t) + \left(\left.\frac{\partial f_3}{\partial v_1}\right|_{(I_b,0,G_b,v_b)}\right) u(t) \\
&= 0 + (0)x_1(t) + (-G_b)x_2(t) + (-p_1)x_3(t) + (0)u(t) \\
&= -G_b x_2(t) - p_1 x_3(t).
\end{aligned}$$

Finally, we now have

$$\begin{aligned}
x_1'(t) &\approx -nx_1(t) + p_4 u(t) \\
x_2'(t) &\approx p_3 x_1(t) - p_2 x_2(t) \\
x_3'(t) &\approx -G_b x_2(t) - p_1 x_3(t),
\end{aligned}$$

which is identical to the linear system in Equation (3).

References

[1] R. N. Bergman, L. S. Phillips, and C. Cobelli, Physiologic evaluation of factors controlling glucose tolerance in man, *Journal of Clinical Investigation*, Volume 68, pp. 1456-1467, 1981.

[2] A. Roy and R. S. Parker, Dynamic modeling of exercise effects on plasma glucose and insulin levels, *Journal of Diabetes Science and Technology*, Volume 1, Issue 3, pp. 338-347, 2007.