ASEE AMERICAN SOCIETY FOR ENGINEERING EDUCATION

Paper ID #27852

Laboratory Course Development for Biomedical Signals and Systems

Prof. Benjamin Hawkins, Cal Poly, SLO

My professional interests focus on the development and use of microsystems (biosensors, microcontrollers, etc) to matters of human health. Primarily this is focused on microfluidics, but also ranges from wearable devices to laboratory equipment. Applications range from cell measurements to ecological questions. Educationally, I am focused on developing courses and content that connects theory to technology in practice, with an emphasis on rigorous understanding of both.

Dr. James Eason, Cal Poly San Luis Obispo

Laboratory Course Development for Biomedical Signals and Systems

Abstract

We have developed a MATLAB-based set of laboratory experiences for junior level undergraduate students in Biomedical Engineering that focuses on integrating foundational knowledge outside the discipline in to a systems analysis focused set of exercises. Biomedical Engineering curricula tend to focus on a breadth of topics and require the development of significant foundational knowledge outside of core program courses. This often leads to program sequences where students don't interact with major specific courses until their junior year. Students, at this stage, have likely organized knowledge in to isolated "silos"; considering the topics they learned in math, physics, chemistry, electrical engineering, and programming as separate and non-overlapping sets of information. In developing content for their first junior level course in Biomedical Engineering (BMED 310: Biomedical Measurement and Analysis) and the associated lab, a focus was placed on universal systems analysis themes with broad scope and deep applicability. The result is a sequence of "systems and signals" focused exercises that drive students to integrate and apply knowledge and skills from math, electrical engineering, computer programing, biology, and chemistry to problems of biomedical relevance.
An example of this systems analysis approach coupled with biomedical application is a sequence of lab exercises where students create a mathematical model system for glucose and insulin response in the body. Initially, the model is developed as a linear system and solved using circuit analysis techniques. Nonlinearities are subsequently introduced, and the solution method is developed numerically. Finally, students are tasked with designing a PID controller for an external insulin pump to modulate blood glucose concentration. Throughout this development students study system response behaviors such as resonance, time-constants, transfer function, frequency response, and feedback control. They learn to analyze system behavior while developing and applying skills from previous courses in biology, chemistry, calculus, electric circuits, and computer programming.

To date, 3 cohorts of students have engaged with this module. Each cohort is between 50 and 75 students and composed of primarily third-year Biomedical Engineering students, with a small fraction of Electrical Engineering students. The demographics reflect those of the Biomedical Engineering program, with approximately 55% female students. Initial results indicate that students develop significant ability to work with MATLAB as an engineering tool and enter following coursework better prepared to apply prerequisite materials. In a qualitative self-assessment, participating students indicated that the activities could have better reinforced lecture content, but successfully improved their ability to apply MATLAB analysis tools and successfully applied and improved understanding of prerequisite material.

Introduction

The structure of the Biomedical Engineering program at Cal Poly, San Luis Obispo mirrors that of many peer institutions, with background coursework in chemistry, biology, math, and physics offered by other departments being taken before students engage in core BME courses at the junior level. The first junior-level BMED course is BMED 310: Biomedical Measurement and Analysis. After completing BMED 310, students continue to complete core and technical area electives. There are three concentration options: General (no concentration), Bioinstrumentation, and Mechanical Design. Overall, Biomedical Engineering at Cal Poly, SLO is weighted toward

mechanical and electrical engineering disciplines, though program options do exist for pre-med and we also offer a Master of Science in Regenerative Medicine to address relevant biological foci. Regardless of their ultimate degree objective, one of the primary learning outcomes emphasized in the program is the ability to synthesize and apply knowledge from a variety of fields to the design of biomedical systems that improve human health. In support of this, BMED 310 emphasizes general system analysis techniques applicable across disciplines.

In designing the content for the course, our overall goals were (i) to apply and extend knowledge gained in prerequisite coursework and (ii) integrate potentially disparate topics in applications relevant to biomedical engineering. The primary learning outcomes for the course reflect our desire to bring together information and analysis techniques from disparate fields and synthesize them in application to biomedical problems:

1. Apply compartmental analysis to model mass, momentum, charge, and energy in transport biomedical systems
2. Use fundamental time- and frequency-domain circuit analysis techniques to understand the behavior of biomedical systems
3. Analyze biomedical signals using time- and frequency-domain methods
4. Use principles of computer programming to model and analyze biomedical signals and systems

These objectives also reflect our emphasis on building a computational toolset for numerical analysis using MATLAB. Functional programming is one of the skills often highlighted by members of our Industrial Advisory Board. While MATLAB may not be the most rigorous programming tool, it provides versatile analytical capability, does not require adherence to rigid syntax, and coincides with content from prerequisite courses.

The lecture portion of BMED 310 focuses on developing conceptual and analytical tools while the laboratory portion focuses on the computational application of these same processes. Because they have approached their prerequisite coursework in different fields from different departments across campus, students often store this prerequisite knowledge in separate “silos” [1]. For application in multidisciplinary fields like Biomedical Engineering, we must find ways to bridge these “silos” and connect content across fields so that students bring a comprehensive knowledge base to any problem. Figure 1 shows the conceptual map of prerequisite topics used in BMED 310 and which subsequent courses are served by the course.

The framework for the development of analytical skills within the course is also broken down in terms of the approach to an engineering problem. The problem-solving framework is to (i) from an abstract problem, develop a conceptual description applying background knowledge and governing equations, (ii) translate the conceptual problem in to a mathematical form, (iii) perform analysis of the system based on its mathematical representation, and, if necessary, (iv) determine a quantitative response given a system input. At each step along this process, students will develop and implement a variety of analytical tools. This concept map is arranged graphically in Figure 2.

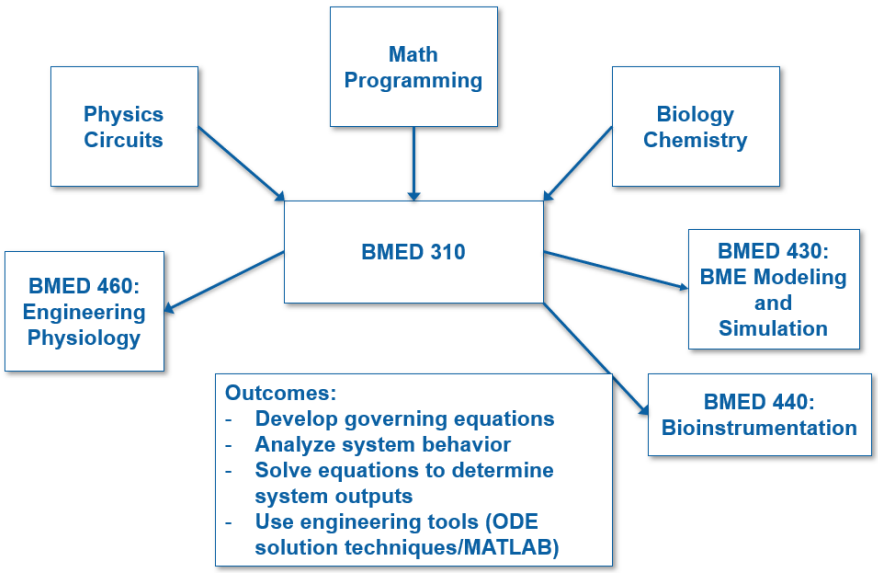

Figure 1: Prerequisite knowledge and outcomes for BMED 310

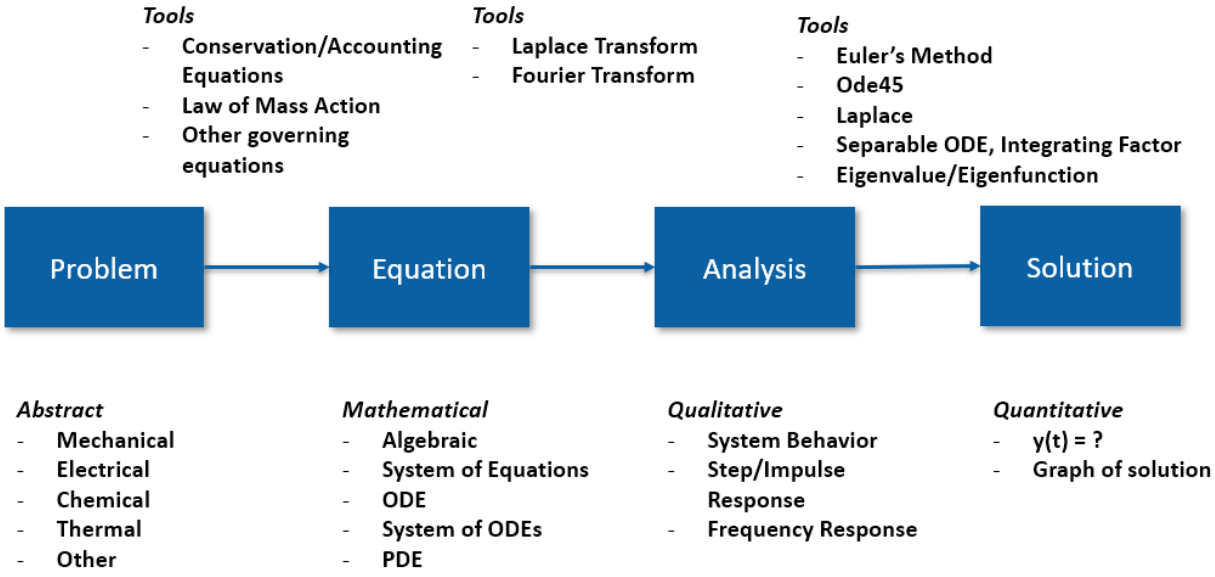

Figure 2: Graphical map of concepts taught in BMED 310 in the framework of a problem-solving process.

Developing these skills independently is possible but does not achieve the goal of connected the separate "tools" across disciplines. One of the best ways to develop cross-disciplinary bridges between disparate knowledge fields is through a multidisciplinary project.

Background

The backdrop for this multidisciplinary project is the blood-glucose response regulated by pancreatic insulin production. This relevant biomedical model system has several existing

models for its behavior which are leveraged in the development of this module. The development of the analytical model follows the work of [2] and [3] who, in turn, implement the minimal Bergman model, developed by Richard Bergman and colleagues [4].

The first step to developing the model is understanding the physiology. The body regulates blood glucose concentration via pancreatic secretions called endocrines (or hormones). Low blood glucose concentration causes the pancreas to produce glucagon and high blood glucose concentration causes the production of insulin. In patients with diabetes (both type 1 and type 2), the production of insulin is diminished due to damage of beta-cells in the pancreas. If we consider the body as a single compartment, and consider the mass balance of glucose, we can translate our understanding of physiology to mathematical form:

$$\begin{aligned} &rate\ of\ change\ of\ glucose \\ &\quad = liver\ production + glucose\ intake - insulin\ control - metabolism \\ &\quad - renal\ removal \end{aligned}$$

The rate of change of blood glucose is dependent on several factors: the production of glucose by the liver, the influx of glucose from dietary sources, the removal of glucose due to insulin response, metabolism of glucose, and filtering of excess glucose by the kidneys. Renal removal only occurs above a certain threshold, and so we have a piecewise description for blood glucose concentration:

$$\begin{aligned} C_g \frac{dG}{dt} &= Q + I_n(t) - G_g G I - D_d G && if\ G < G_k \\ C_g \frac{dG}{dt} &= Q + I_n(t) - G_g G_s I - D_d G - M_u(G - G_k) && if\ G > G_k \end{aligned}$$

The parameters in the above equation are described in *Table 1*.

Table 1: Parameter definitions for blood glucose concentration model.

Variable	**Explanation**
C_g	Total volume of system for glucose
G	Glucose concentration variable
Q	Liver release of glucose rate
$I_n(t)$	Glucose intake rate, a defined function of time
G_g	Controlled glucose loss, effect of insulin
I	Insulin concentration parameter
D_d	First-order glucose loss due to metabolism
M_u	Renal clearance rate, used when $G > G_k$
G_k	Renal clearance threshold, for $G > G_k$ kidneys remove glucose

A similar approach is taken for insulin concentration:

$$rate\ of\ change\ of\ insulin = -insulin\ reduction + pancreatic\ insulin\ release$$

The rate of change of insulin concentration is dependent on how rapidly the body binds insulin as a signaling factor and how fast the pancreas releases it to the blood stream. Again, since insulin

release is triggered by a high concentration of blood glucose, we arrive at a piecewise description:

$$C_i \frac{dI}{dt} = -A_a I \qquad if\ G \leq G_0$$
$$C_i \frac{dI}{dt} = -A_a I + B_b(G - G_0) \quad if\ G > G_0$$

The parameters in the above equation are described in Table *2*.

Table 2: List of variable names and descriptions for insulin mass balance.

Variable	Explanation
G	Glucose concentration variable
I	Insulin concentration parameter
C_i	Total volume of system for insulin
A_a	Insulin reduction rate, used in metabolism and control
B_b	Pancreas insulin release rate, variable passed in to your function by the user
G_0	Pancreas threshold, for $G > G_0$ pancreas secretes insulin (this control function is not used in our model, it is always on)

Laboratory Module

The following sequence of laboratory activities was designed to build on background knowledge in math, chemistry, and biology while developing computational skill:

1. ODEs
   Students develop a set of tools for solving ordinary differential equations and systems of ordinary differential equations. They then apply these skills to a model for blood glucose concentration that includes pancreatic insulin production. The model is simplified to be linear.
2. System Response
   Expanding on the previous lab, students employ the techniques for solving ODEs numerically to a circuit containing resistive, inductive, and capacitive elements which leads to a system of linear ODEs that models the behavior of the linear blood glucose model. Next, they solve the full, nonlinear model for blood glucose concentration. Finally, students apply their numerical analysis techniques to characterize the system behavior and observe the effect of nonlinearity in both the RLC circuit and blood-glucose models. The blood-glucose model is also explored in the context of disease (diabetes) and changing system responses.
3. Euler's Method, Insulin Pump (PID)
   In this last laboratory exercise, refocusing on computational skills, students are tasked with two major challenges: developing the appropriate mathematical representation of proportional (P), integral (I), and derivative (D) feedback and writing a differential equation solver applying Euler's method (a technique discussed in prerequisite courses and developed in lecture).

MATLAB® Grader™

Each laboratory exercise is developed and tested using MathWorks MATLAB® Grader™ online tool. This tool is an excellent platform for developing coding assignments, providing automated feedback, and completing automated grading of submitted work. Grader provides an interface for enrolling students in a course with a sequence of exercises. Each exercise can be broken down in to separate problems and within each problem solutions can be subjected to a variety of tests to assess code functionality and performance. Each test can be given a weighted value and a score given for each problem. Feedback on failed tests is automated as well, freeing the instructor to work on more conceptual and/or unique challenges in the classroom. Each problem has a description of the goals of the exercise as well as relevant background information. Additionally, students are provided with a starting "template" upon which to build their code. This serves two purposes: to make sure that their code is compatible with the Grader™ framework and automated assessment (e.g., that the function name matches and that the right variables are returned in the right order) and to provide students hints on where to begin their coding work. For example, the following template code is provided for the linearized glucose-insulin model in Laboratory 1:

```
%% function to model basic glucose/insulin behavior
function [t, GI] = GluIns_lin(Gt, Bb)
    % set tolerances
    options = odeset(???)
    % set initial conditions
    GI0 = ???
    % set time span
    % solve ODE
    [t, GI] = ode45(@(t, GI) ??? );
end
function dGIdt = GluIns(t, GI, Gt, Bb)
    % define constants
    ????
    % define In conditionals
    if t >=0 && ???
    ????
    % define glucose ODE including conditionals
    if G < ????
    % define insulin ODE
    ???
end
```

Additionally, a test case is provided for students to run their code and debug as they develop their algorithms:

```
Bb = 14.3;
Gt = 0;
%Gt = 80000;
[t, GI] = GluIns_lin(Gt, Bb);
yyaxis left;
plot(t,GI(:,1));
yyaxis right;
plot(t,GI(:,2));
```

For this module focusing on blood-glucose modeling, each exercise is broken up in to 3 or 4 problems and within each problem there are 2 to 4 tests. The "in-class" portion of the lab focuses on developing functional code that can be used for later system analysis in "post-lab" exercises. While the "in-class" portion focuses on teaching students how to use and apply a particular tool within MATLAB, the "post-lab" exercises emphasize the application of these tools to system analysis. The results of these "post-lab" exercises are written up and submitted for grading by the instructor.

Laboratory Exercise 1: ODEs

The first lab develops facility with two tools within MATLAB: the symbolic solver, "dsolve", and the numeric solver, "ode45", along with associated plotting tools. In the lecture portion of the course, compartmental modeling and mass conservation in chemical and biochemical systems are being developed, so in the lab, we solve the general equation for a one-compartment system as presented by [5] with an exponentially decaying input function.

$$\dot{q}_1 = f_1(t) - K_{10}q_1$$
$$f_1(t) = 100e^{-at}$$

Students are provided a framework for coding the symbolic and numeric solutions. Figure 3 shows the forcing function and ODE solution using ode45.

The next step is to modify the input forcing function to be a nonlinear input. In this case a pulse train is chosen. The new forcing function and system response (ODE solution using ode45) shown in Figure 4 brings students closer to completing a simulation of the glucose tolerance test in which the glucose intake function is a square pulse.

The last problem posed to students is to use the ode45 solver to solve the coupled ODE for glucose and insulin concentrations. The equation is modified slightly to ensure that the terms are linear and the piece-wise insulin response is omitted for brevity:

$$C_g \frac{dG}{dt} = Q + I_n(t) - G_g G_s I - D_d G \qquad if\ G < G_k$$
$$C_g \frac{dG}{dt} = Q + I_n(t) - G_g G_s I - D_d G - M_u(G - G_k) \quad if\ G > G_k$$

for glucose (G) and

$$C_i \frac{dI}{dt} = -A_a I + B_b(G - G_0)$$

for insulin (I). Note that we have linearized the insulin control term in the glucose function by replacing the G term with a constant G_s. The glucose input function, $I_n(t)$, is a piecewise function, according to:

$$I_n = \begin{cases} G_t & 0 < t < 0.5 \\ 0 & t > 0.5 \end{cases}$$

G_t is a parameter that can be modified to correspond to the conditions of the glucose tolerance test. Typically, it is set to 0 for determining baseline values and 80000 for performing the test. The initial conditions are $G(0) = 81.14$ and $I(0) = 5.671$. The glucose and insulin concentration responses for $G_t = 80000$ are shown in Figure 5.

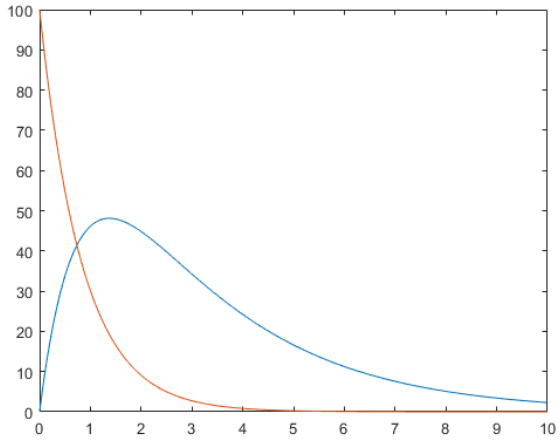

Figure 3: Solution to the general one-compartment model with a decaying exponential forcing function, using ode45. The red line represents the forcing function and the blue line the solution or response.

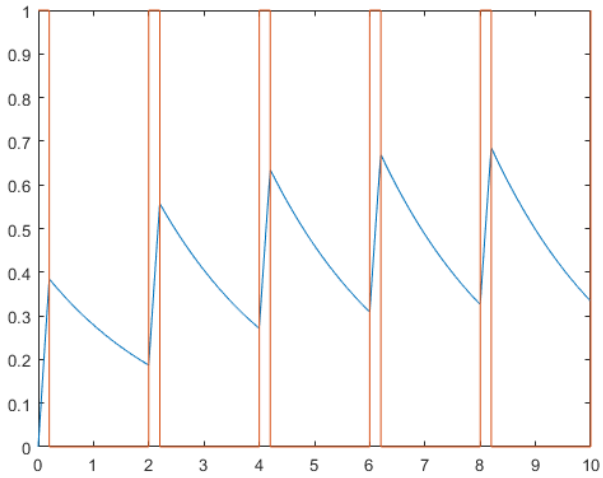

Figure 4: Solution to the general one-compartment model with a pulse train forcing function, using ode45. The red line represents the forcing function and the blue line the solution or response.

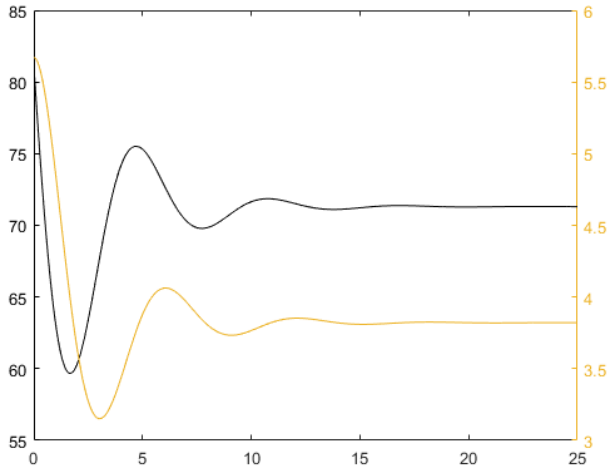

Figure 5: Solution to the linearized glucose-insulin model using ode45. The black line corresponds to the left-hand y-axis and represents glucose level, the yellow line corresponds to the right-hand y-axis and represents insulin level.

This solution marks the completion of the in-class portion of the laboratory exercise. In "post-lab" review, the students are posed questions that highlight: (i) the difference between the numeric ode45 calculated solution and an analytical solution and the relationship between this error and the time-steps taken by the numeric solver, (ii) the need for appropriate tolerancing by changing the solver tolerance across a range of values for the pulse-train solution, and (iii) investigating the glucose-insulin response for healthy patients, patients with increased pancreatic sensitivity to glucose (insulin overproduction), and patients with a decreased pancreatic sensitivity to glucose (insulin insufficiency). The last question highlights the application of modeling and numeric solution techniques, to physiology and disease.

Laboratory Exercise 2: System Response

In the second portion of this module, students analyze the series RLC circuit shown in Figure 6.

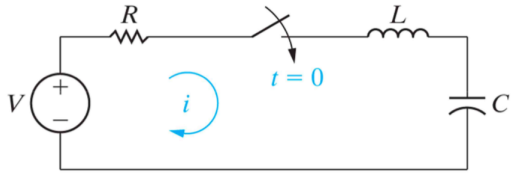

Figure 6: Series RLC circuit analyzed to characterize system linearity.

Circuit and equation parameters are given as $L = 1\,H, R = 1.5\,\Omega, C = 0.5\,F, V = 80\,V$, $V_C(0) = 100\,V, I(0) = 0\,A$. Using ode45, students obtain the solution given in Figure 7.

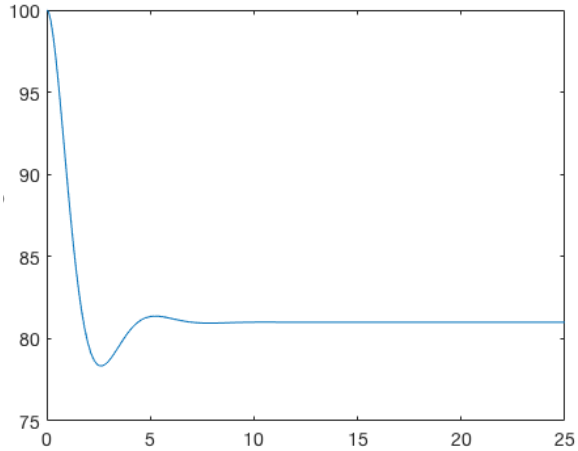

Figure 7: Solution for current through a series RLC circuit using ode45.

The second exercise students are tasked with implementing the "full" minimal Bergman model for glucose-insulin response:

$$C_g \frac{dG}{dt} = Q + I_n(t) - G_g G I - D_d G \qquad \text{if } G \leq G_k$$
$$C_g \frac{dG}{dt} = Q + I_n(t) - G_g G I - D_d G - M_u(G - G_k) \qquad \text{if } G > G_k$$

For glucose (G) and

$$C_i \frac{dI}{dt} = -A_a I \qquad \text{if } G \leq G_0$$
$$C_i \frac{dI}{dt} = -A_a I + B_b(G - G_0) \qquad \text{if } G > G_0$$

The results of this analysis are shown in Figure 8 for the nonlinear system.

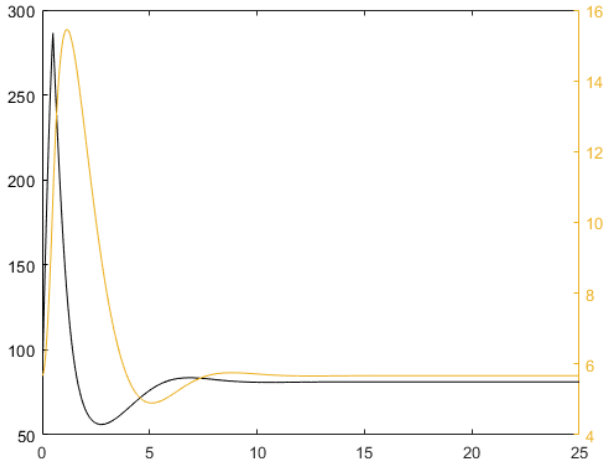

Figure 8: Nonlinear glucose-insulin response using the full minimal Bergman model, solved using ode45. The black line corresponds to the left-hand y-axis and represents glucose level, the yellow line corresponds to the right-hand y-axis and represents insulin level.

After completing the "in-class" portion of the lab, students are then tasked with several questions to (i) determine the time-constant of glucose-insulin response and the systems resonant frequency, (ii) examining the linearity or nonlinearity of their solutions by applying the principle of additivity – the property of linear systems that indicates the sum of outputs for multiple inputs

is the same as the output of a sum of inputs – and (iii) tuning the output of the RLC model to most closely match the output of the glucose-insulin model, thereby connecting a circuit model and equation to a physiological model.

Laboratory Exercise 3: Euler's Method, Insulin Pump (PID)
In the third week of this sequence, we revisit concepts from circuits (equivalent sources), control theory (PID controller), and numerical methods (Euler integration). Each element is used incrementally to design a system that mimics control of glucose using an insulin pump.

First, the voltage which drives the RLC circuit in Figure 6 is replaced by a current source as shown in Figure 9. In an analogy to the glucose model, the current source, I_{dist}, represents glucose ingestion. The second current source, I_m, will be used for the output of the PID control system.

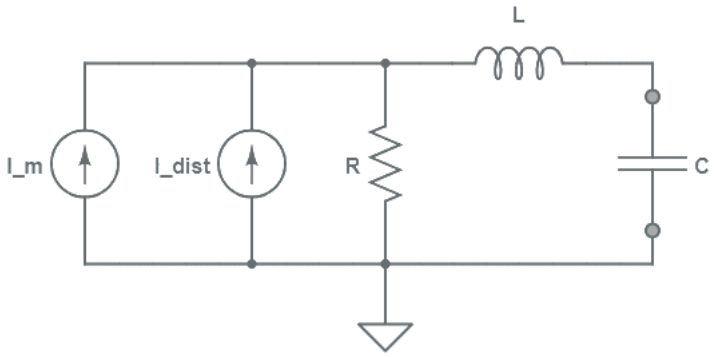

Figure 9: Circuit analog for the PID controlled insulin-glucose system. I_{dist} represents glucose intake and I_m is the output of the control system.

Students design an Euler's method solution to the resulting pair of differential equations that govern this circuit analog.

$$\frac{dV_C}{dt} = \frac{I_L}{C}$$
$$\frac{dI_L}{dt} = \big((I_m - I_L)R - V_C\big)/L$$

With $I_m = \frac{V}{R} = 53.33\ A$, and the initial value of the output voltage across the capacitor $V_C(0) = 100\ V$, students can verify that the results of this system are identical to Figure 7. Students are next asked to develop a PID control system for the current source, I_m:

$$I_m = K_p e + K_i \int_0^t e\, dt + K_d \frac{de}{dt}$$

where the error term, e, is the difference between the setpoint, $r = 80\ V$, and the output voltage, V_C.

$$e(t) = r - v_{out}(t)$$

Using the control parameters $K_p = 10$, $K_i = 1$, and $K_d = 1$, the analog circuit rapidly reaches the steady state defined by the setpoint as shown in Figure 10.

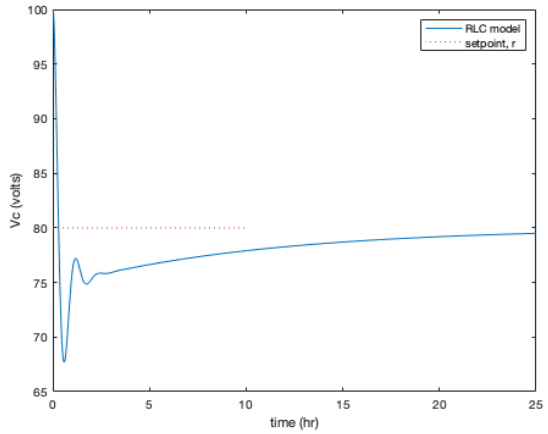

Figure 10: Simulation results from PID controlled RLC circuit (Figure 9) using control parameters $K_p = 10$, $K_i = 1$, and $K_d = 1$.

Finally, students add the same type of PID controlled source to introduce insulin into the full, nonlinear glucose-insulin system. Since insulin is a negative feedback variable, the error term is calculated as the difference between the glucose concentration and the glucose setpoint, $r = 81.14$.

$$e(t) = G(t) - r$$

$$I_m = \begin{cases} K_p e + K_i \int_0^t e\,dt + K_d \dfrac{de}{dt} & \text{for } G > r \\ 0 & \text{for } G \leq r \end{cases}$$

When the glucose concentration falls below the setpoint, the insulin pump turns off and remains idle until glucose concentration once again exceeds the setpoint.

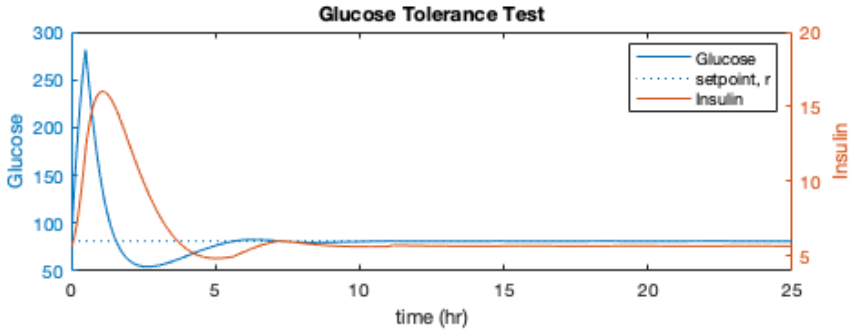

Figure 11: Results from PID-controlled insulin pump simulation with full minimal Bergman model of glucose-insulin balance. Glucose intake during the first 30 minutes causes a spike in glucose which is quickly reduced through insulin infusion by the simulated device.

In the post-lab exercises for this activity, students measure characteristics of the glucose-insulin system response and then use these characteristics to optimize the parameters in the PID controller. Using this optimized system, they will then quantify the improvement in glucose regulation afforded by this device when implanted in a person with diabetes.

Discussion

The development of this core concept and its evolution over three laboratory sessions means that students receive a relatively comprehensive experience related to solving ODEs and systems of ODEs using both MATLABs included ode45 function as well as writing their own simple numeric solver based on Euler's method. By applying the same analytical tools to circuits and biological systems, they connect previously disparate knowledge sources. They also explore the concept of feedback and control and observing the effects of different control parameters on damped responses, and the physiological backdrop of diabetes disease and an insulin pump as a biomedical device engage students in design-thinking from a whole system perspective.

A qualitative self-assessment survey was conducted where students were asked to reflect on their experiences in the course. Students were asked to score on a Likert scale ("Strongly disagree" to "Strongly agree") outcomes in two main areas:

1. "For the following statements, please consider how the lab activities in BMED 310 contributed to improving your skills and achieving course outcomes."
2. "For the following statements, please consider how the BMED 310 curriculum integrated knowledge from prerequisite courses into the development of new analytical techniques as applied to biomedical systems."

Out of 181 participants, 44 completed the survey (24% return). The first category specifically focuses on the MATLAB activities discussed here, had a large percentage of students indicating "Strongly agree" with each outcome question.

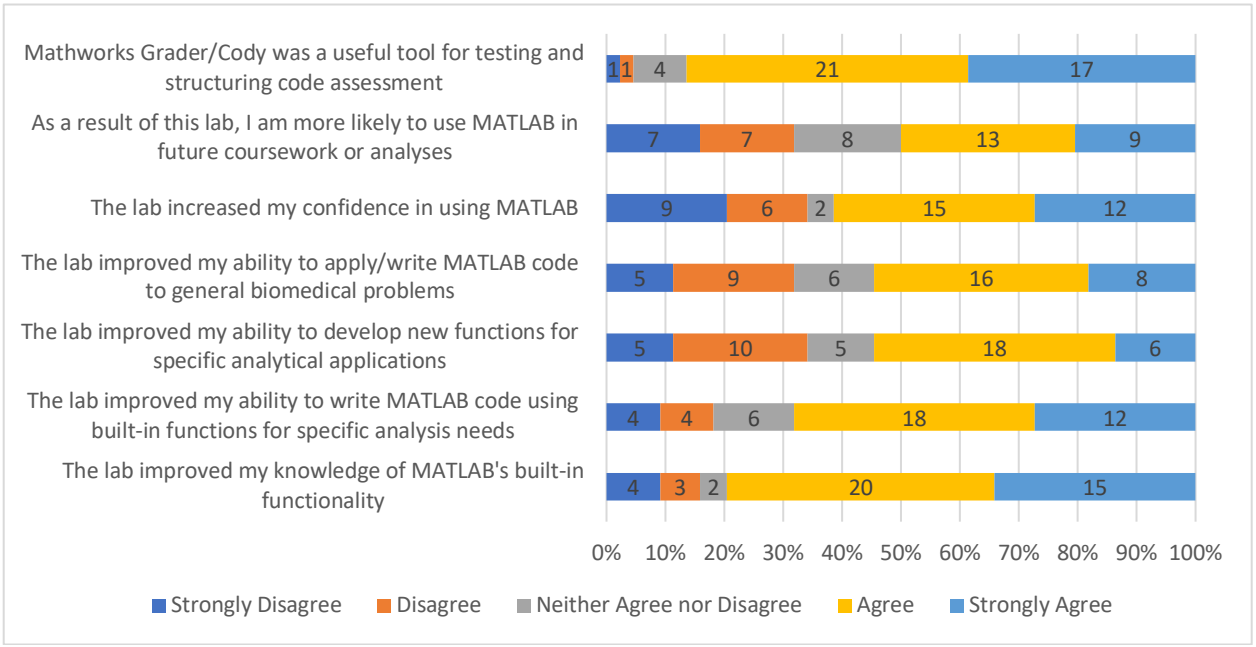

Figure 12: Survey response data for questions focusing on the MATLAB portion of the course.

The questions and distributions shown in Figure 12 indicate the effectiveness of the lab activities at improving MATLAB proficiency and ability to apply course concepts.

The third category addresses the integrative goals of the course. Like the first category, responses were split, but more respondents indicated "Agree" than any other category. Questions and distributions can be seen in Figure 13.

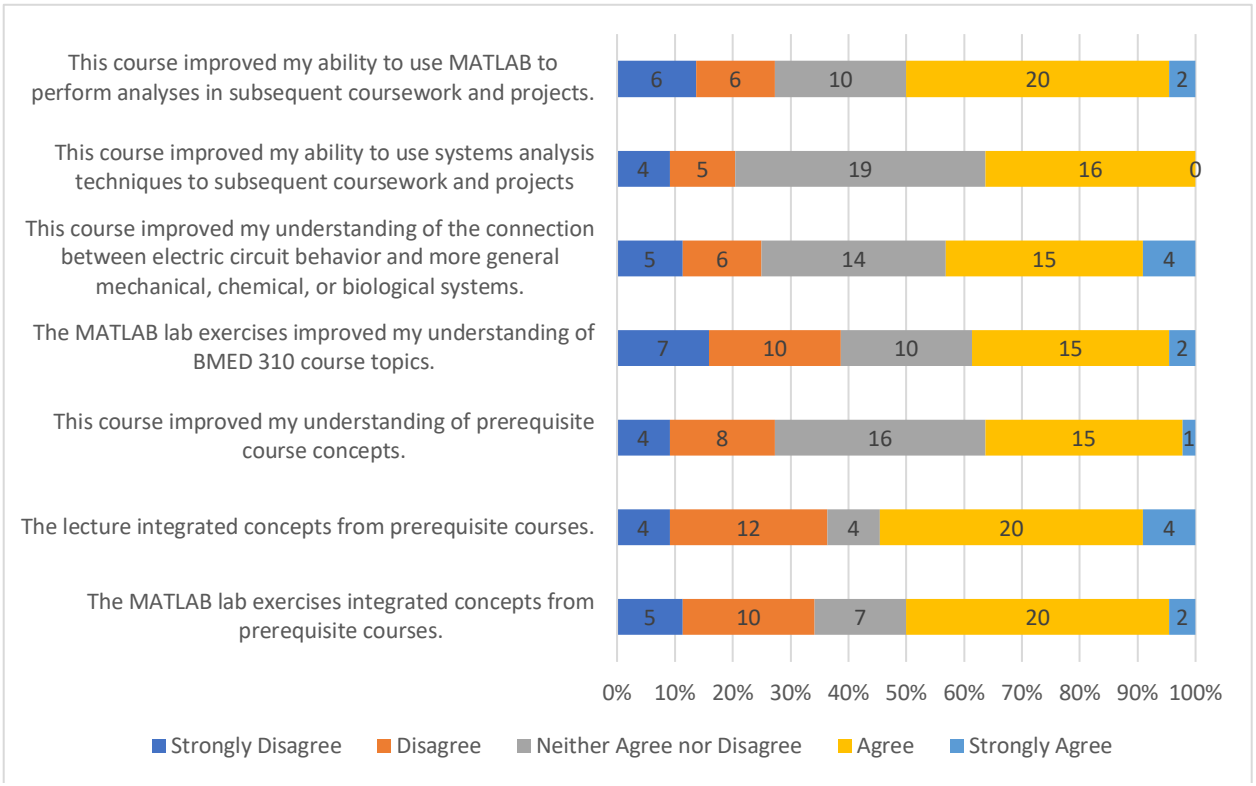

Figure 13: Survey response data for questions focusing on curricular integration objectives for the course.

The main challenges with this sequence of modules center around time. Each laboratory session is 3 hours long, which allows time for a small amount of background information to be provided, along with some preparatory discussion of the code to be written (introducing new functions, etc.). Typically, students are not able to complete all of the problems in a given exercise during the laboratory session. While students are allowed to complete their work independently outside of class time, the combination of completing ostensibly "in-class" work along with "post lab" analysis is frustrating to some students.

Additionally, while the topic coverage within this module is relatively comprehensive, there isn't sufficient time to provide all necessary background material, so by necessity, the students don't get to engage as meaningfully with the model development side of the process. Students who are not keen to follow the model development are often still able to complete the exercises without connecting all the parts of the big picture. Also owing to the compressed timeline, students often become myopic in pursuit of functional code and miss out on engagement with the "big picture" being presented.

Feedback from students and faculty after implementation of the course indicate that the experience was positive. They the higher degree of integration of knowledge across disciplines made the course feel for cohesive as a part of their Biomedical Engineering education. Faculty in courses for which BMED 310 is a prerequisite also indicate that students are entering their courses better prepared for modeling, programming, and systems level thinking after implementation of this module and the development of a quarter-long sequence of signals and systems analysis focused on biomedical topics.

Conclusion

This course module focusing on blood-glucose system modeling has improved outcomes for students within the course, based on student and faculty responses to informal questions. Qualitative assessment of student outcomes using a survey instrument indicated success in several of our target outcomes as well as some areas for future improvement. As we continue to develop this course material, additional quantitative assessments will be included to provide more objective measures of student progress and outcomes. This type of problem and module will also serve as a template for future modules of other biomedical systems that have well-studied behaviors. In subsequent courses, students perform the glucose tolerance test modeled in this module on themselves and record the results. Efforts are currently underway to integrate these results with this module, and future work as well. We are hopeful that this type of integrative module will continue to be successful and that it will initiate the development of additional modules that can be used to both develop student's computational skill and systems-level thinking, while also serving as a research platform for faculty seeking to develop or modify existing engineering models of biomedical system.

Works Cited

[1] M. Borrego and L. K. Newswander, "Definitions of Interdisciplinary Research: Toward Graduate-Level Interdisciplinary Learning Outcomes," *The Review of Higher Education,* pp. 61-84, 2010.

[2] W. E. Schiesser, Differential Equation Analysis in Biomedical Science and Engineering: Ordinary Differential Equation Applications with R, Hoboken, NJ, USA: John Wiley & Sons, 2014.

[3] E. Friis-Jensen, "Modeling and simulation of glucose-insulin metabolism," Kongens Lyngby, Kongens Lyngby, Denmark, 2007.

[4] C. R. Bowden, R. N. Bergman, G. Toffolo and C. Cobelli, "Minimal modeling, partition analysis, and identification of glucose disposal in animals and man.," *IEEE Transactions on biomedical engineering,* pp. 129-135, 1980.

[5] J. D. Enderle, "Compartmental Modeling," in *Introduction to Biomedical Engineering*, Burlington, MA, Elsevier, 2012, pp. 359-447.