Development of a Laboratory-Based Course in Experimental Physiology for Biomedical Engineering Undergraduates

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Introduction

In its program criteria for Biomedical Engineering, the Accreditation Board for Engineering and Technology (ABET) requires that graduating undergraduate students have an understanding of biology and physiology and demonstrate an ability to make measurements on and interpret data from living systems. In the Department of Biomedical Engineering at Worcester Polytechnic Institute (WPI), these criteria have been addressed through the development and implementation of a laboratory-based course in experimental physiology (BE 3110). The objective of this paper is to describe this course in sufficient detail to enable replication.

Course objective and outcomes

The primary objective is to develop in each student a basic skill set and knowledge base necessary for working with a rodent animal model in the laboratory. Included in this skill set is an ability to make measurements on and interpret data from this animal model using a computer-based data acquisition system. Six course outcomes, relating directly to the ABET criteria for bioengineering programs, are identified:

- Demonstrate an understanding of the fundamental physiologic principles necessary for working with animals in the laboratory (ABET program criteria for Bioengineering).
- Appreciate the ethical responsibilities associated with working with animals in the laboratory (ABET criterion 3f).
- Perform basic anesthetic and surgical procedures on the rat animal model (ABET criterion 3b and program criteria for Bioengineering).
- Utilize modern engineering tools to make measurements on and interpret data from a living system (ABET criteria 3b, 3k, and program criteria for Bioengineering).
- Apply knowledge of mathematics and statistics to the analysis and interpretation of laboratory data (ABET criterion 3a and program criteria for Bioengineering).
Effectively communicate the laboratory experience in a well-written report (the laboratory notebook) (ABET criterion 3g)

Course structure and administration

The course, taught at the junior-level, is based upon a series of integrated laboratory modules. Each module incorporates traditional lectures in biology and physiology, computer-based physiology simulations, some engineering and mathematics content, and a hands-on laboratory experience that includes fundamental surgical procedures and the measurement of important physiologic variables using a computer-based data acquisition system in the rat animal model. Table 1 provides an overview of the educational content in each laboratory module. Important administrative elements of the course include:

- **Seven week duration**: At the undergraduate level, WPI operates on seven-week terms and accelerates the delivery of courses over the term by increasing the number of contact hours-per-week. As such, this course is approximately equivalent to two-thirds of a standard semester course.

- **Three one-hour lectures per week**: Lectures are used to discuss the relevant physiology and procedures needed to complete the laboratory exercises. Previous exposure to an undergraduate-level physiology course is helpful, but not required. A standard undergraduate physiology textbook is used.

- **One three-hour laboratory per week**: Each laboratory is restricted to eight students working in groups of two. There are four laboratory sessions per week and total enrollment is capped at 32 students. The instructor and one trained teaching assistant are present at all times during the labs.

- **Online course administration**: Most of the course material, including lecture notes, homework assignments, laboratory exercises, and answer keys are distributed online through the Blackboard® community portal system at WPI. This system controls when material becomes available to the student and makes it much easier to distribute and collect time-sensitive assignments.

- **Use of a computer-based physiology simulator**: The SimBioSys® human physiology simulator allows each student to manipulate the physiology of a virtual patient in parallel to the experiments done in lab. It also allows students to perform “experiments” far too difficult for an undergraduate-level physiology laboratory.

The student’s final grade is calculated from his/her effort in five different areas:

- **Pre-laboratory exercises (20%)**: Designed to prepare each student for the upcoming laboratory, either through the analysis of pre-existing experimental data or the completion of physiology simulator exercises. Questions addressing the student’s understanding of the physiology and engineering background material needed for the lab are also assigned.
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<td>Engineering and Mathematics</td>
<td>Animal / Laboratory Procedures</td>
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<td>• Theory and use of a computer-based data acquisition system.</td>
<td>• Handling and anesthetizing the rat.</td>
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<td>• Anesthesia.</td>
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<td>Nerve and muscle physiology (Lab #2)</td>
<td>• Cell and membrane physiology.</td>
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<td>Lab #1 procedures, plus:</td>
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<td>• Membrane transport.</td>
<td>• Derivation and application of the Nernst equation.</td>
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<td>• Intracellular communication and signal transduction.</td>
<td>• Derivation and application of the Goldman-Hodgkin-Katz equation.</td>
<td>• Isolating and electrically stimulating the sciatic nerve.</td>
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<td>• Membrane potential and the electrochemical gradient.</td>
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<td>• Neurons and synapses.</td>
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<td>• Skeletal muscle structure and function.</td>
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<td>• Forces, twitch, and tetanus.</td>
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<td>• Electrical stimulation of tissues.</td>
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<td>Electro-physiology (Lab #3)</td>
<td>• Overview of the cardiovascular system.</td>
<td>• Calculation of the mean electrical axis of ventricular depolarization from ECG data.</td>
<td>Lab #1 procedures, plus:</td>
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<td>• Characteristics of cardiac cells.</td>
<td>• Calculation of the mean electrical axis of atrial depolarization from ECG data.</td>
<td>• Recording ECG leads I, II, and III.</td>
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<td>• Electrical conduction in the heart and the electrocardiogram (ECG).</td>
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Table 1. (continued).

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| Circulatory physiology (Lab #4) | • Pumping action of the heart and the cardiac cycle.  
• Frank-Starling law, preload, afterload, and contractility.  
• Intrinsic regulation of the heart.  
• Physics of cardiovascular transport.  
• Arterial pressure and its regulation.  
• Response to physiologic stress.  
• The autonomic nervous system.  
• Pharmacological influences on the heart and peripheral circulation  
• Structure, mechanics, and ventilation of the lung.  
• Mechanics of breathing and artificial respiration.  
• Diffusion and gas exchange in the lung.  
• Arterial blood gases.  
• Convection and gas transport in the blood.  
• Control of respiration.  
• Theory and use of a blood pressure transducer.  
• Derivation and application of the Law of Laplace.  
• Derivation and application of Poiseuille’s law.  
• Derivation and application of Fick’s first law of diffusion.  
• Lab #1 procedures, plus:  
• Cannulating the carotid artery.  
• Cannulating the femoral vein.  
• Calibrating and using an arterial blood pressure transducer.  
• Recording arterial blood pressure and heart rate response to an epinephrine injection.  
• Euthanasia by direct cardiac puncture. |  |
| Respiratory physiology (Lab #5) | • Bicarbonate buffer system and acid-base status.  
• The renal system and regulation of pH.  
• Blood gases and base excess.  
• Clinical determination of acid-base status.  
• Application of the Henderson-Hasselbalch equation.  
• Calculation of acid-base status and base excess.  
• Clinically-based acid-base diagnosis.  
• Lab #4 procedures, plus:  
• Cannulating the trachea.  
• Programming and using a volume-controlled mechanical ventilator.  
• Measuring arterial blood-gases.  
• Adjusting artificial ventilatory parameters to normalize arterial blood-gases.  
• Assessing the effects of hyperoxia on arterial blood-gases.  
• Direct observation of beating heart and ventilated lungs.  
• Lab #5 procedures, plus:  
• Assessing the effects of hypercapnia on arterial blood-gases and acid-base status.  
• Assessing the effects of sodium bicarbonate injection on arterial blood-gases and acid-base status. |  |
Laboratory Notebook (20%): Consistent with ABET criterion 3g, students are asked to maintain a laboratory notebook according to a strict set of guidelines and are graded on their ability to fully describe the lab preparation and setup, the anesthetic and surgical procedures, and the experimental procedures including raw data collection. Following each laboratory, notebooks are turned in and hand-graded. To ensure that students develop appropriate laboratory note-taking skills, weekly review and grading of the notebooks is absolutely necessary.

Post-laboratory exercises (30%): Constitutes the analysis portion of the lab. Because there is insufficient time to analyze the raw data collected during the actual laboratory period, students are asked questions that require the detailed analysis of their raw experimental data. Mathematics, statistics, and quantitative analyses are emphasized. Students are given one week to complete the appropriate exercises after a lab.

Midterm (15%) and final (15%) exams: Multiple-choice, one-hour examinations covering the fundamental physiology and engineering content of the lectures and laboratories.

Laboratories

Six laboratories are delivered over the period of a seven week term:

Animal Care and Anesthesia (Lab #1): Students observe basic rat behavior, become familiar with handling the rat, and, when ready, immobilize and inject an anesthetic. Following this injection, students monitor the different stages of anesthesia and maintain core body temperature using a rectal probe and heating pad. In the post-lab exercises, students are asked to describe how anesthesia affected their animal’s behavior and physiology.

Nerve and Muscle physiology (Lab #2): Students isolate and electrically stimulate the sciatic nerve innervating the muscles of the leg. The effects of electrical stimulation frequency on muscle force generation and fatigue are assessed using an isometric force transducer attached to the Achilles tendon. Blunt surgical dissection and animal euthanasia are introduced for the first time. In the post-lab exercises, students are asked to compare their isometric force data to textbook definitions of twitch, twitch summation, and tetanus.

Electrophysiology (Lab #3): Students record traditional electrocardiogram leads I, II, and III (Einthoven’s triangle) using surface electrodes placed on the animal’s limbs. In the post-lab exercises, students are asked to compute various ECG amplitudes and intervals and compare them to human averages. They are also asked to calculate the mean electrical axis of ventricular and atrial depolarization.

Circulatory Physiology (Lab #4): This laboratory is the first of three integrated laboratories designed to introduce nearly all of the important laboratory skills necessary for maintaining an anesthetized animal under tight physiologic control. Students cannulate the carotid artery and the femoral vein and then record the arterial blood
pressure and heart rate response to an intravenous bolus injection of epinephrine. In the post-lab exercises, students are asked to quantitatively describe how epinephrine affects heart rate and arterial blood pressure and predict how epinephrine might, given their data, affect cardiac output and total peripheral resistance.

- **Respiratory Physiology (Lab #5):** In addition to repeating the surgical exercises of Lab #4, students also cannulate the trachea and place the rat’s respiratory system under the control of a volume-controlled mechanical ventilator. Using a clinical blood gas machine, students adjust the artificial ventilatory parameters to normalize arterial blood-gases and then assess the effects of hyperoxia on arterial blood-gases. Following this procedure, the chest wall is opened and students observe the beating heart and artificially ventilated lungs. In the post-lab exercises, students are asked to justify their strategy for bringing the animal’s blood gases values to normal and to consider how hyperoxia affects blood-gases.

- **Acid-Base Physiology (Lab #6):** In the final lab, students perform all of the surgical and experimental procedures outlined in Lab #5 and then assess the effects of hypercapnia and sodium bicarbonate injection on arterial blood-gases and acid-base status. In the post-lab exercises, students are asked to perform a detailed assessment of their animal’s acid-base status with each blood-gas, including a calculation of base excess and bicarbonate deficiency.

New surgical and experimental techniques are incrementally introduced and integrated into each laboratory module, such that the final laboratory has a level of complexity equivalent to that at most animal research facilities or veterinary hospitals.

**Laboratory Equipment**

A dedicated animal teaching laboratory, containing four independent operating/experimental stations, is used. Students work in groups of two and use the following major pieces of equipment:

- **Computer-based data acquisition system** (model MP 100, Biopac Systems, Inc, Santa Barbara, CA, USA), which includes 3 conditioning modules for measuring temperature (model SKT100B, Biopac), the electrocardiogram (model ECG100B, Biopac), and arterial blood pressure (model DA100B, Biopac). This system is used to: 1) measure core body temperature using a rectal probe thermistor (model 402, YSI, Dayton, OH, USA), 2) measure the electrocardiogram using surface electrodes, 3) measure arterial blood pressure using a blood pressure transducer (model TSD104A, Biopac), 4) measure isometric muscle force using an isometric force transducer (Harvard Apparatus, Holliston, MA, USA), and 5) stimulate the sciatic nerve using a subminiature electrode (Harvard Apparatus), a stimulus isolation adapter (ISO STIM, Biopac), and a stimulation module (STM100A, Biopac).

- **Water-filled heating blanket** (Cole Parmer, Chicago, IL, USA), which circulates warm water to a thermal blanket under the animal’s body.
• **Gas-mixing flowmeters** (Cole Parmer), which allow for the control of nitrogen, oxygen, and carbon dioxide concentrations in the inspiratory gas.

• **Artificial ventilator/respirator** (model CIV-101, Columbus Instruments, Inc., Columbus, OH, USA), for mechanical ventilation of the rat in Labs #4 and #5.

• **Blood-gas machine** (model ABL5, Radiometer America, Inc., Westlake, OH, USA), for measuring pH, PO$_2$, and PCO$_2$ in arterial blood samples.

**Ethics and Alternatives**

As with any course that requires the sacrifice of animals to meet an educational objective, there are substantive ethical and emotional considerations that must be addressed up front and continuously throughout the course:

• **Role of animals in biomedical research and teaching**: In the first lecture, the important historical and present-day role of animals in biomedical research and teaching is discussed and students are asked directly to consider their position on the use of animals in research and teaching. Because it is not possible to complete the course without animal surgery and sacrifice, students who raise a moral objection are permitted to withdraw without prejudice or penalty.

• **Animal welfare**: The important distinction between animal rights versus animal welfare is also addressed in the first lecture. Students are introduced to the function and scope of the Institutional Animal Care and Use Committee (IACUC), review the responsibilities of the course instructor, and are instructed as to their own rights and responsibilities regarding animal use. The right of the student to withdraw from the class without penalty should they have an ethical or moral objection to animal welfare is stated clearly again.

• **Student fear and apprehension**: With very few exceptions, students are justifiably nervous and apprehensive about the prospect of handling and working with a living creature. This apprehension is particularly evident in the first lab when they are asked to handle and anesthetize the rat, in the second lab when they are asked to perform their first surgical exercise, and in the fourth lab when they have their first significant exposure to arterial blood. Successful strategies to address and allay these fears include ample time to complete the anesthetic and surgical procedures, intensive one-on-one assistance and guidance during the lab, and the incremental introduction of new procedures with each new laboratory. In addition, students are told that academic success is not associated with surgical success.

• **Judicious use of animals**: Two non-surgical labs (Labs #1 and #3), where recovery from anesthesia is justified, are interspersed with four surgical lab (Labs #2, #4-6), where euthanasia is the logical end-point. This scheduling minimizes the number of animals used, permits the gradual introduction of complicated surgical procedures, and prevents a single animal from being anesthetized more than twice. Because students are generally unskilled surgeons and do not follow aseptic procedures, recovery from invasive surgery is never considered acceptable.
• **Alternatives:** The physiology simulator allows students to engage in limited physiologic experimentation without additional animal sacrifice. For example, the simulator is used to: 1) monitor the effects of different pharmacological agents on cardiac pressure-volume loops, 2) investigate the cardiac and respiratory effects of positive-pressure ventilation, and 3) assess the effects of hemorrhage on the autonomic nervous system. The simulator also gives each student an opportunity to investigate the physiological consequences for a few of the experimental procedures that will actually be performed lab. Equally important, students are directly exposed to the advantages and limitations of computer-based physiology simulators. By witnessing physiologic variability in the laboratory, they come to understand that physiology simulators can never fully replace live animal experimentation.

• **Euthanasia:** In general, while students do not regard the laboratory rats as pets, they do express significant concern, and some sadness, when their first animal is euthanized in Lab #2. Before injecting a euthanizing agent for the first time, I work intensely with each individual laboratory group to address the need for euthanasia and how the agent will work. Students are encouraged, but not required, to witness the animal’s death. Most students are comforted by the knowledge that there is no pain and suffering associated with anesthesia and euthanasia.

**Course evaluation**

This course has now been delivered five times, beginning in 1999, to 107 students. As a result of this experience, the following comments can be made:

• Approximately 95% of the two-student lab groups are capable of completing all surgical procedures by the end of the course. This surprisingly high rate of success can be mostly attributed to the fact that: 1) new surgical procedures are introduced incrementally, 2) the more difficult procedures are repeated multiple times, and 3) intensive and continuous assistance is available from the instructor and TA. For example, only 30% of the lab groups successfully cannulate the carotid artery the first time without assistance in Lab #4, but most are ultimately successful given the opportunity to try it two more times in Labs #5 and #6. Group success is higher than individual success, as approximately 20% of the students lack the technical skills to complete all surgical exercises. Thus, surgical success is never a basis for grading. The instructor and TA intervene only as necessary to insure that all surgical procedures are completed successfully. This insures that experimental procedures can be completed on all animals.

• Of the students that have taken this course to date, only two have raised a moral objection with me. Neither chose to withdraw from the course, citing the importance of this material to their chosen career as a biomedical engineer. This statistic is undoubtedly skewed by the fact that most students are already predisposed to the position that animals should be used for research and teaching. Approximately 15% of the students never become comfortable working with rats and, while they all viewed the course as a positive learning experience, state that they will never voluntarily work with animals again. At the other end of the spectrum, approximately 20% of the students absolutely revel in the opportunity to work with animals.
• Student evaluation of the course and instructor has been outstanding to date. Following its most recent offering (Fall 2002), all students either agreed (20%) or strongly agreed (80%) with the fourteen questions designed to assess the effectiveness of the instructor and the course. This was the highest instructor rating at WPI for that time period. Summarized over the five offerings of the course, student evaluations have been 31% agree and 68% strongly agree. In the spring of 2002, the instructor won WPI’s Romeo L. Moruzzi Young Faculty Award for Innovation in Undergraduate Education.

Future developments

Because this course has now been delivered five times, its general structure and operation are well established. Based on recommendations following a recent ABET accreditation visit, more statistically-based hypothesis testing will be incorporated into future offerings. Specifically, the application and use of the student t-test, repeated-measures analysis of variance, and linear regression will be more formally incorporated into the lectures and used explicitly in the post-laboratory exercises.

Conclusion

As an evolving field-of-study that uses traditional engineering principles to solve important problems in medicine and biology, undergraduate biomedical engineering programs must deliver an engineering curriculum that is strongly grounded in the life sciences. These criteria are formally defined by ABET in their program criteria for bioengineering programs\(^1\) and were specifically integrated into the development and delivery of this course. While the costs associated with its delivery are somewhat high, both in terms of materials and instructor effort, the educational and practical experience provided is viewed as absolutely vital to the training of biomedical engineering students. In an era where the use of animals for teaching is declining, WPI is graduating biomedical engineering students who are fully prepared to engage in biomedical research involving animals, appreciate the important role of animal experimentation and, most importantly, empowered with the knowledge to make informed ethical decisions regarding the use of animals in biomedical research.

References


2. Course URLs: http://www.wpi.edu/+bme/Course/BE3110 or through http://my.wpi.edu.


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