A COURSE IN BIOPROCESS ENGINEERING

Engaging the Imagination of Students Using Experiences Outside the Classroom

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Bioprocess Engineering has the potential to become one of the leading chemical engineering fields due to the explosive discoveries that are occurring and continue to occur in the field of life sciences. Since the rate of progress is so accelerated in this field, we must train future engineers to be willing to go beyond the conventional classroom education with initiative, motivation, and creativity.

We have developed a course that engages students' imaginations and participation outside the classroom, that offers real-life experiences through field trips, and that provides a chance for students to express their enthusiasm by publishing their own newsletter. Through these activities, students find that although life sciences is not an exact science, it is filled with tremendous need for challenging and novel conceptual development, which can be exciting to pursue through quantitative numerical analyses and expression.

In the chemical engineering department at the Notre Dame University, which has no formal bioengineering degree program, the second-semester senior/graduate-level bioprocess engineering course attracts students with various backgrounds. By the time they have completed the course, some will have established a strong foundation for embarking on graduate research, while others will have acquired sufficient practical knowledge to become entry-level bioprocessing engineers.

To fulfill the educational goals outlined in the ABET assessment criteria, this course introduces essential biology, biotechnology, and computational concepts while providing an environment in which the student can improve their skills in design, analysis, problem solving, teamwork, and communication. In order to develop a fast-paced, attractive, and self-motivated course, the leading roles for learning are shared between the students and the instructor. The students attend traditional lectures on the fundamentals of bioprocessing and are then asked to take the initiative in using the laboratory learning modules, in organizing a field trip to a local bioprocessing factory, and in publishing a newsletter on bioprocess engineering. They are evaluated based on their performance in all of these aspects, and the course is improved by assessing the results of a standard student Course Evaluation and additional questionnaires.

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OBJECTIVES OF COURSE

Recent advancements in molecular biology demand a new way of thinking in bioprocess engineering. During the last decade, explosive amounts of information have become available in the life sciences and it has become almost impossible for engineering students to know all there is to know about the field. In order to introduce such a wealth of information in one semester to students with little biological background, while maintaining an emphasis on traditional bioprocessing, there must be a carefully crafted set of course objectives. We have identified the following goals:

- *Students should know the structures, natural habitat, and industrial use of various microbes. Since most of the bioprocessing topics discussed in class will be*

TABLE 1
Course Syllabus

Goals By the end of this course, you should be able to
- Identify basic structure and types of microbes found in nature and used in industry
- Culture microbes—sterile method
- Design and operate bioreactors
- Harvest and characterize microbial products
- Describe intercellular function and structure models of cell growth
- Describe the strategy of genetic engineering and molecular cloning to improve product yields
- Describe metabolic engineering with solid understanding of enzyme kinetics and its historic evolution
- Communicate with the others and work as a team

Text Required: none
Supplemental Reading: Hand-Out Materials

Class Tuesdays and Thursdays 9:30 - 10:45

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Grades Grades will be based on your performance in
- Take-home exam (30%)
- Homework problems, including interactive exercises with reports (55%)
- Field trip with a follow-up lab (5%)
- Participation in publishing Bioeng. Newsletter (10%)

Course Outline
I *Introduction to Bioprocessing: Concept through Application*
II *Traditional Bioprocessing*
  a. Biological cells, bioenergetics, and cell metabolism
  b. Microbial growth and modeling
  c. Bioreactor design
  d. Recovery and Purification of products
III *Enzymes and Applications*
IV *Contemporary Bioprocessing*
  a. Genetic engineering
  b. Metabolic engineering
  c. Nonconventional systems

TABLE 2
Source Textbooks Used in Course

- *Bioprocess Engineering,* W. Veith; Wiley Interscience, New York, NY (1994)
- *Bioreaction Engineering Principles,* J. Nielsen and J. Villadsen; Plenum Press, New York, NY (1994)
- *Cell and Molecular Biology,* 2nd ed., G. Karp; Wiley, New York, NY (1999)
- *Biochemical Engineering Fundamentals,* J. Bailey and D. Ollis, McGraw-Hill, New York, NY (1986)
- *Bioprocess Engineering Principles,* P. Doran; Academic Press, San Diego, CA (1995) (Out of print)
- *Fundamental Laboratory Approaches for Biochemistry and Biotechnology,* A. Ninfa and D. Ballou; Fitzgerald Science Press, Bethesda, MD (1998)
- *Bioprocess Engineering,* 2nd ed., M. Shuler and F. Kargi, Prentice Hall International Series in Physical and Chemical Sciences, Englewood Cliffs, NJ (2002)

related to microbes, students should have a good understanding of the subject area.

- *Students should have a good grasp of the analysis of microbial cultures and be able to describe quantitatively their growth and scale-up.*
- *Students should be able to design bioreactors for different microbes when provided with sufficient knowledge about the growth culture supply, gas supply, release of waste products, and heat transfer.*
- *Students should be familiar with microbial product recovery and purification. They need to know the common methods used in product recovery.*
- *Students should be made aware of genetic engineering methods to design microbes to achieve improved product yield.*
- *Students should have some laboratory experience in microbial culturing and enzyme kinetics with sufficient computational, statistical, large-scale bioprocessing, and error analysis skills.*
- *Students should learn to work as a team, improve their communication skills, and be aware of the outside activities related to their fields.*

The course syllabus that reflects such goals is shown in Table 1, and a list of useful texts is given in Table 2.

In order to accomplish these goals, two general postulates were introduced to set the direction of the lecture section of the course. First, biological phenomena and concepts were deductively introduced in the class.[1,2] By approaching the subject from organisms to molecules, it was possible to focus continually on the theme of bioprocess engineering, while introducing the subjects of molecular and cellular events as needed. Future engineers must be trained to direct process development and to pioneer new discoveries in biology and genetics by bringing traditional engineering functions to bear in this novel field. Bioprocessing in a cell can be described in terms of various linked cellular "unit operations" (organelles) in which internal functions are driven by molecular-scale bioprocessing units (proteins and nucleotides) within the cell. This approach differs from the order of presentation typical in many bioprocess engineering textbooks, which start with an in-depth description of the chemical basis of biological systems and enzyme kinetics before introducing the cell, growth models, and unit operations. The choice between the two approaches may well be decided by the number of credit hours students are allowed to take in biology.

The second postulate used in course development was that while traditional bioprocess engineering addresses the issues of development and optimization of organism growth and product recovery, contemporary bioprocess engineering must also address the issues of engineering new organisms to better suit the purpose. The impact of recent advances in genomics and proteomics is quickly coming to bioprocess engineering and must be used by bioprocess engineers. For this, discussions of proteins, DNA, enzyme kinetics, and other biochemical processes both inside and outside the cell are critical.

ACTIVITIES OUTSIDE THE CLASSROOM

While classroom instruction continued, the students initiated activities outside the classroom to enhance their understanding of concepts and their knowledge of real-world applications. Active participation of the students made this course a more exciting learning experience.

Take-Home Examination • A take-home examination was given about midway into the semester to test the students on their ability to model and design fermentation processes. They should show good grasp of microorganisms and their regulated growth. Students appreciated the opportunity to express their knowledge in a relaxed environment.

Regular Homework • Traditional problem-solving homework exercises were assigned to develop and test student comprehension of the various analytical approaches used in this field.

Interactive Homework • In addition to traditional problem-solving homework, interactive modules were developed in order to engage student participation in the learning process. Rather than providing students with a set of numbers to plug into equations and submitting the computational results as homework, we arranged opportunities for them to find these numbers experimentally. We hoped the students would have a better feel for the significance and the range of errors that come with these numbers and how they would affect the final outcome if they were provided with interactive homework.

Relying on the laboratory instruction provided, students performed two laboratory experiments outside the regular classroom hours to generate data. These data were subsequently used to answer the homework problems. Students were divided into groups of 3-4 team members and used the learning laboratory modules. Each module was a mobile unit equipped with analytical instruments to conduct a specific laboratory experiment. Consulting with the graduate teaching assistants, students planned and set up the experiments by themselves, arranging their work schedule as demanded by the experimental procedures. With proper management of student schedules and the learning modules, this flexible arrangement could accommodate 22 students to complete the two experiments described below before the end of the semester. A high degree of student initiative was the key to the success of this arrangement.

• **Growth Analysis of *E. coli*:** Students had already been exposed to the growth analysis of bacteria in the lecture. The objectives of this experiment was to 1) learn the use of a pH meter, a spectrophotometer, and a centrifuge, 2) learn sterile techniques, 3) numerically analyze growth of bacteria, and 4) determine the mass transfer of glucose to the organism. Using a well-established method[3] in microbiology, the teaching assistant provided the original colony of *E. coli* to the students and they cultured bacteria in Luria-Bertani liquid culture medium[4] while intermittently determining the growth spectrophotometrically. A similar experiment was conducted with glucose, observing the rate of its uptake with Benedict solution.[5] Students reported quantitative kinetic analyses with degrees of errors on the lag phase, exponential growth phase, declining phase, stationary phase, and death phase during bacterial culture. The rate of transfer of glucose to the organisms was also reported. Most of the teams were able to obtain reliable data, but some failed and had to borrow data from colleagues. This highlighted the need to perform careful, well-recorded experiments and encouraged students to work together to achieve the long-term goal. The entire process took a little over two weeks, during which the students expended a similar number of hours as they would have spent doing regular homework.

• **Collision and Diffusion Limited Enzyme Catalysis:** Through this experiment the students also become familiar with the use of a pH meter and spectrophotometer. In addition, they learn how to run a LabView module, to understand the importance of pH in enzyme kinetics, to construct the three basic plots used in enzyme analysis (Lineweaver-Burk Plot, Eadie-Hofstee Plot, and Hanes Plot), and to understand the effect of collision frequency and kinetic energy of collision on the rate of enzyme catalysis. After becoming familiar with the conventional enzyme kinetic study in a buffer, the students performed a similar experiment in glycerol to mimic real-world bioprocessing where diffusion-limited reactions would take place in non-Newtonian fluids. Since all the reagents were prepared in advance, well-coordinated teams completed the experiments in two sessions of 2-3 hours.

First, students carried out the enzyme kinetics analysis of urease in water, using urea as the substrate, to understand the importance of buffered solution for enzyme kinetics. The rest of the experiments were conducted in HEPES buffered solution at pH 9.0. The rates of reactions were determined using Berthelot color assay[6] and the concentrations of the enzyme and substrate were adjusted to obtain the constants for the

Michaelis-Menton model at room temperature. This was a relatively simple system and the students were able to obtain data with a relatively small range of standard deviations.

In the second part, similar experiments were performed in a different concentration of glycerol to demonstrate the effect of increasing viscosity of the solvent on the enzyme reaction. The students were asked to explain the significance of high viscosity solvent on enzyme kinetics and its effect on the various constants.

The students considered this type of homework as somewhat taxing, but in general appreciated the firsthand experience in wet biochemical experiments.

Real-Life Bioprocess Manufacturing and Laboratory Practice • About halfway into the semester, a mandatory 3-hour tour to a local microbrewery was scheduled.[7] The students experienced scaling up of laboratory procedures, integration of chemical and mechanical engineering in flows of liquids and a number of regulatory systems, and communication between the administrative personnel, engineers, and technicians. The students embarked on a small-team project to brew three types of bottled beer, starting with the kits purchased from the brewery. Brewing took up to four weeks, and the grade was judged by student participation as recorded by the TA. In general, the excitement level for this module was highest, and an increase in registration was noted in the following year, with specific requests for a repeat of this module.

Publication of Bioengineering Newsletter • A major semester-long team project, the Bioengineering Newsletter, was assigned as the final project for the course. It provided an opportunity for the students to practice long-term team-based project execution and negotiation skills, to use written and verbal communication skills, to develop better literature review techniques, and to become aware of current events in the area of bioprocessing. The entire class of 22 individuals comprised the publication staff of the newsletter. Class members were assigned specific roles and responsibility levels, such as editor, writing team, design and layout team, financial team, and printing and distribution teams. Each responsibility level was given a list of duties, and team leaders were told to report regularly on their progress to their immediate senior in the publishing-team hierarchy. General guidelines and a timeline were provided, and the team leaders were asked to set and enforce deadlines for their own teams. The goal was to produce the final publication on time.

In order to keep some control over the progress of the project throughout the semester, each team leader was expected to provide copies of their regular reports to the instructor and to the editor, indicating the accomplishments of their team for the preceding reporting period and reporting any difficulties that may have arisen. The editor was asked to provide a final comprehensive report on the project on the activities of each team and suggestions for the future. The concept of multi-layered reporting within a large team, although realistic, is sometimes difficult to achieve in the classroom since some students may be reluctant to assess the performance of their peers or to pay strict attention to deadlines. When a very detailed calendar of events was provided, there was more compliance with the structure.

Each student was asked to write a one-page single-spaced article with references and properly sourced graphics relating to a subject relevant to bioprocess engineering. The writing team was to provide a specific theme for that year's newsletter along with a list of suggested topics for the students to write about. Students were free to choose any topic, but if it was not on the list, they had to obtain approval from the writing team. Eventually, students reached a consensus and instructor intervention was minimal.

The design and layout team was responsible for creating the electronic publication using Microsoft Publisher. This group defined the manuscript size and graphical elements, and provided a mock-up to the editor, who proofread the copy before printing. The financial team raised money to cover the cost of printing by soliciting donations from student engineering organizations on campus, such as AIChE, SWE, MEP, and various departments. Excess funds were used to provide pizza and drinks for the inevitable last-minute "push to publish" just before finals week. Each member of the class and each financial donor received a paper copy, and five went to the instructor. Distribution of printed newsletters takes place during finals week. Wider distribution was achieved through website dissemination at <http://www.nd.edu/aostafin/ben1>.

STUDENT PERFORMANCE EVALUATION

Students were evaluated based on

- Their ability to comprehend and express bioprocess engineering subjects quantitatively: *take-home examination (30%)*
- *Problem-solving homework (30%)*
- Taking initiative in conducting two experiments and the ability to analyze the results quantitatively: *Interactive homework (25%)*
- Ability to apply knowledge to the real world: *site visit and follow-up experiments (5%)*
- Communication skills and ability to work as a team:

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participating in publishing a Bioengineering Newsletter (10%)

ASSESSMENT

This course has been taught only once under its present title, "Bioprocess Engineering"—in the spring of 2002. Assessment of whether or not the learning goals were achieved in this class was determined through exit surveys and teacher course evaluations. Some examples of questions that were asked of the students were

- *Did they feel the amount of learning they experienced was better, as good as, or less than in other core engineering courses?*
- *Did they think this course helped them to see where key issues of transport, thermodynamics, and reaction kinetics play a role in biological systems?*
- *Did they feel confident in their ability to begin employment in a field related to bioprocess engineering?*

The responses were divided: about 2/3 of the class participants responded positively to the course and felt it was a good introductory course to enable their further advanced studies in this area, while the other 1/3 did not find the course particularly beneficial. Some commented that the course was "very interesting," "tied in concepts previously learned in other courses in bioprocessing," and "the homework laboratories made the corresponding parts of the lecture more colorful." Because there was no formal text for the course, some students "had difficulty in finding additional information to solve some homework problems." A reserve list of library texts covering the course material was always made available in the Engineering Library, but access to on-line resources may be a more effective way to disseminate these materials.

CONCLUSIONS

To our surprise, most of the ambitious goals set for the course were accomplished. Such excellent accomplishments were due to the students' willingness to participate in the outside classroom activities. We could have done even better if more students had had some university-level biology background.

The student engineers adapted well in the conceptual and computational analyses in the classroom dealing with the biological system, but some had difficulty in growing microbial culture. This was quite understandable, and the Department of Chemical and Biomolecular Engineering is moving toward requiring one semester of biology for all engineering students in the future.

Many students who took the course were excited about the prospect of molecular-biology driven bioprocess engineering and appeared to have enjoyed the less stressful approach to the subject, although it was a demanding course. We intend to improve the quality of the course by analyzing formal and informal assessments of the course. In the future, it would be advisable to solicit an external evaluation of the course.

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ChE letter to the editor

To the Editor:

The recent article (Pitt, M.J., and J.E. Robinson, "Using a Commercial Movie for an Educational Experience," *Chem. Eng. Ed.,* **37**(2), 154, 2003) on the use of movies for educational experience is interesting, and may I suggest another possible movie for study...*The Man in the White Suit.* A brilliant young polymer chemist, working unofficially in a corporate research laboratory, develops a fabric that "never gets dirty, never wears out." At first this is seen as a blessing, but very soon it is seen as a threat to the entire textile industry, and attempts are made to suppress it.

Although *The Man in the White Suit* was made as a comedy, it says much about the role of industrial research and its economic and social impact. In some ways it is very dated, as it was made over fifty years ago; but today's students who see it could be asked to explain how it is dated and also to identify the aspects that are still highly topical. When I first saw it as a teenager, it reinforced my interest in applied chemistry, and that eventually led me to chemical engineering.

Malcolm Baird
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