Pioneering the Incorporation of Cell Culture in A New Biomolecular Engineering Program

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Abstract

The Milwaukee School of Engineering (MSOE) has brought a new BioMolecular Engineering program (BioE), an interdisciplinary engineering which overlaps skill set between chemical engineering and biology. BioEs often manipulate DNA and proteins in order to design, modify, or improve molecular products or processes. Knowledge of proper cell culturing techniques is vital to such a discipline. The cell culture course includes basic housekeeping topics such as cryo-banking, sterilization, BSL-2-LS, and passaging and manipulating live monolayers with COS-7, L-cells, keratinocytes and/or embryonic stem cells. These acquired skills are then applied to a mini-design project that merges life science with chemical engineering. The purpose of this course is to apply an innovative teaching philosophy of the new biomolecular engineering program at MSOE which is centered on thinking and designing at the molecular level. The success of this teaching philosophy has been shown through the collected data measured against the ABET student outcomes. The BioE program has presented and enabled the introduction of new and unconventional courses into the engineering field at MSOE such as the cell culture laboratory course.

The History of Tissue and Cell Culture

Tissue culture, developed during the beginning of the twentieth century was a tool for studying animal cells outside of the living organism[1]. This *in vitro* environment was to mimic *in vivo* events in tissues and cells[1].

Some of the first tissue sources for cell culture were performed in cold-blooded animals, such as frogs, that do not require incubation[1]. Medical science later adapted the use of warm-blooded animals to more closely represent the development and pathology of humans[1]. Due to accessibility and ease of growth, the chick embryos were an initial warm-blooded tissue source, but later mouse cell lines with well-established genetic backgrounds were developed[1].

Why Cell Culture for Engineers?

Since engineering is becoming diverse, the following was considered when introducing a cell culture course into the new BioMolecular Engineering program at the Milwaukee School of Engineering (MSOE).

- Historically, cell culture was a traditional *in vitro* tool established and accepted as a data rich discipline in both the natural sciences and engineering fields worldwide.
- Mammalian cell culture presented an opportunity to work with complicated design projects of the cell, such as post-translational modifications and energy models. These kinds of design projects have brought new challenges to the field of engineering.
- Production of cell products, such as insulin, interferon, and antibodies via gene expression, has further established the power of the cell culture discipline. Engineers directly working in the field of biology or other bio-based areas have accepted the importance of cell culture applications.
- Cell signaling in cell differentiation and development have led to the development of a new area called tissue transplantation[1]. Since this area has applications in grafting and reconstructive surgeries using the patient's own cells, the area has become of interest for molecular and macro level engineers.
- A related area established by cell culture is the insertion of a gene's working copy into a faulty functioning cell which allows for the cell to regain function and be placed back into the patient[1]. Such advances are of interest for the engineers who wish to explore genetic engineering.
- Neuronal engineering has been benefited from cell culture. Since the routine propagation of neuronal cells was not possible due to the nature of this cell type, neuronal cells could now be produced through the replication process of embryonic stem cells that may produce useful models for neuronal diseases[1]. This field is of interest to biochemical, chemical and biomolecular engineers.
- Various other applications, such as *in vitro* fertilization (IVF), clinical diagnoses (i.e. amniocentesis), and toxicity reports (environmental pollutants), can now can be assayed *in vitro* through cell culture. This kind of genetic and bioengineering has made bio-based engineering disciplines closer to human health and has presented new ethical and societal issues.

Overall, cell culture has become a powerful tool to both researchers and engineers in modern times. It has allowed for the design of *in vitro* experiments at the same level as those experiments previously carried out *in vivo*. This is an exciting time in the field as it transitions from fundamental descriptive molecular biology to a mathematically driven field that allows cell and tissue design and its applications. This is a time when biology has joined the ranks with chemistry, physics and math for all fields of engineering.

Biomolecular Engineering - On the Horizon of Engineering

As biology started changing from a data poor to a data rich science in 1990s due to the high throughput analytical techniques, the large amount of data produced became a force behind changing molecular biology from a qualitative to a quantitative science. Therefore, it started to overlap interests in chemical engineering with biology as well as biology with chemical engineering [2]. Due to the overlapping interests of chemical engineering and biology, and because of the new found applications of the fields such as biotechnology, cell culture and biochemistry in engineering, a new field of engineering, “biomolecular engineering” emerged which is an interdisciplinary engineering. The term “Biomolecular engineering was defined by National Institutes of Health (NIH) for a December 1992 meeting as… ‘research at the interface of chemical engineering and biology with an emphasis at the molecular level’” [2].

Construction of the BioMolecular Engineering Program

The initial groundwork for the launch of BioMolecular Engineering Program at MSOE started in 2000. The proposal for the program was prepared in 2006 by Dr. Afshan (one of the authors of this paper). The curriculum of this program was constructed and approved in 2008 with the new undergraduate degree for the BioMolecular Engineering program launched in the fall of 2009. The curriculum of the BioMolecular Engineering Program at MSOE consists of 192 trimester credits divided among 3 categories: general education, math and science, and engineering including a series of three senior design project courses[3] **(Figure 1)**. Each category serves a specific purpose within the program. The general education courses, such as humanities, social sciences, English and business, prepare the students for social aspects while the math and science courses “prepares the students with the necessary principles and skills needed for all forms of engineering and gives them a background” in the biology specifically needed for biomolecular engineering[3]. Finally, the engineering curriculum “prepares the students for the engineering principles and skills essential for biomolecular engineers”[3]. This is to expose the students to the “conceptual, technical, ethical, and cultural diversity” of biomolecular engineering[3]. Twenty-five brand new courses were designed to meet the needs of the new BioMolecular Engineering Program at MSOE. This ranged from courses similarly found in traditional chemical or biochemical engineering curricula to courses on micro and nano principles and applications to diverse concepts and technologies related to molecular biology[3]. In addition, courses to address the long term future of the field, such as Cell Culture, Molecular Nanotechnology, Engineering of Controlled Drug Delivery and Biopolymer Engineering were designed. Students spend 270 hours in the laboratory which includes numerous hands-on activities. “The choices and the sequence of the engineering courses in this newly designed curriculum provide the diversity and flexibility needed for the Biomolecular Engineering field”[3].

Pioneering a Cell Culture course in the MSOE Biomolecular Engineering Curriculum

The first ever Cell Culture course introduced at MSOE for the BioMolecular Engineering students is a 3-credit laboratory course. Students registered in the course meet every week in lecture for one hour and in the biosafety level-2 (BSL-2) cell culture laboratory for four hours. Each student is required to take on a cell culture design project after they learn and successfully manipulate a mammalian cell line without contamination. The course, designated as EB-3530, has been successfully running for three years.

Basic cell culture housekeeping and its applications required students to be clear on biology, math and some design concepts. The work also demanded maturity, time, and clear conception on ethical and safety rules and regulations. In the light of all aforementioned considerations, the cell culture course was placed in the program’s curriculum at the end of the student’s junior year.

This allowed for the student to have a solid foundation for handling this course. The strategic position of the course also trained students in cell culture prior to a 3-course senior design capstone project sequence, so that the cell culture skills can be utilized for the senior design project as needed. The cell culture laboratory is a required course for biomolecular engineers at MSOE.

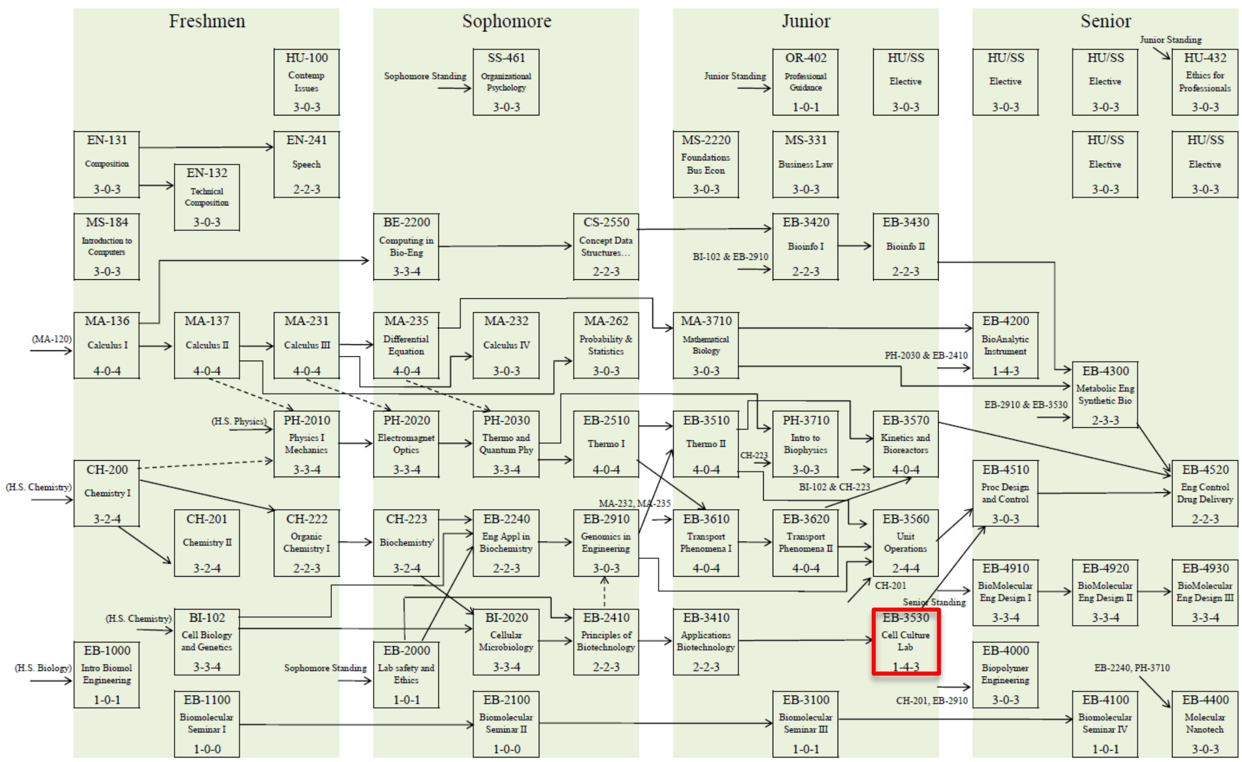


Figure 1. Curriculum of the BioMolecular Engineering (BioE) Program at MSOE. The following flow diagram represents the BioE track for all four years (freshman through senior year) to obtain a BioMolecular Engineering degree from MSOE. Twenty-five brand new courses were developed for the BioE program which ranged from traditional chemical engineering courses, to courses on the principles and applications of micro and nano concepts to molecular biology concepts and techniques to futuristic courses (i.e. cell culture). Note that the cell culture course is offered in the junior year and is highlighted in red.

The course incorporated a "hands-on experience in cell culturing aseptic techniques and their applications in industrial manufacturing and biomanufacturing" (i.e., BSL-2-LS)[4]. Topics covered include: "basics of cell culture techniques, controls and conditions, safety and hazards, types of cell culture, cell environment, cryopreservation and good cell banking practices, alternative cell culture systems, process protocols, bioreactor design and operation, cell growth models and emerging technologies"[4]. Students are exposed to the culturing techniques associated with COS-7, L-cells, keratinocytes and/or embryonic stem cells.

Biomolecular tools or applications of biotools such as smart drug development, gene therapy (DNA or RNA) and bioremediation as well as cell based therapeutics and diagnostic products[3] may use cell culture at some point during the design and developmental stages of such projects. The cell culture course was critical for the program graduate's "flexibility of careers opportunities in a dynamic job market"[3].

A Success Story

The cell culture laboratory course was one of the targeted courses that is used to collect data on the attainment of the ABET student outcomes (a), (k) and (l). The quantitative and qualitative data collected for three years was used for the assessment process and was also valued as an indicator of the success of the core cell culture concepts and techniques taught in the course. The assessment for the BioMolecular Engineering program was defined as, one or more processes that identify, collect, and prepare data to evaluate the attainment of student outcomes and program educational objectives[5].

The tools used for the attainment of students outcomes (a), (k) and (l) were a laboratory individual oral exam and a cell culture mini-design project. The assessment scale used to measure validity of success ranged from 1 to 5 with 1 being the lowest (beginning) to 5 being the highest (exemplary) **(Table 1)**. The performance bar set by the program was to have at least 70% of the students at a proficiency or higher level, which in terms of numbers is 3 or higher. Each student outcome mapped to the course utilized performance indicators (PIs) to validate the attainment of the respective student outcome. The questions asked during the oral exam and the assessment of the mini-design project and its report were measured against a rubric.

Table 1. Assessment Scale. One is lowest level of attainment on the assessment scale and corresponds to a beginner student whereas a five is the highest level of attainment on the assessment scale and corresponds to an exemplary student with a range in between.

Assessment Scale	Description
1	Beginning
2	Developing
3	Proficient
4	Accomplished
5	Exemplary

Oral exam questions ranged from performing direct cell culture calculations to the safety measures, rules and regulation, and ethics associated with the field. All results obtained were tabulated in a program student outcome assessment form. A sample form showing such data on the oral exam results is shown in **Figure 2**.

The objective of the mini-design project was to mentally and intellectually train the students for the real senior design project. Students of the course worked in teams of three or four. Each team identified and reported a problem statement, constructed a Microsoft Visio flow sheet diagram to address the constraints and multiple solutions to the project, as well as discussed the commercialization or scale-up in the market or industrial levels, respectively in which the center of thinking and designing was at the molecular level. Students then completed a portion of the project in the cell culture lab and submitted both the written and experimental data.

EB-3530 Cell culture for BioEs Spring 2013
Section(s): 11 & 21
Course Instructor(s): Afshan, Hassemer
Course Coordinator: Afshan
Course Assessors(s): Afshan, Hassemer

Assessment of Student Outcome "a"

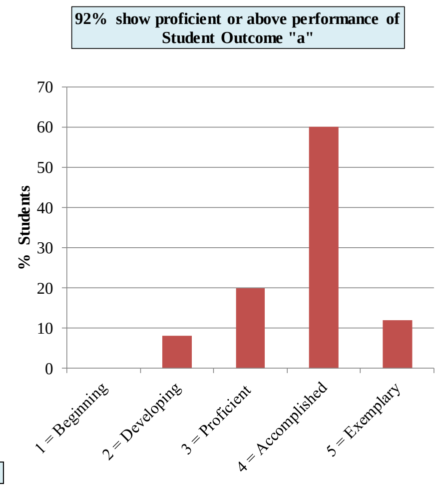
an ability to apply knowledge of mathematics, science, and engineering.

Assessment Tools: Three Oral Lab Ex Qtns were constructed

Q1 a) A viability count was used to determine the total number of living cells/mL. The total number counted (from 3 squares of hemacytometer) was 63, 74 and 65 living cells. The total amount of the suspension is 10 mL. How many cells are there total in these 10 mL?

Q1b)Viability count was used to determine the total number of living cells/mL. The total number counted (from 4 squares of hemacytometer) was 63, 78, 60 and 65 living cells. The total amount of the suspension is 15 mL. How many cells are there total in these 15 mL?

Scale Used	Range			% students
1 = Beginning	0	-	1.99	0
2 = Developing	2.00	-	2.99	8
3 = Proficient	3.00	-	2.79	20
4 = Accomplished	3.80	-	4.79	60
5 = Exemplary	4.80	-	5	12



Student code	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
ability to communicate by making diagrams																									
ability to do calculations	4	4	4	5	5	5	4	4	4	3	3	3	2	2	4	4	4	4	4	4	3	3	4	4	4
reason to lead to conclusions																									
Individual performance average on a scale of 1-5	4.0	4.0	4.0	5.0	5.0	5.0	4.0	4.0	4.0	3.0	3.0	3.0	2.0	2.0	4.0	4.0	4.0	4.0	4.0	4.0	3.0	3.0	4.0	4.0	4.0

Performance average of cohort on a scale of 1-5 3.8

Figure 2. Program Student Outcome Assessment Form. Every mapped student outcome has the form filled out by all participating faculty members. Each outcome contains multiple performance indicators (PIs) upon which faculty agree upon and choose prior to the start of assessment. These PIs are used in the assessment process to rank the degree of attainment (scale of 1-5 with one being the lowest and 5 being the highest).

From the assessment data collected so far, it can be reasonably concluded that a large majority of students learned from this course and student outcomes assigned to this course are also met. Another reflection on the success of the course is the fact that the program's first graduates have utilized the techniques learned in this course at their place of employment. Recently, the feedback from graduates indicates that suspension cell techniques besides the monolayer techniques would be useful in the industrial settings.

Conclusions

"Biomolecular engineering is a diverse, application-driven discipline in the areas of medical, agricultural, environmental, biotechnical and other life-science fields"[3]. Incorporation of cell culture skills has been considered vital to such a diverse and futuristic discipline. Since biomolecular engineers use biomolecules to design, modify, or improve products and processes at the molecular level, it was considered essential to expose students to live cells which house these biomolecules, in general and their manipulation in particular. The BioMolecular Engineering Program at MSOE is a pioneer in introducing a biosafety level 2 cell culture facility and a cell-based laboratory course for the program. The purpose is to make a leading example for other programs. The assessment data collected over three years and input from one class of graduates so far indicates that key concepts and techniques of cell culture have been acquired and the skill sets attained by the cell culture course and practiced by many in the senior design three course sequence have been utilized in the industry in protein and microorganism design work. For the authors, it is a work in progress. From the small data pool collected, it indicates that the value of the cell culture in the field of biomolecular engineering is going to increase with time as the application of the field for engineering keeps increasing. At least one cell culture course, therefore should be considered a requirement for all four year biomolecular engineering degree programs.

Authors' affiliation

[*]Coauthors contributed equally to this paper.

[‡]Drs. Afshan and Hassemer initiated the first biosafety level-2 (BSL-2) cell culture facility at MSOE and currently are team teaching the cell culture laboratory course to all BioMolecular engineers. Dr. Afshan is the course coordinator for the course.

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