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Board 28: Work-in-progress: Transforming the Molecular and Cellular Engineering Educational Experience in Biomedical Engineering

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Abstract

In recent decades, biomedical engineers have capitalized upon the "molecular revolution" that fundamentally changed the study of biology through discovery, design, and commercial production of molecular and cell-based therapeutics that form the foundation and future of modern medical treatment. Advances in tissue engineering, computational protein design, and high-throughput bioanalytical techniques across academia and industry motivate the need to develop curricula that provides opportunities for students to interact and design early in their undergraduate careers. To meet this need, we created two new junior-level courses: Molecular Engineering (BME305L) and Cellular Engineering (BME306L) that were offered in the Fall and Spring of 2022, respectively. We have emphasized student-centered experimental and laboratory practice as the backbone of these courses to prepare students for authentic research experiences in any industry. Molecular Engineering integrates computational and experimental learning outcomes that bridge the *in silico* to *in vitro* pipeline of protein engineering. Students combine their "wet" and "dry" lab experiences into a final month-long project to design novel protein fusions or protein affinity binders with the potential to inhibit an aberrantly expressed protein. Cellular Engineering prepares students with continuous engagement in mathematical modeling of cellular phenomena, mammalian cell culture, analytical techniques (fluorescence microscopy, Western blotting, and quantitative real-time PCR), and studying morphological and cytoskeletal changes in 3D culture models.

Preliminary student feedback from Cellular Engineering and Molecular Engineering emphasizes the impact of "hands-on lab experiences" that scaffold knowledge with lecture content. Students value that these authentic experiences help to answer "overarching scientific question[s] for most of the labs and we were doing the lab for a purpose." Course evaluations for Cellular Engineering report a 4.83/5 overall evaluation score, with a 5/5 score for intellectually stimulating content. Likewise, Molecular Engineering course evaluations report a 4.00/5 overall evaluation score, with a 4.53/5 score for intellectually stimulating content. Additional questions on integrating these new gateway courses with advanced topics and electives are pending, along with long-term success of the new courses on student engagement in primary research at Duke University, industry connections and career success.

Introduction

Linsenmeier and Saterbak [1] have analyzed the nearly 120 ABET-accredited biomedical engineering/bioengineering (BME/BioE) programs in the U.S. to identify commonalities in the multidisciplinary curriculum and how university programs develop discipline-based "tracks" based on historical significance, growing workforce needs, and student interests. One such track in molecular, cellular, and tissue engineering (MCTE) has garnered significant attention this decade with increased access to mammalian cell culture, CRISPR/Cas9 genome engineering [2], and synthetic biology education [3]. In addition, the U.S. presidential administration enacted Executive Order 14081 [4] in 2022 to launch a National Biotechnology and Biomanufacturing Initiative that "train[s] a diverse skilled workforce" and increase federal funding for research & development in this sector. This identified need is compounded by the Covid-19 pandemic and the weak bio-infrastructure [5] to support the production of mRNA vaccines, monoclonal antibody therapies, and cellular testbeds for validating the activity of biologics. As careers in biotechnology industry and research increase in the past five years [6] with growing student interest, we address the need to improve the MCTE track within biomedical engineering education.

The rapid technological advancements in the MCTE field require concomitant curricular changes formed on a student-centered pedagogical approach that emphasizes hands-on engagement with research and deliberate practice in biological settings [7]. This work-in-progress paper will outline our strategies for transforming the MCTE track at Duke University, including the needs identification, initial findings of student and curricular success, infrastructure changes to support our enhanced tract, and future directions to iterate on our courses. We also present the first iteration of our improved MCTE track courses, learning objectives for lecture and student-centered laboratories, and feedback on further improving these core courses to reflect the dynamic change in the biomedical engineering space.

From traditional engineering courses to an enhanced MCTE track

Our BME curriculum requires students to take Bio201L: Molecular Biology as a prerequisite for their initial required BME courses, which is completed by second-year first semester for most students. Bio201L introduces students to the molecular mechanisms that comprise the Central Dogma; protein folding, structure and function; and cell metabolism and energetics. The hands-on laboratory experiences introduce recombinant DNA technology that covers restriction digest-ligation cloning; *Escherichia coli* transformation; Sanger sequencing; and introduction to bioinformatics using sequence alignment.

Our BME students take four required 200-level BME courses that don't provide a dedicated examination of engineering basics at the cellular level. Instead, courses fall into the more traditional engineering prerequisite categories which prepare them for the broad scope of BME (Signals and Systems, Biomaterials, Modeling Cellular and Molecular Systems, Quantitative Physiology and Biostatistical Applications). These courses are taken throughout the student's sophomore year and first semester of their junior year. While labs are offered for these courses, none emphasize molecular and cell biology experimentation—only computational modeling in molecular and cellular engineering applications.

During their junior year, students take three 300-level BME courses. The one required course is Introduction to Medical Instrumentation, while the other two can be selected based on the student's interest in a particular track of BME. These areas are Biomechanics and Biomaterials; Electrobiology; Imaging and Measurement Systems; and Molecular, Cellular and Tissue Engineering. These tracks are led by a gateway area core class with an identical (or nearly

identical) title, apart from the MCTE track—this track is led by BMEXXX: Transport Phenomena in Biological Systems. We reflect in the next section why this core class alone is insufficient to prepare our students for depth in the MCTE track.

In their final year of study, students must complete two advanced electives in their chosen area of focus and one capstone design course. Advanced electives within the MCTE track (listed in Appendix B) offered in the past five years have skewed as much as 4 to 1 in favor of molecular/cellular-focused content over transport phenomena (Fig. 1), with few pre-requisite molecular/cellular engineering coursework and experiential laboratory experiences to scaffold learning appropriately. The increase in advanced electives in the MCTE area over the past several years coincides with new faculty hires within these fast-growing research areas, but student enrollment in electives has increased on a per class basis, reflecting topical interest. Along with the advanced electives, Biotechnology Design I/II courses have been developed over the past several years and is now one of our most popular year-long design courses within our program.

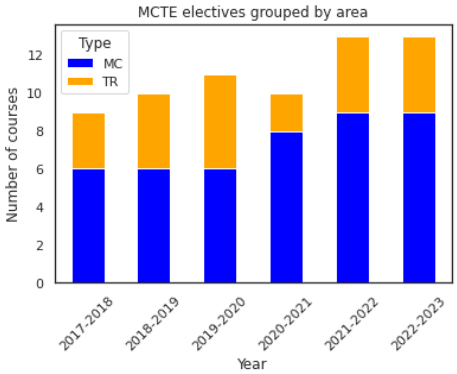

Figure 1: MCTE electives offered at XXX University BME since 2017 are mostly in molecular and cellular (MC) versus transport (TR) offerings by nearly 2:1.

ABET Criterion 5(d) [8] states that the engineering curriculum for undergraduate students must contain "a culminating major engineering design experience that 1) incorporates appropriate engineering standards and multiple constraints, and 2) is based on the knowledge and skills acquired in earlier course work." Arguably, our Biotechnology Design sequence did not meet this criterion, as we did not have the appropriate coursework prior to this class, nor did we provide laboratory skills to apply to later capstone designs. For students that followed the standard BME curriculum in our department at that time (i.e., no additional majors, minors, or certificates) or did not have access to primary research experiences, they did not have any hands-on molecular or cell biology laboratory experiences for two to three years (Appendix A).

Developing the BME305L: Molecular Engineering and BME306L: Cellular Engineering gateway area core courses

To address this gap in MCTE and biotechnology education with technical content and skills development, a subcommittee of the undergraduate curriculum committee was convened to identify learning objectives, laboratory skills, and prospects of undergraduates who pursue this track in 2018. Led by BME faculty, the committee identified the conceptual and technical skills that comprise a transformative educational experience that will prepare students to be the future leaders in molecular and cellular engineering. Lab and lecture content of these courses is presented in Table 1, along with course examples that align to ABET Student Outcomes in Appendix B:

- *Students completing BMEXXX: Molecular Engineering will be able to* describe the principles of biological and synthetic DNA production; utilize basic experimental and computational techniques to analyze DNA; apply principles from thermodynamics to understand protein structure-function relationships; develop a quantitative understanding of key protein functions, including binding and enzymatic activity; and use basic experimental and computational approaches to analyze proteins in bacterial cells.
- *Students completing BMEXXX: Cellular Engineering will be able to* quantitatively describe fundamental cell processes including energy and mass production, growth, differentiation,

adhesion and migration; mathematically model the transfer of information within the cellular environment to alter gene expression; provide quantitative and qualitative descriptions of cellular responses to the external environment including within tissue; and quantitatively measure viability, proliferation, transfection, and differentiation in mammalian cells.

Table 1: Summary of lecture and lab components in transformed MCTE gateway area courses

BMEXXX: Molecular Engineering		**BMEXXX: Cellular Engineering**	
Lecture Content	Lab Skills	Lecture Content	Lab Skills
• DNA, RNA, protein structure • Protein folding • Directed evolution • Positive/negative selection • Enzyme kinetics • Entropy • X-ray/cryo-EM structure determination • Functional RNA molecules	• Gibson Assembly • RNA secondary structure • Protein purification • Site-directed mutagenesis • Flow cytometry • PyRosetta and Alphafold computational labs • Surface plasmon resonance	• Cell types • Stem cell • Central Dogma • Protein sorting/trafficking • Respiration and metabolism • Adhesion and extracellular matrix • Tissue engineering scaffolds • Cell-based therapies	• Mammalian cell culture and aseptic technique • Fluorescence microscopy • Collagen tissue scaffolds • Electroporation and transfection • Cell viability • Western blotting • Real-time quantitative PCR

Preliminary evidence of MCTE track enhancement and growing student interest

Within the track-based system used at XXX University BME, the MCTE track has risen in popularity from 18.8% of students (18, n=96) in 2018 to 27.6% (27, n=98) in 2023 selecting this area of focus. While confounding variables such as the Covid-19 pandemic and limited enrollment due to laboratory spaces cannot be controlled, we expect to enhance the education and training opportunities for 40-50 students during the first years of track rollout. Course evaluation scores were overwhelmingly positive and presented in Table 2. We believe that differences between course ratings range from instructor variability to smaller sample sizes. End-of-semester student feedback emphasized the importance of "hands-on" skills and "reinforcing holes" from previous experiences, motivating the importance of these courses to bridge topics from introductory biology to biotechnology design.

Official Course Evaluations	**Molecular Engineering (n=17/21)**	**Cellular Engineering (n=6/9)**
Overall Course	4.00	4.83
Intellectually Stimulating	4.53	5.00
Course Difficulty	3.53	4.00
Overall Instructor	4.59	4.83

Future Directions

Enhancing the MCTE track at Duke University will provide more BME students with the curricular excellence and scaffolding to succeed in upper-level advanced electives and future careers in the biotechnology sector. We will equip our BME undergraduates with the technical and conceptual expertise to foster an engineering perspective to the world-class multidisciplinary MCTE field. Our plans emphasize curricular updates to BME305L & BME306L that reflects students' comments on better preparations for these area core classes, measuring BME student success in research and industry careers in this sector, and assess improvements in Biotechnology Design I/II projects and ventures as a capstone design course.

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Appendix A: List of course titles offered within the MCTE track as molecular/cellular-focused versus transport-focused

Molecular and Cellular Engineering		**Transport Phenomena**	
Course Title	Number of offerings	Course Title	Number of offerings
Genome Science Lab	2	HIV Transport	5
Intro to Biomolecular EGR	8	Transport: Cells and Organs	2
Gene Circuits	7	Biofluid Mechanics	3
Cell Mech and Mechanotransduction	6	Cardiovascular EGR	5
Quant Cell and Tissue EGR	3	Drug Delivery	5
Biology by Design	7	Vascular Bioengineering	2
EGR Living Systems	2		
Genome Engineering Lab	4		
Biomanufacturing: Upstream	2		
Protein Design and Deep Learning	1		
Machine Learning in Pharmacology	2		

Appendix B: Summary of lecture and lab components between first year and fourth year in the MCTE track emphasizes the gaps in student knowledge prior to independent design and track revision

First Year		**Third Year**	**Fourth Year**	
BioXXX: Molecular Biology		**BMEXXX: Transport Phenomena**	**BMEXXX: Biotechnology Design**	
Lecture Content	Lab Skills	Lecture Content (No lab)	Lecture Content	Lab Skills
• DNA, RNA, protein structure • Energy and metabolism • Genome organization • Central Dogma • DNA repair • Cell cycle • Cancer	• Pipetting • *E. coli* and yeast culture • Plasmid isolation • Restriction digest • Agarose gel electrophoresis • Sanger sequencing • BLAST	• Conservation of mass • Steady state/unsteady diffusion • Bernoulli's principle • Conservation of linear momentum • Transport with reaction • Drug delivery • Blood rheology • Finite element analysis • Krogh tissue cylinder	• Needs finding • Diagnostics • Therapeutics • Vaccine • Intellectual property • Nucleic acid biotechnology • Cell and gene therapy	• Recombinant protein expression • Plasmid design • Aseptic technique • Protein polyacrylamide gel electrophoresis • Assay development • Quality control standards

Appendix C: Mapping MCTE gateway area courses to ABET Student Outcomes

We considered how our new courses corresponded to ABET student outcomes (SO) to ensure our learning objectives and activities were preparing our BMEs for success as future engineers [7]. Notably, we focus on student outcomes 1, 3, 6, and 7 within both courses:

- SO1: *an ability to identify, formulate, and solve complex engineering problems by applying principles of engineering, science, and mathematics.*
    - *Molecular Engineering:* Homework assignments required students to calculate the potential energy and thermodynamic parameters of biomolecular complexes to assess favorability of interactions or activity. Computational labs applied similar principles in energy scoring functions, intermolecular forces, and optimization to study and design novel biomolecules.
    - *Cellular Engineering:* Students complete homework and project assignments where they are expected to formulate and manipulate mathematical models to investigate cellular processes as well as the effectiveness of various therapeutic and process design strategies. Examples include the investigation of the effectiveness of non-specific versus specific chemotherapy targets when modeling tumor growth using the cancer stem cell hypothesis, examining the effect of various rate limiting nutrients and the level of toxic metabolites on the production level of extracellular IgG within bioreactors, and quantifying intracellular protein levels while varying transcription, mRNA degradation, translation, and protein degradation rates.
- SO3*: an ability to communicate effectively with a range of audiences;* and SO7*: an ability to acquire and apply new knowledge as needed, using appropriate learning strategies.*
    - *Molecular Engineering:* Laboratory exercises required students to prepare sections of a manuscript at different stages (e.g., introduction, materials & methods, results) and present to a technical audience. Final projects focused on applying computational protein folding algorithms such as PyRosetta [9] to design novel peptide-based protein degraders or miniprotein binders for a novel antigen [10]. Students prepared an oral presentation for a general audience and a full manuscript draft subject to best practices in data analysis and presentation.
    - *Cellular Engineering:* While the final course project has a targeted audience of those within the field of MCTE, students write a proposal for a project topic of their choosing within the MCTE field, receive feedback on their proposal from the instructor, complete the project report, and receive another round of feedback from the instructor. The ability to effectively communicate is 20% of the total project grade, which is broken down into the following categories: organization, articulation, visual aids, and writing style.
- SO6*: an ability to develop and conduct appropriate experimentation, analyze and interpret data, and use engineering judgment to draw conclusions.*
    - *Molecular Engineering:* Homework assignments and an exam provide students an opportunity to outline a potential experimental plan to assess if their proposed molecular design from computational to *in vitro* testing would be valid. Examples include: Design a positive/negative selection screening for improved antibody binders for a ligand of interest, explain why acidic amino acids are favored in DNA binding vs. nonpolar and identify critical residues of a protein involved in activity, and which experimental assays would you employ to measure RNA aptamer binding affinities.
    - *Cellular Engineering:* Homework and post-lab assignments provide several opportunities for students to meet this outcome. There are several homework problems

in which students must use given experimental data along with mathematical relationships discussed in lecture to perform linear and non-linear curve fitting to estimate unknown parameters along with their 95% confidence intervals. These models often require manipulation to incorporate experimental limitations not accounted for in the original models. Most lab activities are designed in a way in which students are attempting to answer a scientific question. These include: Does ethanol affect cell viability, does the percent serum affect cell proliferation rate, does LPS treatment affect COX-2 mRNA and protein levels. Students complete the measurements in the lab, and then use the class data to perform the appropriate hypothesis testing to determine if the null hypothesis should be rejected or not. The experimental designs require students to perform either t-testing; ANOVA and post-hoc testing; or the non-parametric equivalents given the data being analyzed.

Appendix References

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