Putting the "Engineering" into Tissue Engineering: Development of Undergraduate Tissue Engineering Course Materials and Laboratory Experiments

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Tissue engineering is inherently multidisciplinary, requiring an understanding both of cell and molecular biology and basic materials science and engineering. According to the report of the International Technology Research Institute (WTEC Division) on Tissue Engineering Research (http://wtec.org/loyola/te/final/te_final.pdf), while there are a number of strong interdisciplinary research programs in the US that effectively bridge the gap between biology and materials science and engineering, there is a critical need to transfer this knowledge base to a potential work force. This is particularly challenging for undergraduate programs in biomedical engineering. Students are unlikely to develop significant expertise in both cellular and molecular biology or materials/mechanical engineering independently. Undergraduate course materials that provide opportunities for integration of these two areas are necessary. NC State Biomedical Engineering faculty with expertise in biomaterials, biomechanics, and tissue engineering are collaborating on design and development of course and laboratory materials that provide tissue engineering learning experiences for students in the sophomore, junior and senior years.

At the junior level, students analyze the effects of mechanical loading on differentiation of mesenchymal stem cells in a human physiology course (BME 301). Students will use concepts of solid and fluid mechanics in describing ideal stress and strain conditions for developing engineered tissues. Diffusion and mass transport, as well surface and polymer engineering concepts for tissue scaffolds are presented in TE/BME 466, Polymer Biomaterials Engineering. Students in the senior level biomechanics class learn different constitutive models for both hard and soft tissues, then take measurements on and model biological materials that have elastic and a visco-elastic responses. All three courses address the effects of local stresses on cellular differentiation and tissue formation and organization, and require integration of basic engineering concepts with cell physiology and molecular biology. The authors will present their strategies for integration of these concepts and discuss the ways in which students meet ABET criteria and the professional component.

Biomedical Engineering Applications

In our Biomedical Engineering Applications (BAE 382) course[*], we are bringing mechanical engineering to life by analyzing the effects of mechanical loading on human mesenchymal stem cell differentiation. Mesenchymal stem cells are multipotent, adult stem cells that have the capability to differentiate into a variety of cells comprising skeletal tissue. Work in Dr. Loboa's previous laboratory showed that mesenchymal tissue differentiation could be guided by the mechanical environment to which the mesenchymal tissue was exposed. Specifically, low levels of cyclic hydrostatic stress and tensile strain allow for bone formation, high hydrostatic pressure

[*] This material will be covered in the future in BME 301, Human Physiology for Engineers

leads to cartilage formation, high tensile strain to fibrous tissue formation, and a combination of both high hydrostatic pressure and high tensile strain to fibrocartilage formation[1, 2, 3]. Dr. Loboa now focuses on bringing these tissue-level concepts to the cell level and provides the students in her classroom with an opportunity to test these concepts themselves.

In BAE 382, our students obtain a thorough introduction to the field of biomedical engineering. Topics include biomedical sensors, biomaterials, bioelectricity, bioinstrumentation, tissue engineering, imaging modalities, signal processing, and other subspecialties in the field. However, in addition to being introduced to the theory involved with these subjects, the students also participate in a major team project that allows them to put some of the theory they learn into practice. For their project, students are split into teams of 3 or 4 individuals. After being introduced to the major principles associated with the mechanobiology of mesenchymal tissue differentiation, the students are asked to perform research to determine the optimal tensile strain, duration of strain, and other factors to best promote the differentiation of mesenchymal stem cells down an osteogenic (bone forming) pathway. They provide a preliminary report in the form of an "Introduction" for a major peer-reviewed journal article that provides a thorough background and analysis of why they chose the mechanical loading protocol they did. They then discuss their team findings as a class and have an interactive analysis of their protocols. At this point, they break into their teams again and implement specific tensile strain protocols in the Cell Mechanics Laboratory that trigger either bone or fibrous tissue formation. Their experiments run for two weeks and are concluded with a team presentation and a project report in the form of a journal article discussing their major findings.

This project gives students the opportunity to apply mechanical engineering theory to tissue engineering practice (ABET criteria 3.a., 3.b., 3.c.), to work as a team, to present their results professionally both verbally and in writing (ABET criterion 3.g.), and to make decisions about how best to proceed to achieve desired results prior to performing experiments in the laboratory.

Polymer Biomaterials Engineering

At the completion of TE 466, Polymer Biomaterials Engineering, students are expected to be able to:

1. Identify polymeric biomaterials, describe the properties of different types of polymeric biomaterials, explain those properties based on the chemical composition and structure of the polymer, identify material properties which may affect biocompatibility and explain those effects, provide examples of surface modification techniques that improve biocompatibility, and describe surface analysis techniques. (ABET criterion 3.a.)
2. Describe a number of different polymeric biomaterials in use today, and their primary functions. Select polymeric materials suitable for desired implant specifications, and justify selection based on biocompatibility, durability, and mechanical properties. (ABET criteria 3.a., 3.e., 3.j.)
3. Work on a multidisciplinary team to either design and produce a polymer implant or tissue scaffold, or modify a polymer biomaterial or tissue scaffold. Characterize mechanical properties, biocompatibility, surface chemistry and morphology. Present this work to a group of scientists and engineers. (ABET criteria 3.a., 3.b., 3.c., 3.d., 3.f., 3.g., 3.h., 3.i., 3.j., 3.k.)

The students in this course are either biomedical engineering or textile engineering seniors. Students are first introduced to important concepts in polymer science and engineering, including polymer synthesis, polymer structure/property relationships (including rubbery elasticity), and polymer transitions. The text used for this introduction to polymer engineering is *Fundamental Principles of Polymeric Materials for Practicing Engineers* (Stephen L. Rosen), chapters 1 – 13. Lectures are supplemented with problem-based learning activities and in-class demonstrations. Students read about polymer processing and see a demonstration of fiber extrusion at the College of Textiles at NC State. Students are asked to do additional readings on polymer viscoelasticity, rubbery elasticity, and mechanical properties, and are asked to identify and explain methods used in research papers to study polymer biomaterials. Polymer gel formation and properties are reviewed. Chapter 22 from *Principles of Tissue Engineering* (Lanza, Langer and Vacanti) is used as a reading for resorbable polymers. There are several lectures on surface modification techniques, including gas plasma etching (with a demo) and self-assembled monolayers. The interface between living and non-living systems is a major topic in the course (ABET criterion 8) (Chapters 18, 19, *Principles of Tissue Engineering*).

The culmination of the learning experience is a multidisciplinary team project that allows students to synthesize and apply materials engineering and cellular biology concepts to the selection of polymers for biomaterials applications, in particular, tissue engineering scaffolds. The project incorporates both materials design/treatment and characterization (physical, chemical, mechanical), and cell culture in our new Tissue Engineering Teaching Laboratory. In the first year, students investigated cell adhesion to plasma-treated and plasma-treated, protein coated substrates. Next year, projects will include three-dimensional tissue cultures (in gels or on substrates). Mechanical properties of the tissue cultures will be measured by a combination of rheological and dynamic mechanical testing. New course materials to support the project will include a chapter on diffusion through polymers, and more extensive coverage of polymer viscoelasticity.

Biomechanics

An important aspect of tissue engineering is an understanding of the complex mechanical loads that an engineered tissue will have to endure if it is to adequately replace a natural biological tissue. This is particularly true for those tissues that perform a structural role.

In BME 441, a senior level biomechanics class, students learn how to calculate the loading on a tissue and are introduced to the various constitutive models that are used to describe the mechanical responses of biological tissues (ABET criteria 3.b., 3.e., 8). Students also get hands-on lab experience manipulating tissues and testing their material properties. Thus students develop both a theoretical and practical appreciation of the complexity of biological tissues.

Students begin the semester with a dissection of a canine knee joint performing both a gross and microscopic analysis of the various structural tissues. This experience gives students an important hands-on look at the materials that they will be studying and allows them to see the dimensions and the physical relationships between the different tissues that make up the knee joint.

In later labs students harvest bone tissue, anterior and posterior cruciate ligaments, and cartilage tissue from animal parts obtained from a local slaughterhouse in order perform mechanical property tests. This exposes students to the inherent difficulties in collecting, handling, measuring, and testing biological materials and gives them an appreciation of the complex material behavior that normal tissues exhibit, and that their replacements should mimic. Students must fit their experimental data to various theoretical constitutive models including elastic, viscoelastic or biphasic models. Lab write-ups are in the form of short journal articles to introduce students to accepted methods of reporting their results (ABET criterion 3.g.).

Bibliography

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