Teaching
A GRADUATE-LEVEL COURSE IN TISSUE ENGINEERING

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What goes into teaching a tissue engineering course in a chemical engineering or bioengineering department? Developing any new course presents numerous challenges such as topics to cover, textbook selection, and types of assignments to give. Additionally, in an area such as tissue engineering where the technology is constantly evolving, the course must stay current on cutting-edge research. With the increasing demand for improved healthcare, bio-focused fields such as tissue engineering have gathered increased attention. We surveyed 80 universities across the country, and found that at least 40 universities currently offer a course in tissue engineering. Of the 20 universities that comprise the top-10 lists of chemical engineering and bioengineering graduate programs from the 2006 *US News & World Report* survey, 16 currently offer a tissue engineering course. Many courses are offered by the chemical engineering department, although most are taught in the growing number of bioengineering/biomedical engineering departments across the country.

As more faculty with tissue engineering expertise begin their academic careers, the number of institutions with tissue engineering courses will likely increase. Furthermore, existing "bio" faculty generally familiar with tissue engineering may develop an interest in creating a tissue engineering course, or perhaps incorporate a tissue engineering component into a broader engineering course. This article, containing examples and insights from our experiences teaching tissue engineering at the University of Kansas and the University of Michigan-Ann Arbor, aims to serve as a guide both to those developing a new course in tissue engineering and those

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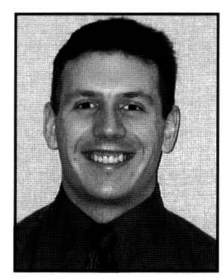

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looking for ideas to supplement an existing tissue engineering course. We will discuss key administrative details, such as textbook selection, class level, prerequisites, and types of assignments and exams, as well as course curricula. Moreover, we will offer suggestions for incorporating quantitative material into the course.

TEXTBOOK AND READING SELECTIONS

Selection of textbooks and/or reference reading material presents a difficult task for this course, due to the rapidly changing state of tissue engineering technology and the number of choices available. One good option is to choose a large edited book, which can offer an ample volume of information on a broad variety of topics.[1-5] Other books offer more focus, which may be useful to instructors with a given expertise or to refer students to a focused topic.[6-10]

Alternatively, one may choose a textbook written entirely by the same author(s), which offers continuity between chapters in the traditional style of a course textbook. We are aware of three such textbooks written in the past couple of years.[11-13] In fact, textbooks are now available that include homework problems,[12, 13] which can reduce the amount of time the instructor spends on creating homework sets.

Rather than choose any single book, some instructors may decide to assign select chapters from a combination of these texts and/or supplement them with chapters from reference texts and journal articles about current advances in tissue engineering. This approach exposes the students to the basic concepts in engineering (*e.g.*, transport, materials science, mechanics) along with biochemistry and cell biology. It also introduces students to contemporary strategies and issues in the field.

Whatever type of reading material the instructor chooses, however, we highly recommend that additional books on select subjects be suggested as optional, recommended, or on reserve. Related-reading topics of special importance include basic and cell biology. Depending on the course focus, literature on immunobiology, polymer science, biomechanics, and biomaterials could also be suggested for students who need more background in certain areas or who wish to read further into a particular area of interest.

FURTHER READING

- **Background**
  - General texts on tissue engineering[1-7]
- **Cell biology**[8]
  - Physiology[9]
- **Chemical signals**
  - Kinetics and transport[10,11]
  - Chemotaxis[12]
- **Mechanical signals**[13]
  - Single-cell mechanics[14-22]
  - Viscoelasticity[23-26]
- **Stem cells**[27-32]
  - Embryonic stem cells[33-37]
- **Scaffolds**[5, 7, 38-40]
  - Hydrogels[41]
- **Bioreactors**[42]
  - Perfusion[43-50]
  - Rotating wall[51-53]
- **Engineering of Specific Tissues**
  - Skin[54, 55]
  - Cartilage[6, 56-59]
  - Bone[6, 56, 60-62]
  - Kidney[63]

Figure 1. *Abbreviated example of a "Further Reading" supplement to distribute to students. A bibliography of corresponding references would follow.*

This approach will serve the potential educational diversity of the students: Those from chemical or mechanical engineering may need a stronger understanding of biology concepts, and vice versa for science students. In this way, the instructor can foster learning outside the classroom (thereby encouraging lifelong learning), *and* prevent covering topics in class that some portion of the student population has learned prior to the course. A strategy one of us has used is to compile a "further reading" list, with references numbered throughout the outline as in a journal article (Figure 1). These references include texts as well as several journal articles, and are updated with every iteration of the course. The advantage of this format is that it provides a resource to those students interested in learning more about specific topics, whether for their research, course projects, or sheer curiosity. It preempts the inevitable question, "Can you recommend a book or some articles about . . . ?"

In summary, we recommend instructors be aware of all available options. Every instructor will choose a format that best fits his or her course design, whether that means using a conglomeration of selected sections of various texts given as handouts, a large edited volume, or a textbook with homework problems, etc. In any event, it stands to reason that each approach would benefit from supplementing with optional or reserved reference materials and perhaps a further reading list.

COURSE LEVEL AND PREREQUISITES

A course in tissue engineering is often intended to be a graduate-level course, which can be open to advanced junior- and senior-level undergraduates. We feel that in an area such as tissue engineering, which is perpetually in a state of flux, the best way to teach is by focusing a major portion of the class on researching the current literature — a method more amenable to a graduate-level course.

Tissue engineering can certainly be tailored to an undergraduate curriculum, which a few universities offer (typically as an earlier version of the graduate-level tissue engineering course). Likewise, junior and senior undergraduates with a solid background of engineering and biology classes can be permitted to enroll in the graduate course.

Prerequisites may be minimal, as this course can appeal to a broad student audience. Students outside of engineering, however, may not be prepared for the quantitative rigor of the course, so it may be prudent to at least require prior coursework in differential equations. Moreover, some instructors may choose to require bioscience courses to ensure a basic understanding of biochemistry and cell biology among those taking the course. At the University of Kansas, we require only senior/graduate standing in engineering or instructor permission. At the University of Michigan-Ann Arbor, we require biochemistry and another upper-level biology or biotechnology course and senior standing.

COURSE CURRICULUM

Selecting pertinent topics for a course that comprehensively covers all relevant aspects of tissue engineering is a challenging and sometimes overwhelming task. While tissue engineering courses will vary from university to university, some common themes define the course, and we believe these constitute a set of "required" topics. Table 1 provides, in random order, specific topics to cover that fall under the umbrella of required discussion; also provided are additional topics that are commonly covered and can be chosen based on instructor expertise and available time in the course. Inevitably, debate will surround any discussion of required versus optional topics, as is presented here. Of course, we realize that arguments could be made for moving certain items from core to supplemental, or for including additional suggested topics. These topic designations are merely our best suggestions based on our own experience and on surveying tissue engineering curricula at various other universities; a brief explanation is provided for each topic we have designated as required. We recognize that the list of supplemental topics is not all-inclusive, nor should it be, for the sake of brevity.

At minimum, the instructor should introduce students to the three main components used to create tissue-engineered constructs, often referred to as "the tissue engineering triad" — cells, signals, and scaffolds. All other concepts can subsequently build upon this foundation.

Cells *Cell sources can be discussed from a few perspectives, namely autologous versus nonautologous sources and stem cells versus differentiated cells. Of course, stem-cell discussion can be separated into discussion of embryonic and extraembryonic cells compared to adult stem cells.*

Signals *Discussing cell signaling provides an excellent opportunity for integrating quantitative material, covering both mechanical and chemical signals. For mechanical signals, mechanotransduction at the single-cell level can be addressed, including integrin receptors and ranging all the way up to large-scale mechanical-stimulation bioreactors. Discussion of chemical signals is an excellent way for bioengineering and chemical engineering to incorporate transport and kinetics equations, including controlled-release applications. Transport equations can be expanded upon with a mathematical description of chemotaxis of cells toward a chemical signal[14] and transport of nutrients through the blood and tissue.*

Scaffolds *Although the depth of the course related to scaffolds will vary from instructor to instructor, certain central themes should be covered, including the components,*

TABLE 1
Suggested Topics To Be Covered in Every Tissue Engineering Course (Core) and Possible Additional Topics to Include Based on Instructor Expertise (Supplemental)

SUGGESTED CORE TOPICS	Tissue Engineering Triad	Cell sources	
		Cell signaling	Chemical
			Mechanical
		Scaffolds	
	Immune response, biocompatibility, and associated strategies		
	Structure/function of native tissue		
	Tissue engineering strategies for specific tissues		
	Tissue engineering practice	Equipment Cost Design of experiments	
SUGGESTED SUPPLEMENTAL TOPICS	Stem cells		
	Cell culture, sterile technique		
	Gene therapy, drug delivery		
	Tissue repair, remodeling, angiogenesis		
	Bioreactors		
	Construct validation	Mechanical testing Quantitative biochemical analysis Histology/immunohistochemistry	
	Ethical issues		
	FDA regulations and patents		

> *structure, and function of the extracellular matrix, natural and synthetic scaffolds, and comparisons between these matrices along with modern fabrication and seeding techniques.*

Furthermore, immune response and biocompatibility are central to the success of any implanted tissue, as any transplant surgeon would attest. Therefore, the instructor needs to instill student awareness of these issues, impart understanding of the basic underlying principles, and expose students to strategies to overcome potential problems (*e.g.*, autologous cells, immunosuppression, immunoisolation, reduction of protein adsorption, and HLA tissue typing). Structure and function of native tissues is a crucial topic, as native-tissue properties serve as the design criteria for tissue engineering efforts. Basic information on the extracellular matrix would be relevant, as would mechanical properties of musculoskeletal tissues. Every course should highlight select tissues, which can be done by the instructor (in which case recent review articles are quite useful) or by students in group-project presentations to the class (discussed later). Discussions of select tissues and the current tissue engineering strategies for these tissues show the students how all the various concepts are integrated (*e.g.*, cells, signals, scaffolds, and immune response) and how the elements can be applied for real-world use.

Finally, in the spirit of balancing theory and practice — providing the link between concept and application desired in engineering education — we would like to offer a few strategies to address tissue engineering practice. A strategy we have employed is to briefly cover the function and cost of the major pieces of equipment in a tissue engineering laboratory (*e.g.*, biosafety cabinets, incubators, autoclave, inverted microscope, cryostat, plate readers, centrifuge). An excellent follow-up to this discussion is a class tour of an actual tissue-culture facility, which the students enjoy. In our experience, this serves to create a tangible and practical understanding of what is involved in tissue engineering, as it helps to paint a mental picture of the work being done in the articles the students read. Time and resources permitting, a laboratory component may also be useful if an equivalent component of an existing laboratory course is not already offered. Another practical application is experimental design, in which students can learn to determine sample sizes, calculate the amount of growth factor to buy, and so forth.

In addition to these topics, contemporary information is crucial to the success of the course and should be incorporated into each topic of the course whenever possible. The instructor should follow topics in the current literature and those in the political arena and bring them to class for discussion. Class discussions on ethical and political topics such as embryonic stem-cell research policy, gene therapy, and cloning — if moderated carefully and appropriately — can raise the students' level of interest in the class *and* expose them to the controversies surrounding advancements in medical treatments. Assignments directed at contemporary literature will also serve to familiarize students with the latest breakthroughs in their areas of interest.

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Class discussions also help facilitate and promote new exercises in active learning — a style of learning increasingly incorporated into engineering courses. In active learning, students are encouraged to interact with the instructor and/or each other throughout or at certain times in the lecture via class exercises and discussions. The benefits of active learning include increased student awareness and interest, immediate feedback of student comprehension of the material, and increased understanding of the material. For a tissue engineering course, the instructor may begin adding active learning elements into the lecture using the ethical discussions mentioned above.

An exercise we used at the University of Michigan-Ann Arbor was a discussion of skin-tissue engineering strategies. Before we discussed it as a class, students were asked to chat in small groups for five or 10 minutes and come up with four or five key design considerations for creating a tissue-engineered skin construct. In another example, the class was asked to list the pros and cons of different bioreactors and mechanical-conditioning devices. This approach engages students and allows them to reflect on newly presented lecture material and think critically about its implications. At the University of Kansas, we discussed the ethical considerations of embryonic stem-cell research after students became informed on the topic via lectures and outside reading. The students enjoy participating and it helps break up long lecture periods as well, so these discussions should often be distributed throughout the lecture period.

If the instructor wishes to incorporate more quantitative exercises, he or she may present a conceptual problem based on a governing equation. For example, we asked students which geometry provides the best transport to cells seeded inside immunoisolated devices: slab, cylinder, or sphere. Students were asked to first solve the problem individually and then in groups, since peer interaction can improve student comprehension. In this way, the instructor can gain feedback on student understanding by either polling the students prior to discussion or by listening in on group discussions about the solution. One drawback to active-learning exercises is that they demand significant portions of lecture time, which may necessitate that students be required to study any uncovered lecture material outside of class.

COURSE ASSIGNMENTS AND EXAMS

To complement the course material, an instructor for a tissue engineering course must also decide whether to offer assignments, and if so, what types of assignments should be given. The purpose of assignments is to encourage students to review their notes, gain comprehension of basic concepts and key topics, prepare for exams, and learn about the latest technology. We have accomplished this objective by assigning a variety of tasks as needed, such as homework problems, literature critiques, NIH-style proposals, and quizzes and/or exams.

Occasional quizzes covering lecture material and required readings help ensure understanding of the material and prepare for exams. Homework assignments can draw from textbook problems, topics covered in class, and/or literature reviews and article critiques; they can emphasize quantitative problem-solving skills, practical application of concepts, and/or critical-thinking skills. Literature-critique assignments can serve as a means to keep the course current by requiring students to prepare a short presentation (10-15 minutes) on a newsworthy tissue engineering topic of their choice. To develop students' ability to review and critique the literature and use the concepts learned in class to create a novel research plan, the instructor may choose to assign a semester-long NIH-style proposal assignment, which will be discussed later. Finally, in light of the fact that this *is* an engineering course, effort should be made to include a significant quantitative component that can be reflected in the assignments and in the exams — an issue we address in the following section.

MAKING TISSUE ENGINEERING A QUANTITATIVE COURSE

One of the most difficult tasks in teaching a course in tissue engineering is adhering to the expectation that a graduate-level course in chemical engineering (or *any* engineering discipline) should be highly quantitative. One strategy to add more quantitative weight to the course is to assign more points to quantitative homework problems and to quantitative material on exams. Another is to include a greater proportion of quantitative problems on a given assignment. Of course, the instructor should make these strategies exceedingly clear to the students and adequately illustrate example problems in the lectures. As engineering students, they will tend to respect and even welcome this policy. It is entirely feasible to write a fair exam in this course that is more than 50 percent quantitative in point distribution. The topics listed in Table 2, some of which were mentioned earlier, lend nicely to quantitative evaluation.

Many forms of traditional engineering problems can be incorporated into a tissue engineering course to reinforce basic concepts, introduce advanced material, and demonstrate practical applications. Chemical engineering principles can be applied to discussions of signal diffusion, chemotaxis, controlled release, and receptor-ligand interactions. Moreover, we can demonstrate to students that an understanding of the equations can lead to a practical understanding. For example, the mass transport equation applies to addressing nutrient- and waste-transport limitations (*e.g.*, a rotating-wall bioreactor increases concentration gradient and hence driving force; a direct-perfusion bioreactor introduces a convection term). Likewise, single-cell mechanics and viscoelasticity are great ways to keep the mechanical engineers in the class entertained as well as provide a little variety for the chemical (and other) engineers. Space limitations prevent exploration of either of these topics in depth, but a review of key concepts and methods provides useful information and a refreshing change of pace while lending more quantitative material to the course. Such a review can also reinforce the multidisciplinary nature of the field.

Other quantitative material may be drawn directly from aspects of the tissue engineering triad, particularly with regard to cells and scaffolds. The compartmental model for differentiation provides an opportunity for students to use the software of their choice (*e.g.*, Matlab, Maple, Mathcad) to solve a series of ordinary-differential equations to quantitatively evaluate and conceptually understand the effects of varying self-renewal rates, initial cell numbers, and growth rates. While cell migration is enormously complex and actively studied, important parameters can be distilled for students, such as performing calculations to determine the random-motility coefficient, persistence time, and root-mean-square migration speed. Calculations for scaffolds can range from simple molecular-weight calculations to more complex calculations associated with polymer science, drug delivery, and scaffold development. Another quantitative aspect not listed in Table 2 is design of experiment calculations, *i.e.*, teaching students to make calculations that would be typical in the early stages of an experiment. For example, have them determine a safe but conservative margin of error for what is needed when ordering expensive biochemicals (*e.g.*, growth factors and antibodies) and accounting for statistical significance.

It should be noted that although we have presented a number of alternatives that we have used to make a tissue engineering course more quantitative, it will be beneficial to continue to strengthen the quantitative aspects of this engineering course.

SEMESTER PROJECT

The semester project is arguably the single most important component of the course. A common and successful strategy has been to make students prepare a research plan based on a literature search in a given area of interest. This project distinguishes the course as a graduate-level course *and* serves as a crucial means to educate students in contemporary tissue engineering methodology. Moreover, it will introduce many students to conducting literature searches, learning experimental techniques and assessments, and formulating a plan of research — facilitating their transition to a graduate-student mentality. The semester project is an exercise in problem-based learning (PBL), which is a forum for students to actively engage a problem as a group and ultimately further develop skills to become independent and lifelong learners.[20] Fung[21] presents one possible sequence in a bioengineering class project that instructors may find useful, where innovative thinking is the basis of the project.

In our classes, we place students in groups of three or four and require them to prepare a hypothesis-driven, NIH-style grant proposal. The literature search provides the background information from which the students critique current approaches, identify a need for new technology, formulate a hypothesis and supporting aims, and argue the feasibility of methods and choice of operating parameters. In addition to imparting technical knowledge, this project reinforces the importance of developing strong teamwork skills. The projects are evaluated by criteria of the instructor's discretion, with weight given to originality of the idea, quality of the background research, and logical organization of the research design.

TABLE 2
Selected Quantitative Topics in Our Tissue Engineering Courses with Example Equations

Topic	Example Equation	Explanation
Diffusion of signals[14, 15]	$\frac{\partial c}{\partial t}=D\nabla^2 c-\nabla\cdot(\vec{v}c)+P$	Standard macroscopic species balance
Chemotaxis[14]	$\frac{\partial n}{\partial t}=\mu\nabla^2 n-\chi(\nabla n\cdot\nabla c+n\nabla^2 c)$	Constitutive equation with random motility and chemotaxis
Cell signaling	$\frac{\partial C}{\partial t}=k_f(R_T-C)\left(L_o-\frac{Cn}{N_{AV}}\right)-k_r C$	The rate of change of receptor ligand complexes on a cell
Single-cell mechanics[16]	$P_o-P_p=2T_c\left(\frac{1}{R_p}-\frac{1}{R_c}\right)$	Cortical tension from micropipette aspiration[10]
Viscoelasticity[17]	$\sigma(t)=E_R\varepsilon_o\left[1+\left(\frac{\tau_\sigma}{\tau_\varepsilon}-1\right)e^{-t/\tau_\varepsilon}\right]$	Stress relaxation profile from a step strain
Proliferation & differentiation[13]	$\frac{dx_i}{dt}=2(1-f_{i-1})\mu_{i-1}x_{i-1}+(2f_i-1)\mu_i x_i$	Compartmental model for differentiation
Cell migration[13, 18]	$\mu=\frac{1}{2}S^2P$	Motility coefficient in terms of RMS migration speed and persistence time
Scaffolds[19]	$M_W=\frac{\Sigma w_i M_i}{\Sigma w_i}=\frac{\Sigma N_i M_i^2}{\Sigma N_i M_i}$	Simple weight-average molecular weight of a polymer
Drug delivery	$\frac{dM}{dt}=\frac{2\pi hDK\Delta C}{\ln\left[\frac{r_o}{r_i}\right]}$	Drug release from a cylindrical polymeric reservoir device

In the spirit of practical education, the instructor may choose to ask that students adhere to NIH formats — using face pages, biosketches, and half-inch margins with single-space writing.

In addition, the instructor may choose to require some form of itemized budget, as is typically requested for an NIH grant. Asking students to identify and estimate the necessary personnel, travel, equipment, materials, (bio)chemical, and lab-supply expenses will foster comprehension and appreciation for the significant cost of scientific research. As with any course, the instructor should allot one or two class periods to introduce and follow-up on the project, as well as encourage (or require) the groups to meet with the instructor periodically to make sure they are on track. The project can be comprised of two parts: a written proposal and an in-class group presentation.

The following strategy is a combination of our approaches. During the oral presentation, the class critiques the presentation along with the instructor, both on format and content. Following the presentation, the presenting group leaves the room and the class discusses the strengths and weaknesses of the presentation. Each remaining student is required to turn in a one-page critical review of the proposal. The presenting group's written proposal is turned in on the same day as the oral presentation, graded by the instructor, and returned the next period. Then on the last day of class, a "resubmission" is turned in, which gives the group that presents first the most time to incorporate revisions and vice versa. The advantage to this approach is that the instructor has the opportunity to provide thorough, constructive criticisms, and the students have the opportunity to critically assess others' research plans, learn from these suggestions, and incorporate them into a solid final piece of work. As incentive to turn in quality work the first time, and to lend more flavor of reality to the proposal, groups that earn an "A" on their first submission are not required to resubmit — analogous to being funded the first time around. The criteria for earning an "A" is, of course, at the instructor's discretion, allowing you to decide which groups must resubmit.

CONCLUSIONS

A course in tissue engineering affords the instructor a great deal of flexibility, and will appeal to a broad range of students with diverse backgrounds. The heart and soul of the students' educational experience will come from completion of the semester project, supplemented with focus areas identified earlier, and strengths from the instructor's area of expertise. Several ways to bring a quantitative component into this course have been described, although certainly others exist that each instructor can bring to his or her classroom.

We wish our colleagues the best in their endeavors to develop or to continue and improve upon their tissue engineering courses. Have fun, and keep the class discussions lively.

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