Massachusetts Institute of Technology

Chemical-Biological Engineering Laboratory
Course 10.28
Syllabus fall 2016

Instructor-in-charge	**Teaching Assistants**	**CI Instructor**	**Industry Guest (OSIsoft)**
Dr. Jean-François Hamel Email: jhamel@mit.edu	Stephanie Doong Won Jun Jo Alexander Kendrick 1028-tas@mit.edu	Mary E. Caulfield Email: mcaulf@mit.edu	Dr. Erica Trump

Location
Meeting room: Room 66-0042 (the room facing the elevators of building 66, at **the sub-basement level**)
Laboratory: Room 66-0044 (adjacent to 66-0042)

Schedule
Term September 7 to December 14, 2016
1st class on Wednesday September 7th, 1:05 – 5:00 PM Room 66-0042

Number of Credits 15

Course Documents
There is no textbook but course materials and assignments will be available on MITx. Material will be posted on line and you are expected to do the assigned readings there. You will be given the link in week 1.

Required Materials
Please bring a laptop, a smart phone or digital camera, paper and pen. If you do not have a smart phone or digital camera, a Camcorder will be available to the class at all times. Safety glasses or side shields and a lab coat will be provided to you, a subject we will discuss on Day 1.

COURSE DESCRIPTION

This fall, course 10.28, the Chemical-Biological Engineering Laboratory, offer experiment-based projects in both Biochemical Engineering and Energy. You will have an opportunity to do hands-on, real-life, research combining techniques of biochemistry and chemical engineering and applying them to solving some of today's biggest global challenges. You will have a chance to put "principles into practice," using state-of-the-art equipment and software, including bioreactors, mass spectrometry and a software management tool that monitors real-time data and events in an integrated systems approach.

Technical component

In the course, you will participate in one of two microbial research projects: 1) a newly-developed project using mammalian cells (cultivation of IgG-producing CHO and a Programmable Robotic Bioreactor System and a novel microfluidics-based perfusion culture system), and 2) a microalgae (growth and CO_2 capture under chemotrophic

and phototrophic conditions) which is being used for growing lipids that can be used as fuel to replace oil that needs to be extracted from the ground and that adds long-stored carbon to the atmosphere. In this case, we can use oil who carbon was pulled from the atmosphere in the past month or two, helping with climate stabilization in the long-run.

In this course, new digital tools will be introduced to enhance learning opportunities, such as with Web-based applications for video peer reviewing, communication with external experts, and multimedia reporting.

The Course is open to ALL majors and all MIT-affiliated programs, with a prerequisite of one lab course (5.310 or 7.02) and biochemistry (5.07 or 7.05) (or equivalent). This course meets the elective requirement in the MIT Energy Studies Minor.

Individual writing component (part of the Communication Intensive program)

Your individual CI writing assignment will be based on **the evaluation of innovative technologies** you will use, and others that you handle in the lab (e.g., squared, accordion, and hexagonal reactors; rocked (Wave), air-lift, and rotating reactors; large-scale stainless-steel and miniaturized plastic reactors; gravity-based settlers, alternating tangential flow filtration, tangential-flow filtration, centrifugal, and microfluidics-based separators, online analytics (e.g., NIR-spectroscope, mass spectrometry, glucose analyzer) and real-time monitoring & control tools (e.g., the Pi software system, which will allow you to predict and display cell growth kinetics based on measured metabolic events (i.e., O_2 and glucose consumption rates and CO_2 production rate), in real time).

You will participate in self evaluating your work.

READINGS

There is no textbook. Reading materials will be posted on MITx and/or distributed during class.

COURSE OBJECTIVES

Students will gain knowledge on:

- Concepts of Chemical-Biological Engineering and Bioprocess Engineering, such as cell growth and product kinetics, oxygen transport, tuning process controllers, yield coefficients, carbon-mass balance, process scale-up, batch vs. continuous fermentation, traditional vs, single-se bioreactor, cell recovery by filtration, substrate and product quantification by HPLC, bioanalyzer, and protein assays
- Online analytical tools (e.g., mass spectrometry for off-gas) for studying cell metabolism (e.g., respiratory quotient)
- Varied biological platforms (i.e., yeast, Chinese Hamster Ovary cell, microalgae) important for applications in biotechnology, bioengineering, environmental and bioenergy research
- Real-time visualization tools for monitoring and estimating process parameters 24 h a day (e.g., cell concentration), while in lab or at home
- Working in teams and Project Management (with MS Project software)
- Addressing original research questions and designing experiments (DoE approach)
- Improving methodologies
- Producing unified research results through written and oral communications using multimedia tools

COURSE FORMAT

The Research Projects

In this course, you will learn how to design and conduct original experiments using important concepts and approaches common to the biotechnology and/or energy fields, such as batch and fed-batch, process control, design of experiment (DoE) methodology, continuous bioprocessing and real-time analysis and visualization of data. You will be able to monitor your results in the lab and remotely.

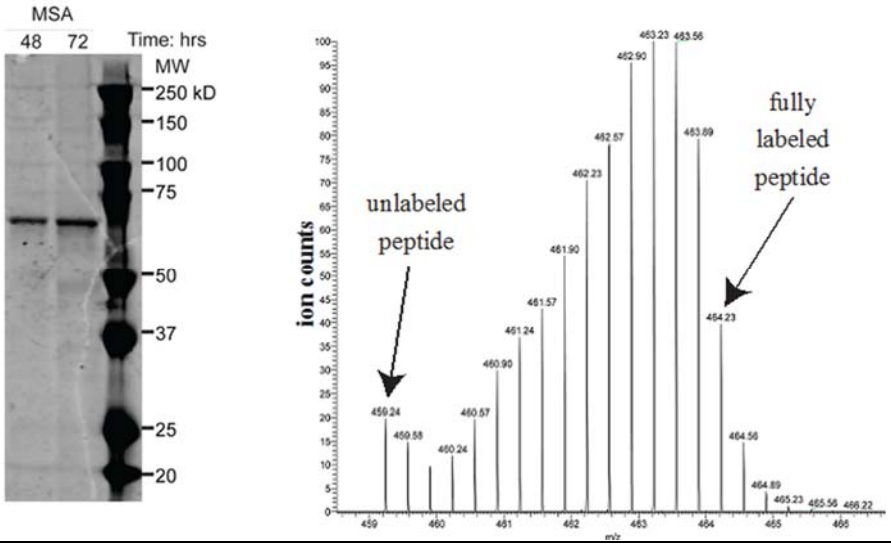
With faculty guidance, you will select specific original objectives, formulate your hypothesis, carry out, validate, and refine experimental procedures, design and execute experiments, and present results in oral and written form. The course strengthens analytical, communications, and cooperative problem-solving skills while teaching concepts such as reaction kinetics, cell metabolism, gas transport, yield and productivity, how to monitor O_2 consumption and CO_2 production in real-time, and product recovery.

More Information on the Biotech Project

The biotech project will be examining the production of ^{13}C-albumin from recombinant yeast *Pichia pastoris*, using glucose as the carbon source. This project seeks to generate a stable isotope-labeled albumin as a model for how to optimize the yield of a useful bioprocess product. Human serum albumin (HSA), a protein transporter for small molecules in blood, is used to treat trauma patients. It is normally produced from fractionation of blood, a method restricted by blood shortages and the pathogenic contamination of blood donations.

This project seeks an alternative path for a stable source of recombinant HSA (rHSA). Additionally, isotopically-labeled albumin is used as a research tool in the field of proteomics, however, the price for such albumin is prohibitively high (thousands of dollars per gram). This project will attempt to produce it at a much lower cost. Motivated by these two challenges, the project aims to maximize recombinant albumin production. Computationally, the teams working on this project will carry out a simple economic analysis to determine the production cost for making 13C-albumin, using a powerful and easy-to-use simulation software.

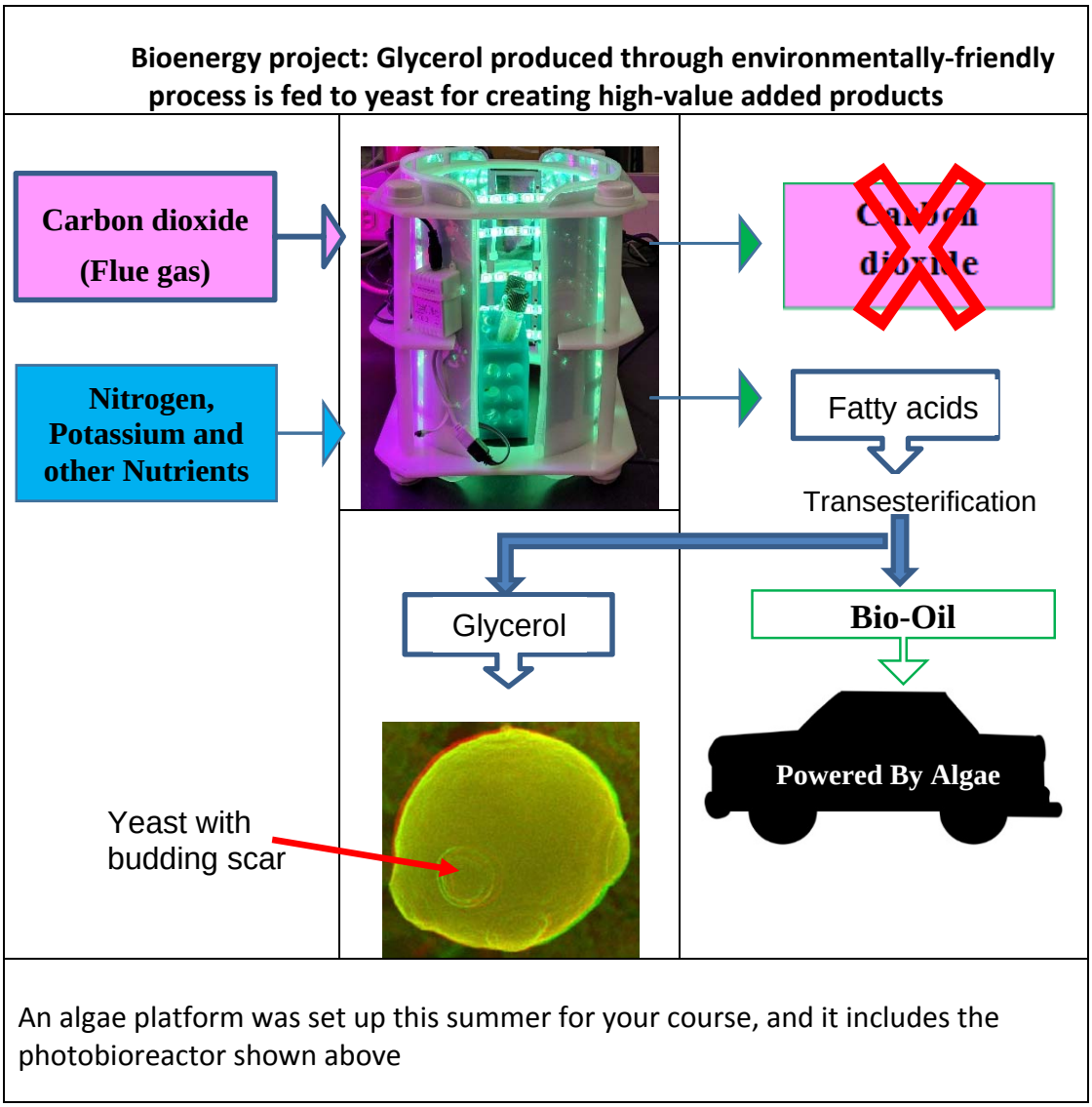
Biotechnology theme: Albumin for biomedicine and for cancer research at the Koch Center (once isotopically labeled)



SDS PAGE gel of culture supernatant from shake-flask cultures of *P. pastoris* expressing albumin (66 kDa) at indicated time points (left). Isotopic enrichment can subsequently be validated through MS of the purified protein (right)

More Information on the Bioenergy Project

The bioenergy project this year will be in the form of an environmentally-friendly process for creating high-added value products from waste carbon sources, such as glycerol. Glycerol is a waste product of biodiesel production process, and is in abundance. Making cells and albumin via cells grown on glycerol rather than glucose might be advantageous, but the data are lacking. In addition, because $^{13}C_3$-glycerol is 4 times more expensive to buy (on a mass basis) than $^{13}C_6$-glucose, it opens the possibility to develop a two-step process for making cells from glycerol and using them to make ^{13}C-albumin with ^{13}C-glucose. Computationally, the teams working on this project will carry out a simple economic analysis to determine the production cost for making albumin from glycerol in one step, and 13C-albumin in two steps, using a powerful and easy-to-use simulation software.



Both projects will be studied using Internet-connected bioprocess equipment (e.g., the bioreactor or fermenter) and powerful analytical tools, either online (e.g., mass spectrometry) or off-line (e.g., HPLC and biochemical analyzers).

REGULAR COURSE (10.28) SCHEDULE

wk	Date	Classroom or Lab activity - Students will:	Homework Assignment
1	9/7	1. Receive course overview (1 hour, in classroom) 2. Get oriented in the lab and receive the specific lab safety orientation (1 hour, including break) 3. Learn about the communication-intensive program Part I (1 h) 4. Participate in a project management session (1 h)	1. Watch videos on PI topics, experimental techniques and team building 2. Scan Reviews and select field of interest for TAP
	9/9	1. Revisit past experiments with PI Coresight (1 h) 2. Discover past ProcessBook displays & construct new one (1 h) 3. Visualize real-time data (on-going agitated reactor with water) with PI ProcessBook (1 h) 4. Prepare their first assignment through communication-intensive program Part II (1 h)	1. Construct a ProcessBook display for the bioreactor (start in class) 2. Study the Review paper for TAP and the articles for the main project 3. Complete the EHS training
2	9/12	1. Setup PI analyses for Reactor Volume and Total Glucose, where Total Glucose is calculated from the real-time values of substrate pump total (Analytics - Part I). 2. Initiate an experiment over 30 minutes: sample bioreactor every 5 minutes and measure glucose, by turn. 3. "Register" each sample, at the time that it is taken, using a dedicated Excel sheet. Reactor volume will be calculated in real-time based on manual data inputs.	1. Complete the bioreactor, ProcessBook display, in preparation for the mass transfer experiments in Week 3 2. Watch video on PI Analytics and short intro videos to real-time analytics in Biopharma (David Spiese, OSIsoft)
	9/14	1. Review glucose results and class results, w/ given PI Coresight 2. Compare calculations and measurements and identify potential discrepancies between them 3. Set up equations for cell productivity by OD (Analytics-Part II) 4. Learn about off-gas data to determine cell concentration, cell productivity, cell metabolism and carbon mass balance (Analytics – Part II)	
	9/16	1. Appreciate importance of DO control in the bioreactor and learn tuning of pH and DO controllers (2 h) 2. Learn Design of Experiments (2 h)	Review Datalink workbook and familiarize yourselves with the add-on
3	9/19	1. Learn to interface information from DataLink to Excel (1.5 h) 2. Learn mass transport (0.5 h)	Review video of basic lab techniques Use DataLink to access reactor data and validate analytical results
	9/21	1. Perform mass transfer experiments I (water, medium, no cell) 2. Compare you mass transfer data with class' data, in real time 3. Prepare medium	Use DataLink, data from at least three modes of bioreactor mass transfer operation Produce report
	9/23	Student Holiday: no class	Submit DoE of plate or flask study
4	9/26	1. Launch Pichia Bioscreen or shake-flask experiments I 2. Learn Cell Growth Kinetics	CI: Submit a copy of your second article and justify your choice of it.
	9/28	1. Perform mass transfer experiments II (with cells) 2. Compare your real-time mass transfer data with that of the class 3. Measure OD and calculate cell productivity 4. Initiate off-gas analysis study and determine cell concentration and cell productivity.	Access any data through DataLink, and compare them with yours to produce an original report
	9/30	Measure protein from Pichia flask study Determine dry cell weight (Pichia project)	

5	10/3	Prepare medium for Pichia flask study II and for bioreactor Opportunity for Pichia Bioscreen experiment II	Produce Bioscreen/flask report
	10/5	Launch flask study II Launch CHO cell study I Prepare bioreactor for autoclaving	
	10/7	Measure protein from Pichia flask study Determine dry cell weight (DCW) – Pichia project	Produce Bioscreen/flask report Submit batch bioreactor proposal
6	10/10	Columbus Day: no class	
	10/12 10/14	Launch Pichia batch bioreactor study Opportunity for Pichia Bioscreen experiment III Conclude CHO cell study I Prepare chemotrophic algae medium	CI: Submit Data Presentation and Analysis section (due on 10/12)
7	10/17 10/19 10/21	Measure protein and DCW – Pichia project Prepare medium and bioreactor for Pichia fed-batch study Opportunity for Pichia Bioscreen experiment IV Launch CHO cell study II Launch chemotrophic algae study	Produce batch bioreactor report Propose fed-batch bioreactor I CI : Submit First peer review (due on 10/21)
8	10/24 10/26 10/28	Launch Pichia bioreactor fed-batch study I Opportunity for Pichia Bioscreen experiment V Prepare medium for Pichia chemostat Conclude CHO cell study II	Design chemostat and perfusion studies
9	10/31 11/2 11/4	Opportunity for Pichia Bioscreen experiment VI Analyze samples from Pichia bioreactor fed-batch study I	
10	11/7 11/9	Launch Pichia chemostats I and II, and perfusion I	Propose fed-batch bioreactor II Study algae class data
	11/11	Veterans Day: no class	
11	11/14 11/16 11/18	Receive Orientation to Oral Presentations Launch Pichia bioreactor fed-batch study II Prepare chemotrophic and phototrophic media	CI: Submit TAP2 on 11/14 and ; peer review on 11/18
12	11/21 11/23	Launch phototrophic algae bioreactor study	
	11/25	Thanksgiving Holiday	
13	11/28 11/30 12/2	Rehearsals I Rehearsals II Rehearsals III	
14	12/5 12/7 12/9	Conclude phototrophic algae bioreactor study Lab Clean-up Final Presentations I	CI: Submit final TAP on 12/5
15	12/12 12/14	Final Presentations II Final Presentations III	

COURSE GRADING (still in progress)

This course requires active participation in all activities including experimental design, bench work, data analysis, and post lab discussion.

COURSE POLICIES AND REGULATIONS

Attendance

Both attendance and participation are extremely important for this class. Because of the nature of the experiments, make-up lab sessions cannot be offered. In fact because biological experiments cannot always fit in a 4-hour session, there is flexibility in the system for team members to distribute their weekly work between normal lab time and outside of it, provided that a staff member is present to supervise students, all team members are on board with the team schedule and it benefits the project. Any planned absence should be discussed openly with the team, communicated with the instructor and TAs, and will be accommodated, as much as possible. Teams should also have a plan in case of a sudden absence of a team member. In both cases, please alert the instructor and your team of your absence as soon as possible. Also, please plan to arrive on time as a courtesy to the class and to your team members.

Lab Conduct and Safety -

1. Food/drink only in Room 66-0042 (no lab coat or chemical should be brought in the room)
2. Lab coats, protective eyewear, and gloves must be worn at all times when conducting experiments in the laboratory; when working with the computers in the lab, only protective eyewear is required
3. Protective closed toed shoes must be worn in the laboratory
4. Use of smart phone, digital camera or video recorder is encouraged as part of documenting the lab work, and preparing the multimedia lab reports; **a Camcorder and a dedicated laptop PC for downloading files will be available to you at all times in lab, if you do not have a smart phone, camera or by preference.**
5. Since cell reception is poor or inexistent in the lab, you are welcome to use the landline telephone in 66-0042 to support your work in the lab (e.g., reaching team members, contacting vendors of equipment in the lab, reaching EHS, lab emergency). The phone number in 66-0042 is (617) 253-4573
6. If you need to communicate by phone or computer for personal reasons, please do this outside the lab

Disability Statement

It is the policy of MIT to accommodate students with disabilities, based on the Americans with Disabilities Act of 1990 (ADA) and the Rehabilitation Act of 1973.

For any questions, please contact the Instructor, Dr. Jean-François Hamel, at jhamel@mit.edu.

This year's course is being offered thanks to a grant from MIT's Energy Initiative and the Bechtel Foundation, donation of PI system and technical support from OSIsoft, and the loan of the Aquos interactive Board from SHARP.