Danmarks Tekniske Universitet
Department of Systems Biology
http://www.bio.dtu.dk/

27405 Cell Factories: Design, engineering and analysis

Language: English
Point (ECTS): 10
Course type: Advanced course
Taught under: Open University
Technological Specialisation Course, Chemical and Biochemical Engineering
Technological Specialization Course, Bioinformatics and Systems Biology
Technological Specialization course, Biotechnology

Schedule:
E4 DTU Time Block
Tuesdays, 13:00-17:00
Fridays, 8:00-12:00

Location: Campus Lyngby

Scope and form: Lectures, group exercises, seminars, and problem solving

Duration of Course: 13 weeks

Date of examination: TBA

Type of assessment: Oral examination
without preparing time - all exam questions are available approx. 2 weeks prior to
the exam, which counts 75%. Written report of a group assignment which counts
25%. Approval of written report is a prerequisite for participation in the exam.

Evaluation: 7 step scale, external examiner

Qualified Prerequisites: 27032 (Fermentation Technology) /27416 (Fermentation Processes),
Fundamental knowledge on basic principles of fermentation technology and
biotechnological products produced by microorganisms. Knowledge of the basic
quantitative elements, the underlying science, and the general concepts of
biotechnological processes. Knowledge of cellular metabolism.
Optional prerequisites:
28020 (Introduction to Chemical and Biochemical Engineering)
27611 (Introduction to Bioinformatics)

This is a Technical University of Denmark (DTU) course open to DIS students.
Please ensure you read the full details on taking external courses through DIS.
Cell Factories: Design, Engineering, and Analysis | DIS
General course objectives:
The aim of the course is to give the students a fundamental understanding of the interplay between the many different intracellular reactions in a cell factory, and especially how the fluxes through the different pathways are regulated. A special focus is given to pathways leading to industrially relevant products like primary metabolites, antibiotics, industrial enzymes, and pharmaceutical proteins. A central aspect of the course is to identify the optimal strategy for introducing directed genetic changes in the microorganisms with the aim of obtaining better production strains. Analysis of the interaction between different cellular reactions is a central element in the course, and tools for systems level strain characterization and design will be described.

Learning objectives:
A student who has met the objectives of the course will be able to:
- Describe the synthesis and analysis elements of metabolic engineering and how they interact.
- Describe the concepts behind metabolic flux analysis, and discuss advantages and disadvantages with different methods.
- Describe the principles of transcriptome, proteome and metabolome analysis and how data from these analyses can be applied in cell factory engineering.
- Describe how one constructs a genome-scale metabolic model.
- Discuss the application of genome-scale models in design of optimal cell factories.
- Design an experimental strategy for obtaining data to be used in cell factory design.
- Design a cell factory optimization strategy based on metabolic knowledge, quantitative physiology and omics data.
- Write a scientific report and give an oral presentation on a real-life cell factory engineering example.

Content:
The course gives an overview of the different elements of cell factory design with a number of examples on how directed genetic modification have been introduced with the aim of obtaining improved strains for production of different compounds in the bioindustry. There is especially focus on the different tools of cell factory design.

The course covers the following topics:
- Introduction to cell factory design.
- Overview of biochemical pathways.
- Regulation of pathways.
- Examples of cell factory design.
- Design of experiments for characterization of strains.
- Metabolic flux analysis: Theory and applications.
- Application of 13C-isotopes for quantification of metabolic fluxes.
- Genomics. Whole genome transcription analysis.
- Proteome analysis.
- Metabolome analysis.
- Methods for evaluation of omics data.
- Different case stories are used to illustrate the topics.

Students will work independently with examples and with a group task, which will be presented both orally and in a written report. In the group task, students are introduced to a real-life cell factory design case and are supposed to suggest innovative strain improvement strategies.

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**Remarks:**
The course is aimed at biotechnology students, but the course can also be taken by students with a chemical engineering background. There is a chance to carry out strategies suggested in the group assignment in practice in the 3-weeks course 27432.

**Responsible:**
Mikael Rørdam Andersen, Building 223, room 224

**Department:** 27 Department of Systems Biology

**Department involved:** 28 Department of Chemical Engineering

**Suggested Reading Material for Lectures:**

**Lecture 1 - INTRODUCTION**

(Article that gives an overview of different approaches used for construction and optimization of cell factories. Can be nice to skim through it now to get an overview, but several methods mentioned we will first talk about later in the course so do not worry if you do not get it all now. We will also get back to the article later in the course to look more specific at different examples given)

**Lecture 2 - METABOLISM**

*Comment: You are not expected to know all details about the different metabolic pathways. Focus on understanding the overall purpose of the metabolic pathways.*

Information about cellular metabolism may also be found in:

**RATES, YIELDS, MASS BALANCES**

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Lecture 3- METABOLIC FLUX ANALYSIS

Lecture 4- METABOLIC NETWORK ANALYSIS

Lecture 5 - Michaelis-Menten kinetics:
Villadsen et al 2011 (http://www.springerlink.com.globalproxy.cvt.dk/content/978-1-44199687-9/contents/ and in File sharing)
Read pp 215-220 (top)

Lecture 7 - Introduction to genome-scale models and network topology
The lecture of today will focus on the concept of rational design of microbial cell factories, specifically through the application of genome-scale networks. The mathematics and concepts for this is in effect an extension of the principles covered in Lecture 3. The review by Oberhardt et al. examines the reported uses of these models and provides a good overview of the organisms for which this type of models is available. In reading the reference, the text on “Category 4: Interrogation of multispecies relationships” may be skipped in this context.

Reading materials
2. Bernhard Ø. Palsson – Systems Biology – properties of reconstructed networks, Chapter 7: Topological properties (11 pages)

Lecture 8 -Reconstruction of genome-scale models
For this lecture we will approach how to reconstruct the metabolic networks in microorganisms with the ultimate result of generating a genome-scale metabolic model. Reference 1 is a general walk-through of the reconstruction process with a list of essential web-services at the end of the reference. This reference will be the main focus of the lecture. Reference 2 is a detailed protocol for how to produce a validated metabolic model, and is included here as an example of the practicalities of performing the reconstruction. While the introduction, Table 1 and Figure 1 should be studied in detail, the remainder of the reference can be read cursorily.

Reading materials

Lecture 10- Application of genome---scale models for insilico predictions

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Lecture 11 – Proteomics and its application in cell factory design

In this lecture we will cover the underlying principles for the large field of proteomics including gel based and gel free proteomics. The use of proteomics in cell factory design and analysis of cell factory performance is briefly touched, and will elaborated more in lecture 12 in combination with the field of metabolomics.

Proteomics has exploded as a research field in the last ten years with the application of more and more methods from the field of analytical chemistry. Earlier research was based upon two-dimensional gel electrophoresis of intact denatured proteins and identification of protein spots by extraction and Edman degradation (sequential digestion of N-terminal and chromatographic identification of the amino acids). Today, cutting edge proteomics is performed using fast HPLC coupled to super precise mass spectrometry. Since the full procedure does not lead to reproducible quantification, the determination of relative levels in different samples require co-analysis during mass spectrometry. Mass spectrometry identifies molecules based upon their molecular mass and charge, so co-analysis require that the masses of the two samples can be distinguished from each other. The article by Fang et al reviews these techniques.

The ultimate goal of proteomics is to identify and quantify all proteins in a cell, both for the unmodified form and for all additional protein forms containing post translational modifications. An equally important area of proteomics is the identification and extent of interactions between all these protein forms in vivo.

Reading materials


Lecture 13 Cell Factory Engineering- generic strategies and illustrative cases

Lecture 15- Transcriptomics and its application in cell factory engineering

Lecture 16- Omic data integration

In this lecture we will follow up on some of the examples of integrating multiple types of data to support functional genomics and metabolic engineering. Reference 1 (note the page numbers) gives an introduction to the discipline of data integration in this context. We will be shortly re-examining some of the articles from the earlier lectures as well as the examples of refs. 2 and 3.

Reading materials


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Lecture 24- Cell factories of the future
This Lecture will sum up on key concepts from the course, and attempt to look into the future. How does the cell factory of tomorrow look like? Is it even a cell? The reading material should be seen as a primer for the lecture and a recap of the previous statements from the course.

Reading materials