**AIM OF THE COURSE**

The aim of the course is to teach state of the art methods of quantitative metabolomics to industrial and academic research professionals (i.e. MSc, PhD). The focus is to gain insights into the complex metabolic control of central carbon metabolism and connected product formation pathways in industrial micro-organisms.

The course covers recent developments in rapid sampling methods, measurement techniques and modeling approaches for microbial systems. The first two days are mainly dedicated to experimental techniques, from steady-state analysis to stimulus response experiments. Proper sampling and sample handling procedures for reliable and reproducible metabolome analysis will be discussed and calculation exercises are performed. The main measurement techniques addressed are based on liquid and gas chromatographic separation, coupled to mass spectrometry.

The third and fourth day focus on theoretical and modeling aspects of Systems Biology. Approaches from network reconstruction, stoichiometric and thermodynamic network analysis and in-vivo kinetic modeling will be covered. $^{13}$C tracer methods will be discussed to increase the information content of stationary state as well as dynamic experiments.

Day five will be dedicated to future developments and advanced applications of quantitative metabolomics to tackle specific biological questions, whereby also other hierarchical levels of the cell will be taken into account.
COURSE DESCRIPTION
This one-week course is given in English and has intensive and long days. To ensure active participation by those attending, a combination of theoretical (lectures) and practical work (exercises and computer simulations) is offered. Some online preparatory materials will be given to facilitate all participants to have the same basic knowledge.

LECTURES
In the lectures, attention will be paid to the following themes:
• Rapid sampling and quantitative analysis
• Metabolite quantification and validation using Isotope Dilution Mass Spectrometry, IDMS
• Perturbation strategies
• Estimation of extra- and intracellular rates from experimental data
• Kinetic modeling and approaches to handle parameter identification problems
• Outlook and future developments

EXERCISES AND COMPUTER SIMULATIONS
Several exercises will be performed to familiarize the participants with the theory and practice and to illustrate the utility and utilization of quantitative metabolomics in modern biotechnology. IDMS calculations will be carried out using Microsoft Excel. Flux analysis and dynamic simulations are performed using the numerical computing environment MATLAB. Prior knowledge of MATLAB is needed - a tutorial for learning the required (basic) MATLAB knowledge will be sent prior to the course.

WHO SHOULD ATTEND?
This Advanced Course is aimed at participants from industry, universities and research institutions who want to update and extend their theoretical knowledge and practical insight in quantitative metabolomics and modeling.

The course is intended for postgraduates (MSc, PDEng, PhD), with a sound background in microbiology, microbial physiology, biotechnology, biochemistry or biochemical engineering, with an affinity to applied mathematics.

COURSE BOARD
Dr. Walter van Gulik
Systems Biology
Delft University of Technology
Delft, the Netherlands

Dr. Aljoscha Wahl
Systems Biology
Delft University of Technology
Delft, the Netherlands

COURSE COORDINATION
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LECTURERS
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Dr. Martin Pabst
Cell Systems Engineering, Proteomics
Delft University of Technology, the Netherlands

Prof. Bas Teusink
Vrije Universiteit Amsterdam
Systems Bioinformatics group (AIMMS)
Amsterdam, the Netherlands
PROGRAM

MONDAY 18 JUNE 2018
Theme: Rapid sampling and quantitative analytics
08:30 Registration
09:00 Short introduction on Surfaces and BioTech Delft
09:15 Outline of the course and introduction of participants
Walter van Gulik
09:45 Introduction to microbial metabolomics
Walter van Gulik
10:45 Rapid sampling for quantitative metabolomics
Walter van Gulik
12:30 Lunch
13:30 MS-technologies
Martin Pabst
14:15 Identification of compounds using high-mass-resolution GC-TOF-MS
Marco Oldiges
15:15 Understanding penicillin G production pathway using stimulus response strategy and targeted metabolite analysis by LC-MS/MS
Marco Oldiges
16:00 Understanding penicillin G production pathway using stimulus response strategy and targeted metabolite analysis by LC-MS/MS
Martin Pabst and Amit Deshmukh
16:45 NMR for metabolomics
Martin Pabst
17:30 Social drink and buffet

TUESDAY 19 JUNE 2018
Theme: Quantification and validation using isotope dilution mass spectrometry and perturbation and validation strategies
09:00 Development of quantitative analysis of metabolites using GC isotope dilution mass spectrometry
Aljoscha Wahl
10:00 Exercises: calculating concentrations from ID-MS data and validation of sampling and extraction protocols
Walter van Gulik and Martin Pabst
12:15 Lunch
13:45 Perturbation strategies for estimation of in-vivo kinetic properties of enzymes
Walter van Gulik
14:30 Thermodynamic validation of metabolite data
Aljoscha Wahl
15:30 Tackling cellular compartmentalization: application of sensor reactions
Walter van Gulik
16:15 Futile cycles during Penicillin production: mimic large scale on the bench using a feast/famine regime
Aljoscha Wahl
17:15 Introduction Matlab (optional)
Aljoscha Wahl
18:00 End of the day

WEDNESDAY 20 JUNE 2018
Theme: Estimation of extra- and intracellular rates from experimental data
09:00 Calculation of net conversion rates from reactor mass balances
Walter van Gulik
09:45 Analysis, validation and estimation of rates
Walter van Gulik
10:45 Introduction to metabolic flux analysis
Aljoscha Wahl
11:30 Computer exercises on metabolic flux analysis
Aljoscha Wahl
12:45 Lunch
13:30 Continuation
15:45 Steady state flux analysis using 13C labeling at isotopic transient states
Katharina Nöh
17:00 Computer demonstration/exercises on 13C isotopomer modeling
Aljoscha Wahl and Katharina Nöh
18:00 End of the day

FRIDAY 22 JUNE 2017
Theme: Outlook and future developments
09:30 Analytics in industry
Denise Jacobs
10:45 Regulation of metabolism: navigating between desired and fatal states
Bas Teusink
11:45 Lunch
13:30 How E. coli integrates growth rate regulation with amino acid and fatty acid anabolism
Greg Bokinsky
14:45 Imaging metabolites and metabolic pathways in cancer tissues
Liam McDonnell
15:45 Evaluation and Farwell Drink

THURSDAY 21 JUNE 2018
Theme: Kinetic modeling, parameter identification and visualization approaches
09:00 Steady state flux analysis using 13C labeling at isotopic transient states
Katharina Nöh
10:00 Setting up a kinetic model using mechanistic enzyme kinetics
Aljoscha Wahl
11:00 Computer exercise: kinetic ODE models
Aljoscha Wahl
12:45 Lunch
13:30 Continuation
14:30 Hybrid systems modelling approach for efficient dynamic flux estimation
Aljoscha Wahl
15:30 Model analysis and visualisation techniques
Katharina Nöh
16:15 Computer demonstration on model analysis and visualisation
Peter Droste
18:00 Canal Tour by Boat
19:00 Course Dinner

LOCATION
The course will be held at the Delft University of Technology
Department of Biotechnology
Van der Maasweg 9
2629 HZ Delft, The Netherlands
http://bt.tudelft.nl

ACCOMMODATION
Hotel accommodation can be arranged at your request addressed to biotechdelft@tudelft.nl.
BioTech Delft organises courses in biotechnology at postgraduate level. BioTech Delft closely cooperates with the department of Biotechnology of Delft University of Technology. Since its foundation, in 1987, BioTech Delft has very successfully organised various types of postdoctoral education.

Currently BioTech Delft offers various Advanced Courses given each year covering the multidisciplinary spectrum of biotechnology. The courses have a long track-record dating back to 1988.

- **Microbial Physiology and Fermentation Technology (1988)**
- **Downstream Processing (1989)**
- **Biocatalysis and Protein Engineering (1999)**
- **Environmental Biotechnology (1993)**
- **Genomics in Industrial Biotechnology (2005)**
- **Metabolomics for Microbial Systems Biology* (2010)**
- **Bioprocess Design** **(2014)**

* in partnership with Forschungzentrum Jülich
** in partnership with Wageningen University & Research

FURTHER INFORMATION

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