Biochemical Engineering

Bioprocess Technology
Our Vision

We build bridges between the “omics” sciences, process development and scale up for industrially relevant biopharmaceutical processes

Our Goal

Method development for efficient and scientifically based biopharmaceutical process development
Research Area Biochemical Engineering

Integrated Quality by Design Approach

Red Biotechnology
- On-line Monitoring of biomass, metabolites, internal components and recombinant protein
- direct and indirect determination of specific rates and Yields in Real Time
- Metabolic Modelling
- Transient experiments for quick derivation of Design Space

Integrated Bioproces Development

Process understanding across unit operations
- Quality by Design Studies on propagation of effects from fermentation to purification
- Debottleneck DSP
- Alternatives chromatography
- Strategies for optimized multiproduct facilities

CO₂ Fixation and Renewable Energy

Renewable Energy from Waste
- Biohydrogen and Biomethane production from Waste streams
- Strikthy Anaerobic Cultivations
- Quantitative bioprocess development

Straw Biorefinery

Development of an efficient, low temperature biomass fractionation process for the production of value-added chemicals and materials from annual plants.

Wood Decay and Wood Aging Processes

Biotechnology for Wood and Forest Industry

Enzymatic, biomimetic, or microbial treatment of wood materials or living plants.

Emission control

Bio-control

Function-alization

FTIR-microscopy to trace fungal wood decay processes on the subcellular level (10 µm)
Quantitative Bioprocess Development for Production of Biofuels and cocurrent CO₂ Fixation

Motivation

- CO₂ emissions are made responsible for climate change.
- Source of renewable energies (such as wind or solar energy) need to be made storeable.

Mission

- Development of a robust and economic competitive process for biofuels
- Using raw material from renewable energy sources
- Fixation of CO₂
- Prove the feasibility to use real emission gases

Methods and Results

On-line and off-line analytics as well as PAT are used for real time data exploitation

<table>
<thead>
<tr>
<th>H₂</th>
<th>CO₂</th>
<th>Integration</th>
<th>CH₄</th>
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Facultative and strict anaerobic bacteria

S. cerevisiae for bioethanol and concomitant CO₂ production

Automation & bioprocess control

Methanogenic Archaea convert H₂ and CO₂ to CH₄

Output

Our research focuses on:
- Technology development and integration of 2nd and 4th generation of biomass utilization
- Quantification and scale up of biohydrogen, bioethanol and biomethane production
- Comprehensive and quantitative process development aiming for industrial application

The technology will be very important in respect to the global carbon cycle and renewable energy production.
**Generic Tools for QbD, PAT and Bioprocess Identification**

**Motivation**

Quality by Design (QbD) is used to extract process knowledge and information from experimental data to reach process understanding. Quantitative robust variables must be derived for identification of critical process parameters (CPPs) for critical quality attributes (CQAs). Generic approaches must be provided to allow the paradigm change from empirical to science based bioprocess development.

**Mission**

Develop generic tools to apply the PAT/QbD approach to different cultures and bioprocess modes.

**Experimental Design**

- **Design of Experiments**
  - Identification of CCPs/CQAs
  - Risk based approach to identify non critical parameters
  - Definition of analytics: What signal quality is needed for which CCPs/CQAs?

**Data**

- **Real Time Measurements**
  - Off-gas
  - Feed rates, base consumption
  - In-line sensors: FT-MIR, capacitance
  - At-line: GC, Enzymatic Photometric

- **Morphology**
  - High throughput,
  - Automated light microscopy
  - x,y,z axis scanning
  - Feature extraction algorithms

**Information**

- **Data Mining**
  - Calculation of scale-independent specific rates and yields
  - Determination of morphologic key parameters

- **Soft Sensors**
  - Kinetic Models, Metabolic Analysis Observers
  - Calculation of non-measured quantities

**Knowledge**

- **Reconciliation**
  - Consistency check
  - Establishment of design space
  - Control strategies

**Output & Outlook**

- Extraction of process understanding in a real-time automated bioreactor setup
- Generic approach: extension to different cultures, bioprocess setups and culture modes
- Development of quality processes robust regarding quality and productivity
- Extrapolate Approach to dynamic process conditions: quicker and more exhaustive metabolic analysis
Biopharmaceutical Downstream Processing and Integrated Bioprocess Development

Introduction

The bottleneck for many biopharmaceutical production processes lies in the purification of the product by chromatography, as product titers will increase. Therefore R&D activities are needed to debottleneck the Downstream Process (DSP) by:

- understanding propagation of effects across the unit operations, employing Quality by Design (QbD) principles using Design of Experiments (DoE)
- development of alternative unit operations for purification, mainly for the capture step and strategies for optimization of the use of multiproduct facilities

Goals and activities

Process understanding across unit operations

By employing QbD principles, it is our goal to analyze and understand the effect of changed process parameters in the USP area on the resulting product quality attributes in the DSP area.

The variations of the different process parameters are carried out according to DoE. We thereby understand the propagation of the CPP to CQA relationships across unit operations. This allows the analysis of the whole process: from the cryo-tube to the purified and frozen protein.

Debottleneck DSP

Upstream Output Considerations (Titer g/L) for the next ten years in the biopharmaceutical industry

Due to the expected future high titers from optimized expression systems, we aim to establish new methods beyond chromatography such as

- crystallization
- precipitation
- membrane assisted Aqueous 2-phase systems (ATPS)
- membrane adsorber

Strategies for optimized multiproduct facilities

Integrated time & motion analysis tools allow the analysis of the rate limiting step for increased productivity in a given multiproduct facility.

Outlook

Biochemical Engineering is interdisciplinary. We need to look beyond the fermentation. The combination of all activities shown allow the determination of how to fit the process to facility or fit the facility to process.
We carry out

- Quantitative Strain Characterization
- Analysis of Physiological Regulations Responding to Stress conditions
- Metabolic Engineering
- Cell Modeling, e.g. Metabolic Flux Analysis
- Media Optimization using on-line decision making tools

We conduct

- Characterization & Development of On-line Monitoring Instruments
- Determination of On-line Measurement of Specific Compound

We investigate

- Innovative DoE strategies using dynamic process conditions
- Limits of the design space, such as maximum metabolic (intrinsic) rates and adaptation times, using on-line exploitation methods

We integrate

- Instruments and data analysis tools in ready made exploitation tools which are commercially available for the industry for efficient process development
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