Department of Mechanical Engineering
Technical University of Munich

Annual Report 2019

TUM Mechanical Engineering
Technik für Menschen

Biochemical Engineering

Industrial biotechnology

Industrial biotechnology ('white biotechnology') makes use of microorganisms or enzymes for the industrial production of chemicals like special and fine chemicals, building blocks for agricultural or pharmaceutical products, additives for manufacturing, as well as bulk chemicals and fuels. Renewable resources and CO_2 are the favored raw materials for industrial biotechnology. The Chair of Biochemical Engineering deals with all aspects of the technical use of biochemical reactions for industrial biotechnology. The research focus is on bioreactors and biocatalysis, as well as on (gas-) fermentation and isolation of bioproducts.

A new digitized bioprocess laboratory is under construction at the Institute of Biochemical Engineering for the knowledge-based automation and digitalization of bioprocess development in order to be able to drastically shorten development cycles in industrial biotechnology in the future (photo: Tobias Hase, TUM)

Bioreactors and digitalization

The effective generation of process information represents a major bottleneck in microbial process design and optimisation. An approach to overcome the necessity for a large number of time- and labour-consuming experiments is miniaturisation and parallelisation of stirred-tank reactors along with automation of process management and digitalization of bioprocess development.

Highlight

Experimental design, resource planning of the devices in the bioprocess laboratory and evaluation of the experimental results have so far only been carried out intuitively according to the level of education and individual knowledge of the respective scientist. Consequently, the objective of a new digitized bioprocess laboratory at the Institute of Biochemical Engineering is the use of intelligent software components for knowledge-based experimental design, for the procedural control of parallelised and automated laboratory experiments in real time and for on-line data evaluation, in order to be able to drastically shorten development cycles in bioprocess design in the future.

Projects

- Multi-parameter analytics in parallel bioreactors
- Automation of bioprocess development
- Digitalization of bioprocess development

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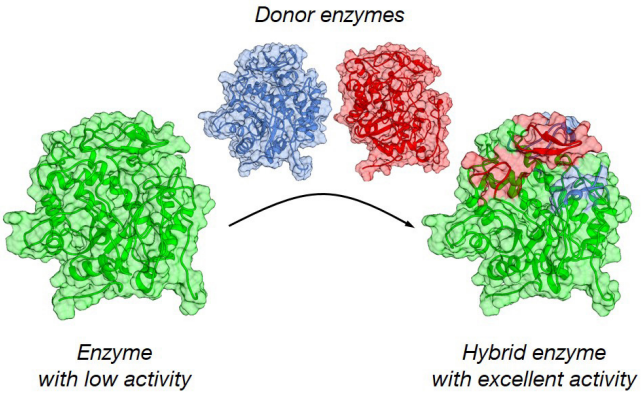
Biocatalysis

Great demands are placed on the optical purity of building-blocks for the production of pharmaceuticals. Due to the high natural selectivity of biocatalysts, biocatalysis appears to be a favorable method for the purpose of chiral syntheses. Major research interests are the development of new reaction engineering methods and devices to intensify whole cell biotransformations of hydrophobic, unstable and/or toxic substrates up to the technical scale.



Model of an enzyme useful for the stereoselective reduction of alkenes (colored in green) which was improved by rational exchange of loop regions (colored in red and blue) (copyright: Christoph Mähler, TUM)

Highlight
The activity of an industrially important enzyme isolated from a cyanobacterium which catalyzes the stereoselective reduction of alkenes was improved by a factor of 10 by rational exchange of loop regions of the protein which are supposed to interact with the electron transport metabolite nicotinamide adenine dinucleotide (NADH). A whole-cell biotransformation process was developed for efficient production of a chiral precursor useful for the synthesis of e.g. an anti-malaria drug.

Projects
- Biocatalytic conversion of D-galacturonic acid with recombinant *Saccharomyces cerevisiae*
- Cellular envelopes for multi-enzyme syntheses
- Asymmetric synthesis with optimised ene-reductases
- Production of terpenoid glucosides by recombinant *Escherichia coli*
- Oxidations with recombinant *Gluconobacter oxydans*

Fermentation

Making use of microorganisms for the production of chemicals from renewable resources is the core of industrial biotechnology. Reaction engineering analyses of metabolically optimized producer strains and metabolic analyses of microorganisms in production processes are necessary for efficient bio-production on an industrial scale.

Highlight
A new microbial production process was designed for the production of the aromatic amino acid L-tryptophan (dietary supplement for use as an antidepressant) from the byproduct of biodiesel production (glycerol) and ammonia making use of recombinant *Escherichia coli*.

Projects
- Population heterogeneity in industrial scale bioprocesses
- Metabolic control analyses of microbial production processes
- Production of aromatic amino acids with recombinant *Escherichia coli*
- Production of single-stranded DNA with recombinant *Escherichia coli*
- Reaction engineering analysis of recombinant *Aspergillus niger*

A fermentation process for the microbial production of L-tryptophan is studied on a 40 L-scale at the Institute of Biochemical Engineering (photo: Tobias Hase, TUM)

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Gas Fermentation

Special microorganisms are able to produce chemicals with carbon dioxide as the sole carbon source. Electrons may be supplied from sunlight, hydrogen or carbon monoxide. Bioprocess engineering is the key to make use of these energy sources for the microbial production of chemicals from carbon dioxide emissions.

Special syngas-converting microorganisms are studied in fully controlled stirred-tank bioreactors operated in a syngas (CO_2, H_2, CO) compartment of the lab ensuring safety requirements are met. (photo: Tobias Hase, TUM)

Highlight

A new continuous process was established for the microbial production of alcohols from CO-rich synthesis gas in a cascade of stirred-tank bioreactors. The strictly anaerobic bacterium *Clostridium carboxidivorans* grows in the first pH-controlled reactor and produces organic acids from synthesis gas. Biomass and organic acids are continuously transferred into the second reactor where the acids are reduced by the bacteria to alcohols making use of the synthesis gas as well.

Projects

- Mass production of microalgae in open photobioreactors
- Production of anti-oxidants with microalgae
- Microalgae processes in open photobioreactors with reduced water consumption
- Gas fermentation with *Clostridium carboxidivorans*
- Gas fermentation with *Clostridium aceticum*
- Multi-purpose reactor for gas fermentations

Bioprocess Integration

In many cases, downstream processing is by far the most cost-intensive step of a bioprocess. Often, multiplestep bioseparations are required, yielding rather low product yields. Therefore, existing bioseparation processes should be improved and combined to reduce the number of process steps. The focus is on bioprocess integration of fermentation/biocatalysis and downstream processing.

Highlight

Technical protein crystallization may become an economically attractive alternative to chromatography but so far protein crystallization is not applied due to an incomplete understanding. An industrially important enzyme was rationally modified, expressed, purified and crystallized to generate large crystals suitable for neutron diffraction studies at the Heinz Maier-Leibnitz Center (MLZ) in Garching. The neutron structure provided new insights into the reasons why divalent magnesium (Mg^{2+}) or manganese (Mn^{2+}) ions are necessary for its activity. Molecular-dynamics simulations enabled rational modifications of this enzyme to improve the crystallization process.

Protein crystallization is studied in parallel in a temperature-controlled incubator. Crystal formation is monitored automatically with a microscope (photo: Tobias Hase, TUM)

Projects

- Novel methods for packing of preparative chromatography columns
- Preparative purification of proteins via extraction
- Engineering of proteins for the control of crystallization processes
- Modeling and molecular dynamics simulation of protein crystals

Biochemical Engineering

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Research Focus
- Micro-bioprocess engineering
- Bioreactors
- Biocatalysis
- Fermentation
- Gas fermentation
- Microalgal bioprocesses
- Bioprocess integration

Competence
- Design and automation of bioreactor systems
- Bioprocess development and optimization
- Metabolic analysis of microbial reactions in bioreactors
- Metabolomics
- Downstream processing

Infrastructure
- Stirred-tank bioreactor systems up to a 100 l scale
- Flat-panel photobioreactor systems with high-power LEDs
- Parallel bioreactor systems automated with lab robots
- Anaerobic work benches/sterile laminar flow work benches
- Syngas lab (CO_2, CO, H_2)
- Phage lab
- Cooled lab (4° C)
- Digitized bioprocess lab
- Mechanical workshop
- Analytical lab (LC-MS, flow cytometry, GC, LC, etc.)

Courses
- Biochemical Engineering Fundamentals
- Biochemical Engineering
- Bioprocesses
- Bioprocesses and Bioproduction
- Industrial Bioprocesses
- Bioreactors/Bioreaction Engineering
- Environmental and Biochemical Engineering
- Separation of Macromolecular Bioproducts
- Practical Training on Biochemical Engineering
- Practical Training on Bioprocess Engineering

Selected Publications 2018

- Heins AL, Weuster-Botz D (2018): Population heterogeneity in bioprocesses – the diversity of single cells. Bioproc Biosys Eng 41: 889-916.
- Priebe X, Daschner M, Schwab W, Weuster-Botz D (2018): Rational selection of biphasic reaction systems for geranyl glucoside production by *Escherichia coli* whole-cell biocatalysts. Enz Microb Technol 112: 79-87.
- Tröndle J, Trachtmann N, Sprenger GA, Weuster-Botz D (2018): Production of L-tryptophan from glycerol using recombinant *Escherichia coli*. Biotechnol Bioeng 115: 2881–2892.
- Doll K, Rückel A, Kämpf P, Weuster-Botz D (2018): Two stirred-tank bioreactors in series enable continuous production of alcohols from carbon monoxide with *Clostridium carboxidivorans*. Bioproc Biosys Eng 41: 1403-1416.
- Hermann J, Nowotny P, Schrader TE, Biggel P, Hekmat D, Weuster-Botz D (2018): Neutron and X-ray crystal structures of *Lactobacillus brevis* alcohol dehydrogenase reveal new insights on hydrogen bonding pathways. Acta Cryst F74: 754-764.

Book 2018

- Chmiel H, Takors R, Weuster-Botz D (Editors): Bioprozesstechnik. 4. Auflage, Springer-Verlag GmbH, Berlin, 2018. ISBN 978-3-662-54041-1.

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