

TUM Mechanical Engineering Technik für Menschen

Industrial biotechnology

■ Industrial biotechnology ('white biotechnology') makes use of cells, microorganisms and 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 favoured 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 integration of up- and downstream processing.



Knowledge-based automation and digitalisation of bioprocess development is studied in the digitised bioprocess lab in order to be able to drastically shorten development cycles in industrial biotechnology in the future (photo: Tobias Hase, TUM).

Bioreactors and digitalisation

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 digitalisation 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 digitised bioprocess lab is the use of intelligent software components for knowledge-based experimental design, for the 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 development in the future.

Projects

- Multi-parameter analytics in parallel bioreactors
- Automation of bioprocess development
- Digitalisation of bioprocess development
- High-throughput bioprocess design

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 favourable method for the purpose of chiral syntheses. Major research interests are the development of new reaction engineering methods and devices



Study of Gluconobacter oxydans strains in parallel controlled stirred-tank bioreactors for the regioselective oxidation of sugar alcohols (photo: Tobias Hase, TUM).

Fermentation

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

Highlight

Parallelised short-term perturbation experiments with various substrates were employed to characterise the metabolism of recombinant *Escherichia coli* from fedbatch processes for the production of aromatic amino acids by analysing intracellular fluxes and metabolites. Metabolic control analysis allowed the identification of limiting metabolic reactions during the production of L-tryptophan from glycerol.

Projects

- Population heterogeneity in industrial scale bioprocesses
- Metabolic control analyses of microbial production processes
- Production of aromatic amino acids with recombinant Escherichia coli

to intensify whole cell biotransformations of hydrophobic, unstable and/or toxic substrates up to the technical scale.

Highlight

Multideletion strains of *Gluconobacter oxydans* expressing selected membrane integrated dehydrogenases were characterised in controlled stirred-tank bioreactors with respect to the single-step oxidation from *meso*-erythritol to L-erythrulose and the two-step oxidation from glucose to 5-ketogluconate. High product concentrations (> 240 g L⁻¹) and space-time yields were thus achieved by applying resting cells of *Gluconobacter oxydans* at complete substrate conversion in simple batch processes.

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



Flux control coefficients of intracellular enzymes during the production of L-tryptophan from glycerol with recombinent Escherichia coli in a fedbatch process (green: postitiv control, red: negativ control). Three enzymes show positive control (should be more active) and one enzyme shows negative control (activity should be reduced) of fluxes in the biosynthetic pathway to L-tryptophan (last 6 fluxes) (copyright: Julia Tröndle, TUM).

- Production of single-stranded DNA with recombinant Escherichia coli
- Reaction engineering analysis of recombinant Aspergillus niger
- Analysis of population heterogeneity with reporter strains

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



Process performances of marine microalgae are studied in open thin-layer cascade photobioreactors with a surface area of up to 50 m² at physically simulated climate conditions (day-night cycles) useful for microalgae production e.g. Mediterranean summer climate (photo: Tobias Hase, TUM).

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 upstream and downstream processing.

Highlight

Packed bed liquid chromatography is a key purification step in the industrial production of biopharmaceuticals. A new method for the 3-dimensional reconstruction of packed beds using X-ray tomography was established and used on polymethylacrylate and agarose-based chromatographic particles. Vibration packing of liquid chromatography columns was studied applying ultrasound or mechanical vibration. Ultrasound reduced particle sedimentation but was not strong enough to compact consolidated beds, whereas vertical linear vibration delivered denser and more efficient column packings. of these energy sources for the microbial production of chemicals from carbon dioxide emissions.

Highlight

Two open thin-layer cascade photobioreactors in series enabled continuous production of lipids from CO_2 with *Microchloropsis salina* applying a physically simulated Mediterranean summer climate. Microalgal cells were produced continuously in the first photobioreactor, whereas continuous lipid production with up to 46% total lipids in dry cell mass was enabled in the second, nitrogen-limited photobioreactor resulting in high space-time yields and high CO_2 conversion efficiencies of > 85%.

Projects

- CO, valorisation with microalgae and yeasts
- Production of anti-oxidants with microalgae
- Microalgae processes in open photobioreactors with reduced water consumption
- Conversion of syngas with acetogens
- Combination of biomass gasification and syngasfermentation
- Co-cultivation of clostridia for syngas-fermentation



Packing of liquid chromatography columns is studied experimentally and theoretically applying CFD-DEM simulation (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 crystallisation processes
- Modelling and molecular dynamics simulation of protein crystals



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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 optimisation
- 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 (CO₂, CO, H₂)
- Phage lab
- Cooled lab (4° C)
- Digitised 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 2019

- Phillip Nowotny, Johannes Hermann, Jianing Li, Angela Krautenbacher, Kai Klöpfer, Dariusch Hekmat, Dirk Weuster-Botz (2019): Rational Crystal Contact Engineering of *Lactobacillus brevis* Alcohol Dehydrogenase to Promote Technical Protein Crystallization. Crystal Growth and Design 19: 2380–2387.
- Christina Evi Pfaffinger, Timm Steffen Severin, Andreas Christoph Apel, Johanna Göbel, Julia Sauter, Dirk Weuster-Botz D (2019): Lightdependent Growth Kinetics Enable Scale-up of Well-mixed Phototrophic Bioprocesses in Different Types of Photobioreactors. Journal of Biotechnology 297: 41–48.
- Christoph Mähler, Franziska Kratzl, Melina Vogel, Stefan Vinnenberg, Dirk Weuster-Botz, Kathrin Castiglione (2019): Loop Swapping as a Potent Approach to Increase Ene Reductase Activity with NADH. Advanced Synthesis and Catalysis 361: 2505–2513.
- Christian Burger, Constantin Kessler, Simone Gruber, Armin Ehrenreich, Wolfgang Liebl, Dirk Weuster-Botz (2019): L-erythrulose Production with a Multideletion Strain of *Gluconobacter oxydans*. Applied Microbiology and Biotechnology 103: 4393–4404.
- Torben Schädler, Daniel Caballero Cerbon, Luis Oliveira, Daniel Garbe, Thomas Brück, Dirk Weuster-Botz (2019): Production of Lipids with *Microchloropsis salina* in Open Thinlayer Cascade Photobioreactors. Bioresource Technology 289: 121682.

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