Technische Universität Braunschweig

pvz Zentrum für Pharmaverfahrenstechnik

Center of Pharmaceutical Engineering

Research Profiles

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Zentrum für
Pharmaverfahrenstechnik

Editorial

Photo credit: Marisol Glassermann; PVZ / TU Braunschweig

Center of Pharmaceutical Engineering, PVZ

PVZ Structure

Four interdisciplinary divisions
- Pharmaceutical Biological Processes
- Pharmaceutical Chemical Processes
- Formulation & Packaging Technology
- Microdevices and Analytics

flanked by two cross-sectional groups
- Multi-scale Simulations of Pharmaceutical Processes
- Pharmaceutical Manufacturing Engineering

People
- about 20 participating institutes
- 3 PVZ junior professorships
- about 60 doctoral candidates and Postdocs

Core Research Topics
- Biomolecule Engineering
- Digital Twins
- Human-on-Chip
- Individualised Production & Therapy
- Miniaturisation / Parallelisation
- Optimisation of Processes

Pharmaceutical production has many facets and the societal need to produce innovative and tailor-made drugs cost-efficiently is still increasing in an ageing society. Providing patients with effective and innovative drugs that are produced by optimised processes is one of the greatest challenges facing the healthcare system of the future.

Combining expertises of pharmacy, process and production engineering as well as microtechnology enable us to face this challenge. At Technische Universität Braunschweig these key disciplines are joined under the roof of the Center of Pharmaceutical Engineering. Established in 2017, the PVZ bridges the gap between the identification and characterization of active pharmaceutical ingredients, APIs, on the one hand and the subsequent GMP-compliant production, testing and application of the drug on the other hand. With our work we support the cost-efficient production of individualized novel drugs and the development of innovative pharmaceutical manufacturing techniques.

Tandem teams consisting of pharmacists and engineers are working closely together in six research areas to speed up Pharmaceutical Engineering research. Altogether, more than 90 staff and researchers of about 20 institutes bundle their research capacities to meet the PVZ overall goal of customized high value drugs & processes and intelligent production systems.

The research profiles provide a short overview of PVZ members‘ research interests and competences. The PVZ is part of the university's strategic research area "Infections and Therapeutics". Together with its national and international partners from academia and industry, PVZ provides a unique multidisciplinary network to strengthen Pharmaceutical Engineering research.

Find out more about our research!

Prof. Dr.
Ludger Beerhues
Board Member

Prof. Dr.
Heike Bunjes
Board Member &
Vice-spokeswoman

Prof. Dr.
Andreas Dietzel
Board Member

Prof. Dr.-Ing.
Arno Kwade
Board Member &
Spokesman

Prof. Dr.-Ing.
Stephan Scholl
Board Member

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PVZ Research Area

Pharmaceutical Biological Processes

The development and optimization of innovative methods for the cost-effective and efficient production of biomolecular drugs is based on integrated operations for a holistic approach of upstream processing, cultivation and downstream processing.

The most important challenge is the development and optimization of highly productive pharmaceutical cell factories for labile and poorly soluble ingredients in an active shape at high concentrations. Analyzing effects of changes in the product spectrum is important for the development of efficient downstream strategies. Using miniaturized systems early process decisions reduce development times.

For patient-friendly, personalized biopharmaceuticals reliable methods for flexible, demand-driven, reproducible and procedural concepts have to be developed. Synthetic biotechnology will help cost effective personalized drug production in miniaturized systems, i.e. tailor-made cell factories with optimal power of synthesis.

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PVZ Principal Investigator • Research Profile

Institute of Pharmaceutical Biology

Prof. Dr. Ludger Beerhues

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Pharmaceutical Biology
PVZ Research Area
Pharmaceutical Biological Processes

Research Interest & Competences

Our research aims at **providing production platforms.** The focus is on **plant-derived active pharmaceutical ingredients (API),** which have challenging chemical structures and intriguing pharmacological activities. To produce these **difficult-to-synthesize API** biotechnologically, we use both **native producers** such as root cultures and heterologous hosts such as **engineered micro-organisms.** For reconstructing plant biosynthetic pathways in microorganisms via metabolic engineering, the enzymes and genes involved are identified using *omics* and bioinformatics techniques. In the context of synthetic biology, additional directed modification and design strategies yield **tailored production platforms and API.** Plants that are preferably studied involve *Hypericum* species, which contain an amazing array of complex **polyprenylated polycyclic acylphloroglucinols (PPAP),** the prototype molecule of which is **hyperforin.**

Major Research Methods

- *In vitro* plant tissue cultivation
- Transcriptomics and bioinformatics
- Gene/cDNA cloning and functional expression
- Metabolic engineering
- Synthetic biology tools

Photo credit: Ludger Beerhues; IPB / TU Braunschweig

Hypericum perforatum (St. John's wort)

Selected Publications

- Nagia M, Gaid M, Biedermann E, Fiesel T, El-Awaad I, Hänsch R, Wittstock U, Beerhues L. Sequential regiospecific gem-diprenylation of tetrahydroxyxanthone by prenyltransferases from Hypericum sp. New Phytol. 2019; 222:318-334.
- Gaid M, Biedermann E, Füller J, Haas P, Behrends S, Krull R, Scholl S, Wittstock U, Müller-Goymann C, Beerhues L. Biotechnological production of hyperforin for pharmaceutical formulation. Eur J Pharm Biopharm. 2018; 126:10-26.
- El-Awaad I, Bocola M, Beuerle T, Liu B, Beerhues L. Bifunctional CYP81AA proteins catalyse identical hydroxylations but alternative regioselective phenol couplings in plant xanthone biosynthesis. Nat Commun. 2016; 7:11472.
- Gaid M, Haas P, Beuerle T, Scholl S, Beerhues L. Hyperforin production in Hypericum perforatum root cultures. J Biotechnol. 2016; 222:47-55.
- Gaid MM, Sircar D, Müller A, Beuerle T, Liu B, Ernst L, Hänsch R, Beerhues L. Cinnamate:CoA ligase initiates the biosynthesis of a benzoate-derived xanthone phytoalexin in Hypericum calycinum cell cultures. Plant Physiol. 2012; 160:1267-80.

Key words
Plant-derived API • Production platforms • Engineered microorganisms • Hypericum

Contact
Mendelssohnstraße 1 • 38106 Braunschweig • Phone: +49(0)531 391-5689 • l.beerhues@tu-braunschweig.de
www.tu-braunschweig.de/pharmbiol

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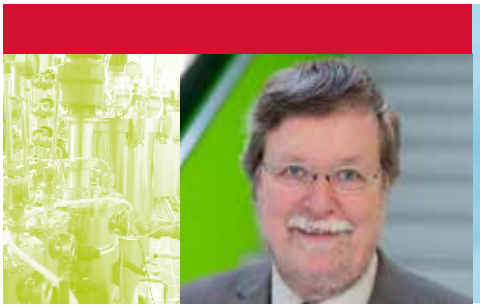


PVZ Principal Investigator • Research Profile

Institute of Biochemistry, Biotechnology and Bioinformatics

Prof. Dr. Stefan Dübel

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Biochemistry, Biotechnology and Bioinformatics
PVZ Research Area
Pharmaceutical Biological Processes

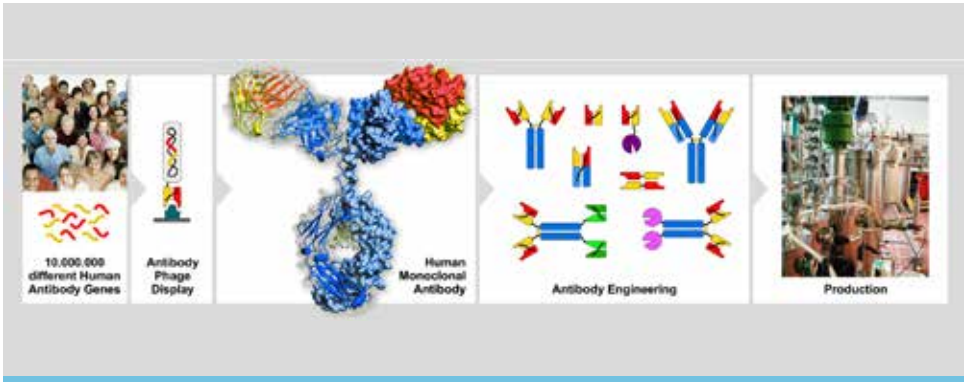
Research Interest & Competences

Phage display and human antibody discovery. We continue to generate and refine human antibodies both by adding novel functions allowing **new therapeutic paradigms** and developing **high-throughput in vitro antibody generation** to substitute animal experiments. We partner with academia and pharma in the generation of new drugs against cancer, autoimmune diseases and infections using our world leading antibody phage display systems, including the first truly comprehensive naïve functional human antibody gene repertoire. The control of biochemical milieu during the in vitro selection step can be employed to **predetermine antibody properties** at the very moment of selection, e.g. to avoid cross-reactivity or generating compatible sandwich pairs. **Engineering of antibodies for novel applications** like intracellular protein knockdowns, or allosteric switches for affinity modulation, complement the animal-free antibody generation pipelines for reserach.

Major Research Methods

- Phage display and human antibody discovery
- Designer antibodies
- Discovery of novel disease biomarkers
- Antibody fusions & bispecific antibodies
- Protein knock down *in vivo* by intrabodies

Photo credit: Stefan Dübel; bbt biotech / TU Braunschweig



From human antibody genes to therapeutic concepts.

Selected Publications

- Wenzel EV, Bosnak M, Tierney R, Schubert M, Brown J, Dübel S, Efstratiou A, Sesardic D, Stickings P, Hust M. Human antibodies neutralizing diphtheria toxin in vitro and in vivo. Sci. Rep. 2020; 10:571.
- Froude JW, Herbert AS, Pelat T, Miethe S, Zak SE, Brannan JM, Bakken RR, Steiner AR, Yin G, Hallam TJ, Sato AK, Hust M, Thullier P and Dye JM. Post-Exposure Protection in Mice against Sudan Virus by a Two Antibody Cocktail. Viruses 2018; 10:286.
- Russo G, Theisen U, Fahr W, Helmsing S, Hust M, Köster RW, Dübel S. Sequence defined antibodies improve the detection of Cadherin 2 (N-Cadherin) during Zebrafish development. N. Biotechnology 2018; 45:98-112 https://doi.org/10.1016/j.nbt.2017.12.008.
- Dübel S. & Reichert, J.M. (eds.) Handbook of Therapeutic Antibodies, 2nd ed. 4 Vol., Wiley-VCH, Weinheim 2014; ISBN 978-3-527-32937-3.
- Marschall ALJet al. Functional knock down of VCAM1 in mice mediated by ER intrabodies. mAbs 2014; 6:1394-1401.

Key words
Antibody engineering • Phage display • ORFeome display • Intrabodies • Biomarkers

Contact

Spielmannstraße 7 • 38106 Braunschweig • Phone: +49(0)531 391-5731 • biotech@tu-braunschweig.de
www.tu-braunschweig.de/bbt/biotech

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PVZ Principal Investigator • Research Profile

Institute of Biochemical Engineering

Prof. Dr. Rainer Krull

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Biochemical Engineering
PVZ Research Area
Pharmaceutical Biological Processes

Research Interest & Competences

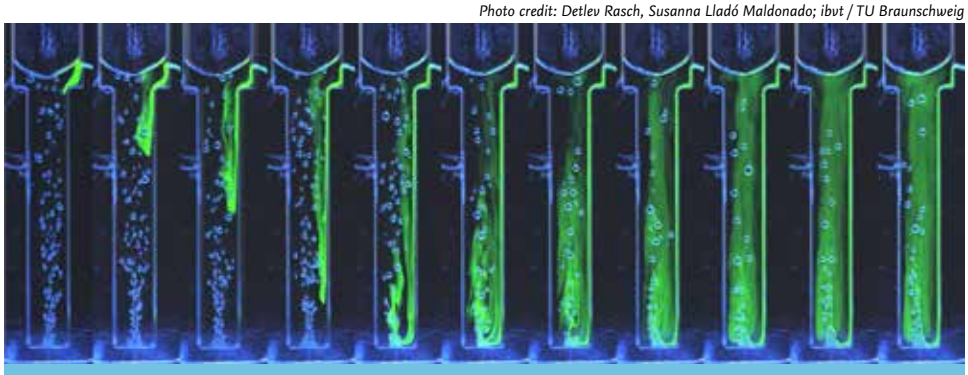
The Institute of Biochemical Engineering, ibvt, has a broad expertise in **morphology engineering,** which is the development of methods for tailor-made highly productive cell morphologies of filamentous microorganisms, e.g. for the improved production of new antibiotics by actinomycetes. The generation of physiological stress by *microparticle-enhanced cultivation* and by *salt-enhanced cultivation* was found to be a sophisticated method to conduct morphology to increased productivity.

A second research area is **fluid dynamic induced stress on shear sensitive microorganisms** which has long been the subject of intensive research activities. Methods have been developed for the determination of particle stress in multiphase reactors with a shear sensitive non-biological clay-polymer-floc system and biological systems, e.g. fungi, actinomycetes, plant cells, and mammalian cell cultures. Additionally, the ibvt developes **microbioreactors** (MBR) as a screening platform for biotechnological applications. The MBR demonstrated all the features for autonomous, inexpensive cultivation and showed potential for online analytics and parallelization. Currently, integrated sensing strategies for bioprocess analysis are investigated to develop MBR for pharmaceutical applications.

Major Research Methods

- Microparticle- and salt-enhanced cultivation
- Characterisation of cell morphology
- Fluid dynamic induced stress on shear sensitive microorganisms
- Fully, online sensor-equipped, disposable multiphase microbioreactor as a screening platform

Photo credit: Detlev Rasch, Susanna Lladó Maldonado; ibvt / TU Braunschweig



Mixing time experiments in a microbubble column-bioreactor (working volume 60 µL). Time-lapse image series with a superficial gas velocity set at 1.3 x 10^{-3} m/s after the injection of a pulse of 2 µL of the fluorescent tracer solution through a needle pump.

Selected Publications

- Pommerehne K, Walisko J, Ebersbach A, Krull R. The antitumor antibiotic rebeccamycin – Challenges and advanced approaches in production processes. Appl Microbiol Biotechnol 2019; 103:3627-3636.
- Lladó Maldonado S, Panjan P, Sun S, Rasch D, Sesay A, Mayr T, Krull R. A fully, online sensor-equipped, disposable multiphase microbioreactor as a screening platform for biotechnological applications. Biotechnol Bioeng 2019; 116:65-75.
- Walisko J, Vernen F, Pommerehne K, Richter G, Terfehr J, Kaden D, Dähne L, Holtmann D, Krull R. Particle-based production of antibiotic rebeccamycin with *Lechevalieria aerocolonigenes.* Proc Biochem 2017; 53:1-9.
- Krull R, Peterat G. Analysis of reaction kinetics during chemostat cultivation of *Saccharomyces cerevisiae* using a multiphase microreactor. Biochem Eng J 2016; 105:220-229.
- Wucherpfennig T, Hestler T, Krull R. Morphology engineering – Osmolality and its effect on *Aspergillus niger* morphology and productivity. Microb Cell Fact 2011; 11:58.

Key words
Cell morphology • Shear sensitivity • Microbioreactor • Sensing • Biological reaction kinetics

Contact
Rebenring 56 • 38106 Braunschweig • Phone: +49(0)531 391-55311 • r.krull@tu-braunschweig.de
www.ibvt.de

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PVZ Principal Investigator • Research Profile

Institute of Biochemistry, Biotechnology and Bioinformatics

Prof. Dr. Anett Schallmey

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Biochemistry, Biotechnology and Bioinformatics
PVZ Research Area
Pharmaceutical Biological Processes

Research Interest & Competences

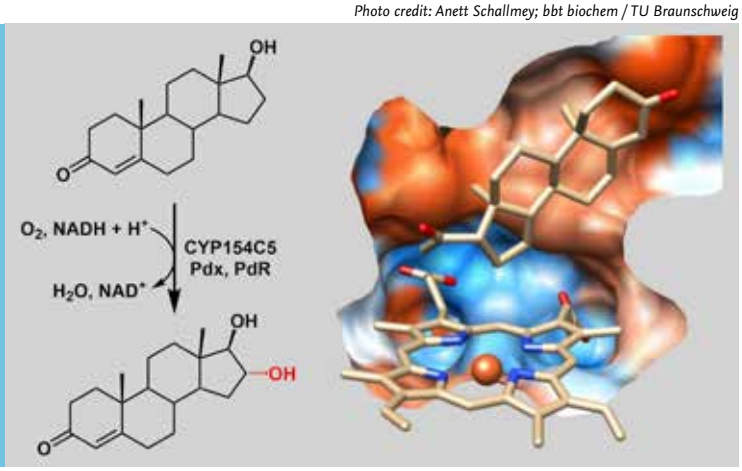
My research in general focuses on the investigation, utilization and engineering of **enzymes as biocatalysts** for industrially relevant applications. The major advantage of enzymes compared to chemical catalysts is their intrinsic **high selectivity,** which is a major driver for their use in pharmaceutical industry. In the PVZ context, we are exploring the regio- and stereoselectivity of various oxidoreductases and lyases for the selective **synthesis of active pharmaceutical ingredients** (APIs) and their precursors. This not only involves the application of free enzymes but also the generation of suitable whole-cell biocatalysts as well as the **combination of** different **enzyme activities in biocascades.** Many naturally occurring enzymes, however, do not exhibit all characteristics required for their application in industrial processes. Hence, we apply different **protein engineering** techniques to modify the activity, selectivity or stability of our biocatalysts.

Major Research Methods

- Sequence database mining for novel enzymes
- Heterologous enzyme production in *E. coli*
- Enzyme purification and biochemical characterization
- Protein engineering using semirational design and directed evolution
- Biocatalysis and chemo-enzymatic cascade reactions

Photo credit: Anett Schallmey; bbt biochem / TU Braunschweig

Cytochrome P450 catalysed steroid hydroxylation and molecular evidence for the enzyme's high regio- and stereoselectivity.



Selected Publications

- Solarczek J, Klünemann T, Brandt F, Schrepfer P, Wolter M, Jacob CR, Blankenfeldt W, Schallmey A. Position 123 of halohydrin dehalogenase HheG plays an important role in stability, activity, and enantioselectivity. Sci Rep. 2019; 9:5106.
- Calderini E, Wessel J, Süss P, Schrepfer P, Wardenga R, Schallmey A. Selective ring-opening of di-substituted epoxides catalysed by halohydrin dehalogenases. ChemCatChem. 2019; doi: 10.1002/cctc.201900103.
- Koopmeiners J, Diederich C, Solarczek J, Voß H, Mayer J, Blankenfeldt W, Schallmey A. HheG, a halohydrin dehalogenase with activity on cyclic epoxides. ACS Catal. 2017; 7:6877-6886.
- Bracco P, Janssen DB, Schallmey A. Selective steroid oxyfunctionalisation by CYP154C5, a bacterial cytochrome P450. Microb Cell Fact. 2013; 12:95.
- Hollmann F, Arends IWCE, Buehler K, Schallmey A, Buehler B. Enzyme-mediated oxidations for the chemist. Green Chem. 2011; 13:226-265.

Key words
Biocatalysis • Protein engineering • Biocascades • Database mining

Contact

Spielmannstraße 7 • 38106 Braunschweig • Phone: +49(0)531 391-55400 • a.schallmey@tu-braunschweig.de
www.tu-braunschweig.de/bbt/biochem

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PVZ Principal Investigator • Research Profile

Institute of Biochemical Engineering

Prof. Dr.-Ing. Antje C. Spieß

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Biochemical Engineering
PVZ Research Area
Pharmaceutical Biological Processes

Research Interest & Competences

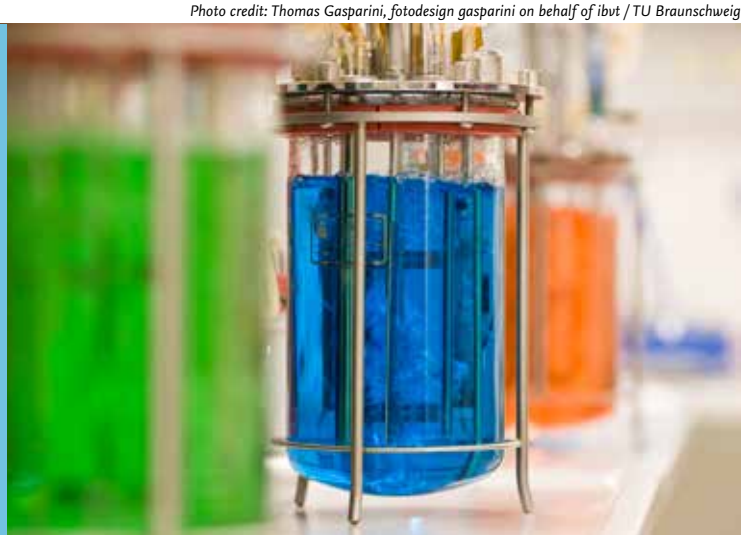
Our research aims at **moving mechanistic knowledge on metabolic and transport processes in bioreactors towards rational bioprocess development.** We specialize on complex enzymatic carboligation and redox reactions as well as on the cultivation of shear sensitive microorganisms, e.g. actinomycetes, filamentous fungi, plant root cultures, or leading to mostly small molecule pharmaceutical active ingredients, e.g. antiinfectives and anticarcerogenics.
To achieve our goal, we apply quantitative, automated and parallel experimentation on micro- to laboratory scale to characterize the corresponding enzymatic reaction, whole cell biotransformation, or cultivation. We use the obtained data to develop mechanistic models for simulations studies, model-based optimal experimental design, and process optimization both in the area of upstream and downstream processing.

Major Research Methods

- Reaction and cultivation operations:
  Parallel and automated µL – to L bench-scale bioreactors, 20 and 100 L bioreactor
- Rheological and morphological analysis, including confocal laser scanning microscopy
- Mechanistic kinetic modelling and model-based experimental analysis
- Downstream operations: Cross-flow filtration, Äkta purifier, explorer, and pilot
- Electrochemical quartz crystal microbalance

Photo credit: Thomas Gasparini, fotodesign gasparini on behalf of ibvt / TU Braunschweig

Series of stirred tank reactors with active gassing on bench-scale for the development and optimization of biological processes.



Selected Publications

- Cürten C, Anders N, Juchem N, Ihling N, Volkenborn K, Knapp A, et al. Fast automated online xylanase activity assay using HPAEC-PAD. Anal Bioanal Chem. 2018; 410:57-69.
- Ohs R, Leipnitz M, Schöpping M, Spiess AC. Simultaneous identification of reaction and inactivation kinetics of an enzyme-catalyzed carboligation. Biotechnol Prog. 2018; 34:1081-1092.
- Ohs R, Wendlandt J, Spiess AC. How graphical analysis helps interpreting optimal experimental designs for nonlinear enzyme kinetic models. AIChE J. 2017; 63:4870-4880.
- Grosch J-H, Wagner D, Nistelkas V, Spieß AC. Thermodynamic activity-based intrinsic enzyme kinetic sheds light on enzyme-solvent interactions. Biotechnol Prog. 2017; 33:96-103.
- Begemann J, Ohs RBH, Ogolong AB, Eberhard W, Ansorge-Schumacher MB, Spiess AC. Model-based analysis of a reactor and control concept for oxidoreductions based on exhaust CO2-measurement. Process Biochem. 2016; 51:1397-1405.

Key words
Enzyme kinetic modelling • Shear-sensitive organisms • Rheology, morphology • Biofilms and infection • Transport and adsorption analysis

Contact
Rebenring 56 • 38106 Braunschweig • Phone: +49(0)531 391-55310 • a.spiess@tu-braunschweig.de
www.ibvt.de

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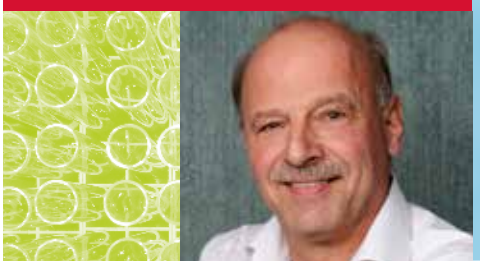

PVZ Principal Investigator • Research Profile

Institute of Food Chemistry

Prof. Dr. Peter Winterhalter

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Food Chemistry
PVZ Research Area
Pharmaceutical Biological Processes

Research Interest & Competences

Isolation and identification of **bio-active natural compounds** using a broad spectrum of **analytical methods** including **preparative countercurrent chromatography** & structural elucidation by modern spectroscopic and spectrometric techniques. **Development of preparative separation systems:** Analysis of complex natural extracts requires preparative separation techniques. We mainly focus on all-liquid countercurrent chromatographic separation systems, such as High Speed Countercurrent Chromatography, Low Speed Rotary Countercurrent Chromatography (LSRCCC) as well as Spiral-Coil LSRCCC for separations in a scale up to 100 g; separation of biopolymers is achieved by Centrifugal Precipitation Chromatography.

Major Research Methods

- High Speed Countercurrent Chromatography
- Spiral-Coil Low Speed Rotary Countercurrent Chromatography
- LC-ESI/APCI-MS/MS
- HRGC-MS
- CE

Photo credit: Peter Winterhalter; ilc / TU Braunschweig

High Speed Countercurrent Chromatography, HSCC (Picture left), Low Speed Rotary Countercurrent Chromatography (LSRCCC) as well as Spiral-Coil LSRCCC (Picture middle). HSCCC separation of red wine pigments (Picture right).

Selected Publications

- Mädge I, Cramer L, Rahaus I, Jerz G, Winterhalter P, Beuerle T. Pyrrolizidine alkaloids in herbal teas for infants, pregnant or lactating women. Food Chem. 2015; 187:491-498.
- Althaus J B, Jerz G, Winterhalter P, Kaiser M, Brun R, Schmidt T J. Antiprotozoal activity of Buxus sempervirens and activity-guided isolation of O-tigloylcycloviro-buxeine-B as the main constituent active against Plasmodium falciparum. Molecules 2014; 19:6184-6201.
- Esatbeyoglu T, Juadjur A, Wray V, Winterhalter P. Semisynthetic preparation and isolation of dimeric procyanidins B1-B8 from roasted hazelnut skins (Corylus avellana L.) on a large scale using countercurrent chromatography. J. Agric. Food Chem. 2014; 62:7101-7110.
- Esatbeyoglu T, Wray V, Winterhalter P. Identification of Two Novel Prodelphinidin A-Type Dimers from Roasted Hazelnut Skins (Corylus avellana L.). J. Agric. Food Chem. 2013; 61:12640-12645.
- Macke S, Jerz G, Empl M T, Steinberg P, Winterhalter P. Activity-guided isolation of resveratrol oligomers from a grapevine-shoot extract using countercurrent chromatography. J. Agric. Food Chem. 2012; 60:11919-11927.

Key words
Analytical techniques • Bioactives • Preparative separations • Countercurrent Chromatography

Contact

Schleinitzstraße 20 • 38106 Braunschweig • Phone: +49 (0) 531 391-7200 • p.winterhalter@tu-braunschweig.de
www.tu-braunschweig.de/ilc

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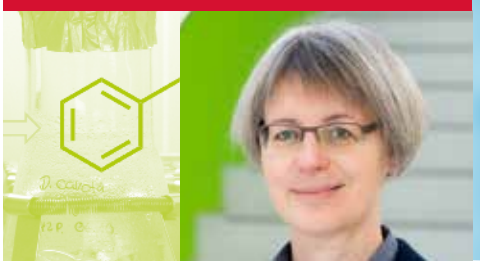


PVZ Principal Investigator • Research Profile

Institute of Pharmaceutical Biology

Prof. Dr. Ute Wittstock

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Phamaceutical Biology
PVZ Research Area
Pharmaceutical Biological Processes

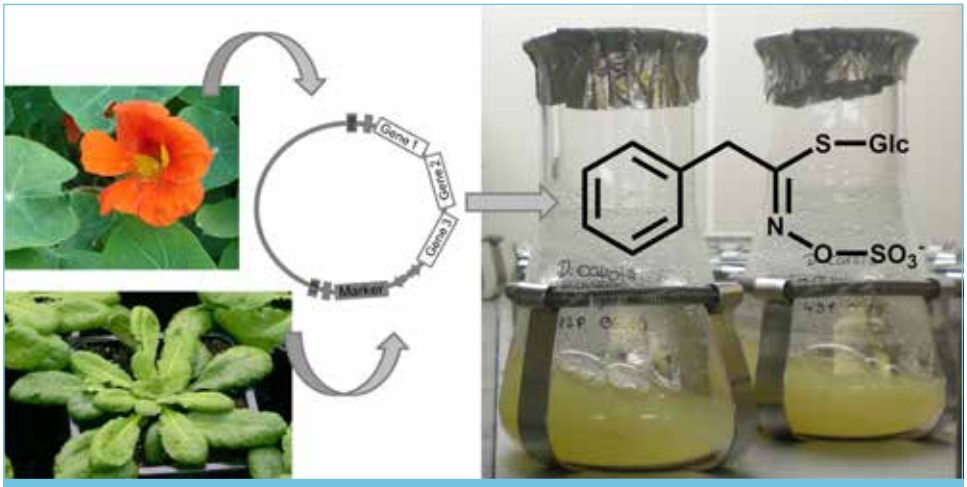
Research Interest & Competences

Secondary metabolites from plants have a long history of medicinal use. However, many interesting compounds occur in only small amounts, complex mixtures and in plants with limited availability. My research is aimed at understanding how and why plants produce so many structurally diverse compounds and at using this knowledge to develop biotechnological processes for their production. I am especially interested in **scalable plant-based production systems** that can be maintained in bioreactors. These include plant suspension cultures that have been transformed to express a foreign **multiple-gene pathway** for a specific secondary metabolite with the potential to apply synthetic biology tools for pathway optimization. Besides the producing cells, media and culture conditions as well as extraction procedures require optimization for high yield production.

Major Research Methods

- Genetic transformation of plant suspension cultures with multiple-gene constructs
- Small molecule analytics (HPLC, GC-MS, HPLC-MS)
- Heterologous expression, purification, and characterization of enzymes

Photo credit: Elena Kurzbach, Ute Wittstock; IPB / TU Braunschweig



Genes from multiple plants are being used to engineer the biosynthetic pathway of a secondary metabolite, e.g. benzylglucosinolate, into suspension cultures of e.g. carrot.

Selected Publications

- Eisenschmidt-Bönn D, Schneegans N, Backenköhler A, Wittstock U, Brandt W. Structural diversification during glucosinolate breakdown: mechanisms of thiocyanate, epithionitrile and simple nitrile formation. Plant J. 2019; 99:329-343.
- Nagia M, Gaid M, Biedermann E, Fiesel T, El-Awaad I, Hänsch R, Wittstock U, Beerhues L. Sequential regiospecific gem-diprenylation of tetrahydroxyxanthone by prenyltransferases from Hypericum sp. New Phytol. 2019; 222:318-334.
- Gaid M, Biedermann E, Füller J, Haas P, Behrends S, Krull R, Scholl S, Wittstock U, Müller-Goymann C, Beerhues L. Biotechnological production of hyperforin for pharmaceutical formulation. Eur J Pharm Biopharm. 2018; 126:10-26.

Key words
Plant suspension culture • Bioreactor • Natural products • Glucosinolates

Contact

Mendelssohnstraße 1 • 38106 Braunschweig • Phone: +49(0)531 391-5681 • u.wittstock@tu-braunschweig.de
www.tu-braunschweig.de/pharmbiol

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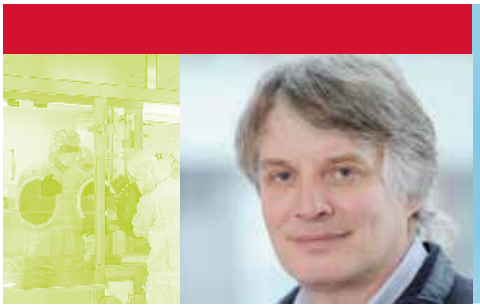

PVZ Principal Investigator • Research Profile

Division Pharmaceutical Biotechnology

Dr. Holger Ziehr

Research Organisation
Fraunhofer Institute for Technology and Experimental Medicine ITEM
Division
Division Pharmaceutical Biotechnology
PVZ Research Area
Pharmaceutical Biological Processes

Selected Publications

- Baydoun L, Ziehr H. Aseptische Abfüllung biopharmazeutischer Prüfarzneimittel. Die Pharmazeutische Industrie 2017; 1:126-132.
- Veith N, Ziehr H, MacLeod R AF, Reamon-Büttner SM. Mechanisms underlying epigenetic and transcriptional heterogeneity in Chinese hamster ovary (CHO) cell lines. BMC biotechnology 2016; 16:6.
- Hecht V, Duvar S, Ziehr H, Burg J, Jockwer A. Efficiency improvement of an antibody production process by increasing the inoculum density. Biotechnology progress 2014; 30:607-615.
- Luer C, Bohle K, Ross A, Ziehr H. Process development for production of pharmaceutical grade plasmid DNA to be used in gene therapy and DNA vaccination. Human gene therapy 2011; 22:A74.
- Hoffmann P, Huelsewig M, Duvar S, Ziehr, H, Mormann M, Peter-Katalinic J, Friedrich AW, Karch H, Müthing J. On the structural diversity of Shiga toxin glycosphingolipid receptors in lymphoid and myeloid cells determined by nanoelectrospray ionization tandem mass spectrometry. Rapid communications in mass spectrometry 2010; 24:2295-2304.

Research Interest & Competences

Key areas of my R&D are pharmaceutical bioprocesses starting at least with an already given cDNA and going through recombinant cell line development, upstream and downstream process development and ending with **early stage GMP manufacturing** of both, **active pharmaceutical ingredient (API)** and **sterile investigational medicinal products (IMPs).**
API targets are proteins and glycoproteins, such as recombinant antibodies and antibody fragments as well as nucleic acids, but also more complex structures like bacteriophages and viruses. Hosts mainly in use are CHO, BHK, HEK293 as well as microbial systems like E. coli and P. pastoris.
The **division is GMP-certified** since 1997 and has beside to process and analytical development labs 700 m² clean room suites grade D – A at its disposal.
Current interests are on **bi-specific antibodies as BiTEs for T-cell and CAR-T-cell therapy** from which already 3 candidates have been translated into clinical. New in focus are **bacteriophages and phage derived lysines as potential anti-infective agents.**

Major Research Methods

- CHO- animal cell culture
- Microbial cultivation
- Biomolecule purification and process chromatography
- Bio-process validation
- Humanized antibodies and bispecific single chain antibodies
- Bacteriophages as anti-infectives
- Recombinant protein and nucleic acid APIs
- Aseptic manufacture of investigational medicinal products
- Analytical method development and validation, stability studies (ICH)
- Pharmaceutical documentation and medical writing

Photo credit: Fraunhofer Institute for Technology and Experimental Medicine ITEM

Clean room with filling machine for the sterile production of Investigational Medicinal Products.

Key words
Biopharmaceutica • Bioprocess development • GMP-manufacture • Investigational medicinal product • Bacteriophage

Contact
Inhoffenstraße 7 • 38124 Braunschweig • Phone: +49(0)531 6181-6000 • holger.ziehr@item.fraunhofer.de
www.item.fraunhofer.de/de/angebot/arzneimittelentwicklung/herstellung-biopharmazeutika

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PVZ Research Area

Pharmaceutical Chemical Processes

Research activities are directed towards the realization of continuous manufacturing processes for synthetic API integrating reactant preparation, synthesis and downstream processing. Specifically, manufacturing processes for protein kinase inhibitors and organic metal complexes, such as gold alkynes, are investigated. Processes are performed in integrated “milli-plants” with typical throughput of 100 to 500 g/h. Selection, design and operation of the individual process steps as well as the corresponding equipment are chosen such that they are representative for large scale processes and may thus serve as basis for scale-up to technical scale. Due to their low solubility in aqueous systems, synthesis and downstream processing of the API require a precise monitoring and control of temperature, concentration, residence time as well as energy management. For the latter, process intensification concepts comprise of ultrasound, micro wave or other techniques.

Process synthesis is supported by high throughput experimental techniques combined with predictive methods for solvent selection and parameter optimization. Additionally theoretical approaches, based on the concept of Elementary Process Functions, are applied to identify alternative process paths. Special attention is dedicated towards integrated process concepts with recycling of solvent streams as well as treatment of side product residual streams. Based on experimental data consistent mass, component and energy balances may be established.

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PVZ Principal Investigator • Research Profile

Institute for Chemical and Thermal Process Engineering

Jun.-Prof. Dr. Julia Großeheilmann

Research Organisation
Technische Universität Braunschweig
Institute
Institute for Chemical and Thermal Process Engineering & Center of Pharmaceutical Engineering
PVZ Research Area
Pharmaceutical Chemical Processes

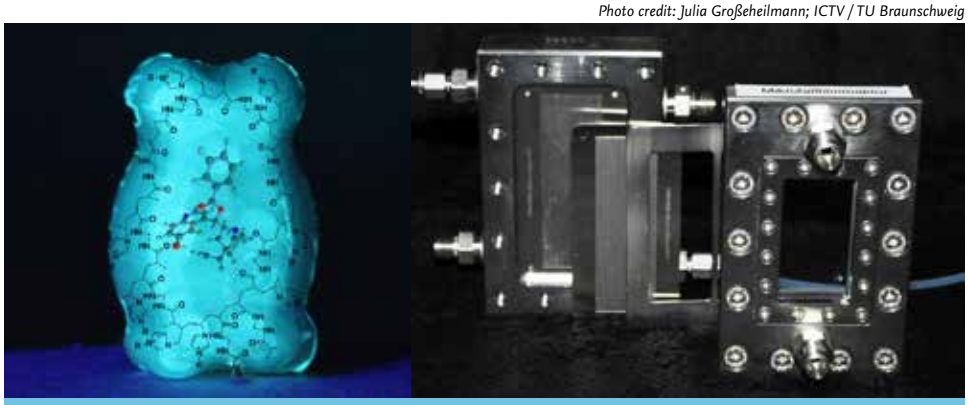
Research Interest & Competences

One of my research fields focuses on the development of **novel drug delivery systems based on polymerized ionic liquids (PILs)-based hydrogels** as innovative drug carriers. This research aims to achieve a **stimulus-responsive** drug release from hydrogels over a defined period and at a specific location. Another research focuses on the development and optimization of **catalytic processes** by considering innovative concepts for catalyst removal **(Organic Solvent Nanofiltration, Switchable Solvent Systems, Switchable Catalysts and novel Immobilization Techniques)** that increase the catalysts productivity. All approaches also provide the advantage of simplifying the **downstream process** for obtaining the crude product without further purification steps, along with the simultaneous **removal of the catalyst. Compartmentalization** as another research focus is a powerful method to entrap catalysts into materials to generate contrary reaction conditions for **chemo-/biocatalytic reactions.** In this project, enzymes and organocatalysts are incorporated into PILs-based hydrogels to optimize a chemo-biocatalytic **cascade process** for the synthesis of **enantiomerically pure compounds.**

Major Research Methods

- Immobilization techniques
- Synthesis procedures
- Micro reaction technology
- Flow chemistry
- Membrane technology

Photo credit: Julia Großeheilmann; ICTV / TU Braunschweig



Process intensification by novel immobilization techniques for drugs and catalysts (left) and by using a falling film micro reactor for catalyst removal (right).

Selected Publications

- Grollmisch A, Kragl U, Großeheilmann J. Enzyme Immobilization in Polymerized Ionic Liquids-based Hydrogels for Active and Reusable Biocatalysts. SynOpen 2018; 2:192-199.
- Großeheilmann J, Kragl U. Simple and Effective Catalyst Separation by New CO2-Induced Switchable Organocatalysts. ChemSusChem 2017; 10:2685-2691.
- Großeheilmann J, Vanderveen JR, Jessop PG, Kragl U. Switchable-Hydrophilicity Solvents for Product Isolation and Catalyst Recycling in Organocatalysis. ChemSusChem 2016; 9:696-702.
- Großeheilmann J, Bandomir J, Kragl U. Preparation of Poly(ionic liquid)s-Supported Recyclable Organocatalysts for the Asymmetric Nitroaldol (Henry) Reaction. Chemistry 2015; 21:18957-18960.
- Großeheilmann J, Büttner H, Kohrt C, Kragl U, Werner T. Recycling of phosphorus-based organocatalysts by organic solvent nanofiltration. ACS Sustain Chem Eng 2015, 3:2817-2822.

Key words
Drug delivery systems • Downstream processing • Process Intensification • Hydrogels • Micro Reaction technology

Contact
Langer Kamp 7 • 38106 Braunschweig • Phone: +49(0)531 391-65581 • j.grosseheilmann@tu-braunschweig.de
www.tu-braunschweig.de/ictv

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Zentrum für
Pharmaverfahrenstechnik

PVZ Principal Investigator • Research Profile

Institute of Medicinal and Pharmaceutical Chemistry

Prof. Dr. Conrad Kunick

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Medicinal and Pharmaceutical Chemistry
PVZ Research Area
Pharmaceutical Chemical Processes

Research Interest & Competences

Design and synthesis of new chemical structures used as **molecular probes** in biological test systems are in the focus of our research. Compounds identified as biologically actives are optimized and the molecular mechanisms of action as well as structure activity relationships are investigated. In this setting we concentrate on inhibitors of protein kinases and on anti-infective agents. Within the PVZ and in collaboration with the other groups of division 2, **production processes** for selected relevant molecules are optimized, for example through batch-to-conti transfer for synthesis procedures or by development of suitable downstream technologies. To address drug-likeness in early stages of drug development campaigns, **physicochemical properties** like solubility and lipophilicity are characterized and optimized by molecular modification.

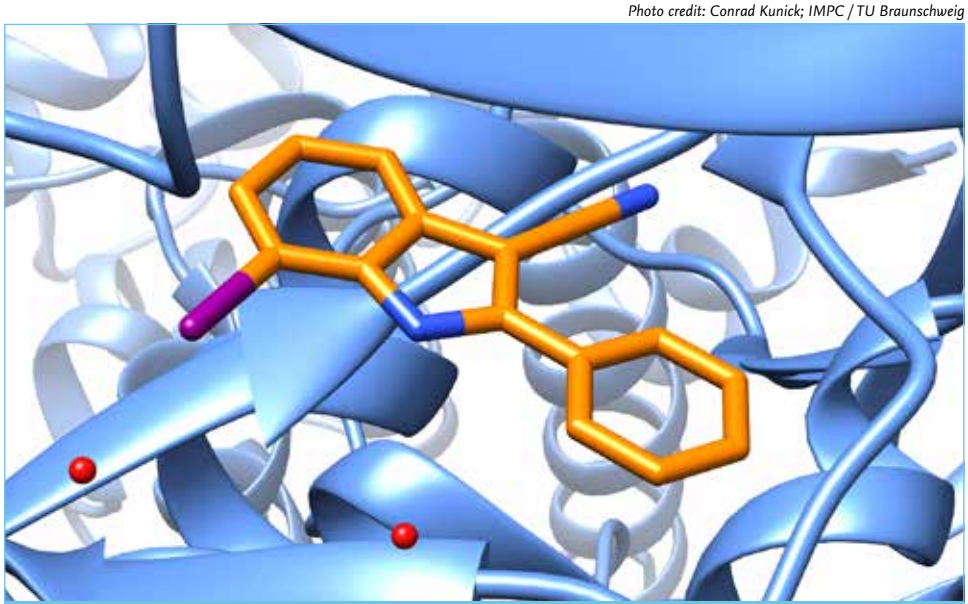
Major Research Methods

- Computer-aided drug design
- Synthesis of bioactive compounds
- Characterization of structure, purity, solubility
- Structure-activity relationships analysis

Selected Publications

- Masch A, Nasereddin A, Alder A, Bird MJ, Schweda SI, Preu L, Doerig C, Dzikowski R, Gilberger TW, Kunick C. Structure-activity relationships in a series of antiplasmodial thieno[2,3-b]pyridines. Malar J. 2019; 18:89.
- Meine R, Becker W, Falke H, Preu L, Loaëc N, Meijer L, Kunick C. Indole-3-carbonitriles as DYRK1A inhibitors by fragment-based drug design. Molecules 2018; 23:64.
- Rehbein MC, Husmann S, Lechner C, Kunick C, Scholl S. Fast and calibration free determination of first order reaction kinetics in API synthesis using in-situ ATR-FTIR. Eur J Pharm Biopharm. 2018; 126:95-100.
- Schlütke L, Immer M, Preu L, Totzke F, Schächtele C, Kubbutat MHG, Kunick C. Scaffold hopping identifies 6,8-disubstituted purines as novel anaplastic lymphoma kinase inhibitors. Eur J Pharm Biopharm. 2018; 126:89-94.
- Meise M, Niggemann M, Dunens A, Schoenitz M, Kuschnerow JC, Kunick C, Scholl S. Early process development of API applied to poorly water-soluble TBID. Eur J Pharm Biopharm. 2018; 126:2-9.

Photo credit: Conrad Kunick; IMPC / TU Braunschweig



A novel chemical probe and two water molecules located in the ATP binding site of the protein kinase DYRK1A.

Key words
Drug design • Molecular probes • Protein kinase inhibitors • Solubility • Synthesis

Contact

Beethovenstraße 55 • 38106 Braunschweig • Phone: +49(0)531 391-2754 • c.kunick@tu-braunschweig.de
www.tu-braunschweig.de/pharmchem/forschung/kunick

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Zentrum für
Pharmaverfahrenstechnik

PVZ Principal Investigator • Research Profile

Institute for Chemical and Thermal Process Engineering

Prof. Dr.-Ing. Stephan Scholl

Research Organisation
Technische Universität Braunschweig
Institute
Institute for Chemical and
Thermal Process Engineering
PVZ Research Area
Pharmaceutical Chemical Processes

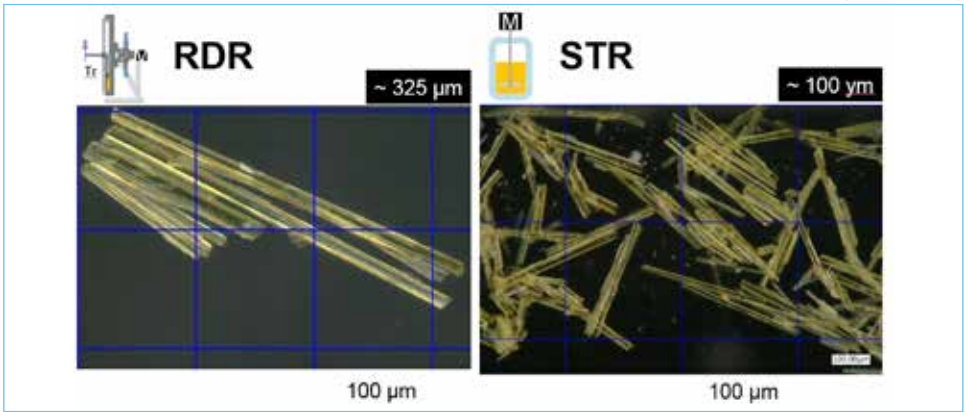
Research Interest & Competences

Our research aims at the development and assessment of **scalable process concepts** together with the corresponding equipment design for **synthesis and downstream processing of active pharmaceutical ingredients API.** These may be originating from plant extracts, chemical or biotechnological synthesis. For chemical synthesis, especially **continuous process concepts** are investigated. Experimental research activities address the application and optimization of individual unit operations, such as **crystallization, extraction, evaporation, chromatography or electro dialysis in manufacturing processes of API,** as well as integrated processes from **synthesis to downstream processing.** Based on comprehensive lab scale experiments, mass, component and heat balances are established using commercial flow sheeting tools to establish the basis for a **multi-criteria process assessment.** Unit operation and process modelling is directed towards the development and optimization of equipment design and scaling rules as well as process guidance concepts.

Major Research Methods

- Lab scale experiments
- Unit operation and integrated process modelling and simulation
- Integration and assessment of process and product analytical technologies
- Design and application of novel equipment technologies

Photo credit: Marius Meise; ICTV / TU Braunschweig



Crystals of the API 4,5,6,7-tetrabromo-2-(1H-imidazol-2-yl) isoindolin-1,3-dione TBID obtained from a seeded precipitation crystallization in a novel Rotating Disc Reactor RDR (left) and a conventional Stirred Tank Reactor STR (right).

Selected Publications

- Rehbein MC, Wolters J, Kunick C, Scholl S. Continuous high-pressure operation of a pharmaceutically relevant Krapcho dealkoxycarbonylation reaction. J Flow Chem 2019; 9:123-131.
- Sauk T, Henke L, Scholl S. Continuous flow di-N-Alkylation of 1H-Benzimidazole in a fixed bed reactor. Chem Eng Technol 2019; 42, DOI: 10.1002/ceat.201900114.
- Haas P, Gaid M, Zarinwall A, Beerhues L, Scholl, S. Downstream processing of hyperforin from Hypericum perforatum root cultures. Eur J Pharm Biopharm 2018; 126:104-107.
- Meise M, Niggemann M, Dunens A, Kunick C, Scholl S. Early Process Development of API applied to Poorly Water-Soluble TBID. Eur J Pharm Biopharm 2018; 126:2-9.
- Hartig D, Waluga T, Scholl S. Expanding the elution by characteristic point method to columns with a finite number of theoretical plates. J Chrom 2015; A 1413:77-84.

Key words
Chemical synthesis and plant extracts • Downstream processing • Continuous processing • Process simulation and assessment • Equipment design

Contact
Langer Kamp 7 • 38106 Braunschweig • Phone: +49(0)531 391-2780 • s.scholl@tu-braunschweig.de
www.tu-braunschweig.de/ictv

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PVZ Research Area

Formulation & Packaging Technology

Research in this field is specially focused on the development of strategies for formulating poorly soluble active ingredients (API) and biomolecular drugs. To improve the bioavailability of poorly soluble API they are, for instance, processed into nanoscale suspensions or incorporated into colloidal carriers. The chemical stability of the drug and the physicochemical integrity of the formulations are controlled to ensure storage stability and applicability at the intended site of administration.

Biomolecular drugs such as proteins are excellent candidates for the development of personalized medicines. Due to the complex and delicate structure of those macromolecules and their sensitivity towards processing, the development of stable and patient-friendly drugs is an important but challenging goal. The fundamental understanding of the respective formulation, its ingredients and their mutual interactions as well as a profound knowledge of the manufacturing processes will provide strategies for developing effective and cost-efficient medicines.

The spectrum of available techniques includes production methods (e.g. milling, high pressure homogenization, spray drying, lyophilization, tabletting), physicochemical and process characterization (e.g. particle size analysis, X-ray scattering, calorimetry, microscopy, HPLC, µ-PIV), evaluation of pharmaceutical product properties such as drug release and cell culture permeation experiments as well as theoretical approaches like molecular modeling and computational fluid dynamics.

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PVZ Principal Investigator • Research Profile

Institute of Pharmaceutical Technology

Prof. Dr. Heike Bunjes

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Pharmaceutical Technology
PVZ Research Area
Formulation & Packaging Technology

Research Interest & Competences

The major research focus of my group is the development of **formulation strategies for poorly soluble drugs** mainly by using **colloidal drug delivery systems** (colloidal lipid dispersions, drug nanoparticles). We aim at establishing **structure-function relationships** for such systems, e.g. concerning the stability, drug carrier capacity and release properties of the formulations depending on their composition, the manufacturing process and their ultrastructure. On this basis, systems with optimized properties are being developed. Our research approach relies on detailed **physicochemical characterization** of the formulations. Moreover, we are concerned with **novel manufacturing methods** for colloidal drug delivery systems (e.g. membrane emulsification, preparation in microfluidic system) and the **influence of further processing** methods (such as sterilization or drying) on the structure and properties of the resulting systems. A smaller research area deals with the development of **formulations for therapeutic proteins** under special consideration of sustained release properties.

Major Research Methods

- High and low energy emulsification
- Particle size analysis
- Differential Scanning Calorimetry
- X-ray diffraction
- Electron microscopy

Photo credit: Katrin Göke; IPhT / TU Braunschweig

Colloidal lipid emulsions as drug carrier systems.

Selected Publications

- Gehrmann S, Bunjes H. Influence of membrane material on the production of colloidal emulsions by premix membrane emulsification, Eur J Pharm Biopharm. 2018; 126:140-48.
- Göke K, Bunjes H. Drug solubility in lipid nanocarriers: Influence of lipid matrix and available interfacial area. Int J Pharm. 2017; 529:617-628.
- Kupetz E, Preu L, Kunick C, Bunjes H. Parenteral formulation of an antileishmanial drug candidate – Tackling poor solubility, chemical instability, and polymorphism. Eur J Pharm Biopharm. 2013; 85:511-20.
- Wöhl-Bruhn S, Bertz A, Harling S, Menzel H, Bunjes H. Hydroxyethyl starch-based polymers for the controlled release of biomacromolecules from hydrogel microspheres. Eur J Pharm Biopharm. 2012; 81:573-81.
- Joseph S, Bunjes H. Preparation of nanoemulsions and solid lipid nanoparticles by premix membrane emulsification. J Pharm Sci. 2012; 101:2479-89.

Key words
Colloidal drug delivery systems • Lipid drug carriers • Drug nanoparticles • Physicochemical characterization • Protein formulation

Contact
Mendelssohnstraße 1 • 38106 Braunschweig • Phone: +49 (0) 531 391-5652 • heike.bunjes@tu-braunschweig.de
www.tu-braunschweig.de/pharmtech

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PVZ Principal Investigator • Research Profile

Institute for Particle Technology

Prof. Dr. rer. nat. Georg Garnweitner

Research Organisation
Technische Universität Braunschweig
Institute
Institute for Particle Technology
PVZ Research Area
Formulation and Packaging technology

Research Interest & Competences

Our core research area is the **synthesis and application of nanoparticles and nanomaterials.** In particular, we apply chemical synthesis strategies to achieve **highly defined inorganic nanoparticles** such as metal oxides and quantum dots. In pharmaceutical applications, these can be utilized in manifold ways according to their functional properties. For example, luminescent materials such as quantum dots are implemented in theranostic systems for bioimaging. By designing **core-shell nanoparticles** with appropriate surface functionalization, **highly stable, non-toxic systems with specific affinity** are realized. We also have **extensive experience in magnetic nanoparticles** that can be utilized in **hyperthermia therapy** but also in **downstream processing,** for example for the separation of therapeutic antibodies from complex biological media. We also work on **nanostructured formulations,** for example **niosomal drug delivery systems, and nanostructured inorganic drug carrier systems.**

Major Research Methods

- Synthesis of inorganic nanoparticles for diagnostics and therapy
- Synthesis and functionalization of magnetic nanoparticles for product purification
- Fabrication of vesicular colloidal systems such as niosomes for drug delivery
- Multifunctional theranostic systems

Photo credit: Cedric Porsiel; iPAT / TU Braunschweig

Dispersions of quantum dots with size increasing from 3.0 to 5.5 nm show UV luminescence in different colors with high efficiency, rendering them suitable for bioimaging and theranostic applications.

Selected Publications

- Stolzenburg P, Lorenz T, Dietzel A, Garnweitner G. Microfluidic synthesis of metal oxide nanoparticles via the nonaqueous method. Chem Eng Sci. 2018; 191:500-510.
- Gädke J, Kleinfeldt L, Biedendieck R, Garnweitner G, Krull R. In situ affinity purification of His-tagged protein A from Bacillus Megaterium cultivation using recyclable superparamagnetic iron oxide nanoparticles. J Biotechnol. 2017; 242:55-63.
- Zellmer S, Garnweitner G, Breinlinger T, Kraft T, Schilde C. Hierarchical structure formation of nanoparticulate spray-dried composite aggregates. ACS Nano. 2015; 9:10749-10757.
- Kockmann A, Hesselbach J, Zellmer S, Kwade A, Garnweitner G. Facile surface tailoring of metal oxide nanoparticles via a two-step modification approach. RSC Adv. 2015; 5:60993-60999.
- Masthoff I-C, David F, Wittmann C, Garnweitner G. Functionalization of magnetic nanoparticles with high-binding capacity for affinity separation of therapeutic proteins. J Nanopart Res. 2014; 16:2164.

Key words
Nanoparticles • Theranostic systems • Niosomes • Magnetic separation

Contact
Volkmaroder Str. 5 • 38104 Braunschweig • Phone: +49(0)531 391-9615 • g.garnweitner@tu-braunschweig.de
www.ipat.tu-braunschweig.de

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PVZ Principal Investigator • Research Profile

Institute for Particle Technology

Prof. Dr.-Ing. Arno Kwade

Research Organisation
Technische Universität Braunschweig
Institute
Institute for Particle Technology
PVZ Research Area
Formulation and Packaging Technology

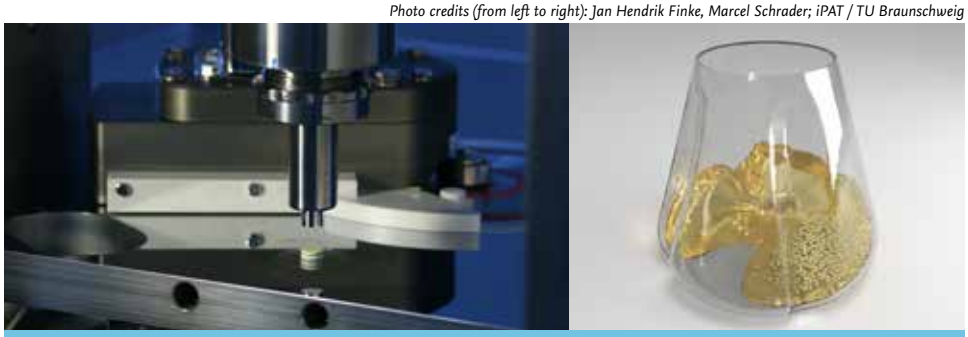
Research Interest & Competences

The research focuses mainly on the formulation and production of advanced and challenging **solid drug products,** especially granules, tablets and orodispersible films for poorly soluble API. An important objective is to determine the so-called process-structure-property relationships. The research covers the entire process chain from tailoring drug particles, especially by **(nano)milling** and **precipitation,** and their further processing by **classification, mixing, granulation** (especially within fluidized bed, high shear mixer) and **tabletting.** Moreover, the mechanical impact on microorganisms in diverse processes is investigated. Special focus lies on **microfluidic** and **continuous production** processes. For the **characterization** of the processes and products advanced measurement methods like nanoindentation, AFM, Raman spectroscopy, Cryo SEM, µCT and µPIV are intensively employed. In order to deeply understand and forecast product properties from the processes multiscale DEM and coupled DEM-CFD **simulations** as well as **population balance model** calculations are carried out.

Major Research Methods

- Nanomilling and precipitation of nanosized API particles
- Granulation by fluidized bed, high shear mixing and tabletting
- DEM (Discrete Element Method) – simulation
- Characterization of powder flowability and particle mechanics
- Characterization of drug products with poorly soluble API

Photo credits (from left to right): Jan Hendrik Finke, Marcel Schrader; iPAT / TU Braunschweig



A compaction simulator is used to tediously analyse the compaction process of multilayer tablets (left) to identify determining mechanisms to enable (cost-)efficient scaling to production presses. The simulation of complex cultivation systems containing glass particles and cells combines different simulation approaches (right, CFD-DEM) to facilitate an enhanced process understanding (right).

Selected Publications

- Göke K, Lorenz T, Repanas A, Schneider F, Steiner D, Baumann K, Bunjes H, Dietzel A, Finke JH, Glasmacher B, Kwade A. Novel strategies for the formulation and processing of poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics 2018; 126:40-56.
- Steiner D, Finke JH, Kwade A. Instant ODFs - Development of an intermediate, nanoparticle-based product platform for individualized medication. European Journal of Pharmaceutics and Biopharmaceutics 2018; 126:149-158.
- Melzig S, Finke JH, Schilde C, Kwade A. Formation of long-term stable amorphous ibuprofen nanoparticles via antisolvent melt precipitation (AMP). European Journal of Pharmaceutics and Biopharmaceutics 2018; 131:224-231.
- Bitterlich A, Laabs C, Krautstrunk I, Dengler M, Juhnke M, Grandeury A, Bunjes H, Kwade A. Process parameter dependent growth phenomena of naproxen nanosuspension manufactured by wet media milling. European Journal of Pharmaceutics and Biopharmaceutics 2015; 92:171-179.
- Gothsch T, Finke JH, Beinert S, Lesche C, Schur J, Büttgenbach S, Müller-Goymann C, Kwade A. Effect of Microchannel Geometry on High-Pressure Dispersion and Emulsification. Chemical Engineering and Technology 2011; 34:335-343.

Key words
Drug nanoparticles • Solid dosage form production • Process and drug product simulation • Poorly soluble drug formulation • High pressure micro systems

Contact

Volkmaroder Straße 5 • 38104 Braunschweig • Phone: +49(0)531 391-9610 • a.kwade@tu-braunschweig.de
www.tu-braunschweig.de/ipat

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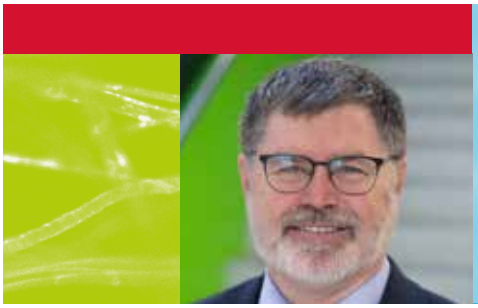


PVZ Principal Investigator • Research Profile

Institute for Technical Chemistry • Polymer Chemistry

Prof. Dr. Henning Menzel

Research Organisation
Technische Universität Braunschweig
Institute
Institute for Technical Chemistry / Polymer Chemistry
PVZ Research Area
Formulation and Packaging Technology

Research Interest & Competences

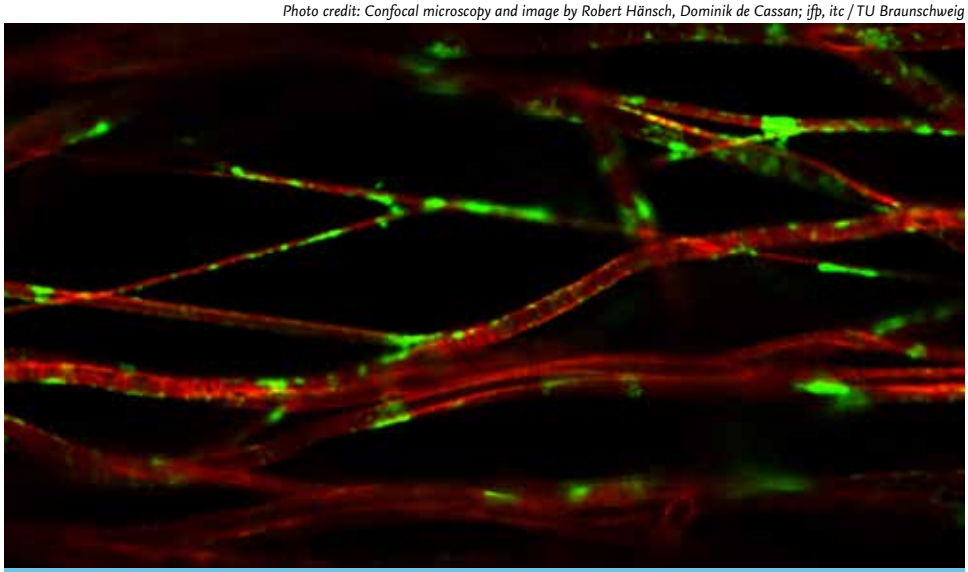
Self-Binding ultrathin copolymer films on implants, just a few nanometer thin, introduce new functionalities to the implant surface, like e.g. the prevention of biofilm formation. For this, the coatings have to have a selective effect, being antibacterial without compromising the integration of the implant in the normal tissue.

Drug delivery systems: Macroscopic hydrogels are prepared to investigate the possibilities to tailor the release profile for therapeutic proteins. The topic was expanded towards micro-particular hydrogels as injectable delivery systems for antibodies or nanogels for immobilization and delivery of growth factors at implant surfaces. The latter are further developed to be a drug release system implemented on electro spun fiber mats. In this way, novel, cell-free implants will be prepared, which activate and instruct endogenous stem cells to "regenerate" junctions of different tissues.

Major Research Methods

- Polymer synthesis
- Surface analytics by e.g. ellipsometry, surface potential measurement or XPS
- Ultrathin polymer coatings by self-assembly of copolymers or layer-by layer technique
- Mikro- and nano- hydrogels as drug delivery systems

Photo credit: Confocal microscopy and image by Robert Hänsch, Dominik de Cassan; ifp, itc / TU Braunschweig



Functionalized fibre mat by fluorescence-labelled nanoparticles.

Selected Publications

- de Cassan D, Sydow S, Schmidt N, Behrens P, Roger Y, Hoffmann A, et al. Attachment of nanoparticulate drug-release systems on poly (ε-caprolactone) nanofibers via a graftpolymer as interlayer. Colloids Surf B Biointerfaces. 2018; 163:309-20.
- Poth N, Seiffart V, Gross G, Menzel H, Dempwolf W. Biodegradable Chitosan Nanoparticle Coatings on Titanium for the Delivery of BMP-2. Biomolecules. 2015; 5:3-19.
- Bertz A, Wöhl-Bruhn S, Miethe S, Tiersch B, Koetz J, Hust M, et al. Encapsulation of Proteins in Hydrogel Carrier Systems for Controlled Drug Delivery: Influence of Network Structure and Drug Size on Release Rate. J Biotechnol. 2013; 163:243-9.
- Pfaffenroth C, Winkel A, Dempwolf W, Gamble LJ, Castner DG, Stiesch M, et al. Self-Assembled Antimicrobial and Biocompatible Copolymer Films on Titanium. Macromol Biosci. 2011; 11:1515-25.
- Menzel H, Wassmann M, Stelljes S, Stiesch M, Winkel A. Verfahren zur Herstellung einer antibakteriellen Beschichtungszusammensetzung für Implantate. Germany Patent: DE102015219139B4. 2017.

Key words
Polymers • Drug delivery systems • Hydrogel • Surface analytics

Contact
Hagenring 30 • 38106 Braunschweig • Phone: +49 (0) 531 391-5360 • h.menzel@tu-braunschweig.de
www.tu-braunschweig.de/itc

pvz
Zentrum für
Pharmaverfahrenstechnik

PVZ Research Area

Microdevices & Analytics

For the development and production of effective, affordable and personalized medicines critical information on the active ingredients as well as on their formulation and production methods has to be provided. Many of the analytical methods currently used in pharmacy require elaborate preparations and large sample volumes. This is costly and time-consuming and requires highly skilled personnel. The aim of this research focus is therefore to provide methods that allow highly selective, precise, rapid and stable analysis with very small amounts of active ingredients, formulations and biological systems. On the other side, micro- and miniaturized systems can also be applied to intensify the production of APIs and medicines. Especially micro fluidic systems enable the reaction, precipitation, emulsification and dispersing in continuous mode at low and high pressures. Moreover, miniaturized devices offer the opportunity to establish cell cultivation in biomimetic environments for the preclinical testing of drug candidates.

For this purpose, different methodological approaches are being pursued: one is the production and application of miniaturized devices, the so-called lab-on-chip and organ-on-chip systems in which fluids controlled in submillimeter dimensions can be manipulated and analyzed, and secondly, the development and adaptation of more classical analysis methods and procedures for small quantities. A challenge is also the design of sampling, sample preparation, and measurement with the least possible interference with ongoing processes.

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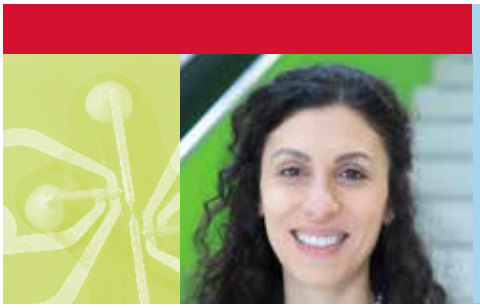


PVZ Principal Investigator • Research Profile

Institute of Microtechnology

Jun.-Prof. Dr. Iordania Constantinou

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Microtechnology &
Center of Pharmaceutical Engineering
PVZ Research Area
Microdevices & Analytics

Research Interest & Competences

My research focuses on the development of **miniaturized sensors and sensing platforms** for the characterization of particles, single cells and tissues. Such sensors can be implemented on **microfluidic platforms** for precise specimen manipulation and control over the experimental conditions. Within the context of the research performed at PVZ, such systems could be used for the **synthesis, manipulation, characterization,** and **sorting** of **drug particles.** Additionally, optical and electrical characterization of live cells and tissues can be performed under different conditions, including in the presence of pharmaceutical products. Finally, we are interested in the development of **miniaturized PAT sensors** for the monitoring and control of pharmaceutical manufacturing processes.

Major Research Methods

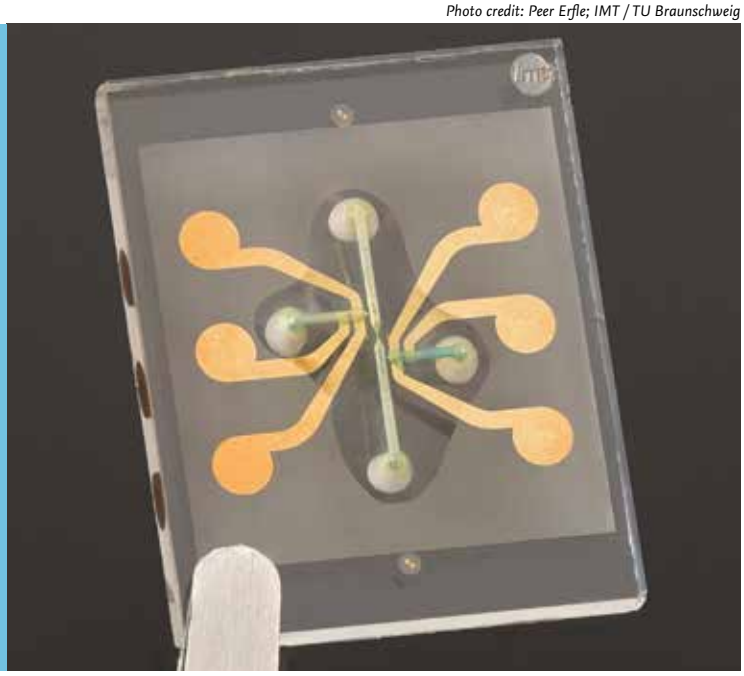
- Micro- / nanofabrication using photolithography and soft-lithography
- COMSOL simulations
- Fluorescence and confocal microscopy
- Impedance/capacitance/resistance sensing

Selected Publications

- Schwarz M, Jendrusch M, Constantinou I. Spatially resolved electrical impedance methods for cell and particle characterization. Electrophoresis 2020; 41:65.
- Constantinou I, Jendrusch M, Aspert T, Görlitz F, Schulze A, Charvin G, Knop M. Self-Learning Microfluidic Platform for Single-Cell Imaging and Classification in Flow. Micromachines 2019; 10:311.
- Constantinou I, Yi X, Shewmon NT, Klump ED, Peng C, Garakyaraghi S, Lo CK, Reynolds JR, Castellano FN, So F. Effect of polymer-fullerene interaction on the dielectric properties of the blend. Adv. Energy Mater. 2017; 7:e1601947.
- Constantinou I, Shewmon NT, Klump ED, Lo CK, Reynolds JR, So F. Photodegradation of metal oxide interlayers in polymer solar cells. Adv. Mater. Interfaces 2016; 3:e160074.
- Constantinou I, Lai TH, Klump ED, Goswami S, Schanze KS, So F. Effect of Polymer Side Chains on Charge Generation and Disorder in PBDTTPD Solar Cells. ACS Appl Mater Interfaces. 2015; 7:26999-27005.

Photo credit: Peer Erfle; IMT / TU Braunschweig

Advanced microfluidic sensing platforms.



Key words
Optofluidics • Advanced sensing • Particle/cell characterization • Materials characterization

Contact

Franz-Liszt-Str. 35a • 38106 Braunschweig • Phone: +49(0)531 391-9769 • i.constantinou@tu-braunschweig.de
www.tu-braunschweig.de/imt

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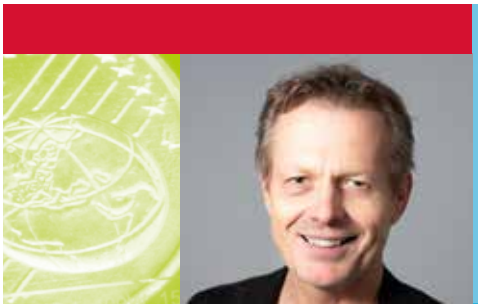

PVZ Principal Investigator • Research Profile

Institute of Microtechnology

Prof. Dr. Andreas Dietzel

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Microtechnology
PVZ Research Area
Microdevices & Analytics

Research Interest & Competences

For fast and effective screening of drugs in different formulations and for more personalized medicine demanding production in very small volumes, the **microfluidic approach** seems ideally suited. With **miniaturized systems** that can be realized by microfabrication processes, new tools for research and development become available. The aim of my research is to investigate **lab-on-chip systems** for the manipulation of fluids, particles, droplets, and cells in microscopic environments that can find applications in pharmaceutical engineering. On one hand lab-on-chip systems can provide **highly selective, and rapid analysis** with very small amounts of active ingredients, formulations and biological systems. A special focus lies on so called **organ-on-chip systems** to be used in the **preclinical testing of drugs and drug formulations.** On the other hand, microsystems can also be applied to intensify the production of APIs and medicines. In particular, microbioreactors and miniaturized nanoparticle precipitation devices are investigated which offer new opportunities for drug development.

Major Research Methods

- Micro- and nanofabrication in cleanroom
- Ultrashort-pulse laser fabrication
- Micro flow characterization by FEM and µPIV
- Electrical / optical sensing

Photo credit: Peer Erfle; IMT / TU Braunschweig

Glass chip for precipitation of nanoparticles, multiphase flow.

Selected Publications

- Lorenz T, Bojko S, Bunjes H, Dietzel A. An inert 3D emulsification device for individual precipitation and concentration of amorphous drug nanoparticles, Lab Chip. 2018; 18:627-638.
- Mattern K, Beißner N, Reichl S, Dietzel A. DynaMiTES - A dynamic cell culture platform for in vitro drug testing PART 1 - Engineering of microfluidic system and technical simulations. Eur J Pharm Biopharm. 2018; 126:159-165.
- Erfle P, Riewe J, Bunjes H, Dietzel A. Optically monitored segmented flow for controlled ultra-fast mixing and nanoparticle precipitation, Microfluidics Nanofluidics 2017; 21:179.
- Schulze T, Mattern K, Früh E, Hecht L, Rustenbeck I, Dietzel A. A 3D microfluidic perfusion system made from glass for multiparametric analysis of stimulus-secretion coupling in pancreatic islets. Biomed Microdevices. 2017; 19:47.
- Petousis I, Homburg E, Derks RJS, Dietzel A. Transient behaviour of magnetic micro-bead chains rotating in a fluid by external fields, Lab Chip. 2007; 7:1746-1751.

Key words
Lab-on-Chip • Organ-on-chip • Microbioreactor • Biosensing • Microfabrication

Contact

Alte Salzdahlumer Str. 203 • 38124 Braunschweig • Phone: +49(0)531 391-9750 • a.dietzel@tu-braunschweig.de
www.tu-braunschweig.de/imt

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PVZ Principal Investigator • Research Profile

Institute of Pharmaceutical Technology

Prof. Dr. Stephan Reichl

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Pharmaceutical Technology
PVZ Research Area
Microdevices & Analytics

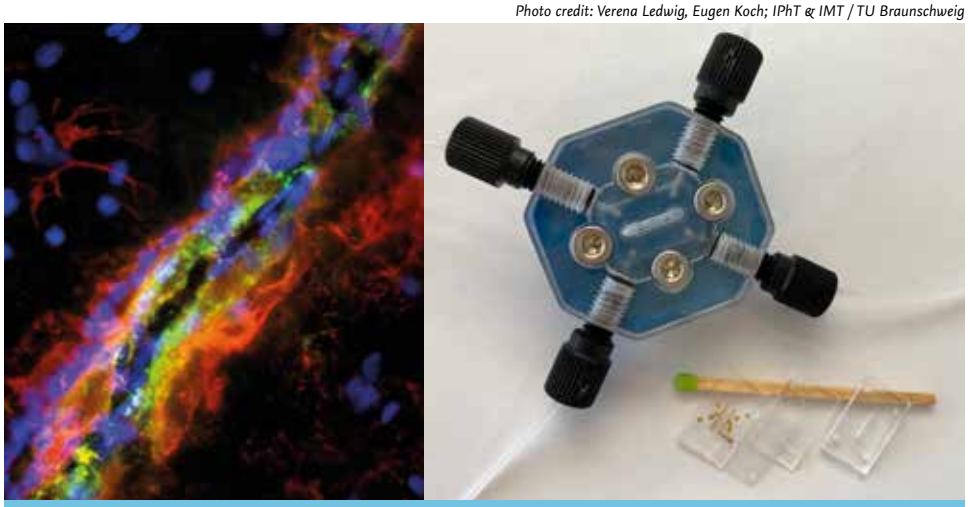
Research Interest & Competences

The research focus of my group is the development, characterization and validation of **3D cell culture models of epithelial and endothelial barriers,** such as cornea, nasal mucosa or blood-brain barrier (BBB) as **alternative to animal models** in preclinical research for the investigation of **drug transport processes.** These artificial tissues are mainly used for the determination of drug absorption, for the evaluation of novel drug delivery systems or **approaches to improve bio-availability,** e.g. by tight junction modulators, as well as for the in vitro assessment of bio-equivalence. Within the PVZ, these tissues are developed by combination with microfluidic elements as organ on chip systems. **Organ-on-chip technologies** offer the potential to perform in vitro tests under more in vivo adapted conditions with very small amounts of active substances. A third research area is concerned with engineering of ocular tissues for the reconstruction of the ocular surface in the field of **regenerative medicine.**

Major Research Methods

- Cell culture, tissue engineering
- Cell characterization (e.g. microscopic techniques, molecular biological methods)
- Drug permeation
- Analytical methods (e.g. chromatography, radiolabeled compounds)

Photo credit: Verena Ledwig, Eugen Koch; IPhT & IMT / TU Braunschweig



Cross section of brain capillary, immunostaining of microvascular endothelial cells, pericytes and astrocytes (left); BBB-on-Chip for drug testing under dynamic conditions (right).

Selected Publications

- Beißner N, Mattern K, Dietzel A, Reichl S. DynaMiTES – a dynamic cell culture platform for in vitro drug testing PART 2 – Ocular DynaMiTES for drug absorption studies of the anterior eye. Eur J Pharm Biopharm. 2018; 126:166-176.
- Dolberg A, Reichl S. Activity of multidrug resistance-associated proteins 1 – 5 (MRP1 – 5) in the RPMI 2650 cell line and explants of human nasal turbinate. Mol Pharm. 2017; 14:1577-1590.
- Verstraelen J, Reichl S. Expression analysis of MDR1, BCRP and MRP3 transporter proteins in different in vitro and ex vivo cornea models for drug absorption studies. Int J Pharm. 2013 30; 441:765-775.
- Hahne M, Zorn-Kruppa M, Guzman G, Brandner J, Haltner-Ukomado E, Wätzig H, Reichl S. Prevalidation of a human cornea construct as an alternative to animal corneas for in vitro drug absorption studies. J Pharm Sci. 2012; 101:2976-2988.
- Reichl S. Films based on human hair keratin as substrates for cell culture and tissue engineering. Biomaterials. 2009; 30:6854-6866.

Key words
3D cell culture • Organ-on-chip • In vitro drug testing • Drug absorption • Pharmacokinetics

Contact
Mendelssohnstraße 1 • 38106 Braunschweig • Phone: +49 (0) 531 391-5651 • s.reichl@tu-braunschweig.de
www.tu-braunschweig.de/pharmtech/

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PVZ Principal Investigator • Research Profile

Institute of Pharmacology, Toxicology and Clinical Pharmacy

Prof. Dr. Ingo Rustenbeck

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Pharmacology, Toxicology and Clinical Pharmacy
PVZ Research Area
Microdevices & Analytics

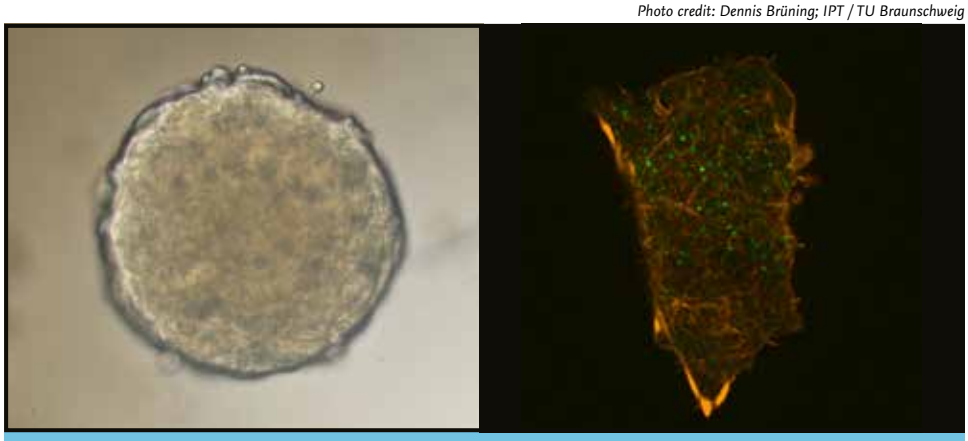
Research Interest & Competences

The scientific interest of our group is directed towards the **mechanisms** which shape the **biphasic kinetics of insulin secretion.** The biphasic kinetics is regarded as indispensable for the maintenance of the glucose homeostasis of the organism. The diminution or even loss of the first phase secretion in response to a glucose challenge is a typical feature of **type 2 diabetes.** Insulin is synthesized and secreted by the beta cells located in the islets of Langerhans in the pancreas. However, pancreatic islets make up only 1 - 2 % of the mass of the pancreas and have to be isolated from the surrounding exocrine tissue by a time-consuming and potentially damaging digestion procedure. The scarce availability of pancreatic islets and beta cells is a major obstacle for research in this field. Thus it is imperative to gain the **most of information out of a minimal number of islets. Microfluidic platforms with integrated analytical function,** such as developed in the PVZ division of microdevices and analytics represent a promising approach to achieve this goal.

Major Research Methods

- Dynamic insulin and glucagon secretion studies
- Life cell imaging
- Electrophysiology
- Standard molecular biology techniques
- Cell and tissue culture

Photo credit: Dennis Brüning; IPT / TU Braunschweig



The left part of the figure shows a collagenase-isolated pancreatic islet of ca. 150 µm diameter. In the right part, a single beta cell is shown. This cell has been adenovirally transduced to label the insulin granules (green) with insulin-EGFP and the actin cytoskeleton (orange) with mTagRFP-T-Lifeact-7.

Selected Publications

- Seemann N, Welling A, Rustenbeck I. The inhibitor of connexin Cx36 channels, mefloquine, inhibits voltage-dependent Ca2+ channels and insulin secretion.Mol Cell Endocrinol. 2018; 472:97-106.
- Gädke J, Thies JW, Kleinfeldt L, Schulze T, Biedendieck R, Rustenbeck I, Garnweitner G, Krull R, Dietzel A. Selective manipulation of superparamagnetic nanoparticles for product purification and microfluidic diagnostics. Eur J Pharm Biopharm. 2018; 126:67-74.
- Brüning D, Reckers K, Drain P, Rustenbeck I. Glucose but not KCl diminishes submembrane granule turnover in mouse beta-cells. J Mol Endocrinol. 2017; 59:311-324.
- Schulze T, Mattern K, Früh E, Hecht L, Rustenbeck I. Dietzel A. A 3D microfluidic perfusion system made from glass for multiparametric analysis of stimulus-secretioncoupling in pancreatic islets. Biomed Microdevices. 2017; 19:47.
- Schulze T, Morsi M, Reckers K, Brüning D, Seemann N, Panten U, Rustenbeck I. Metabolic amplification of insulin secretion is differentially desensitized by depolarization in the absence of exogenous fuels. Metabolism. 2017; 67:1-13.

Key words
Diabetes • Insulin secretion • Pancreatic islets • Cytosolic Calcium • Mitochondria

Contact

Mendelssohnstraße 1 • 38106 Braunschweig • Phone: +49(0)531 391-5670 • i.rustenbeck@tu-braunschweig.de
www.tu-braunschweig.de/ipt

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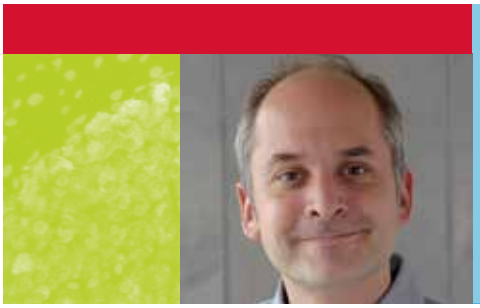


PVZ Principal Investigator • Research Profile

Institute of Pharmacology, Toxicology and Clinical Pharmacy

Prof. Dr. Stephan Scherneck

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Pharmacology, Toxicology and Clinical Pharmacy
PVZ Research Area
Microdevices & Analytics

Selected Publications

- Kluth O, Stadion M, Gottmann P, Aga H, Jähnert M, Scherneck S, Vogel H, Krus U, Seelig A, Ling C, Gerdes J, Schürmann A. Decreased Expression of Cilia Genes in Pancreatic Islets as a Risk Factor for Type 2 Diabetes in Mice and Humans. Cell Rep. 2019; 26:3027-3036.
- Scherneck S, Schlinke N, Beck E, Grupe K, Weber-Schoendorfer C, Schaefer C. Pregnancy outcome after first-trimester exposure to metformin: A prospective cohort study. Reprod Toxicol. 2018; 81:79-83.
- Gorboulev V, Schürmann A, Vallon V, Kipp H, Jaschke A, Klessen D, Friedrich A, Scherneck S, Rieg T, Cunard R, Veyhl-Wichmann M, Srinivasan A, Balen D, Breljak D, Rexhepaj R, Parker HE, Gribble FM, Reimann F, Lang F, Wiese S, Sabolic I, Sendtner M, Koepsell H. Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. Diabetes. 2012; 61:187-196.
- Vogel H, Nestler M, Rüschendorf F, Block MD, Tischer S, Kluge R, Schürmann A, Joost HG, Scherneck S. Characterization of Nob3, a major quantitative trait locus for obesity and hyperglycemia on mouse chromosome 1. Physiol Genomics. 2009; 38:226-232.
- Chadt A, Leicht K, Deshmukh A, Jiang LQ, Scherneck S, Bernhardt U, Dreja T, Vogel H, Schmolz K, Kluge R, Zierath JR, Hultschig C, Hoeben RC, Schürmann A, Joost HG, Al-Hasani H. Tbc1d1 mutation in lean mouse strain confers leanness and protects from diet-induced obesity. Nat Genet. 2008; 40:1354-1359.

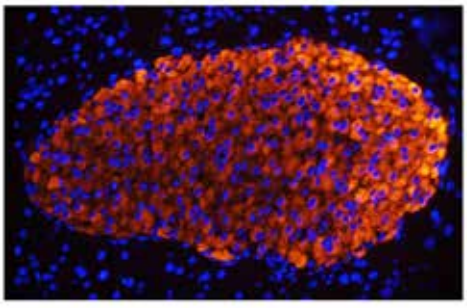
Research Interest & Competences

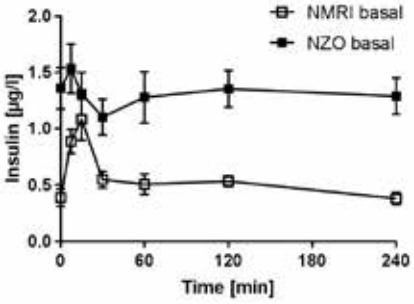
Modern drug therapy considers the **individual characteristics of the patient.** These include (patho-) physiological parameters, such as the presence of **obesity** or **pregnancy,** but also other factors like nutrition and medication for comorbidities. This complex interaction is particularly evident in the treatment of **metabolic diseases** such as **diabetes.** To elucidate the underlying pathomechanisms, we use mouse models that reflect the characteristics of the **human disease.** This enables us to analyze adaptation processes of organs relevant for **glucose metabolism** in conditions of increased insulin demand.
In the context of the PVZ we are focusing on transferring the characteristics of our mouse models to **microfluidic ex vivo-systems.** This provides new and innovative tools for the analysis of impaired metabolic processes and their interaction with compounds for the treatment of the disease. Furthermore, the **safety of drug therapy of diabetes** is the focus of cooperation projects that we conduct with partners in the clinical sector.

Major Research Methods

- Metabolic characterisation of mouse models for human diseases
- *In vivo*- and *ex vivo*- techniques
- Histological and immunohistochemical methods
- Human observational studies on drug safety

Photo credit: IPT / TU Braunschweig





The increased insulin demand during pregnancy is usually compensated by an expansion of beta cell mass. If these or other adaptation mechanisms are deficient, impaired glucose tolerance can develop. In later life, the risk of a manifest diabetes is increasing.

Key words
Metabolic diseases • Diabetes • Drug therapy during pregnancy • Mouse models • Human cohorts

Contact

Mendelssohnstraße 1 • 38106 Braunschweig • Phone: +49(0)531 391-8440 • s.scherneck@tu-braunschweig.de
www.tu-braunschweig.de/ipt

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Pharmaverfahrenstechnik

PVZ Research Area

Multi-scale Simulations of Pharmaceutical Processes

This cross-sectional group of PVZ aims at developing computer-aided models to predict drug properties and production related material parameters. In addition to that, even complex production processes and entire production chains shall be simulated.

Of particular interest are poorly soluble drug candidates. The research topics range from the prediction of suitable solvents for different production steps and ideal excipients for the formulation of poorly soluble compounds with simulations on molecular scale, to microscopic simulations of particulate systems and particulate interactions, up to macroscopic simulations to improve process control and to identify ideal process chains.

The analysis of quantitative structure-property relationships (QSPR), molecular simulation techniques, and quantum chemical computations are employed on molecular scale to predict physicochemical properties of drugs and drug candidates as to support the process of drug synthesis and drug formulation.

Particulate streams, the interaction of streams and biofilms or cells and reactor designs are studied on microscopic scale. Finite element methods, discrete element methods, lattice Boltzmann methods, and finite volume methods are used to solve the simulation of these problems. For coupled mechanics and fluid mechanics problems, combinations of several of these methods are already well established within the group. Simulations for the optimization of process control and flow sheet simulations are investigated on macroscopic scale in order to find efficient process chains for continuous drug production.

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PVZ Principal Investigator • Research Profile

Institute of Solid Mechanics

Prof. Dr.-Ing. Markus Böl

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Solid Mechanics
PVZ Research Area
Multi-scale Simulations of Pharmaceutical Processes

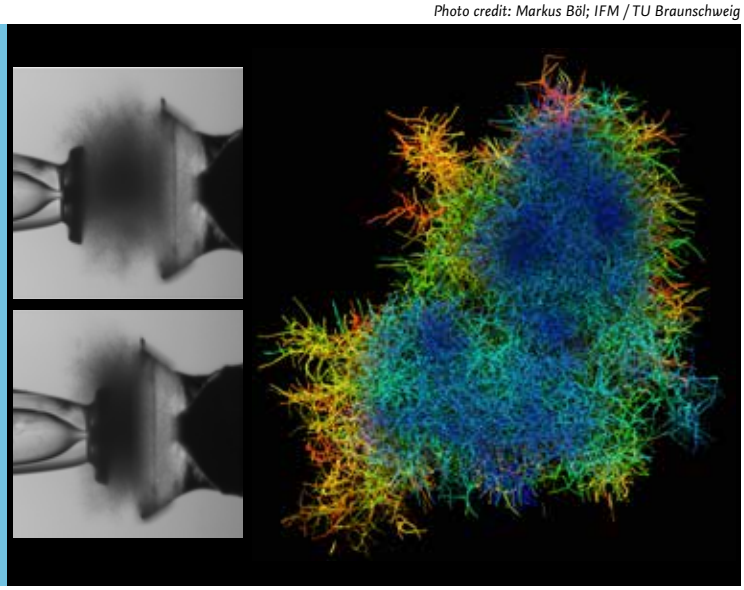
Research Interest & Competences

Main research aim of the Institute of Solid Mechanics is the two-part: On the one hand, we focus on the **three-dimensional multi-scale/field modelling of biological structures** reaching from single cells over biofilms and pellets to large scale objects like biological organs. In doing so, **material modelling approaches** considering mechanical, thermal, chemical, and electrical field can be taken into account, just to name a few. Beside multi-field approaches, we aim to develop comprehensive **modelling concepts** that transfer information on different length scales and thus provide **comprehensive multi-scale information.** On the other hand, another research focus of the IFM is the **mechanical characterisation of biological structures** to calibrate and validate aforementioned model developments. For this purpose, methods are available that enable characterisation at various length scales reaching from cell (micro) to structural (macro) level.

Major Research Methods

- Three-dimensional modelling
- Multi-scale/field modelling
- Finite element modelling/simulation
- Fluid-structure interactions
- Multi-scale/field experiments

Photo credit: Markus Böl; IFM / TU Braunschweig



Filamentous pellet (Actinomadura namibiensis). Large image: Colour-coded pellet (blue: low depth, red: high depth). Small images: Micromechanical compression experiments on a single pellet (top: no compression, bottom: max. compression).

Selected Publications

- Böl M, Iyer R, Dittmann J, Garcés-Schröder M, Dietzel A. Investigating the passive mechanical behaviour of skeletal muscle fibres: Micromechanical experiments and Bayesian hierarchical modelling. Acta Biomater. 2019; 92:277-289.
- Dittmann J, Tesche S, Krull R, Böl M. The influence of salt-enhanced cultivation on the micromechanical behaviour of filamentous pellets. Biochem Eng J. 2019; 148:65-76.
- Dittmann J, Dietzel A, Böl M. Mechanical characterisation of oocytes - The influence of sample geometry on parameter identification. J Mech Behav Biomed Mater. 2018; 77:764-775.
- Morales-Orcajo E, Siebert T, Böl M. Location-dependent correlation between tissue structure and the mechanical behaviour of the urinary bladder. Acta Biomater. 2018; 75:263-278.
- Beißner N, Bolea Albero A, Füller J, Kellner T, Lauterboeck L, Liang J, Böl M, Glasmacher B, Müller-Goymann CC, Reichl S. Improved in vitro models for preclinical drug and formulation screening focusing on 2D and 3D skin and cornea constructs. Eur J Pharm Biopharm. 2018; 126:57-66.

Key words
Material modelling • Material characterisation • Cell characterisation • FEM

Contact
Langer Kamp 8 • 38106 Braunschweig • Phone: +49(0)531 391-7050 • m.boel@tu-braunschweig.de
www.tu-braunschweig.de/ifm

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PVZ Principal Investigator • Research Profile

Institute of Thermodynamics • Molecular Thermodynamics

PD Dr.-Ing. Gabriele Raabe

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Thermodynamics /
Group Molecular Thermodynamics
PVZ Research Area
Multi-scale Simulations of Pharmaceutical Processes

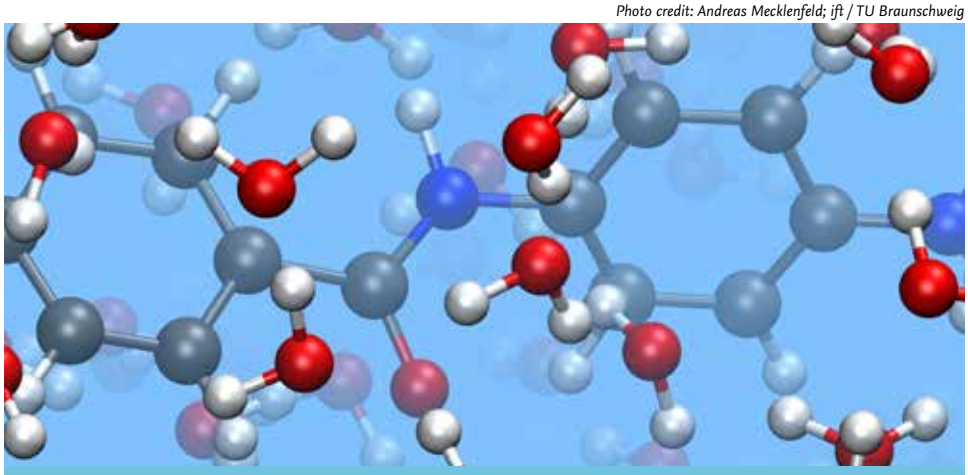
Research Interest & Competences

My research in general is aimed at employing **molecular simulation methods** for the prediction of thermophysical properties, and for gaining a molecular level insight into systems to allow for an identification of relevant molecular interaction patters. A further research focus of my group is the development of the underlying molecular models (force fields) for simulations studies. For this, we are also applying ab initio simulations.
In the PVZ context, our major research interest is the **optimization** of both **simulation algorithms and molecular models** for **efficient and reliable predictions** of solvation free energies for various solute/solvent pairs – including metallodrugs and lipid solvents. Beyond that, we are interested in **molecular simulation** studies on the molecular determinants for the solubilization of drugs in colloidal carrier systems, and in analyzing the drug – carrier – stabilizer interactions.

Major Research Methods

- „Pathfinder" = optimized algorithms for efficient and reliable ΔG_{solv} simulations (by MBAR, TI)
- „GAFF/IPolQ-Mod + LJ-Fit"= optimized molecular models for ΔG_{solv} predictions
- Molecular dynamics simulations on thermophysical and structural properties, using various simulation packages (GROMACS, Lammps, DL_POLY, VMD)
- Ab initio simulations for force field development (using Gaussian, ESPRESSO)

Photo credit: Andreas Mecklenfeld; ift / TU Braunschweig



Exemplary snapshot of N-(4-aminophenyl)benzamide dissolved in water during a molecular dynamics simulation. (Visualization generated with VMD 1.9.3. [Humphrey et al. Mol. Graphics 1996, 14, 33–38]).

Selected Publications

- Mecklenfeld A, Raabe G. Comparison of RESP and IPolQ-Mod Partial Charges for Solvation Free Energy Calculations of Various Solute/Solvent Pairs. J. Chem. Theory Comput 2017; 13:6266-6274.
- Mecklenfeld A, Raabe G. Applicability of a Thermodynamic Cycle Approach for a Force Fields Parametrization Targeting Non-Aqueous Solvation Free Energies. J. Computer-Aided Molecular Design (JCAM) 2020; 34:71-82, DOI: 10.1007/s10822-019-00261-5.
- Mecklenfeld A, Raabe G, Efficient Solvation Free Energy Simulations: Impact of Soft-Core Potential and a New Adaptive λ-Spacing Method. Mol. Phys. 2017; 115:1322-1334.
- Raabe G, Molecular Simulation Studies on Thermophysical Properties, Springer, Series Molecular Modeling and Simulation: Application and perspectives 2017 ISBN 978-981-10-3545-6.
- Raabe G, Sadus RJ. Molecular dynamics simulations of the dielectric constant of water: the effect of bond flexibility. J Chem Phys. 2011; 134:234501.

Key words
Molecular simulation • Molecular modelling • Solvation free energy • Molecular interactions

Contact
Hans-Sommer-Straße 5 • 38106 Braunschweig • Phone: +49 (0) 531 391-2628 • g.raabe@tu-braunschweig.de
www.tu-braunschweig.de/ift

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Zentrum für
Pharmaverfahrenstechnik

PVZ Principal Investigator • Research Profile

Institute for Particle Technology

Jun.-Prof. Dr.-Ing. Carsten Schilde

Research Organisation
Technische Universität Braunschweig
Institute
Institute for Particle Technology &
Center of Pharmaceutical Engineering
PVZ Research Area
Multi-scale Simulations of
Pharmaceutical Processes

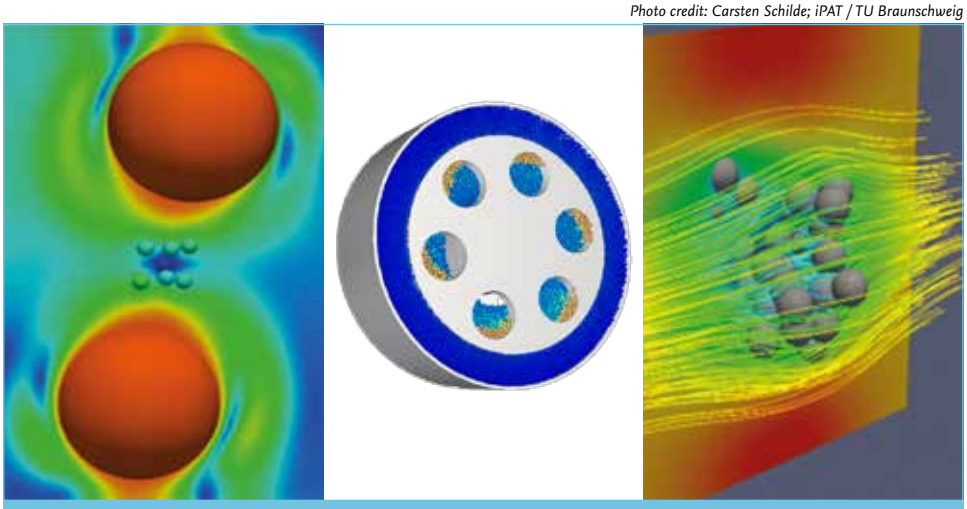
Research Interest & Competences

The goal of the research area **"Particle Simulation and Functional Structures"** is the **targeted design of particle interfaces and structures** as well as their formulation and further processing into innovative, novel products. The resulting structures determine the subsequent product properties and are significantly influenced by the underlying micro and macro processes along the production chain. In order to gain an understanding of the structure formation along the process chain, the particulate systems are supported on the process and formulation level but also on the microscale by numerical simulation methods, in particular the **Discrete Element Method (DEM)** and its coupling with **Computational Fluid Dynamics (CFD)** as well as **methods of artificial intelligence.** A prerequisite for the numerical modeling of particles is the establishment of strategies for the calibration and validation of the simulation parameters by defined model experiments or measurements.

Major Research Methods

- Simulation-based design, optimization and formulation development
- CFD-DEM software development
- DEM (LIGGGHTS, ROCKY), CFD (OpenFoam, Fluent), PBM (Dyssol), AI
- Particle manipulation, processing and characterization

Photo credit: Carsten Schilde; iPAT / TU Braunschweig



Coupled CFD-DEM simulations of particles between grinding beads (IBM, left), grinding media movement in a horizontal stirred media mill (center) and aggregate in shear flow (IBM, right).

Selected Publications

- Beinert S, Kwade A, Schilde C. Strategies for multi-scale simulation of fine grinding and dispersing processes: Drag coefficient and fracture of fractal aggregates. Advanced Powder Technology 2018;29:707-718.
- Kubiak M, Storm K, Kampen I, Schilde C. Relationship between Cross-Linking Reaction Time and Anisotropic Mechanical Behavior of Enzyme Crystals. Crystal Growth & Design 2019;19:4453-4464.
- Schrader M, Pommerehne K, Wolf S, Finke B, Schilde C, Kampen I, Lichtenegger T, Krull R, Kwade A. Design of a CFD-DEM-based method for mechanical stress calculation and its application to glass bead-enhanced cultivations of filamentous Lentzea aerocolonigenes, Biochemical Engineering Journal 2019;148:116-130.
- Zellmer S, Garnweitner G, Breinlinger T, Kraft T, Schilde: C. Hierarchical structure formation of nanoparticulate spray-dried composite aggregates. ACS Nano 2015;9:10749-10757.
- Beinert S, Fragnière G, Schilde C, Kwade A. Analysis and modelling of bead contacts in wet-operating stirred media and planetary ball mills with CFD–DEM simulations. Chemical Engineering Science 2015;134:648-662.

Key words
Discrete Element Method • Particle simulation • Functional structures • Artificial intelligence

Contact

Volkmaroder Straße 5 • 38104 Braunschweig • Phone: +49(0)531 391-65551 • c.schilde@tu-braunschweig.de
www.tu-braunschweig.de/ipat

pvz
Zentrum für
Pharmaverfahrenstechnik

PVZ Research Area

Pharmaceutical Manufacturing Engineering

Working towards the pharmaceutical factory of the future this cross-sectional group takes a comprehensive approach to establish sustainable production technologies for pharmaceutical drugs and dosage forms. Research and development is based on the processes established in the other divisions of PVZ, especially in pharmaceutical-biological and -chemical process technologies as well as formulation and packaging technology. Special focus is on methods and technologies with regard to up-scaling, energy- and resource-efficient manufacturing, digitalisation in manufacturing and production systems enabling individualised production and/or cost-efficient mass production.

The cross-group aims to elaborate, assess, optimize and provide customized production technologies and methods taking into account the specific regulatory, plant-specific, infrastructural and operational conditions of a pharmaceutical production. Flexible, integrated and tailored production concepts from drug extraction or biotechnological or chemical drug synthesis to packaged medicines for a defined capacity are designed and evaluated. This includes the implementation of instruments and plant technology together with process management, analytics, quality control based on models and parameters, and quality assurance as well as aspects on regulation and operating technology.

Furthermore, adequate methods and tools for an early-stage economic as well as environmental assessment support the sustainability-oriented planning and design of processes, process chains, and plants. Depending on the demands of the product and the targeted capacity the most feasible production technology can be identified and adapted.

Zentrum für Pharmaverfahrenstechnik

PVZ Principal Investigator • Research Profile

Institute of Machine Tools and Production Technology

Prof. Dr.-Ing. Christoph Herrmann

Research Organisation
Technische Universität Braunschweig
Institute
Institute of Machine Tools and Production Technology, Sustainable Manufacturing and Life Cycle Engineering and
Fraunhofer Institute for Surface Engineering and Thin Films IST
PVZ Research Area
Pharmaceutical Manufacturing Engineering

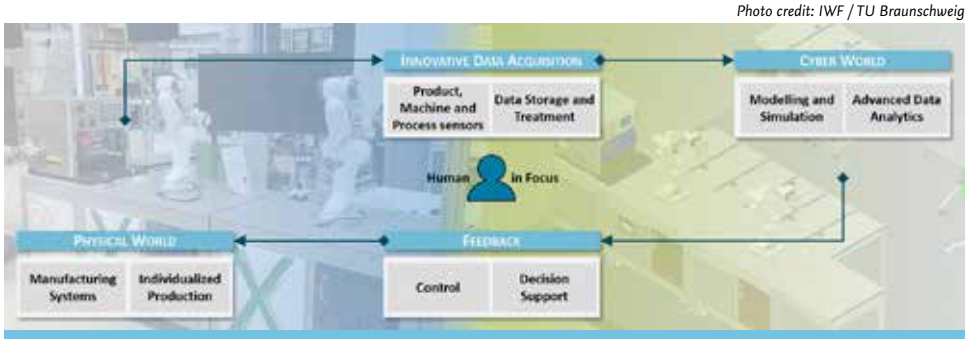
Research Interest & Competences

The manufacturing of individualized drugs embedded in resilient supply chains is a major scientific and social challenge of the 21st century. The Chair of Sustainable Manufacturing and Life Cycle Engineering at the Institute of Machine Tools and Production Technology (IWF) works with methods, tools and technologies in pharmaceutical manufacturing from a production engineering point of view. Two major scopes are decentralized manufacturing systems enabling a close-to-customer production of individualized pharmaceutical products as well as cost-efficient mass production. In addition, life cycle engineering methods and tools are investigated that support decisions with respect to economic and environmental requirements.
The research fields can be clustered in sustainability, digitalized production and innovative production systems. Within the research field of sustainability, life cycle assessment based engineering of pharmaceutical products and processes, the development of symbiotic internal and external process chains as well as energy and resource-efficiency are in focus. In the context of digitalized production, tracking and tracing along the value chain, modelling and simulation and cyber-physical production systems are investigated. In the field of innovative production systems, all scales from unit processes up to a plant level are considered. The focus is on concepts and technologies (e.g. smart devices), enabling flexible and scalable production of pharmaceutical products.

Major Research Methods

- Multi-Scale modelling and simulation of manufacturing systems
- Cyber-physical production systems
- Life Cycle Engineering
- Systems of Systems Engineering

Photo credit: IWF / TU Braunschweig



Framework of a cyber-physical production system embedded in a flexible production cell for individualized drugs.

Selected Publications

- Leiden A, Cerdas F, Noriega D, Beyerlein J, Herrmann C. Life cycle assessment of a disposable and a reusable surgery instrument set for spinal fusion surgeries. Resources, Conservation and Recycling 2020; 156:104704.
- Thiede S, Schönemann M, Kurle D, Herrmann C. Multi-level simulation in manufacturing companies: The water-energy nexus case. Journal of Cleaner Production 2016; 139:1118-1127.
- Bueth L, Broderius N, Herrmann C, Thiede S. Introducing agent-based simulation of manufacturing systems to industrial discrete-event simulation tools. International Conference on Industrial Informatics (INDIN) 2017; Emden, Germany, IEEE.
- Schönemann M, Herrmann C, Greschke P, Thiede S. Simulation of matrix-structured manufacturing systems. Journal of Manufacturing Systems 2015; 37:104-112.
- Herrmann C, Thiede S, Kara S, Hesselbach J. Energy oriented simulation of manufacturing systems – Concept and application. CIRP Annals – Manufacturing Technology 2011; 60:45-48.

Key words
Sustainability • Production • Digitalization • Life Cycle Engineering • Cyber-physical production systems

Contact
Langer Kamp 19 B • 38106 Braunschweig • Phone: +49(0)531 391-7149 • c.herrmann@tu-braunschweig.de
www.tu-braunschweig.de/iwf

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Zentrum für
Pharmaverfahrenstechnik

PVZ Principal Investigator • Research Profile

Pharmaceutical Manufacturing Engineering

Dr. Michael Thomas

Research Organisation
Fraunhofer Institute for Surface Engineering and Thin Films IST
Department
Department Atmospheric Pressure Processes
PVZ Research Area
Pharmaceutical Manufacturing Engineering

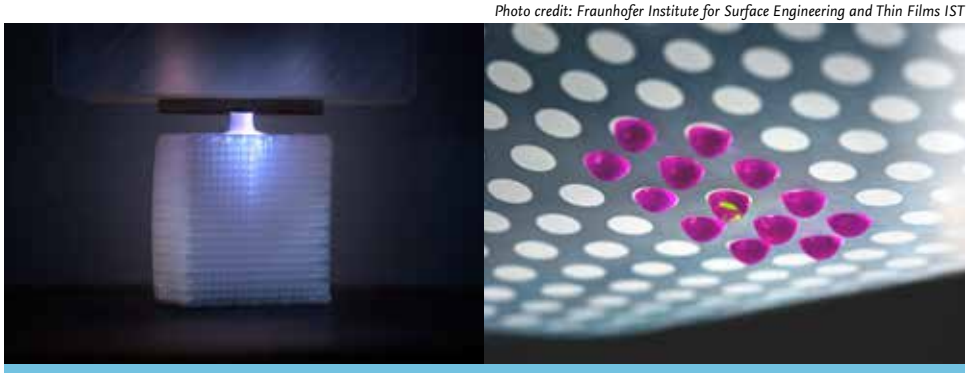
Research Interest & Competences

The surface of medical and pharmaceutical devices plays an important role for their functionality and usability. The Fraunhofer Institute for Surface Engineering and Thin Films IST focuses on the development and simulation of innovative surface modifications, sustainable processes and process chains using a wide range of thin film technologies to adjust the surface towards the desired function. This is supplemented by extensive capabilities in surface analysis.
One major scope are dry plasma-chemical processes for creating chemical reactive surfaces, which can be used for covalent bonding of e.g. bio-molecules or for developing new bonding technologies for packaging processes. Even on particles or complex geometries coatings and surfaces can be created to retain the adhesion of proteins or liquids or to achieve anti-fouling, tribological or barrier properties. Due to the flexibility and efficiency of the plasma processes the technology can easily be adapted to pharmaceutical process chains.
Micro plasma-based process chains and sources were developed for the complete and local modification of microfluidic devices as well as for area-selective surface treatments for producing bio-sensor structures or microarrays.

Major Research Methods

- Plasma chemical modifications
- Surface analytics
- Microplasmas and micro-structuring
- Tribological and barrier coatings

Photo credit: Fraunhofer Institute for Surface Engineering and Thin Films IST



Development of new functional coatings on porous materials by plasma processes, e.g. for regenerative medicine (left). Labbag® for stem-cell research in hanging droplets: Section with a hydrophobic layer and local hydrophilic spots by an atmospheric pressure plasma coating process (right).

Selected Publications

- Thomas M, Herrmann A, Dohse A, Borris J, Weidlich ER. Printing of µm structures with nano inks using a novel combination of high-resolution plasma printing and subsequent rotogravure printing. Plasma Processes and Polymers. 2019; 16:1900080
- Herrmann A, Lachmann K, Fischer L, Kovac J, Thomas, M. Area-selective epoxy coatings by DBD-PECVD in 3D cavities for protein coupling. Surface Innovations. 2015; 3:206-214.
- Thomas M, Eichler M, Lachmann K, Borris J, Hinze A, Klages CP. Adhesion Improvement by Nitrogen Functionalization of Polymers Using DBD-based Plasma Sources at Ambient Pressure. Atmospheric Pressure Plasma Treatment of Polymers; Relevance to Adhesion. Edited by Thomas M, Mittal KL. 2013; 251-273.
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- Barreto MC, Borris J, Thomas M, Hänsel R, Stoll M, Klages CP. Reduction of Plasticizer Leaching from PVC by Barrier Coatings Deposited Using DBD Processes at Atmospheric Pressure. Plasma Processes and Polymers. 2012; 9:1208-1214.

Key words
Sustainability • Plasma • Surface chemistry • Adhesion • Sensors

Contact
Bienroder Weg 54 E • 38018 Braunschweig • Phone: +49(0)531 2155-525 • michael.thomas@ist.fraunhofer.de
www.ist.fraunhofer.de

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Zentrum für
Pharmaverfahrenstechnik

Notes

Center of Pharmaceutical Engineering, PVZ

IMPRINT

Published by
TU Braunschweig
Center of Pharmaceutical Engineering

Franz-Liszt-Straße 35a
38106 Braunschweig

Phone +49 531 391-65502
pvz@tu-braunschweig.de
www.tu-braunschweig.de/pvz

Editorial Office
Dr. Gerlinde Benninger
Center of Pharmaceutical Engineering

Layout & Design
Livingpage® GmbH & Co. KG