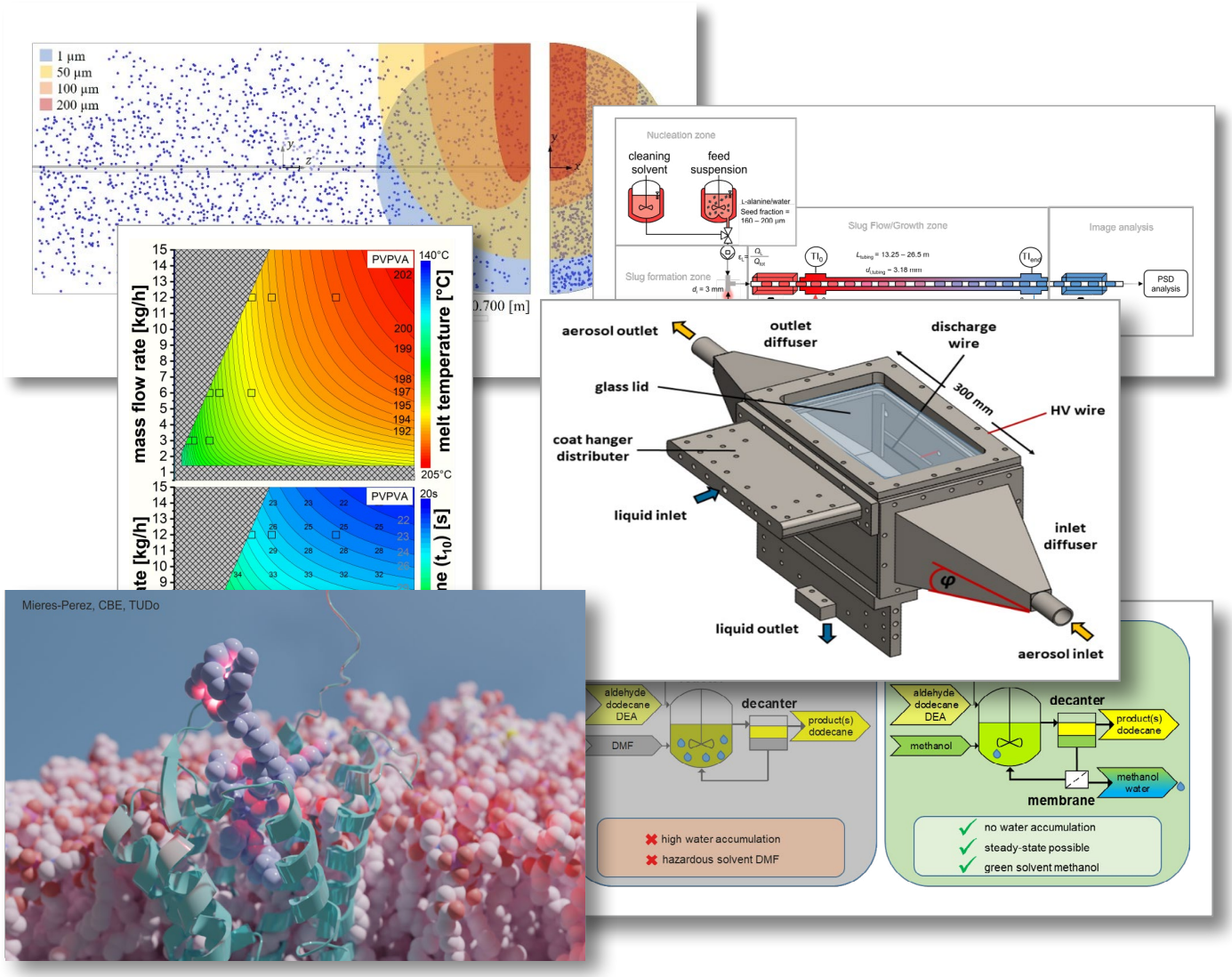
technische universität
dortmund

2023

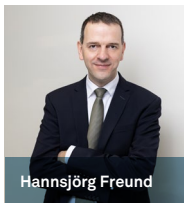
SCIENTIFIC HIGHLIGHTS

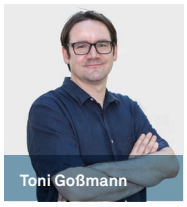
Annual Report

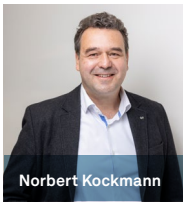


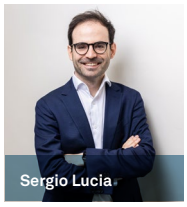
Fakultät Bio- und
Chemieingenieurwesen

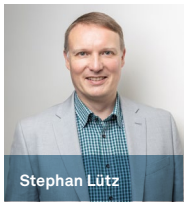
Content

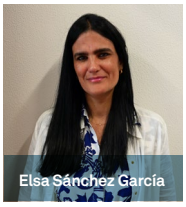


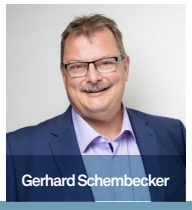


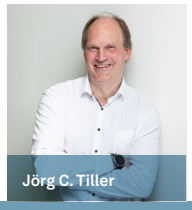


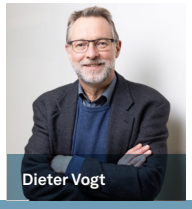


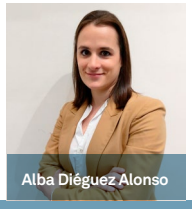












Department of BCI

Preface

Dear Reader,

Annually publishing the „Best of Science" of the Department of Bio- and Chemical Engineering of the TU Dortmund has become a long-standing tradition. The present Scientific Highlights of the year 2023 – the 14th edition - are testament of the booming research activities of the department. They include many aspects of modern process engineering in the chemical, biochemical, and pharmaceutical industry. Focus of the Highlights are often sustainability and computational science. The scientific work was mostly achieved by our students in their bachelor, masters, and doctoral theses, which are the backbone of our department. The faculty is composed of engineers, chemists, pharmacists, and computer scientists. This ensemble was strengthened last year by Prof. Alba Diéguez Alonso, who is leading the group of transport processes. She is working on biomass conversion, which as greatly adding to our main research emphasis sustainability. I wish her a great start. I hope the present collection of Scientific Highlights inspires you, the readers, to remain or become our collaboration partners.

Enjoy the reading,

Prof. Joerg C. Tiller

Equipment Design (AD)

Extending Ontologies Assisted by Natural Language Processing

Gathering the semantic knowledge for FAIR data management by automated text crawling

Alexander S. Behr, Lukáš Korel, Uladzislau Yorsh, Martin Holeňa, Norbert Kockmann

Ontologies store semantic knowledge in a machine-readable way and represent domain knowledge in controlled and connected vocabulary. Human-readable texts often contain a lot of semantic knowledge. With natural language processing (NLP) methods, it is possible to extend ontologies with text-based semantic information, facilitating Findable, Accessible, Interoperable, Reusable (FAIR) data workflows. In order to compare different ontologies, the textual definitions of the vocabulary are contrasted using NLP.

Ontologies facilitate the formalized expression of knowledge, providing explicit representation of knowledge. As manual creation leads to diverse representations, ways to extend and develop ontologies using natural language processing (NLP) techniques were investigated.
First, automating the selection of relevant ontologies for scientific texts to reduce experts' workload was studied. The overall workflow is depicted in Figure 1 and could be used to classify scientific texts. With this, the ontologies fitting best to the text can be determined, leading to automated labeling of textual data, fit for further use in machine learning applications. Significant differences between scientific texts and ontology annotations were identified, prompting a proposal for an entity recognition step utilizing various classifiers. Testing this in fields related to the domain of catalysis research, the Support Vector Machine displayed the highest confidence and margin. With no ground truth for article classification, methods to mitigate the impact were investigated, including interpolation between annotations using public alternatives to GPT. Future experiments aim to explore various transformers, leverage neural networks, and extend ontologies using graph neural networks. [1]

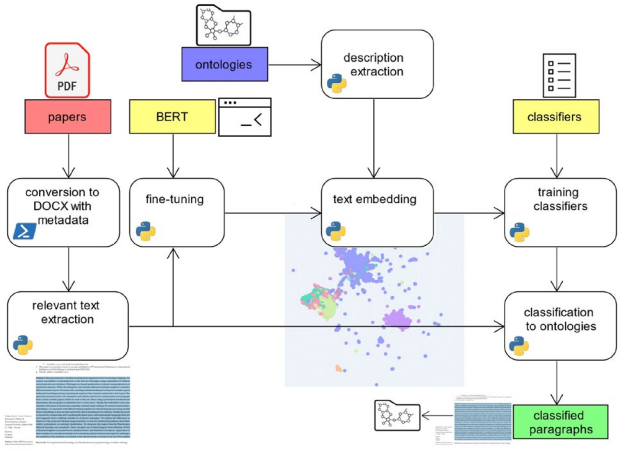


Figure 1: Overall workflow for text-to-ontology mapping via NLP with to search for relevant ontologies in catalysis research leading to classified text paragraphs fit for further application in e.g. machine learning. [1]

In another study, the automatic extension of ontologies using NLP techniques was demonstrated, focusing on a text dataset related to catalytic methanation of CO_2. The workflow also depicted in Figure 2 involves extracting concepts from the text, annotating them using NLP, and extending ontologies with new classes and relations. In a proof-of-concept with 28 papers, the workflow annotates 68.97% of text-based concepts and automatically enriches the Allotrope Foundation Ontology with 90 new classes, 74.44% of which are annotated.
With a graph-based approach, a preliminary safety analysis was developed for early integration into automated engineering workflows [3], see Figure 2.

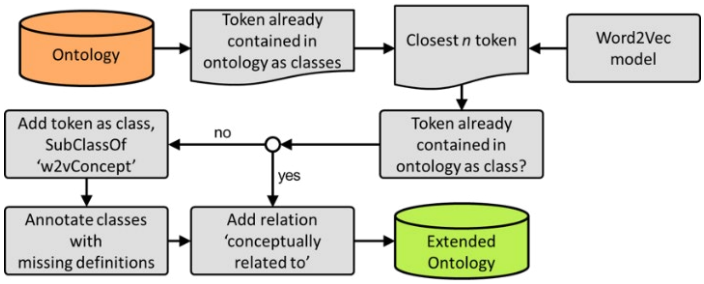


Figure 2: Workflow of code to extend an ontology by new classes based on text dataset. The ontology used as input is denoted red, while the extended ontology, which poses the output of the workflow is colored green. [2, 3]

The adaptable workflow can be applied to other ontologies and text datasets, facilitating automated ontology development for research data annotation in domains like catalysis and process engineering. However, further evaluation by domain experts is recommended to assess the workflow's usefulness in automatically generating valuable classes and relations [2,3].

Publications:
[1] L. Korel, U. Yorsh, A. S. Behr, N. Kockmann, M. Holeňa, Text-to-Ontology Mapping via Natural Language Processing with Application to Search for Relevant Ontologies in Catalysis, MDPI-computers, 12, 14, 2023, doi.org/10.3390/computers12010014
[2] A. S. Behr, M. Völkenrath, N. Kockmann, Ontology extension with NLP-based concept extraction for domain experts in catalytic sciences, Knowledge and Information Systems, 65(12), 5503–5522, 2023, doi.org/10.21203/rs.3.rs-3491129/v1
[3] A. S. Behr, M. Völkenrath, M. Ben Moussa, N. Kockmann, Natural Language Processing-Based Term Extraction for Concept Enrichment of Ontologies for Catalysis Research, 56. Jahrestagung Deutscher Katalytiker, Weimar, 15.-17.03.2023

Contact:
norbert.kockmann@tu-dortmund.de

Artificial Intelligence-assisted engineering for process technology

AI methods exhibit a large potential in assisting the engineering activities in process industries.

Jonas E. Oeing, Laura M. Neuendorf, Norbert Kockmann

Smart process engineering is a thriving topic in the frame of AI tool development. From AI-supported supervision in stirred extraction columns to preliminary safety analysis, and leveraging graph learning of plant topology data, the tools for improved efficiency and safety are developing. Automated P&ID evaluation, powered by DEXPI information, enables streamlined and assisted workflows leading to enhanced productivity. The roadmap ahead is defined by tool´s integration, marking a paradigm shift towards smarter engineering workflows.

The current rapid development of AI-supported methods also affects the process industry and related research. The Laboratory of Equipment Design was co-initiator of the KEEN project (www.keen-plattform.de) and co-edited a special issue of the project´s results in the journal Chemie-Ingenieur-Technik [1]. Beside smart sensor technology [2], the engineering workflow from conceptual design over safety considerations in the early engineering phase [3] to automated processing of pipe & instrumentation diagrams in DEXPI format [4, 5] were addressed (Figure 1) and exhibit new opportunities for engineering activities.

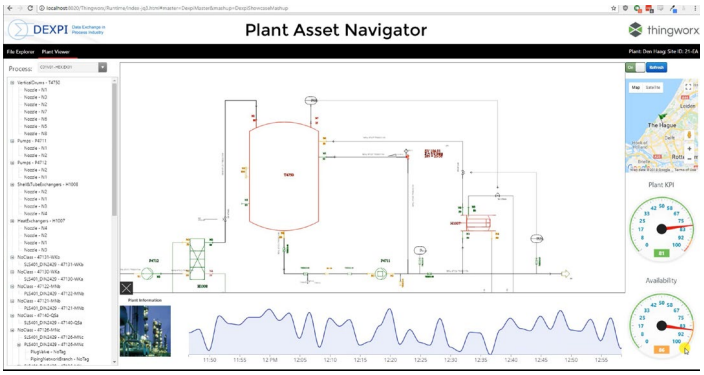


Figure 1: Web-based topology display of a storage vessel in an IIoT platform. Here: a DEXPI plant topology in PTC ThingWorx

A basic requirement for AI tools in process engineering activities is the graph learning in machine-readable plant topology data, here the DEXPI format as well-established, but still developing standard. This assists the necessary shift from a document-oriented to a data-oriented process industry, in particular for describing piping and instrumentation diagrams (P&ID). In the contribution on graph learning [4], industry, software vendors, and research institutions have joined forces to demonstrate the current developments and potentials of machine-readable P&IDs in the DEXPI format combined with artificial intelligence. The aim is to use graph neural networks to learn patterns in machine-readable P&ID data, which results in the efficient engineering and development of new P&IDs. The tool enables for example real-time detection of inconsistencies (e.g. missing equipment or faulty connections). This reduces the development time in detail engineering due to a decrease in error rate and a resulting time saving.
With a graph-based approach, a preliminary safety analysis was developed for early integration into automated engineering workflows [3], see Figure 2.

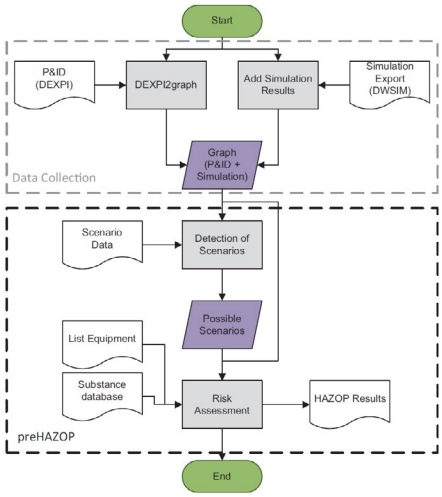


Figure 2: Approach for automated safety analyses with graph-based plant & process models using a deterministic preHAZOP algorithm.

The combination of DEXPI information with those from process simulation enables evaluation of safety-critical scenarios can be in an initial risk assessment.

Contact:
norbert.kockmann@tu-dortmund.de

Publications:
[1] M. Bortz, K. Dadhe, S. Engell, V. Gepert, N. Kockmann, R. Müller-Pfefferkorn, T. Schindler, L. Urbas, AI in Process Industries – Current Status and Future Prospects, Chem. Ing. Technik, 95(7), 975-988, 2023, doi.org/10.1002/cite.202200247
[2] L. Neuendorf, Z. Hammal, A. Fricke, N. Kockmann, AI-based supervision for a stirred extraction column assisted with population balance-based simulation, Chem. Ing. Technik, 95(7), 1134-1145, 2023, doi.org/10.1002/cite.202200241
[3] J. Oeing, T. Holtermann, W. Welscher, N. Kockmann, preHAZOP: Graph-based safety analysis for early integration into automated engineering workflows, Chem. Ing. Technik, 95(7), 1083-1095, 2023, doi.org/10.1002/cite.202200222
[4] J. Oeing, K. Brandt, M. Wiedau, G. Tolksdorf, W. Welscher, N. Kockmann, Graph Learning in Machine-Readable Plant Topology Data, Chem. Ing. Technik, 95(7), 1049-1060, 2023, doi.org/10.1002/cite.202200223
[5] A. Klose, D. Wagner-Stürz, L. Neuendorf, J. Oeing, V. Khaydarov, M. Schleehahn, N. Kockmann, L. Urbas, Automated Evaluation of Biochemical Plant KPIs based on DEXPI Information, Chem. Ing. Technik, 95(7), 1165-1171, 2023, doi.org/10.1002/cite.202200239

AI-assisted sensing and modular control for process equipment and plants

Smart equipment needs new sensors and control measures for improved operations.

Lukas Bittorf, Laura M. Neuendorf, Jonas E. Oeing, Piriyanth Sakthithasan, Norbert Kockmann

For transforming the process industry, AI-driven smart sensors aligned with modular automation standards enhance efficiency in process development and operation. Tailored modular automation with modular type package MTP services are necessary for modular units and process analytics for higher efficiency and robustness. These novel measures are used for advanced extraction cells for improved process conditions. Crystal detection and characterization are supported by convolutional neural networks CNNs for precise size distribution analysis.

Embracing AI for heightened performance and accuracy doesn´t means only new computer algorithms, but also generating a better data base for these tools. Modular automation with design of MTP services for different downstream units and process analytic technology following VDI/VDE/NAMUR 2658 standards [1]. The combination of modular equipment with own automation capability together with an overarching orchestration layer, flexible and rapid adaptation of the plant is possible for new processes, e.g. the distillation of high boiling organic acids [2], see Figure 1.

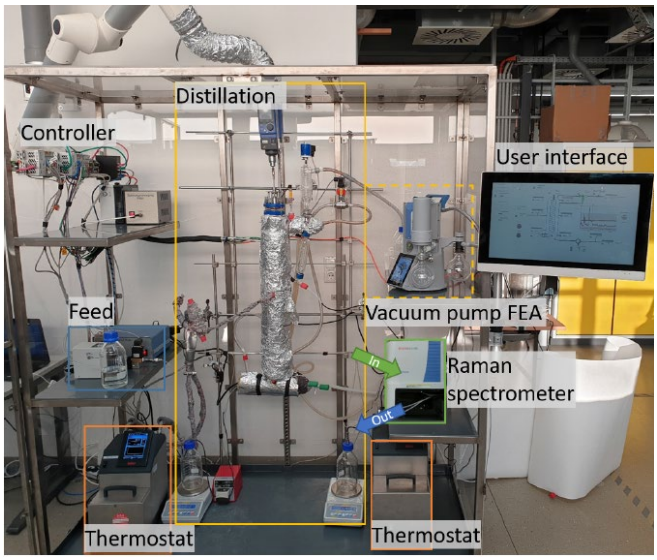


Figure 1: Modular setup of laboratory DN 25 spinning band distillation column and periphery units [1].

In a further step, a digital camera was developed as Artificial Intelligence-based MTP-compatible smart sensor for improved process sensing, control, and automation. Beside a liquid-liquid extraction column, a fermenter was equipped with the digital camera to observe the flooding conditions during aeration of the fermentation broth [3]. Computer vision, powered by convolutional neural networks (CNNs), has been applied to processes like continuous cooling crystallization [4]. Crystals formed in a draft tube baffle crystallizer were monitored in real-time with particle size distribution for optimizing crystal growth and product quality. To widen the operational range of the solvent extraction column, a glass-metal stirred cell was modularly designed for higher temperature and pressure, see Figure 2. Increased temperature range improved the mass transfer, too, and led to improved separation performance with higher mass throughput [5].

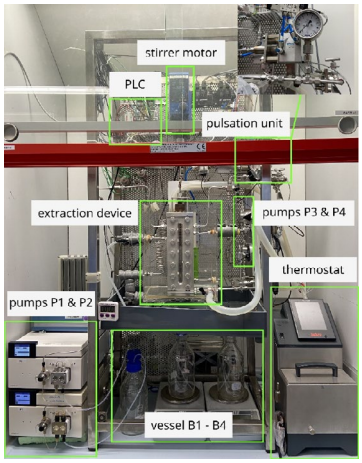


Figure 2: Modular setup of laboratory DN 15 solvent extraction column with periphery units [5].

Contact:
norbert.kockmann@tu-dortmund.de

Publications:
[1] L. Bittorf, J. Oeing, T. Kock, R. Garreis, N. Kockmann, Design of MTP services for modular downstream units and process analytic technology, Chem. Eng. & Technol., 46(7), 1502-1510, 2023, doi.org/10.1002/ceat.202200390
[2] V. Elhami, L.M. Neuendorf, T. Kock, N. Kockmann, B. Schuur, Separation of Crotonic Acid and 2-Pentenoic Acid Obtained by Pyrolysis of Bio-Based Polyhydroxyalkanoates Using a Spinning Band Distillation Column, ACS Sustain. Chem. Eng., 11(12), 4699-4706, 2023, doi.org/10.1021/acssuschemeng.2c07046
[3] L. Neuendorf, V. Khaydarov, C. Schlander, T. Kock, J. Fischer. L. Urbas, N. Kockmann, Artificial Intelligence-based Module Type Package (MTP)-compatible Smart Sensors in the Process Industry, Chem. Ing. Technik, 95(10), 1546-1554, 2023, doi.org/10.3389/fchem.2023.1244043
[4] L. Neuendorf, S. Höving, L. Bennemann, N. Kockmann, Detecting crystals in suspensions: convolutional neural networks vs. a gravity based approach for size distribution detection, Chem. Ing. Technik, 95(7), 1146-1153, 2023, doi.org/10.1002/cite.202200235
[5] P. Sakthithasan, L. Orth, M. Venhuis, N. Kockmann, Design of a process intensified liquid-liquid extraction cell for higher temperature and pressure, Chem. Eng. & Technol., 46(5), 882-890, 2023, doi.org/10.1002/ceat.202200550

Two-Phase Flow Reaction System for DNA-Encoded Amide Coupling

More process information for efficient and reliable process control

Robin Dinter, Suzanne Willems, Mahdi Hachem, Yana Streltsova, Andreas Brunschweiger, Norbert Kockmann

DNA-encoded library (DEL) technologies benefit from automated flow chemistry platforms to facilitate reaction development, building block validation, and high-throughput library synthesis. A liquid-liquid two-phase flow reactor system was designed to enable parallel conduction of reactions with DNA-labeled substrates. The dispersed phase (DP) in the capillary slug flow contained the DNA reaction mixtures, including various carboxylic acids (CA). Fluorocarbon oil FC 40 was introduced as an inert continuous phase (CP) to prevent backmixing. The slugs were successfully generated to act as individual reaction compartments, representing single batch experiments and enabling parallelized reactions. As a widely used exemplar DEL reaction, the amide coupling reaction was successfully transferred from batch to flow chemistry and DNA integrity was ensured.

For process intensification, the coiled flow inverter (CFI) concept was adapted to the DNA encoded chemistry requirements, which considers µL scale reactions, DNA integrity throughout the process, and recovery of the product fraction from the excess unreacted starting material. The tailored CFI for DNA labeled substrates was applied to a liquid-liquid two phase setup, as shown in Figure 1. In order to obtain the µL scale reaction volume, a reproducible slug flow regime was generated. The slugs were pumped back and forth to achieve similar reaction times as in the batch experiments.

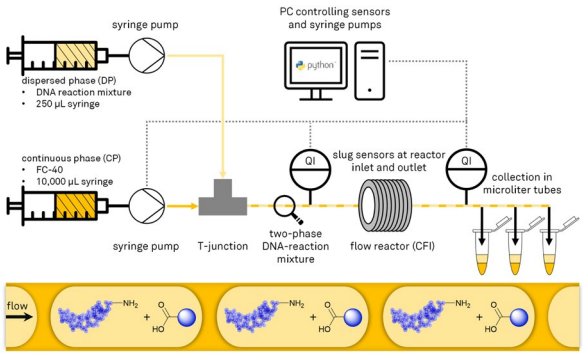


Figure 1: Reaction setup to conduct the DNA encoded amide coupling reaction. The DP was injected using a 250 µL syringe, and the CP using a 10 mL syringe. Slugs were generated with a T junction and collected in microliter tubes for analysis.

Next, the amide coupling reaction with DNA labeled substrates was effectively optimized and conducted in a flow reaction system for the first time. The robustness of the flow reactor design was demonstrated by profiling the reactivity of a small scope of diverse substituted CA, as shown in Figure 2. The main objective in the production of a DEL with different building blocks is to avoid cross contamination. All amide coupling reactions were run in one flow setup for 8 h, with each individual reaction divided into 7 µL slugs. Only the expected product peaks were observed in the MALDI-MS spectra, and no products from other CAs were detected, ruling out cross contamination between slugs containing two different CA. This underlines that the simultaneous reactions in the flow setup worked successfully. In parallel, a batch reaction was performed to compare the performance of the flow.

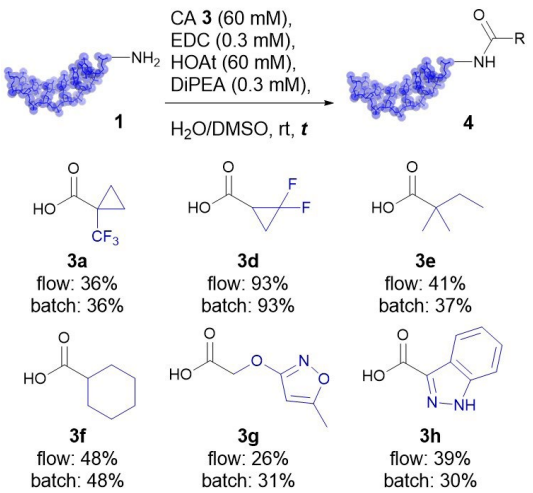


Figure 2: Profiling results of various carboxylic acids (CA) 3 conducted in batch and the flow reaction system after 8 h. A volumetric flow rate of 1.6 mL min^{-1} was set for the flow experiments. The concentration of DNA-labeled amine 1 was 3.6 µmol L^{-1}.

This study showed that the flow and batch setup gave comparable results with moderate to full conversions for a diverse set of CA. More importantly, FC-40 prevented backmixing of the individual slugs without affecting the amide coupling reaction. These results are a successful step towards automatable DEL reactions.

Publications:
[1] R. Dinter, S. Willems, M. Hachem, Y. Streltsova, A. Brunschweiger, N. Kockmann, Development of a Two Phase Flow Reaction System for DNA Encoded Amide Coupling, React. Chem. & Eng., 8, 1334–1340, 2023, doi.org/10.1039/d3re00020f
[2] R. Dinter, S. Willems, T. Nissalk, O. Hastuerk, A. Brunschweiger, N. Kockmann, Development of a Microfluidic Photochemical Flow Reactor Concept by Rapid Prototyping, Front. Chem., 11, 1244043, 2023, doi.org/10.3389/fchem.2023.1244043
[3] R. Dinter, K. Götte, F. Gronke, L. Justen, A. Brunschweiger, N. Kockmann, Development of an Automated Flow Chemistry Affinity-Based Purification Process for DNA-Encoded Chemistry, J. Flow Chem., 13, 361–373, 2023, doi.org/10.1007/s41981-023-00282-0

Contacts:
robin.dinter@tu-dortmund.de
norbert.kockmann@tu-dortmund.de

Reaction engineering tools for flow process engineering

Flow chemistry doesn´t belong to the newest methods in reaction engineering, but still has room for improvement.

Lisa Schulz, Waldemar Krieger, T. Aljoscha Frede, Norbert Kockmann

Flow chemistry is already an established tool in reaction engineering, however, adequate sensing and data analysis are still under development. Reactive intermediates are investigated in the selective monosubstitution on trichlorosilane with ultra-reactive organolithium compounds. With multivariate curve resolution, we facilitate kinetic modeling and scale-up prediction. Seebeck elements in a microcalorimeter enable swift characterization of exothermic reactions supported by data management with a modular Open-Source IoT Platform.

Reaction engineering belongs to the core of chemical engineering and has already many tools in the box. Flow chemistry is a still growing field. We investigated together with the CCB faculty the selective monosubstitution on a trichlorosilane with highly reactive organolithium compounds in a microflow reactor [1]. Since there has been a lack of use in substitution reactions, we used flow microreactors to controllably synthesize highly reactive organolithium compounds and thus create new synthetic opportunities.

Utilizing a microscale flow calorimeter, highly exothermic reactions like thiosulfate oxidation were characterized combined with reactor performance estimation [2]. Through the combination of CFD simulations with reactor performance estimation, we achieved accurate conversion and temperature profiles within the microscale setup (Figure 1). Our approach, tested rigorously for highly oxidative reactions of sodium thiosulfate, demonstrates excellent agreement between estimated and experimental data, showcasing the reliability of our methodology.

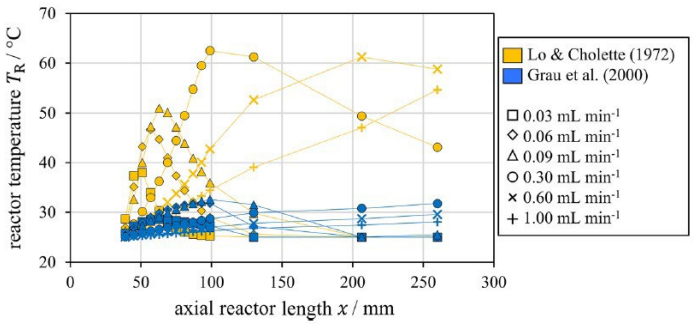


Figure 1: Predicted temperature profile along the reaction channel for thiosulfate oxidation.

For improved kinetic modeling and scale-up prediction, an imine synthesis was investigated in an oscillating segmented flow microreactor at different temperatures using non-invasive Raman spectroscopy [3]. Multivariate curve resolution provided a calibration-free approach for obtaining the kinetic parameters. Taking heat and mass balance into account, the proposed kinetic model was applied for a model-based scale-up prediction from capillary flow conditions to a 0.5 L semi-batch reactor. Observed by in-line Raman spectroscopy and off-line gas chromatography analysis, the scale-up was successfully demonstrated with good agreement between measured and predicted concentration profiles (Figure 2).

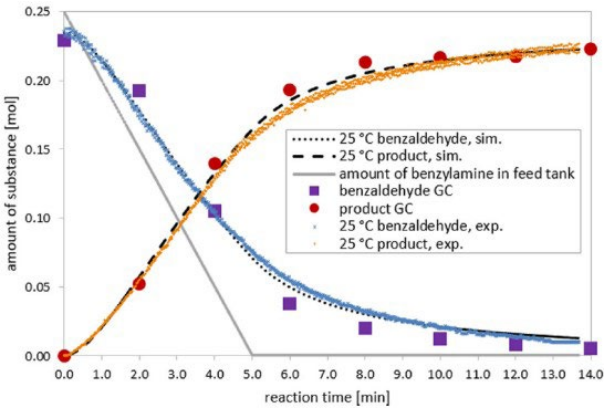


Figure 2: Conversion and yield from multivariate modeling for imine synthesis from benzaldehyde and benzylamine.

The microscale flow calorimeter was connected to the modular open-source IoT-platform d-scover@ from d-fine [4]. The existing OPC UA server was used to stream data into the platform allowing for data visualization, storage, and analysis. The low entry hurdle for operators with little to no programming experience is a key point, since all essential tools for a researcher in the laboratory to store, visualize, and evaluate the measured values are provided without having to install them yourself. In addition, the use of open-source program allows a quick exchange of programs between researchers and the community or forums for help with issues.

Contacts:
norbert.kockmann@tu-dortmund.de

Publications:
[1] M. Achternbosch, L. Zibula, A. Schmidt, W. Krieger, N. Kockmann, C. Strohmann, Selective monosubstitution on a trichlorosilane with highly reactive organolithium compounds in a microflow reactor, J. Flow Chem., 13, 9-12, 2023, doi.org/10.1007/s41981-022-00251-z
[2] T.A. Frede, N. Nikbin, N. Kockmann, Reactor Performance Estimation in Microscale Flow Calorimeter for Rapid Characterization of Exothermic Reactions, J. Flow Chem., 13, 31-44, 2023, doi.org/10.1007/s41981-022-00251-z
[3] L. Schulz, P. Stähle, S. Reining, M. Sawall, N. Kockmann, T. Röder, Multivariate curve resolution for kinetic modeling and scale-up prediction, J. Flow Chem., 13, 13-19. 2023, doi.org/10.1007/s41981-022-00252-y
[4] T.A. Frede, C. Weber, T. Christ, T. Brockhoff, D. Ludwig, N. Kockmann, Data Management of a Microcalorimeter Using a Modular Open-Source IoT Platform, MDPI-processes, 11(1), 2023, doi.org/10.3390/pr11010279

Spatially and Temporally Resolved 3D-Analysis of Bubble Formation in Capillary Flows

Bastian Oldach, Max Schlickewei, Philipp Wintermeyer, Norbert Kockmann

Since its first report, microfluidics is an ever growing trend in various scientific fields and applications as it enables for fast and efficient processes. A deep physical understanding of transport phenomena is essential for the precise control of bubble-based microfluidics. Micro-computed tomography (µCT) is well suited as a non-invasive visualization tool, as it enables for three-dimensional insights into multiphase flow patterns with high spatial resolution, but without need for optical access. This contribution presents the first 3D analysis of bubble formation recorded using µCT.

The 3D analysis (image acquisition: Bruker Skyscan 1275 µCT scanner) provides new insights into bubble formation in different capillary geometries in the micron range (image resolution ~ 15 µm). Image analysis based on artificial intelligence methods is used to identify a defined state of the dispersed phase for each angular position to obtain 3D datasets of periodic flow phenomena. A schematic of the implemented setup inside the µCT and the image evaluation routine can be seen in Figure 1. The investigations cover detailed insights into the squeezing and leaking regimes during bubble formation in capillaries with circular and rectangular cross section (d_h = 1.6 mm). The capillaries are manufactured using stereo lithography and a clear resin.

The bubble volume, the maximum diameter, the interfacial area, and the length of the detaching bubbles are decreasing as the bubble approaches the pinch off stage, as shown in Figure 2. This effect is more relevant for channels of circular cross-sections, where the bubbles fill almost the entire capillary since corner flows prevent these phenomena in rectangular capillaries. The data also provides information regarding the liquid wall film thickness, which approaches a constant value before the bubbles pinch off at t* = 0.4. The phenomena are investigated with air as dispersed phase and polydimethylsiloxane as the continuous phase for flow rates < 1 mL min^{-1}.

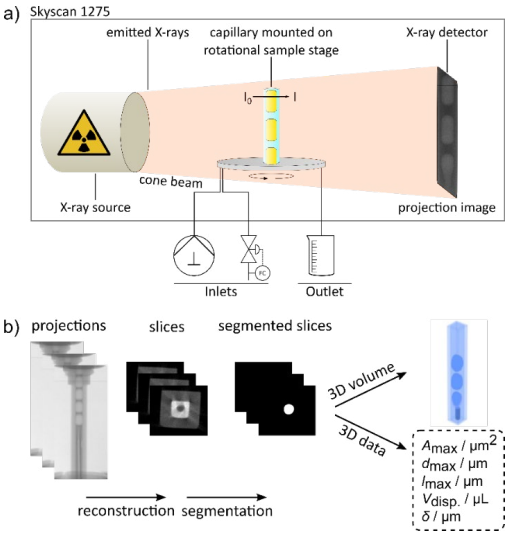


Figure 1: a) Schematic of the setup inside the µCT scanner. The object of interest is mounted onto a rotational disk which is placed between X-Ray source and detector. b) Process of the used image analysis: the projection images are reconstructed to 3D slices, which are then segmented to extract 3D information about the bubble formation.

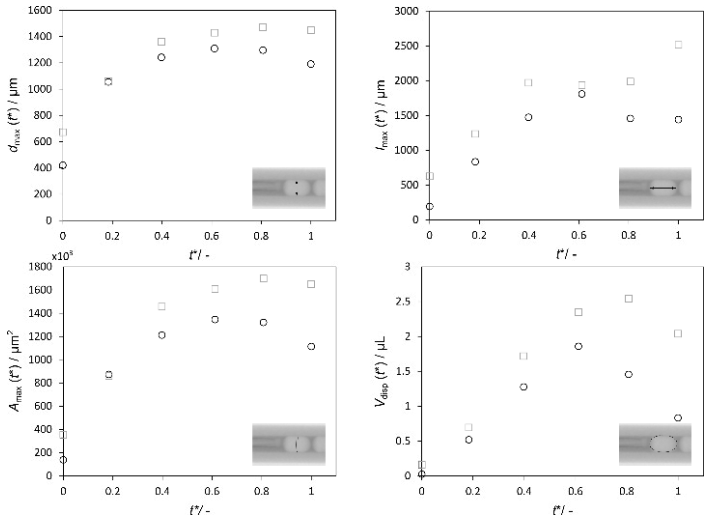


Figure 2: The maximum bubble diameter d_{max}, the maximum bubble length l_{max}, the maximum area A_{max}, and the volume of the dispersed phase V_{disp} are plotted against the dimensionless time t* for six different states during bubble formation in rectangular (grey square) and circular capillaries (black circle).

Publications:
[1] B. Oldach, M. Schlickewei, P. Wintermeyer, N. Kockmann, µTAS Conf. on Miniaturized Systems for Chemistry and Life Sciences, Katowice, Poland, 15.-19.10.2023
[2] B. Oldach, C. Müller, P. Wintermeyer, N. Kockmann, 3D investigation of droplet generation and coalescence in capillary liquid-liquid flows using µ-computed tomography, µFIP Conf. Micro Flow and Interfacial Phenomena, Evanston, IL, USA, 18.-21.6.2023
[3] B. Oldach, L. Ben Achour, C. Müller, P. Wintermeyer, N. Kockmann, Continuous Liquid-Liquid Separation of Segmented Capillary Flows, Flow Chemistry Europe 2023, Hinxton, Cambridgeshire, UK, 25.-26.5.2023

Contacts:
bastian.oldach@tu-dortmund.de
norbert.kockmann@tu-dortmund.de

Smart Image Sensor for Liquid-liquid Systems

More process information for efficient and reliable process control

Inga Burke, Ahmed S. Youssef, Karthik Mannil, Katharina Schmidt, Norbert Kockmann

Smart sensor development for online process monitoring is a growing trend in the process industry. Image analysis offers an effective instrument to analyze product properties during processes and benefits from the fast development of AI-based object detection methods. To use image recognition methods, an optical access to the process of interest is necessary. Therefore, a modular, optical measurement flow cell is designed to capture droplet images during an emulsification process. Automated process control using an AI-based image analysis method is developed and validated for a final design.

Optical methods are a common tool to analyze critical quality attributes (CQA) such as the droplet size distribution (DSD) of emulsification processes [1]. Thus, monitoring and evaluation of the DSD and its changes during an emulsification process is an important field during process efficiency enhancement.

A prototype of an optical flow cell for online monitoring is designed to enable optical access to an emulsification process. Possible challenges during emulsification are high disperse phase content of liquid-liquid systems as well as small droplets. To overcome those challenges, the design of the optical flow cell is based on a modular approach, which enable an adaption of the flow cell concerning the liquid-liquid system. Rapid prototyping of different optical measurement flow cells was realized using SLA-3D printing, which provides flexible design structures and results in an optimized design [1]. The flow cell is designed and evaluated established on an iterative optimization procedure including three key factors during prototyping (device material, channel geometry, and suitability for emulsion systems). This approach to investigate the emulsion system optically builds the fundamental for an AI-based image evaluation.

Smart image sensors enhance the monitoring of multiphase processes [2], such as emulsification. To automatically determine the DSD within the emulsification process, an AI application using different Deep Learning (DL) approaches (YOLOv4 and Mask RCNN) is developed to infer information on how to control the process more efficiently [3]. Figure 1 illustrates the vision-based deep learning framework, incorporating object detection and data processing, which extracts meaningful features from image datasets.

The monitoring of the emulsification process is carried out using the modular, optical flow cell. The captured images are used as the input of the different models. The extracted image information, such as the phase fraction of the used process and the droplet sizes, are used to improve process understanding [4]. Two different AI models for droplet size determination were tested, optimized, and validated. Experimental investigations show that the optical, AI-based evaluation of the droplet size distribution is performable also for higher dispersed phase fractions as well as for droplet sizes of 5 to 100 µm. The final YOLOv4 model is robust and trustworthy for the tested application range. This optical access as well as the performance of both models show promising results and high potential for online process monitoring in emulsification processes.

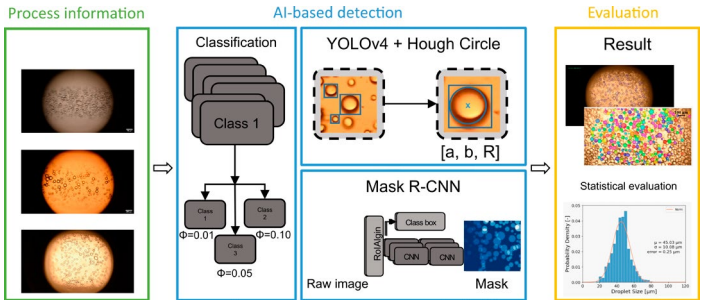


Figure 1: Workflow of the vision-based deep learning framework including process information in the form of process images, the AI-based detection containing classification, and two different DL approaches as well as the results in the form of detection images and a statistical evaluation of the process [3].

Contacts:
inga.burke@tu-dortmund.de
norbert.kockmann@tu-dortmund.de

Publications:
[1] I. Burke, C. Assies, N. Kockmann, Investigation of an 3D-printed Optical Measurement Flow Cell for Process Progress Monitoring of Liquid-Liquid Systems, Flow Chemistry Europe 2023, Hinxton, Cambridgeshire, UK, 25.-26.5.2023
[2] I. Burke, R. Dinter, B. Oldach, A. Frede, A. S. Behr, L. Neuendorf, S. Höving, N. Kockmann, Data-Driven Flow Chemistry - Lab Automation, AI Supported Modules, and Scale-up, Flow Chemistry Europe 2023, Hinxton, Cambridgeshire, UK, 25.-26.5.2023, invited plenary talk
[3] I. Burke, A.S. Youssef, K. Mannil, K. Schmidt, N. Kockmann, Smart image sensor for liquid-liquid systems, µFIP Conf. Micro Flow and Interfacial Phenomena, Evanston, IL, USA, 18.-21.6.2023
[4] I. Burke, C. Assies, N. Kockmann, Investigation and characterization of an 3D-printed optical measurement flow cell for process progress monitoring of liquid-liquid systems, µFIP Conf. Micro Flow and Interfacial Phenomena, Evanston, IL, USA, 18.-21.6.2023

Quasi-Continuous Production of Solids in a Modular and Small-Scale Plant

Integrated processes for efficient particle generation, washing, and drying

Stefan Höving, Thomas Schmidt, Maximilian Peters, Hendrik Lapainis, Phil Bolien, Timo Dobler, Norbert Kockmann

Small-scale continuous apparatuses for solids production are receiving increasing interest due to the demand for the fast market availability of specialty chemical products manufactured in integrated and modular processing plants. Relevant unit operations span from crystallization over solid–liquid separation and filter cake washing to drying. For this purpose, the quasi-continuous filter belt crystallizer (QCFBC) was developed and is presented here.

The functional principle of the apparatus is based on the operation of a horizontal continuous belt filter. Here, the process medium is separated into batch containers that are transported along the operation direction of the plant, covering functional modular units. The concept allows for particle formation, filtration, washing, and drying on a single plant in order to connect the process from solutions to a dry filter cake in a well-controlled manner. The modular units are inter-changeable and the process can therefore be custom-tailored to the specific needs of the substance of interest. The process starts with suspension in the container positioned on the first (red in Figure 1) functional modular unit. Here, the temperature of the suspension is controlled via the functional modules. After, t_{cycle} all the containers travel to the next position. On the last position (green in Figure 1), the product suspension is filtered and the resulting filter cake is washed and dried.

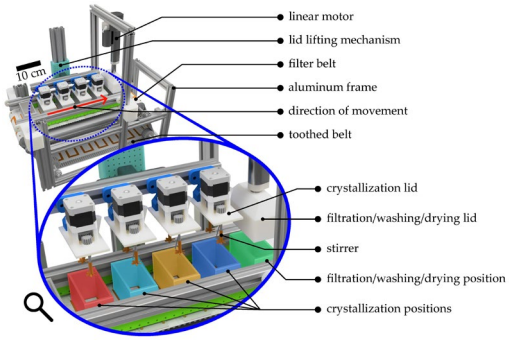


Figure 1. 3D sketch of the modular filter belt apparatus with the five modular functional modules. In the detailed view, the container lids are raised. The first four positions (from left to right) are responsible for the cooling crystallization, while the last container position serves for the filtration, washing, and drying step.

The newly integrated unit operations, positive pressure filtration (Δp_{max}=0.8 bar), filter cake washing ($\dot{V}_{wash}$=55 mL•min^{-1}), and convection drying (T_{dry}=60 °C) have been individually characterized and integrated into the filter apparatus that has been modified and automated for continuous operation. They were synchronized with the flexible cooling crystallization, enabling for a seamless production process. Sucrose in water was used as model substance system. Long-term operations of up to 14 h, as demonstrated in Figure 2, were successfully performed with dry product filter cakes (22.64 g·h^{-1}± 1.64 g·h^{-1}) of constant quality attributes ($x_{50,3}$=216.095 µm±14.766 µm, *span*=0.347±0.109, $Y_{rel.}$=69.9 %±5 %, X_{RM}= 1.64mg·g^{-1}±1.38 mg·g^{-1}).

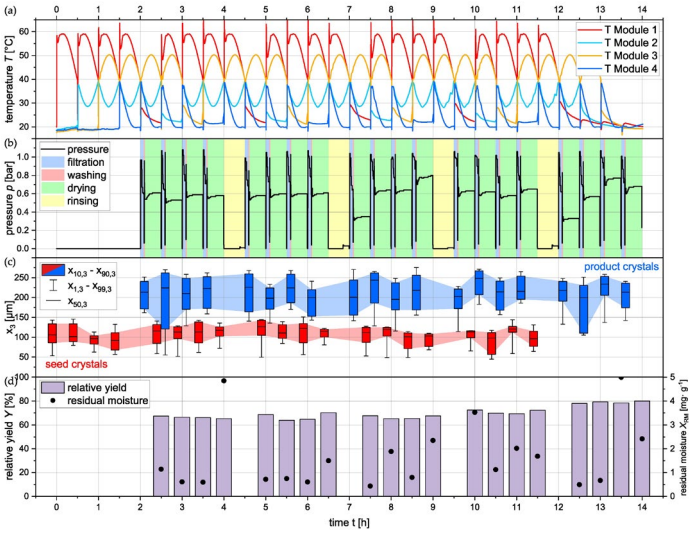


Figure 2. Panel plot of relevant processes and product parameters of the long-term operation of the QCFBC with 20 consecutive containers in total. In (a), the temperature curve of the four temperature modules is plotted. In (b), the pressure during filtration, washing, drying, and the additionally integrated rinsing step (CIP), is plotted. (c) shows the PSD for the seed crystals in red and the product crystals, collected right before the filtration, in blue. In panel (d), the relative yield calculated via the filter cake mass and the residual moisture of each of the product filter cake is plotted.

Publications:
[1] S. Höving, T. Schmidt, M. Peters, H. Lapainis, N. Kockmann, Small-scale Solids Production Plant with Cooling Crystallization, Washing, and Drying in a Modular, Continuous Plant, Processes, 11(8), 2457, 2023, doi.org/10.3390/pr11082457
[2] T. Dobler, S. Höving, C. Dreiser, M. Gleiß, M. Gröschen, A. Henkel, M. Hörne, M. Schäfer, J. Sonnenschein, G. Wiese, K. Wohlgemuth, N. Kockmann, H. Nirschl, From Lab to Pilot Scale: Commissioning of an Integrated Device for the Generation of Crystals, Chem. Eng. & Technol., 46(7), 1511-1520, 2023, doi.org/10.1002/ceat.202200616
[3] S. Höving, P. Bolien, P. Siebers, N. Kockmann, Simplified Approach to Characterize the Cooling Crystallization in a Modular Mini-Plant, Crystals, 13(1), 147, 2023, doi.org/10.3390/cryst13010147
[4] S. Höving, L. Neuendorf, T. Betting, N. Kockmann, Determination of Crystal Size Distributions of Bulk Samples using Micro-Computed Tomography and Artificial Intelligence; Materials, 16(3), 1002, 2023, doi.org/10.3390/ma16031002

Contacts:
stefan.hoeving@tu-dortmund.de
norbert.kockmann@tu-dortmund.de

Numerical modelling of the discharge behavior of particles from gas vessel

Simulating a daily-occurring phenomenon with sophisticated numerical methods to achieve excellent results.

Michael-David Fischer, Simon Baier, Konrad E.R. Boettcher

The characterisation of the outflow of gases from pressure tanks is a fundamental aerodynamic problem. Pressurized tanks can be found in everyday life in many different sizes. From gas capsules, gas cartridges, and spray cans to gas cylinders and tankers, a broad spectrum is covered. Particularly in the case of high internal pressures and flammable, harmful or environmentally hazardous gases, the escape from pressurized containers due to leaks or failure is of safety importance. This problem is extended if the gas flow has a particle load. Especially during the corona pandemic, the discharge of potentially virus-laden particles when exhaled and their spread was omnipresent. As there is hardly any knowledge about particle discharge to date, we have taken a first step and simplified the problem with a pressurized container and uniform particle loading.

In detail, a cylindrical container with a volume of 2 m³ and a length-to-diameter ratio of 2 is considered. The gas is discharged from a circular opening with a diameter of 25 mm in the center of a circular surface of the cylinder. The initial state of the problem is shown in Figure 1.

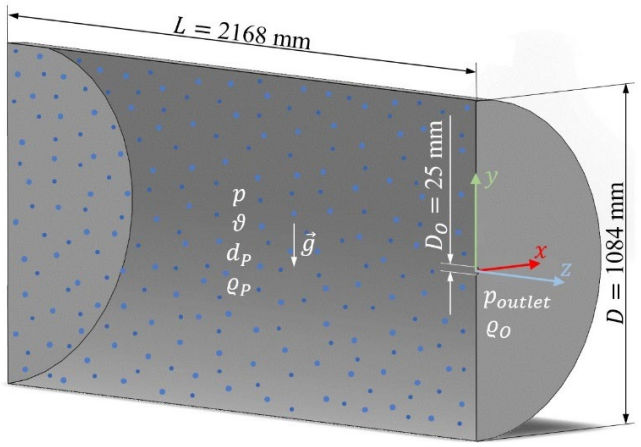


Figure 1: Scale drawing of the thin-walled container. The initial state is sketched here, in which the container contains a particle-laden gas. The particle size is not shown to scale.

For the continuous gas phase, air, helium, hydrogen, methane and nitrogen are considered. In addition, the initial pressure and temperature in the vessel are varied. For the dispersed particle phase, the particle size and the particle density are varied. In addition to the CFD simulations with ANSYS CFX, a similarity analysis of the problem was carried out. For this purpose, the conservation equations for mass, momentum, energy, turbulent kinetic energy and dissipation rate were scaled and dimensionless parameters were derived. This made it possible to derive a prediction model, with which the particle discharge can be determined quickly and accurately without having to carry out complex numerical simulations that take several days. The model is able to capture different gases, pressures, temperatures and particle properties. Figure 2 shows the initial regions from which the particles are entrained by the gas flow and leave the container.

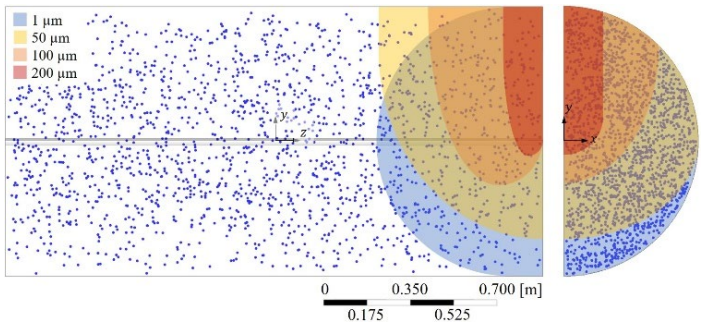


Figure 2: Representation of the initial regions from which particles with a density of 2000 kg/m³ are discharged for different particle sizes.

Figure 3 compares the model with CFD simulations showing deviations of -0.03 %.

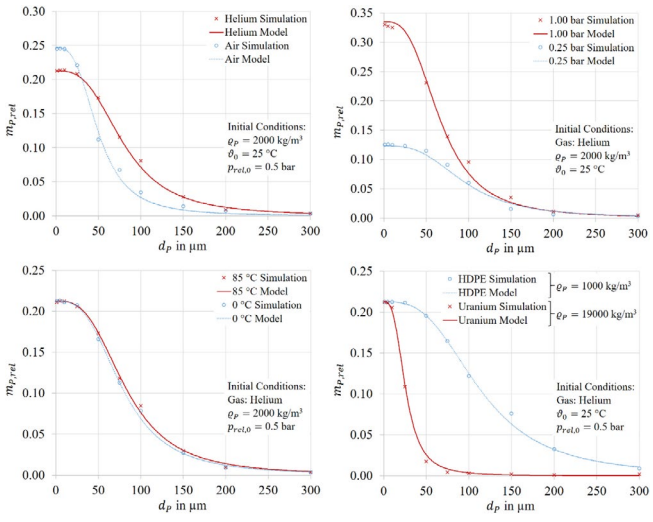


Figure 3: Fractions of discharged particles for each varied parameter plotted against the particle diameter.

Contacts:
michael-david.fischer@tu-dortmund.de
simon.baier@tu-dortmund.de
konrad.boettcher@tu-dortmund.de

Publications:
M.-D. Fischer, S. Baier, K.E.R. Boettcher
Numerical modelling of the discharge behaviour of particles from a gas vessel.
Results in Engineering, 18, 101207, (2023).
https://doi.org/10.1016/j.rineng.2023.101207

Real-World Szenario in a Laboratory Experiment on a Digital Twin to foster Work 4.0 Skills

Konrad E.R. Boettcher, Claudius Terkowsky, Marcel Schade, Dean Brandner, Sabrina Grünendahl

During the corona pandemic, the usual laboratory experiments could not be carried out. Ultra-concurrent or personal remote labs offered a rapid solution, in which an approach was taken to digitize the usual laboratory work. A different path was chosen here and the opportunity for a fundamental didactic redesign was seized to address learning objectives at higher cognitive levels, to introduce constructive alignment as a framework for the instructional design of teaching-learning units, to change the didactic setting from cookbook scripts with low competence growth to scenario-based learning with high competence growth, to enable explorative learning and to increasingly address specific learning objectives that are considered as future skills in life and work 4.0.

The laboratory experiment was developed in cooperation with the Center of Higher Education on the basis of a semi-finished VR environment for the visualization of flows on a jet pump (see Fig 1). Using a checklist for constructive alignment in laboratory instruction in engineering education, an endeavor was made to address as many of Feisel and Rosa's thirteen fundamental laboratory learning objectives as possible in order to enable explorative learning. Since the representation of the jet pump in VR corresponds to a digital twin, further learning objectives of the future skills for life and work 4.0 were addressed. In addition to the organizational design principles of Industry 4.0, these are skills for working autonomously on unclearly formulated problems without a clear goal or clear solution but without much support from superiors and, for example, ethical decision-making skills.

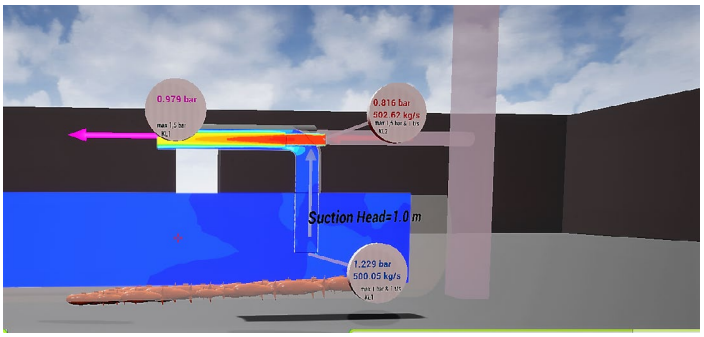


Figure 1. Semi-finished jet pump in VR: the measuring gauges are systematically noisy and noisy according to the accuracy class, errors such as escaping particles need to be analyzed and the fish at the bottom of the tank pose an ethical problem.

In the final scenario, the students work in a development department and only receive a vague work assignment by email from their supervisor. Fulfilling the work assignments confronts the students with an ethical problem that could be solved with a considerable level of creativity. In order not to overwhelm the students with the unfamiliar situation, five defined support levels were defined, whereby only the penultimate level would correspond to a normal laboratory experiment, as parts of a cookbook script are distributed here. In order to strengthen the self-efficacy and resilience of the students, reflection discussions were held after the presentation of the results achieved. Constructive alignment must not forget to check learning objectives. To this end, a competence-oriented Moodle test was designed. The students were able to compare this laboratory experiment with the usual experiments (see Fig. 2). The students rated this test significantly better in terms of professional relevance and learning gain.

The learning objective of teamwork on a meta-cognitive level is currently being increasingly addressed. For example, team role tests according to Belbin are carried out in order to identify the roles the students are aiming for in order to be able to recognize conflicts in teams at an early stage.

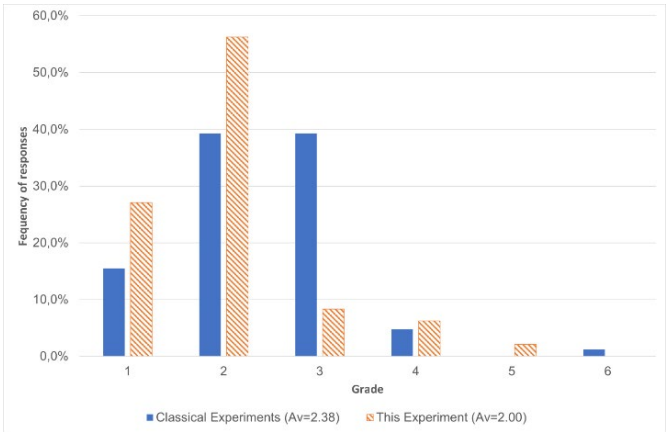


Figure 2: Student responses on learning gains for this experiment (pink) compared to usual experiments (blue) in German school grades.

Publications:
K. Boettcher et al. (2023) Developing a real-world scenario to foster learning and working 4.0 – on using a digital twin of a jet pump experiment in process engineering laboratory education, European Journal of Engineering Education, 48:5, 949-971, https://doi.org/10.1080/03043797.2023.2182184
K. Boettcher, et al. (2023) Work in Progress – Did You Check It? Checklist for Redesigning a Laboratory Experiment in Engineering Education Addressing Competencies of Learning and Working 4.0. In: Auer, M.E., Langmann, R., Tsiatsos, T. (eds) Open Science in Engineering. REV 2023. Lecture Notes in Networks and Systems, vol 763. Springer, Cham. (2023) https://doi.org/10.1007/978-3-031-42467-0_56

Contacts:
stefan.hoeving@tu-dortmund.de
konrad.boettcher@tu-dortmund.de

Publications

2023

Peer-reviewed Journal Articles

- Dinter, R.; Götte, K.; Gronke, F.; Justen, L.; Brunschweiger, A.; Kockmann, N.
Development of an Automated Flow Chemistry Affinity-Based Purification Process for DNA-Encoded Chemistry.
J. Flow Chem, 13, 361–373 (2023).
https://doi.org/10.1007/s41981-023-00282-0

- Behr, A.S.; Völkenrath, M.; Kockmann, N.
Ontology extension with NLP-based concept extraction for domain experts in catalytic sciences.
Knowledge and Information Systems, 65(12), 5503–5522 (2023).
https://doi.org/10.21203/rs.3.rs-3491129/v1

- Neuendorf, L.M.; Khaydarov, V.; Schlander, C.; Kock, T.; Fischer. J.; Urbas, L.; Kockmann, N.
Artificial Intelligence-based Module Type Package (MTP)-compatible Smart Sensors in the Process Industry.
Chem. Ing. Technik, 95(10), 1546-1554 (2023).
https://doi.org/10.3389/fchem.2023.1244043

- Dinter, R.; Willems, S.; Nissalk, T.; Hastuerk, O.; Brunschweiger, A.; Kockmann, N.
Development of a Microfluidic Photochemical Flow Reactor Concept by Rapid Prototyping.
frontiers in chemistry, 11, 1244043 (2023).
https://doi.org/10.3389/fchem.2023.1244043

- Höving, S.; Schmidt, T.; Peters, M.; Lapainis, H.; Kockmann, N.
Small-scale Solids Production Plant with Cooling Crystallization, Washing, and Drying in a Modular, Continuous Plant.
MDPI-processes, 11(8), 2457 (2023).
https://doi.org/10.3390/pr11082457

- Klose, A.; Wagner-Stürz, D.; Neuendorf, L.M.; Oeing, J.; Khaydarov, V.; Schleehahn, M.; Kockmann, N.; Urbas, L.
Automated Evaluation of Biochemical Plant KPIs based on DEXPI Information.
Chem. Ing. Technik, 95(7), 1165-1171 (2023).
https://doi.org/10.1002/cite.202200239

- Oeing, J.; Brandt, K.; Wiedau, M.; Tolksdorf, G.; Welscher, W.; Kockmann, N.
Graph Learning in Machine-Readable Plant Topology Data.
Chem. Ing. Technik, 95(7), 1049-1060 (2023).
https://doi.org/10.1002/cite.202200223

- Neuendorf, L.M.; Höving, S.; Bennemann, L.; Kockmann, N.
Detecting crystals in suspensions: convolutional neural networks vs. a gravity based approach for size distribution detection.
Chem. Ing. Technik, 95(7), 1146-1153 (2023).
https://doi.org/10.1002/cite.202200235

- Oeing, J.; Holtermann, T.; Welscher, W.; Kockmann, N.
preHAZOP: Graph-based safety analysis for early integration into automated engineering workflows.
Chem. Ing. Technik, 95(7), 1083-1095 (2023).
https://doi.org/10.1002/cite.202200222

- Neuendorf, L.M.; Hammal, Z.; Fricke, A.; Kockmann, N.
AI-based supervision for a stirred extraction column assisted with population balance-based simulation.
Chem. Ing. Technik, 95(7), 1134-1145 (2023).
https://doi.org/10.1002/cite.202200241

- Bortz, M.; Dadhe, K.; Engell, S.; Gepert, V.; Kockmann, N.; Müller-Pfefferkorn, R.; Schindler, T.; Urbas, L.
AI in Process Industries – Current Status and Future Prospects.
Chem. Ing. Technik, 95(7), 975-988 (2023).
https://doi.org/10.1002/cite.202200247

- Dobler, T.; Höving, S.; Dreiser, C.; Gleiß, M.; Gröschen, M.; Henkel, A.; Hörne, M.; Schäfer, M.; Sonnenschein, J.; Wiese, G.; Wohlgemuth, K.; Kockmann, N.; Nirschl, H.
From Lab to Pilot Scale: Commissioning of an Integrated Device for the Generation of Crystals.
Chem Eng. & Technol., 46(7), 1511-1520 (2023).
https://doi.org/10.1002/ceat.202200616

- Bittorf, L.; Oeing, J.; Kock, T.; Garreis, R.; Kockmann, N.
Design of MTP services for modular downstream units and process analytic technology following VDI/VDE/NAMUR 2658.
Chem. Eng. & Technol., 46(7), 1502-1510 (2023).
https://doi.org/10.1002/ceat.202200390

- Elhami, V.; Neuendorf, L.M.; Kock, T.; Kockmann, N.; Schuur, B.
Separation of Crotonic Acid and 2-Pentenoic Acid Obtained by Pyrolysis of Bio-Based Polyhydroxyalkanoates Using a Spinning Band Distillation Column.
ACS Sustain. Chem. Eng., 11(12), 4699-4706 (2023).
https://doi.org/10.1021/acssuschemeng.2c07046

- Dinter, R.; Willems, S.; Hachem, M.; Streltsova, Y.; Brunschweiger, A.; Kockmann, N.
Development of a two-phase flow reaction system for DNA-encoded amide coupling.
Reac. Chem. & Eng., 8, 1334-1340 (2023).
https://doi.org/10.1039/d3re00020f

- Frede, T.A.; Weber, C.; Christ, T.; Brockhoff, T.; Ludwig, D.; Kockmann, N.
Data Management of a Microcalorimeter Using a Modular Open-Source IoT Platform.
MDPI-processes, 11(1), 279 (2023).
https://doi.org/10.3390/pr11010279

- Sakthithasan, P.; Orth, L.; Venhuis, M.; Kockmann, N.
Design of a process intensified liquid-liquid extraction cell for higher temperature and pressure.
Chem. Eng. & Technol., 46(5), 882-890 (2023).
https://doi.org/10.1002/ceat.202200550

- Höving, S.; Bolien, P.; Siebers, P.; Kockmann, N.
Simplified Approach to Characterize the Cooling Crystallization in a Modular Mini-Plant.
MDPI-crystals, 13(1),147 (2023).
https://doi.org/10.3390/cryst13010147

- Höving, S.; Neuendorf, L.M.; Betting, T.; Kockmann, N.
Determination of Crystal Size Distributions of Bulk Samples using Micro-Computed Tomography and Artificial Intelligence.
MDPI-materials, 16(3), 1002 (2023).
https://doi.org/10.3390/ma16031002

- Korel, L.; Yorsh, U.; Behr, A.S.; Kockmann, N.; Holeňa, M.
Text-to-Ontology Mapping via Natural Language Processing with Application to Search for Relevant Ontologies in Catalysis.
MDPI-computers, 12, 14 (2023).
https://doi.org/10.3390/computers12010014

- Schulz, L.; Stähle, P.; Reining, S.; Sawall, M.; Kockmann, N.; Röder, T.
Multivariate curve resolution for kinetic modeling and scale-up prediction.
J. Flow Chem., 13, 13-19 (2023).
https://doi.org/10.1007/s41981-022-00252-y

- Frede, T.A.; Nikbin, N.; Kockmann, N.;
Reactor Performance Estimation in Microscale Flow Calorimeter for Rapid Characterization of Exothermic Reactions.
J. Flow Chem., 13, 31-44 (2023).
https://doi.org/10.1007/s41981-022-00251-z

- Achternbosch, M.; Zibula, L.; Schmidt, A.; Krieger, W.; Kockmann, N.; Strohmann, C.
Selective monosubstitution on a trichlorosilane with highly reactive organolithium compounds in a microflow reactor.
J. Flow Chem., 13, 9-12 (2023).
https://doi.org/10.1007/s41981-022-00254-w

Peer-reviewed Conference Contributions

- Behr, A.S.; Abbaspour, E.; Rosenthal, K.; Pleiss, J.; Kockmann, N.
Ontology-Based Laboratory Data Acquisition with EnzymeML for Process Simulation of Biocatalytic Reactors.
1st Conf. Research Data Infrastructure - CoRDI, Karlsruhe, 12.-14.9.2023.
https://doi.org/10.52825/cordi.v1i.324

- Behr, A.S.; Borgelt, H.; Petrenko, T.; Dörr, M.; Kockmann, N.
Investigating the Landscape of Ontologies for Catalysis Research Data Management.
1st Conf. Research Data Infrastructure - CoRDI, Karlsruhe, 12.-14.9.2023.
https://doi.org/10.52825/cordi.v1i.232

- Oldach, B.; Höving, S.; Boettcher, K.E.R.; Kockmann, N.
Ultra-Concurrent Remote Laboratory for Microfluidic Applications.
20th Intl. Conf. Remote Eng. & Virtual Instrum., REV23, Thessaloniki, Greece, 1.-3.3.2023.
https://doi.org/10.1007/978-3-031-42467-0_43

- Behr, A.S.; Neuendorf, L.M.; Sakthithasan, P.; Karan, M.; Fang, Q.; Boettcher, K.E.R.; Terkowsky, C.; Kockmann, N.
Uniting Knowledge and Application in a Hybrid Laboratory Experiment in Virtual Reality - A Cross-Reality Laboratory with Applications of Artificial Intelligence for Industry 4.0.
20th Intl. Conf. Remote Eng. & Virtual Instrum., REV23, Thessaloniki, Greece,1.-3.3.2023.
https://doi.org/10.1007/978-3-031-42467-0_26

Books & Book chapters

- Baerns, M.; Behr, A.; Brehm, A.; Gmehling, J.; Hinrichsen, K.-O.; Hofmann, H.; Kleiber, M.; Kockmann, N.; Onken, U.; Palkovits, R.; Renken, A.; Vogt, D.
Technische Chemie.
Wiley-VCH, Weinheim, 2023.
ISBN 978-3-527-34574-8

- Kockmann, N.; Schuler, J.; Oldach, B.
X-Ray Based Investigations on Multiphase Capillary Flows.
in G.H. Yeoh, J.B. Joshi (Eds.) Handbook of Multiphase Flow Science and Technology, SpringerNature, 2023.
https://doi.org/10.1007/978-981-4585-86-6_29-1

2022

- Peer-reviewed Journal Articles
Frede, T.A.; Greive, M.; Kockmann, N.
Measuring Kinetics in Flow Using Isoperibolic Flow Calorimetry.
MDPI reactions, 3(4), 525-536 (2022).
https://doi.org/10.3390/reactions3040035

- Sonnenschein, J.; Hermes, M.; Höving, S.; Kockmann, N.; Wohlgemuth, K.
Population balance modeling of unstirred cooling crystallization on an integrated belt filter.
Comp. & Chem. Eng., 167, 108024 (2022).
https://doi.org/10.1016/j.compchemeng.2022.108024

- Menke, M.J.; Behr, A.S.; Rosenthal, K.; Linke, D.; Kockmann, N.; Bornscheuer, U.T.; Dörr, M.
Ontology development in Biocatalysis.
Chem. Ing. Technik, 94(11), 1827-1835 (2022).
https://doi.org/10.1002/cite.202200066

- de Cerqueira, R.; Bayomie, O.; Kockmann, N.; Neuendorf, L.M.; Lammers, K.; Kornijez, I.; Kieling, S.; Sandermann, T.
Detecting flooding state in extraction columns: convolutional neural networks vs. a white-box approach for image-based soft sensor development.
Comp. & Chem. Eng., 164, 107904 (2022).
https://doi.org/10.1016/j.compchemeng.2022.107904

- Klose, A.; Lorenz, J.; Bittorf, L.; Stark, K.; Hoernicke, M.; Stutz, A.; Weinhold, H.; Krink, N.; Welscher, W.; Eckert, M.; Unland, S.; Menschner, A.; da Silva Santos, P.; Kockmann, N.; Urbas, L.
Orchestration of modular plants: Procedure and application for orchestration engineering.
automatisierung atp, 63(9), 68-77 (2022).
https://doi.org/10.17560/atp.v63i9.2599

- Götte, K.; Dinter, R.; Justen, L.; Kockmann, N.; Brunschweiger, A.
Development of an Automatable Affinity Purification Process for DNA-Encoded Chemistry.
ACS Omega, 7(32), 28369-28377 (2022).
https://doi.org/10.1021/acsomega.2c02906

- Neuendorf, L.M.; Baygi, F.Z.; Kolloch, P.; Kockmann, N.
Implementation of a control strategy of a stirred liquid-liquid extraction column based on convolutional neural networks.
ACS Engineering Au, 2(4), 369-377 (2022).
https://doi.org/10.1021/acsengineeringau.2c00014

- Sakthithasan, P.; Gerdes, N.; Venhuis, M.; Kockmann, N.
Investigation of strong asymmetric pulsation patterns in a stirred-pulsed extraction measurement cell.
Chem. Eng. Proc - PI, 180, 108757 (2022).
https://doi.org/10.1016/j.cep.2021.108757

- Oeing, J.; Welscher, W.; Krink, N.; Jansen, L.; Henke, F.; Kockmann, N.
Using artificial intelligence to support the drawing of piping and instrumentation diagrams in DEXPI standard.
Digital Chemical Engineering, 4, 100038 (2022).
https://doi.org/10.1016/j.dche.2022.100038

- Markaj, A.; Fay, A.; Kockmann, N.
Definition, characterization, and modeling of hybrid modular-monolithic process plants.
Chem. Ing. Technik, 94(8), 1117-1130 (2022).
https://doi.org/10.1002/cite.202200048

- Schuler, J.; Herath, J.; Kockmann, N.
X-ray based Tomographic Imaging for the Investigation of Laminar Mixing in Capillaries.
Chem. Eng. & Technol., 45(7), 1247-1254 (2022).
https://doi.org/10.1002/ceat.202100530

- Höving, S.; Oldach, B.; Kockmann, N.
Cooling Crystallization with Complex Temperature Profiles on a Quasi-Continuous and Modular Plant.
MDPI processes, 10(6) 1047 (2022).
https://doi.org/10.3390/pr10061047

- Höving, S.; Bobers, J.; Kockmann, N.
Open-source multi-purpose sensor for measurements in continuous capillary flow.
J. Flow Chem., 12, 185-196 (2022).
https://doi.org/10.1007/s41981-021-00214-w

- Grühn, J.; Behr, A.S.; Rosenthal, K.; Kockmann, N.
From coiled flow inverter to stirred tank reactor - Bioprocess development and ontology design.
Chem. Ing. Technik, 94 (6), 852-863 (2022).
https://doi.org/10.1002/cite.202100177

- Frede, T.A.; Maier, M.; Kockmann, N.; Gruber-Wölfler, H.
Advances in continuous flow calorimetry.
Org. Proc. R&D, 26(2), 267-277 (2022).
https://doi.org/10.1021/acs.oprd.1c00437

- Bobers, J.; Hahn, L.K.; Averbeck, T.; Brunschweiger, A.; Kockmann, N.
Reaction Optimization of a Suzuki-Miyaura Cross-Coupling using Design of Experiments.
Chem. Ing. Technik, 94(5), 780-785 (2022).
https://doi.org/10.1002/cite.202100194

- Schmalenberg, M.; Mensing, L.; Lindemann, S.; Krell, T.; Kockmann, N.
Miniaturized Draft Tube Baffle Crystallizer for Continuous Cooling Crystallization.
Chem. Eng. R&D, 178, 232-250 (2022).
https://doi.org/10.1016/j.cherd.2021.12.024

Peer-reviewed Conference Contributions

- Dinter, R.; Helwes, L.; Pillath, M.; Kockmann, N.
Electrical Conductivity Sensor with Open-Source Hardware for the Microfluidic Determination of Reaction Parameters.
16. Dresdner-Sensor Symposium, 5.-7.12.2022.
https://doi.org/10.5162/16dss2022/P03

- Neuendorf, L.M.; Müller, P.; Bergeest, C.; Meijer, A.; Schlander, C.; Kockmann, N.
Künstliche Intelligenz (KI)-basierte optische Sensorik für flüssig-flüssig Systeme.
16. Dresdner-Sensor Symposium, 5.-7.12.2022.
https://doi.org/10.5162/16dss2022/P50

- Burke, I.; Youssef, A.S.; Kockmann, N.
Design of an AI-supported Sensor for Process Relevant Parameters in Emulsification Processes.
16. Dresdner-Sensor Symposium, 5.-7.12.2022.
https://doi.org/10.5162/16dss2022/P48

- Dinter, R.; Willems, S.; Hachem, M.; Mittelstädt, M.; Brunschweiger, A.; Kockmann, N.
Two-Phase Flow Reaction System for Amide Coupling Towards Automated DNA-Encoded Chemistry.
ProcessNet Annual Meeting, Aachen, 12.-15.09.2022.
https://doi.org/10.1002/cite.202255228

Books & Book articles

- Kockmann, N.; Agar, D.W.
Liquid-Liquid Processes - Mass Transfer Processes and Chemical Reactions.
in V. Ranade, R. Utikar (eds.) Multiphase Flows for Process Industries: Fundamentals and Applications Vol. 2, Wiley-VCH, Weinheim, 2022, ISBN 978-3-527-34377-5.
https://doi.org/10.1002/9783527812066.ch5

2021

Peer-reviewed Journal Articles

- Oeing, J.; Neuendorf, L.M.; Bittorf, L.; Krieger, W.; Kockmann, N.
Flooding Prevention in Distillation and Extraction Columns with Aid of Machine Learning Approaches.
Chem. Ing. Technik, 93(12), 1917-1929 (2021).
https://doi.org/10.1002/cite.202100051

- Wiedau, M.; Tolksdorf, G.; Oeing, J.; Kockmann, N.
Towards a systematic data harmonization to enable AI application in the process industry.
Chem. Ing. Technik, 93(12), 2105-2115 (2021).
https://doi.org/10.1002/cite.202100203

- Oeing, J.; Henke, F.; Kockmann, N.
Machine Learning based suggestions of separation units for process synthesis in process simulation.
Chem. Ing. Technik, 93(12), 1930-1936 (2021).
https://doi.org/10.1002/cite.202100082

- Reichmann, F.; Herath, J.; Mensing, L.; Kockmann, N.
Gas-liquid mass transport intensification for bubble breakup employing micronozzles.
J. Flow Chem., 11(3), 429-444 (2021).
https://doi.org/10.1007/s41981-021-00180-3

- Frede, T.A.; Dietz, M.; Kockmann, N.
Software-Guided Microscale Flow Calorimeter for Efficient Acquisition of Thermokinetic Data.
J. Flow Chem., 11(3), 321-332 (2021).
https://doi.org/10.1007/s41981-021-00145-6

- Schmalenberg, M.; Weick, L.; Kockmann, N.
Nucleation for Continuous Flow Cooling Sonocrystallization for Coiled Capillary Crystallizers.
J. Flow Chem., 11(3), 303-319 (2021).
https://doi.org/10.1007/s41981-020-00138-x

- Fath, V.; Lau, P.; Greve, C.; Weller, P.; Kockmann, N.; Röder, T.
Simultaneous self-optimisation of yield and by-product formation through successive combination of inline FT-IR spectroscopy and online mass spectrometry.
J. Flow Chem., 11(3), 285 – 302 (2021).
https://doi.org/10.1007/s41981-021-00140-x

- Schuler, J.; Herath, J.; Kockmann, N.
3D Investigation of Laminar Mixing and Diffusion in Helically Coiled Capillaries by Micro-Computed Tomography.
J. Flow Chem., 11(3), 217-222 (2021)
https://doi.org/10.1007/s41981-021-00161-6

- Kulkarni, A.; Hartman, R.; Kockmann, N.
Editorial of Special Issue on Engineering Aspects in Flow Chemistry.
J. Flow Chem., 11(3), 211-212 (2021).
https://doi.org/10.1007/s41981-021-00197-8

- Bittorf, L.; Pathak, K.; Kockmann, N.
Spinning band distillation column – rotating element design and vacuum operation.
Ind.&Eng. Chem. Res., 60(30), 10854-10862 (2021).
https://doi.org/10.1021/acs.iecr.1c01326

- Wulf, C.; Beller, M.; Boenisch, T.; Deutschmann, O.; Hanf, S.; Kockmann, N.; Kraehnert, R.; Oezaslan, M.; Palkovits, S.; Schimmler, S.; Schunk, S.A.; Wagemann, K.; Linke, D.
A Unified Research Data Infrastructure for Catalysis Research - Challenges and Concepts.
ChemCatChem, 13(14), 3223-3236 (2021).
https://doi.org/10.1002/cctc.202001974R2

- Bittorf, L.; Böttger, N.; Neumann, D.; Winter, A.; Kockmann, N.
Characterization of an automated spinning band column as a module for laboratory distillation.
Chem. Eng. & Technol., 44(9), 1660-1667 (2021).
https://doi.org/10.1002/ceat.202000602

- Schmalenberg, M.; Kreis, S.; Weick, L.; Haas, C.; Sallamon, F.; Kockmann, N.
Continuous Cooling Crystallization in a Coiled Flow Inverter Crystallizer Technology—Design, Characterization, and Hurdles.
MDPI-processes, 9, 1537 (2021).
https://doi.org/10.3390/pr9091537

- Klement, T.; Hanf, S.; Kockmann, N.; Wolff, F.; Schunk, S.A.; Röder, T.
Oscillating droplet reactor – Towards Kinetic Screening for Heterogeneous Catalysis in Hydrogenation Reaction.
Reac. Chem. Eng., 6, 1023-1030 (2021).
https://doi.org/10.1039/D0RE00466A

- Bamberg, A.; Bortz, M.; Kockmann, N.; Bröcker, S.; Urbas, L.
The Digital Twin – Your ingenious companion for process engineering and smart production.
Chem. Eng.&Technol., 44(6), 954-961 (2021).
https://doi.org/10.1002/ceat.202000562

- Frede, T.A.; Burke, I.; Kockmann, N.;
Software-guided Microfluidic Reaction Calorimeter Based on Thermoelectric Modules.
Chem. Ing. Technik, 93(5), 802-808 (2021).
https://doi.org/10.1002/cite.202000223

- Klement, T.; Kockmann, N.; Schwede, C.; Röder, T.
Kinetic measurement of acryl acid polymerization at high concentrations under nearly isothermal conditions in a pendula slug flow reactor.
Ind. Eng. Chem. Res., 60(11), 4240-4250 (2021).
https://doi.org/10.1021/acs.iecr.0c04732

- Grühn, J.; Vogel, M.; Kockmann, N.
Digital Image Processing of Gas-Liquid Reactions in Coiled Capillaries.
Chem. Ing. Technik, 93(5), 825-829 (2021).
https://doi.org/10.1002/cite.202000240

- Bobers, J.; Forys, E.; Oldach, B.; Kockmann, N.
Application of Polyimide-based Microfluidic Devices on Acid-catalyzed Hydrolysis of Dimethoxypropane.
Chem. Ing. Technik, 93(5), 796-801 (2021).
https://doi.org/10.1002/cite.202000224

- Schmalenberg, M.; Frede, T.A.; Mathias, C.; Kockmann, N.
Efficient Short-cut Method for Determining the Process Window in Stirred-pulsed Extraction Columns.
Chem. Ing. Technik, 93(3), 466-472 (2021).
https://doi.org/10.1002/cite.202000066

- Schuler, J.; Neuendorf, L.M.; Petersen, K.; Kockmann, N.
Micro-Computed Tomography for the 3D Time-Resolved Investigation of Monodisperse Droplet Generation in a Co-Flow Setup.
AIChE J., 67(2) e17111 (2021).
https://doi.org/10.1002/aic.17111

Peer-reviewed conference Contributions

- Horsch, M.T.; Petrenko, T.; Kushnarenko, V.; Schembera, B.; Wentzel, B.; Behr, A.S.; Kockmann, N.; Schimmler, S.; Bönisch, T.
Interoperability and architecture requirements analysis and metadata standardization for a research data infrastructure in catalysis.
Oral presentation, DACOMSIN, 26.10.2021.
https://doi.org/10.1007/978-3-031-12285-9_10

Book chapters

- Schlüter, M.; Kexel, F.; von Kameke, A.; Hoffmann, M.; Herres-Pawlis, S.; Klüfers, P.; Oßberger, M.; Turek, S.; Mierka, O.; Kockmann, N.; Krieger, W.
Visualization and Quantitative Analysis of Consecutive Reactions in Taylor Bubble Flows.
pp 507-543 in: Schlüter, M.; Herres-Pawlis, S.; Nieken, U. (Eds.) Reactive Bubble Flow. Fluid Mechanics and Its Applications, vol 128. Springer, Cham, 2021.
https://doi.org/10.1007/978-3-030-72361-3_21

- Kockmann, N.
Historischer Abriss zur Entstehung und Entwicklung der Chemischen Reaktionstechnik.
in: Reschetilowski, W. (Ed.) Handbuch Chemische Reaktoren, Springer, Berlin, 2021.
https://doi.org/10.1007/978-3-662-56444-8_1-2

Plant and Process Design (APT)

Modeling of Continuous Slug Flow Cooling Crystallization towards Pharmaceutical Application

Importance of particle suspension and hydrodynamics for understanding slug flow crystallization.

Anne Cathrine Kufner, Michael Rix, Nico Westkämper, Henrik Bettin, Kerstin Wohlgemuth

The rising trend towards continuous production in the field of small-scale crystallization has generated numerous concepts for apparatuses for the production of active pharmaceutical ingredients (API). One such apparatus is the Slug Flow Crystallizer (SFC), in which a flow segmentation offers advantages such as narrow residence time distributions (RTD), intensified mixing, heat exchange and enhanced particle suspension. To date, realization and process understanding of crystallization inside the SFC required extensive experimental effort. Therefore, a mechanistic model considering hydrodynamics of slug flow, energy and mass balances as well as crystallization phenomena growth and agglomeration inside the apparatus was developed. Its purpose is to facilitate transfer of new substance systems to the apparatus by improving process understanding, estimation of the effects of operating parameters on target properties and the prediction of crystallization behavior with minimal experimental effort.

The general setup of the SFC is shown schematically in Figure 1. In the slug formation zone at the inlet of the apparatus a flow segmentation into slugs of seeded solution and synthetic air is achieved. These slugs pass the tempered growth zone at the end of which an image analysis allows for the determination of slug lengths, slug length distributions and crystal suspension state to ensure ideal growth conditions.

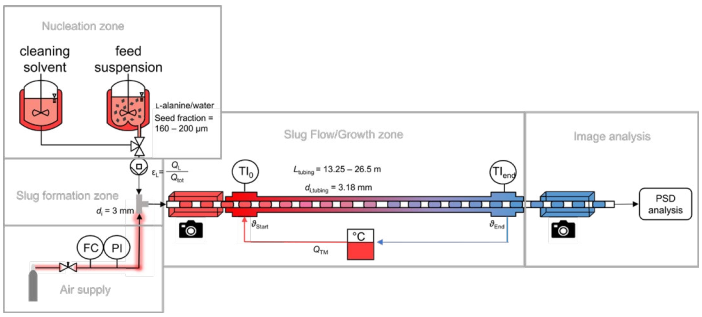


Figure 1: Schematic setup of the slug flow crystallizer.

Despite efforts to describe crystallization behavior inside SFCs, until now no published model has incorporated the hydrodynamics of slug flow, namely the influence of pressure drop, slug length and residence time decrease through gas expansion. Additionally, a satisfactory prediction of agglomeration could not be performed using existing empirical kernels.

Therefore a novel model is presented which is composed of crystallization kinetics, slug flow hydrodynamics as well as mass and energy balances. The crystallization kinetics include a growth and a mechanistic, fitted agglomeration kernel which accounts for the degree of suspension of particles caused by secondary Taylor vortices inside the slugs and is based upon previous work [1]. The additional calculation of slug flow hydrodynamics enables the determination of residence time as a result of acceleration by gas expansion while the energy balance allows for a description of the degressive temperature profile.

As shown in Figure 2 the resulting model is capable of providing a satisfactory calculation of all considered experiments as it provides calculations of residence time, concentration decrease and significant crystal diameters within a ±20 % confidence interval thereby helping in enabling robust and long-term stable operation of the SFC while laying the foundation towards automation of the apparatus [2].

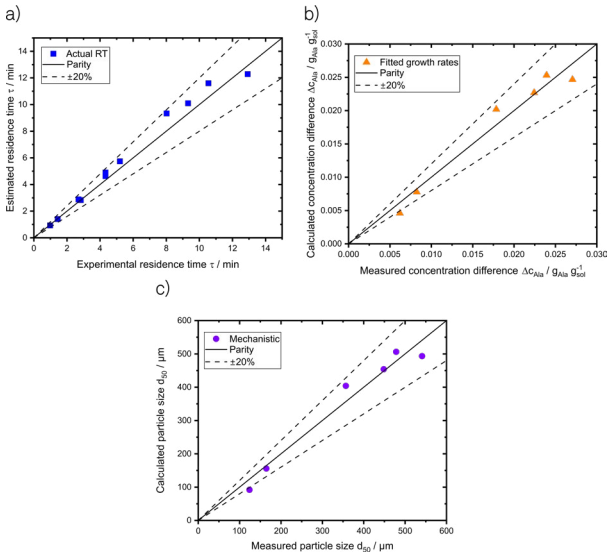


Figure 2: Parity plots comparing the calculated and measured (a) residence time within the SFC; (b) the concentration decreases over the SFC length due to crystal growth; and (c) median particle size d_{50} of the particle size distribution using a mechanistic agglomeration kernel.

Contact:
kerstin.wohlgemuth@tu-dortmund.de

Publications:
[1] Kufner, A.C.; Westkämper, N.; Bettin, H.; Wohlgemuth, K., Prediction of Particle Suspension State for Various Particle Shapes Used in Slug Flow Crystallization. Chem. Engineering 2023, 7 (2), 34. https://doi.org/10.3390/chemengineering7020034
[2] Kufner, A.C.; Rix, M.; Wohlgemuth, K.; Modeling of continuous slug flow cooling crystallization towards pharmaceutical applications. Processes 2023, 11(9), 2637. https://doi.org/10.3390/pr11092637

End-to-End Continuous Small-Scale Drug Substance Manufacturing: From Continuous in-situ Nucleator to Free-Flowing Crystalline Particles

Anne Cathrine Kufner, Marc Meier and Kerstin Wohlgemuth

In the evolving landscape of pharmaceutical manufacturing, a comprehensive continuous production process is being crafted for small-scale active pharmaceutical ingredient production. This study focuses on continuous crystallization with separate nucleation and crystal growth units, as well as continuous downstream processing, encompassing filtration, washing, and drying until the formation of free-flowing particles. We introduce a novel continuous nucleator designed based on solubility data and produced via 3D printing, enabling a fast and precise small-scale manufacturing of a nucleator meeting the requirements for nucleation and for further growth processes. The nucleator was evaluated with regard to its suitability for continuous long-term operation across various coupled crystallizers. As a practical application example, it is connected to a slug flow crystallizer to enable high-quality continuous crystallization. Additionally, the full integration of downstream processes using the continuous vacuum screw filter to achieve free-flowing product particles is realized. Even under non-optimized process conditions, with the help of in-situ generation of nuclei, free-flowing product particles were successfully obtained. This is particularly useful during drug development when no material is available for seed addition and quickly obtain product for further characterization.

Production in the pharmaceutical industry for a small-scale production (250 – 1000 kg a^{-1}) is undergoing a turnaround in terms of processing methods. Thus, more and more research is performed in the direction of continuous production, which, however, brings challenges at a small scale like this. There are already some concepts for continuous cooling crystallization and a few concepts for continuous solid-liquid separation, but there is still a lack of suitable methods that provide continuous nucleation and, thus, continuous in situ seeds for crystallization. Our study introduces a novel continuous nucleator in form of a T-mixer designed based on phase diagrams and making use of antisolvent nucleation. The suitability of the nucleator for continuous, long-term operation in combination with various crystallizers was assessed to ensure an adequate number of nuclei for the subsequent growth process and substantial consumption of supersaturation, minimizing the risk of fouling in subsequent continuous crystallizer. Its implementation was shown for a slug flow crystallizer (SFC) with the aim of producing high-quality product particles. Furthermore, with a connection to a continuous vacuum screw filter (CVSF) for continuous particle isolation consisting of solid-liquid separation, washing, and drying, the fully continuous crystal process chain up to the achievement of free-flowing particles was completed.

The experimental results demonstrate that the fully continuous end-to-end small-scale manufacturing of free-flowing particles is possible. High relative yields in the crystal growth process in the SFC of approximately 80 % are reproducibly achieved, the critical quality attributes during CVSF operation are preserved and residual moistures of around 3 % resulted with the configuration used, despite a low, non-optimal filling degree of 5 % in the CVSF. The modular setup of the CVSF provides the option to add a drying module in order to further reduce the residual moisture below 1 % and obtain dry, free-flowing particles at the end of the integrated process. Additionally, the CVSF offers the potential to realize higher filling degrees independent from the suspension volume flow rate and solid loading by increasing the shaft diameter of the screw. This will further improve the flexibility of the CVSF with regard to compatibility with various types of continuous crystallizers and operation points.

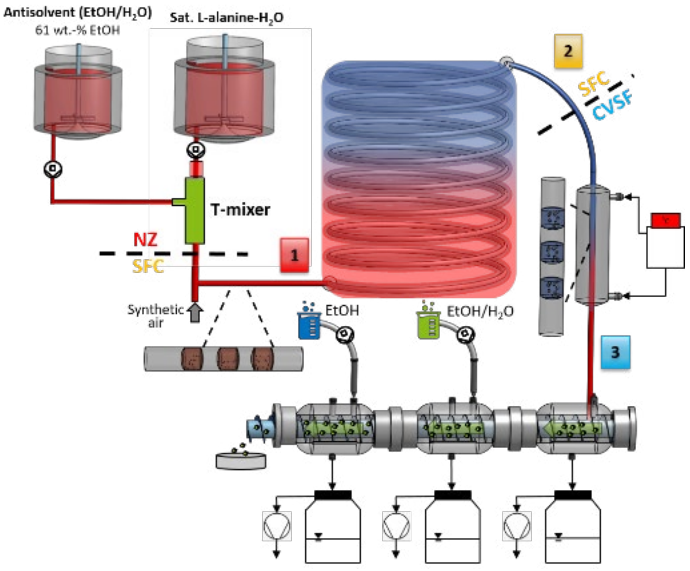


Figure 1: Schematic of experimental setup for end-to-end continuous small-scale manufacturing of free-flowing particles containing a continuous nucleator (T-mixer with 90° inlet configuration) in stage 1, continuous crystallization (SFC) in stage 2, and continuous particle isolation consisting of filtration and two-stage washing (CVSF), as well as a heater between SFC and CVSF, in stage 3.

Publications:
Kufner, A.C.; Meier, M.; Wohlgemuth, K., End-to-End Continuous Small-Scale Drug Substance Manufacturing: From a Continuous In Situ Nucleator to Free-Flowing Crystalline Particles. Crystals, 13 (12), 1675 (2023).
https://doi.org/10.3390/cryst13121675

Contact:
kerstin.wohlgemuth@tu-dortmund.de

Publications

2023

- Qammar, H.; Pyka, T.; Koop, J.; Górak, A.; Schembecker, G.
Radial Temperature Profile Measurements to Understand Mass Transfer in Rotating Packed Bed Distillation
Industrial and Engineering Chemistry Research, 62(38), 15588-15599 (2023)
doi.org/10.1021/acs.iecr.3c01068

- Loll, R.; Nordhausen, L.; Bieberle, A.; Schubert, M.; Pyka, T.; Koop, J.; Held, Ch.; Schembecker, G.
Analysis of Flow Patterns in Structured Zickzack Packings for Rotating Packed Beds Using γ -Ray Computed Tomography
Industrial and Engineering Chemistry Research, 62(38), 15625-15634 (2023)
doi.org/10.1021/acs.iecr.3c02252

- Koop, J.; Bera, N.; Quickert, E.; Schmitt, M.; Schlüter, M.; Held, Ch.; Schembecker, G.
Separation of Volatile Organic Compounds from Viscous Liquids with RPB Technology
Industrial and Engineering Chemistry Research, 62(34), 13637-13645 (2023)
doi.org/10.1021/acs.iecr.3c01597

- Pyka, T.; Ressemann, A.; Held, Ch.; Schembecker, G.; Repke, J.-U.
Impact of Vapor Bypasses on Separation Performance of Rotating Packed Beds in Distillation
Industrial and Engineering Chemistry Research, 62(33), 13274-13279 (2023)
doi.org/10.1021/acs.iecr.3c01947

- Pyka, T.; Brunert, M.; Koop, J.; Bieberle, A.; Held, Ch.; Schembecker, G.
Novel Liquid Distributor Concept for Rotating Packed Beds
Industrial and Engineering Chemistry Research, 62(14), 5984-5994 (2023)
doi.org/10.1021/acs.iecr.3c00248

- Pyka, T.; Backhaus, V.; Held, Ch.; Schembecker, G.
Impact of Number of Rotors in Rotating Packed Beds on Separation Performance in Distillation
Industrial and Engineering Chemistry Research (2023)
doi.org/10.1021/acs.iecr.3c03173

- Kufner, A.; Meier, M.; Wohlgemuth, K.
End-to-End Continuous Small-Scale Drug Substance Manufacturing: From a Continuous In Situ Nucleator to Free-Flowing Crystalline Particles
Crystals, 13(12), 1675 (2023)
doi.org/10.3390/cryst13121675

- Seifert, A.; Wegener, H.; Brühl, K.; Seidensticker, T.; Wohlgemuth, K.
Polymer-Grade Bio-Monomers from Oleochemicals by Combining Homogeneous Catalysis and Selective Product Crystallization in an Integrated Process
Processes, 11 (10), 2861 (2023)
doi.org/10.3390/pr11102861

- Kufner, A.; Rix, M.; Wohlgemuth, K.
Modeling of continuous slug flow cooling crystallization towards pharmaceutical applications
Processes, 11(9), 2637 (2023)
doi.org/10.3390/pr11092637

- Seifert, A.; Wehning, A.; Gutsch, J.; Wohlgemuth, K.
Focusing impurities during inert gassing crystallization of complex mixtures
Organic Process Research & Development, 27, 8, 1485-1498 (2023)
doi.org/10.1021/acs.oprd.3c00171

- Kufner, A.; Westkämper, N.; Bettin, H.; Wohlgemuth, K.
Prediction of Particle Suspension State for Various Particle Shapes Used in Slug Flow Crystallization
Chem. Engineering, 7(2), 34 (2023)
doi.org/10.3390/chemengineering7020034

- Dobler, T.; Höving, S.; Dreiser, Ch.; Gleiß, M.; Gröschen, M.; Henkel, A.; Hörne, M.; Schäfer, M.; Sonnenschein, J.; Wiese, G.; Wohlgemuth, K.; Kockmann, N.; Nirschl, H.
From Lab to Pilot Scale: Commissioning of an Integrated Device for the Generation of Crystals
Chemical Engineering & Technology, 46(7), 1511-1520 (2023)
doi.org/10.1002/ceat.202200616

2022

- Pyka, T.; Koop, J.; Held, Ch.; Schembecker, G.
Dry Pressure Drop in a Two-Rotor Rotating Packed Bed
Industrial an Engineering Chemistry Research, 61(46), 17156-17165 (2022)
doi.org/10.1021/acs.iecr.2c02500

- Buthmann, F.; Pley, F.; Schembecker, G.; Koop, J.
Automated Image Analysis for Retention Determination in Centrifugal Partition Chromatography
Separations, 9(11), 358 (2022)
doi.org/10.3390/separations9110358

- Etmanski, M.; Breloer, M.; Weber, M.; Schembecker, G.; Wohlgemuth, K.
Interplay of Particle Suspension and Residence Time Distribution in a Taylor-Couette Crystallizer
Chrystals, 12(12), 1845 (2022)
doi.org/10.3390/cryst12121845

- Seifert, A.; Simons, J.; Gutsch, J.; Wohlgemuth, K.
Inert gassing crystallization for improved product separation of oleo-chemicals towards an efficient circular economy
Organic Process Research & Development 2/09 (2022),
doi.org/10.1021/acs.oprd.2c00312

- Kufner, A.; Krummnow, A.; Danzer, A.; Wohlgemuth, K.
Strategy for fast decision on material system suitability for continuous crystallization inside a Slug Flow Crystallizer
Micromachines (2022)
https://www.mdpi.com/2072-666X/13/10/1795

- Sonnenschein, J.; Hermes, M.; Höving, S.; Kockmann, N.; Wohlgemuth, K.
Population balance modeling of unstirred cooling crystallization on an integrated belt filter
Journal Computers and Chemical Engineering (2022)
10.1016/j.compchemeng.2022.108024

- Schreiber, M.; Schembecker,G.
Development of an Automated Adsorbent Selection Strategy for Liquid–Phase Adsorption
Chemical Engineering and Technology 45, No. 6, 1124–1132 (2022)
doi.org/10.1002/ceat.202200152

- Lins, J.; Ebeling, U.; Wohlgemuth, K.
Agglomeration Kernel Determination by Combining In-Process Image Analysis and Modeling
Crystal Growth & Design 22, 9, 5363–5374 (2022)
doi.org/10.1021/acs.cgd.2c00461

- Vondran, J.; Seifert, A.; Schäfer, K.; Laudanski, A.; Deysenroth, T.; Wohlgemuth, K.; Seidensticker, T.
Progressing the Crystal Way to Sustainability: Strategy for Developing an Integrated Recycling Process of Homogeneous Catalysts by Selective Product Crystallization
Industrial & Engineering Chemistry Research 61,27,9621–9631 (2022)
doi.org/10.1021/acs.iecr.2c00476

- Sonnenschein, J.; Heming, R.; Wohlgemuth, K.
Archimedes Tube Crystallizer: Design and Operation of Continuous Cooling Crystallization Based on First-Principle Modeling
Crystal Growth & Design 22, 9, 5272-5284 (2022)
doi.org/10.1021/acs.cgd.2c00399

- Lins, J.; Harweg, T.; Weichert, F.; Wohlgemuth, K.
Potential of Deep Learning Methods for Deep Level Particle Characterization in Crystallization
Applied Sciences 12, 5, 2465 (2022)
doi.org/10.3390/app12052465

- Sonnenschein, J.; Wohlgemuth, K.
Archimedes tube crystallizer: Design and characterization for small-scale continuous crystallization
Chemical Engineering Research and Design 178,488-501 (2022)
doi.org/10.1016/j.cherd.2021.12.017

- Steenweg, C.; Habicht, J.; Wohlgemuth, K.
Continuous Isolation of Particles with Varying Aspect Ratios up to Thin Needles Achieving Free-Flowing Products
Crystals 12 (2), 137 (2022)
doi.org/10.3390/cryst12020137

2021

- Sonnenschein, J.; Friedrich, P.; Aghayarzadeh, M.; Mierka, O.; Turek, S.; Wohlgemuth, K.
  Flow Map for Hydrodynamics and Suspension Behavior in a Continuous Archimedes Tube Crystallizer
  Crystals 11, 1466 (2021)
  doi.org/10.3390/cryst11121466

- Steenweg, C.; Kufner, A.; Habicht, J.; Wohlgemuth, K.
  Towards Continuous Primary Manufacturing Processes - Particle Design through Combined Crystallization and Particle Isolation
  Processes 9, 2187 (2021)
  doi.org/10.3390/pr9122187

- Steenweg, C.; Seifert, A.; Böttger, N.; Wohlgemuth, K.
  Process Intensification enabling Continuous Manufacturing Processes using Modular Continuous Vacuum Screw Filter
  Org. Process Res. Dev. 25, 11, 2525–2536 (2021)
  doi.org/10.1021/acs.oprd.1c00294

- Schreiber, M.; Brunert, M; Schembecker, G.
  Extraction on a Robotic Platform - Autonomous Solvent Selection under Economic Evaluation Criteria
  Chemical Engineering and Technology 44, No. 9, 1578-1584 (2021)
  doi.org/10.1002/ceat.202100171

- Koop, J.; Merz,J.; Schembecker, G.
  Hydrophobicity, amphilicity, and flexibility: Relation between molecular protein properties and the macroscopic effects of surface activity
  Journal of Biotechnology 334, 11-25 (2021)
  doi.org/10.1016/j.jbiotec.2021.05.002

- Termühlen, M.; Strakeljahn, B.; Schembecker, G.; Wohlgemuth, K.
  Quantification and Evaluation of Operating Parameters' Effect on Suspension Behavior for Slug Flow Crystallization
  Chemical Engineering Science 243, 116771 (2021)
  doi.org/10.1016/j.ces.2021.116771

- Termühlen, M.; Etmanski, M.; Kryschewski, I.; Kufner, A.; Schembecker, G.; Wohlgemuth, K.
  Continuous Slug Flow Crystallization: Impact of Design and Operating Parameters on Product Quality
  Chemical Engineering Research and Design 170, 290–303 (2021)
  doi.org/10.1016/j.cherd.2021.04.006

- Lukin, I.; Pietzka, L.; Wingartz,I.; Schembecker, G.
  Aroma absorption in rapeseed oil using rotating packed bed
  Flavor and Fragrance Journal, 36,1,137-147 (2021)
  doi.org/10.1002/ffj.3623

- Steenweg, C.; Seifert, A.; Schembecker, G.; Wohlgemuth, K.
  Characterization of a Modular Continuous Vacuum Screw Filter for Small-Scale Solid-Liquid Separation of Suspensions
  Org. Process Res. Dev. 25, 4, 926–940 (2021)
  doi.org/10.1021/acs.oprd.0c00550

- Peterwitz, M.; Schembecker, G.
  Evaluating the potential for optimization of axial back mixing in continuous pharmaceutical manufacturing
  Computers and Chemical Engineering 04.02, 107251 (2021)
  doi.org/10.1016/j.compchemeng.2021.107251

- Lins, J.; Heisel, S.; Wohlgemuth, K.
  Quantification of internal crystal defects using image analysis
  Powder Technology 377, 733-738 (2021)
  doi.org/10.1016/j.powtec.2020.09.015

Biomaterials and Polymer Science (BMP)

Catching and Releasing of Antibiotic Worm Micelles

Highly active worm micelles of amphiphilic polymer CIP conjugates can be deactivated by cross-linking with triblockcopolymers and enzymatically reactivated.

Alina Romanovska, Martin Schmidt, Jonas Tophoven, Joerg C. Tiller

Modification of existing antibiotics towards higher activity particularly against antibiotic-resistant bacteria is a pressing topic in medicine. Modification of the widely used antibiotic ciprofloxacin (CIP) with amphiphilic blockcopoly(2-oxazolines) has been previously shown to activate the antibiotic against CIP resistant bacteria. Since CIP is not cleaved from the conjugated polymer, common formulations to control the delivery of such polymer antibiotic conjugates (PACs) are not applicable. In order to solve this problem, we have developed a novel approach to control the activity of polymer antibiotic conjugates by formation of nanostructured nanoparticles and their disruption with the enzyme lipase.

As shown recently, the conjugation of CIP with amphiphilic poly(2-oxazoline) (POx)-diblock copolymers results in great activation of the antibiotic, which is due to the fact that the conjugates enter the bacterial cells via their efflux pumps, particularly if they form spherical or worm micelles. In order to control the activity of the worm micelles, it was presumed that cross-linking of the latter makes aggregates that are too large and inflexible to enter the bacterial cells anymore. Cleaving the cross-link will then fully recover the activity (see Figure 1).

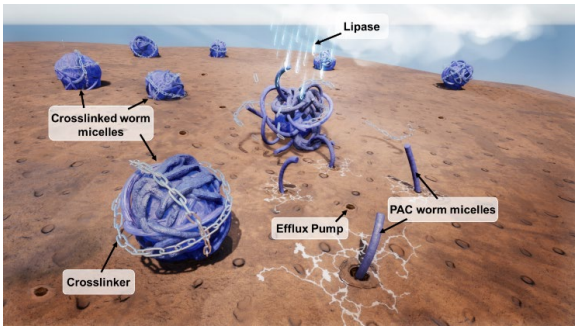


Figure 1: Illustration of the general concept of controlling the activity of cross-linked, antibacterial worm micelles based on CIP-based antibiotic polymer conjugates (PAC) on a bacterial surface.

To find the best suited non-covalent cross-linker for the POx-CIP micelles, a series of POx with two cleavable ester end groups was synthesized. The resulting copolymers were then codissolved with the worm micelle forming highly active CIP conjugate Me-$PMOx_{15}$-b-$PHeptOx_{16}$-EDA-xCIP in ethanol in a 1:1 molar ratio (mol/mol) and then added to thorouhgly stirred water. A successful formation of larger aggregates is initially judged by a visible precipitation.The aggregates with the triblockcopolymers that have PPhOx as middle block seem to contain the unchanged worm micelles in all cases, indicating that the different polymers do not mix and thus, the triblockcopolymer can act as cross-linker only. The triblockcopolymers with a longer hydrophobic middle block C_8-$PMOx_{10}$-b-$PPhOx_{20}$-b-$PMOx_{10}$-C_8 and C_8-$PMOx_{10}$-b-$PPhOx_{40}$-b-$PMOx_{10}$-C_8 afford nanostructured particles, which resemble densly cross-linked worm micelles (see Figure 2A). The aggregate of Me-$PMOx_{15}$-b-$PHeptOx_{16}$-EDA-xCIP with C_8-$PMOx_{10}$-b-$PPhOx_{20}$-b-$PMOx_{10}$-C_8 shows the highest deactivation in antibacterial activity against the clinically relevant strain Staphylococcus aureus of 135 compared to the free conjugate. The deactivation of the CIP-conjugate by the triblock copolymers with a lower PPhOx content or a shorter chain length is less pronounced, which is most likely due to the lower stability of the aggregates. The concept is based on the idea that the structure of the aggregates is majorly stabilized by the hydrophobic end groups of the cross-linking triblockcopolymer. Thus cleaving these groups might reverse the cross-linking process. The esterified triblockopolymers were nano-precipitated in water, isolated by centrifugation and suspended in aqueous NaOH (0.03 M). The cloudy suspension was stirred at room temperature and cleared after 2 h. The aggregates were cleaved into worm micelles of the CIP PAC and spherical micelles originating from the ester end group cleaved triblockcopolymers (see Figure micelles of the CIP PAC and spherical micelles originating from the ester end group cleaved triblockcopolymers (see Figure 2)

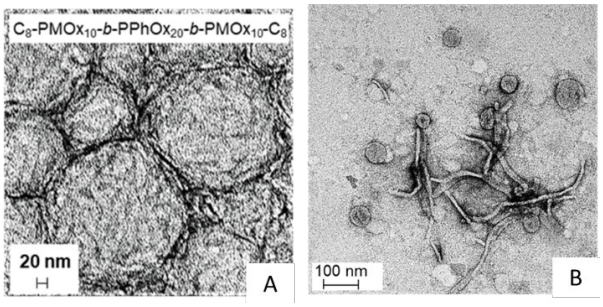


Figure 2: TEM image of cross-linked (A) and NaOH cleaved (B) aggregates of CIP PAC worm micelles and triblockcopolymers.

The cleaved particles fully retained their antibacterial activity and this process was also successful in the presence of the enzyme lipase. This shows the feasibility of the novel concept, which might be transferable to other antibiotics and drugs.

Contact:
joerg.tiller@tu-dortmund.de
jonas.tophoven@tu-dortmund.de

Publications:
Romanovska, A.; Schmidt, M.; Brandt, V.; Tophoven, J.; Tiller, J. C., Controlling the function of bioactive worm micelles by enzyme-cleavable non-covalent inter-assembly cross-linking. Journal of Controlled Release 2024, 368, 15-23. https://doi.org/10.1016/j.jconrel.2024.02.013

Publications

2023

- Milovanovic, M.; Tabakoglu, F.; Saki, F.; Pohlkoetter, E.; Buga, D.; Brandt, V.; Tiller, J. C.
Organic-inorganic double networks as highly permeable separation membranes with a chiral selector for organic solvents.
Journal of Membrane Science 2023, 668, 121190.
doi.org/10.1016/j.memsci.2022.121190

2022

- Benitez-Duif, P. A.; Breisch, M.; Kurka, D.; Edel, K.; Gökcay, S.; Stangier, D.; Tillmann, W.; Hijazi, M.; Tiller, J. C.,
Ultrastrong Poly(2-Oxazoline)/Poly(Acrylic Acid) Double-Network Hydrogels with Cartilage-Like Mechanical Properties.
Advanced Functional Materials 2022, 32 (44), 2204837.
doi.org/10.1002/adfm.202204837

- Milovanovic, M.; Rauner, N.; Civelek, E.; Holtermann, T.; El Jid, O.; Meuris, M.; Brandt, V.; Tiller, J. C.
Enzyme-Induced Ferrification of Hydrogels for Toughening of Functional Inorganic Compounds.
Macromol. Mater. Eng. 2022, 307 (8), 2200051 .
https://onlinelibrary.wiley.com/doi/pdf/10.1002/mame.202200051

- Segiet, D.; Weckes, S.; Austermuehl, J.; Tiller, J. C.; Katzenberg, F.,
On the influence of the amorphous phase on the stability of crystals in poly(cis-1,4-isoprene) networks.
doi.org/10.1002/app.53146

- Wilhelm, S. A.; Maricanov, M.; Brandt, V.; Katzenberg, F.; Tiller, J. C.,
Amphiphilic polymer conetworks with ideal and non-ideal swelling behavior demonstrated by small angle X-ray scattering.
Polymer 2022, 242, 124582.
doi.org/10.1016/j.polymer.2022.124582

2021

- Benski, L.; Viran, I.; Katzenberg, F.; Tiller, J. C.,
Small-Angle X-Ray Scattering Measurements on Amphiphilic Polymer Conetworks Swollen in Orthogonal Solvents.
Macromolecular Chemistry and Physics, 222 (1), 2000292 (2021).
doi.org/10.1002/macp.202000292

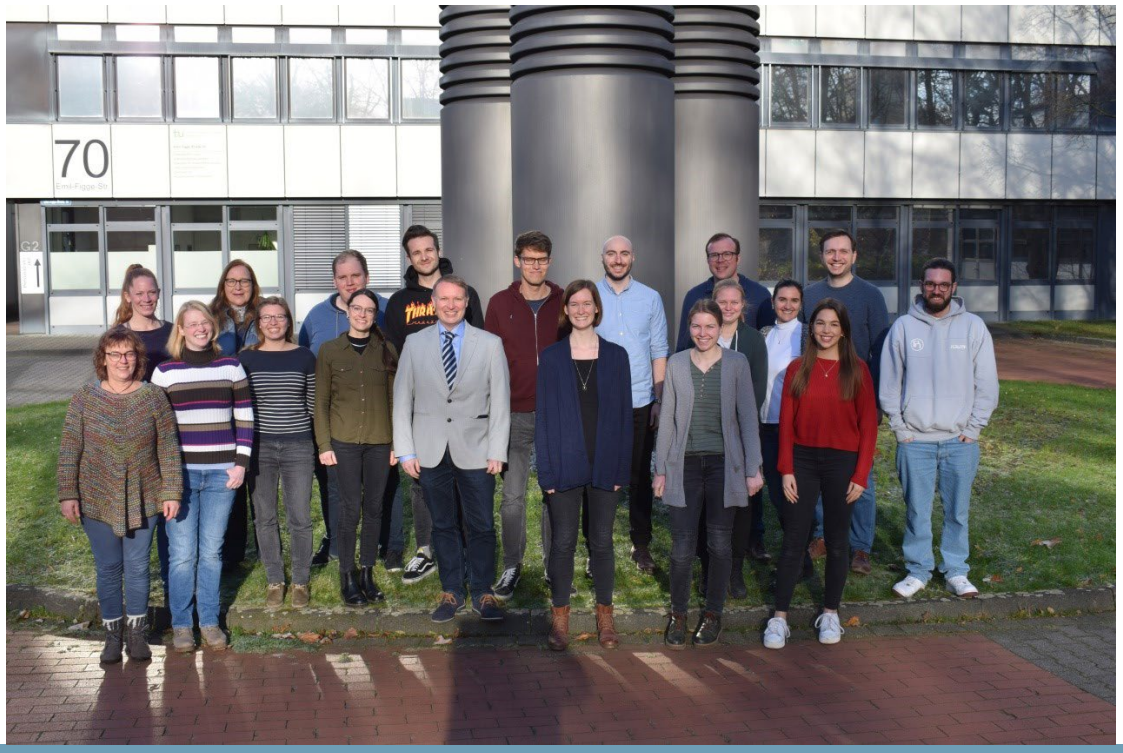
- Milovanovic, M.; Isselbaecher, N.; Brandt, V.; Tiller, J. C.,
Improving the Strength of Ultrastiff Organic–Inorganic Double-Network Hydrogels.
Chemistry of Materials, 33 (21), 8312-8322 (2021).
doi.org/10.1021/acs.chemmater.1c02525

- Milovanovic, M.; Mihailowitsch, L.; Santhirasegaran, M.; Brandt, V.; Tiller, J. C.,
Enzyme-induced mineralization of hydrogels with amorphous calcium carbonate for fast synthesis of ultrastiff, strong and tough organic–inorganic double networks.
Journal of Materials Science, 56 (27), 15299-15312 (2021).
doi.org/10.1007/s10853-021-06204-6

- Niedik, C. F.; Jenau, F.; Maricanov, M.; Segiet, D.; Tiller, J. C.; Katzenberg, F.,
Improvement of high voltage direct current material properties upon tailoring the morphology of crosslinked polyethylenes.
Polymer Crystallization, 4 (6), e10208 (2021).
doi.org/10.1002/pcr2.10208

- Romanovska, A.; Keil, J.; Tophoven, J.; Oruc, M. F.; Schmidt, M.; Breisch, M.; Sengstock, C.; Weidlich, D.; Klostermeier, D.; Tiller, J. C.,
Conjugates of Ciprofloxacin and Amphiphilic Block Copoly(2-alkyl-2-oxazolines)s Overcome Efflux Pumps and Are Active against CIP-Resistant Bacteria.
Molecular Pharmaceutics, 18 (9), 3532-3543 (2021).
doi.org/10.1021/acs.molpharmaceut.1c00430

- Segiet, D.; Stockmann, A.; Sadowski, J.; Katzenberg, F.; Tiller, J. C.,
Insights in the Thermal Volume Transition of Poly(2-oxazoline) Hydrogels.
Macromolecular Chemistry and Physics, 222 (18), 2100157 (2021).
doi.org/10.1002/macp.202100157



Bioprocess Engineering (BPT)

Bivariate One Strain Many Compounds Designs Expand the Secondary Metabolite Production Space in Corallococcus coralloides

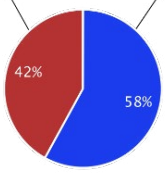
Anton Lindig, Jenny Schwarz, Georg Hubmann, Katrin Rosenthal, Stephan Lütz

*The scarcely investigated myxobacterium **Corallococcus coralloides** holds a large genome containing many uncharacterized biosynthetic gene clusters (BGCs) that potentially encode the synthesis of entirely new natural products. Despite the genomic potential, finding suitable cultivation conditions to trigger the production of new secondary metabolites (SMs) has been challenging. To address this, we employed a bivariate one strain many compounds (OSMAC) approach, combining two elicitors to activate BGCs and induce SM production in **C. coralloides.** The outcomes revealed synergistic effects in the bivariate OSMAC designs, evident through the discovery of entirely new mass features (MFs) not observed in the univariate OSMAC experiments. Molecular network analysis uncovered potential novel natural compounds and chemical derivatives, such as the identification of N-acyl fatty amines and sulfur-containing natural products. This study highlights the robust capacity of bivariate OSMAC designs to broaden the SMs repertoire of microorganisms with large genomes.*

The rather unknown bacterium *C. coralloides* harbors a large and fully sequenced genome of 10.08 Mbp with approximately 13.4% dedicated to the biosynthesis of SMs. Utilizing antiSMASH bacterial version 6.1 for genome mining analysis, only 15 out of 36 BGCs could be linked to potential natural products (Figure 1). However, many of these compounds have not yet been identified. Therefore, the activation of the biosynthetic potential requires a novel approach. Our strategy involves the combination of two stimuli at once to investigate whether synergistic effects in the SMs production of *C. coralloides* can be observed using bivariate OSMAC approaches.

Assigned BGCs (15/36)

NP class	Assigned compound	Sequence similarity
Terpenes	carotenoid	100%
NRPS-like	VEPE / AEPE / TG-1	100%
Terpenes	geosmin	100%
T1PKS-NRPS	myxochelin A / B	83%
T1PKS-NRPS	myxoprincomide-c506	66%
T1PKS-NRPS	nostopeptolide A2	50%
NRPS	APE Ec	36%
T3PKS	alkylpyrone-407 / -393	34%
T1PKS	minutissamide A / C / D	30%
T1PKS-NRPS	chloromyxamide	27%
T1PKS-NRPS	chloromyxamide	13%
Phenazine	streptobactin	11%
T1PKS-NRPS	BE-43547A1 etc.	10%
NRPS-like	myxochromide D	10%
RiPP-like	ficellomycin	5%



Orphan BGCs (21/36)

NP class	# of BGCs
Lanthipeptides	5
PKS-NRPS	4
RiPP-like	4
NRPS	3
Terpenes	2
Others	3

Figure 1: Genome mining of *C. coralloides* using antiSMASH 6.1. The pie chart presents the ratio of assigned and orphan BGCs. Assigned BGCs include the natural product (NP) class, the assigned compound and the sequence similarity to an annotated BGC in the BGC database. Identified orphan BGCs includes their NP class and the number of detected BGCs in the whole genome.

Unique MFs were observed in all conditions including the control condition, the univariate conditions and the bivariate conditions. The specific combination of two stimuli resulted in the production of entirely new unique bivariate-specific MFs. When cultivated with MD1-medium containing 1% v/v Ethanol, 5 new unique MFs were produced. In addition, M9-medium supplemented with supernatant of *Streptomyces griseochromogenes* yielded in 36 MFs, while addition of *Bacillus amyloliquefaciens* supernatant resulted in 4 MFs. Molecular network analysis unveiled a molecular family of 11 MFs belonging to N-acyl fatty amines including N-pentyloctadecanamide that was only produced during cultivation in bivariate condition M9-medium supplemented with supernatant of *S. griseochromogenes* (Figure 2). Additional in silico fragmentation analysis of a bivariate-specific singlet node revealed a potential novel chemical structure including a sulfur moiety, benzene and an oxazole substructure.

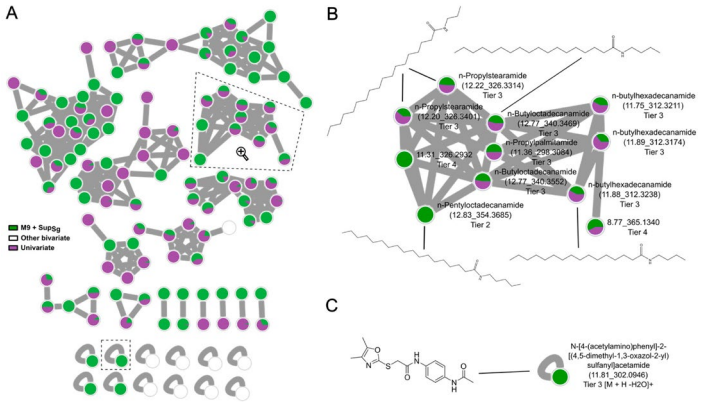


Figure 2: Molecular network and structural elucidation of new mass features in bivariate conditions. (A) Molecular network of all detected unique MFs in bivariate conditions and related MFs in univariate conditions. (B) Molecular family including possible structure of N-acyl fatty amines. (C) Single ion node representing possible novel sulfur-containing natural product.

The findings from this study strongly indicate that employing a combination of multiple elicitors in OSMAC experiments clearly broadens the biosynthetic production space, leading to an increase in the number of chemical derivatives and the potential discovery of novel SMs.

Contacts:
anton.lindig@tu-dortmund.de
georg.hubmann@tu-dortmund.de
stephan.luetz@tu-dortmund.de

Publications:
Lindig, A.; Schwarz, J.; Hubmann, G.; Rosenthal, K.; Lütz, S. Bivariate One Strain Many Compounds Designs Expand the Secondary Metabolite Production Space in Corallococcus coralloides. Microorganisms 2023, 11, 2592. https://doi.org/10.3390/microorganisms11102592

Reaction Engineering and Comparison of Electroenzymatic and Enzymatic ATP Regeneration Systems

Regine Siedentop, Tobias Prenzel, Siegfried R. Waldvogel, Katrin Rosenthal, Stephan Lütz

The investigation into the electrochemical regeneration of the cofactor Adenosine-5'-triphosphate (ATP) was selected as the Front Cover in the ChemElectroChem 22/2023 issue. ATP plays an important role in many enzymatically catalyzed reactions and a regeneration of the cofactor can lead to an increase in performance in cell-free reaction systems. Such an enzymatic ATP regeneration by means of an acetate kinase and pyruvate oxidase could be coupled to an electrochemical reaction for energy supply. The ATP-consuming reaction was compared using the developed electrochemical regeneration as well as other enzymatic regeneration systems and it shows properties and key figures that are promising for an economic bioprocess using regenerative and green energy to drive the electroenzymatic reactions.

TP is a key cofactor for many biocatalytic reactions, but it is expensive and can inhibit or deplete enzymes. Therefore, in situ regeneration of ATP is desirable for improving the performance and feasibility of biocatalytic processes. Various enzymatic methods have been developed for ATP regeneration, but they have limitations such as low yield or high cost.. We aimed to establish an electrochemically coupled ATP regeneration system by using pyruvate oxidase (POX) and acetate kinase (ACK) and expand it by adding polyphosphate kinase (PPK) to enable the phosphorylation of AMP to broaden the application ranges in industrial bioprocesses. The new ATP regeneration system was compared to other enzymatic methods in terms of phosphate donor properties and biocatalytic metrics.

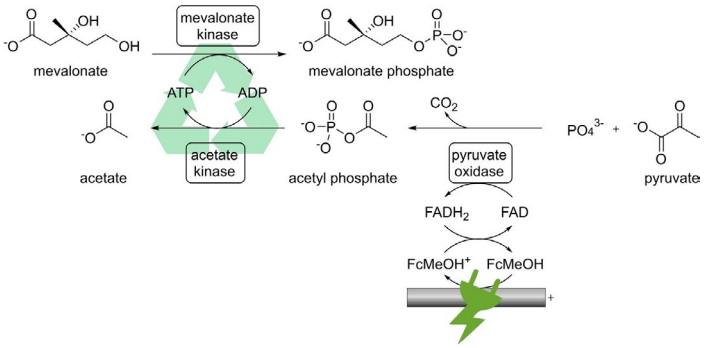


Figure 1: An electrochemically coupled ATP regeneration by POX and ACK for the phosphorylation of mevalonate was established and expanded by PPK.

We used mevalonate kinase (MVK) as a model enzyme that requires ATP for the phosphorylation of mevalonate (MVA) to mevalonate phosphate (MVAP). To evaluate the ATP regeneration efficiency, we measured and calculated the yield, turnover number, and turnover frequency of the reaction using different ATP regeneration systems. . We showed that the electroenzymatic system using POX and ACK achieved a high yield of 84% and a high turnover number of 68 for ADP, which are superior to many other enzymatic systems. Furthermore, we also showed that the regeneration system operate under mild conditions (pH 7, 30 °C) and can be coupled to a renewable energy source. We demonstrated that the system can be extended by adding PPK, which can phosphorylate AMP to ADP, thus increasing the efficiency and versatility of the system.

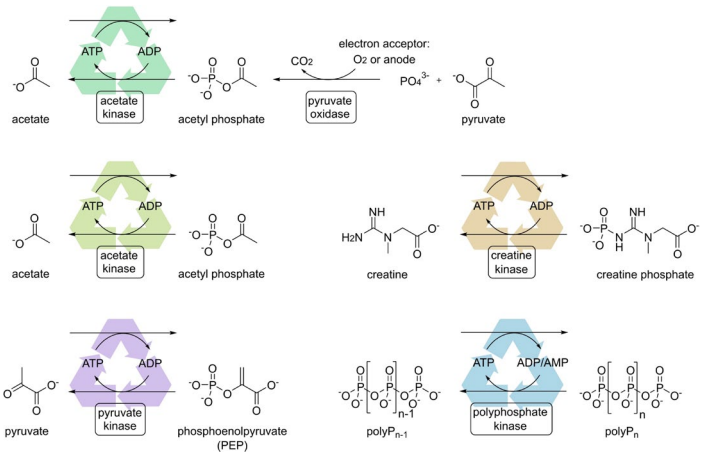


Figure 2: ATP Regeneration systems utilizing various enzymes and phosphate donors.

We conclude that the electroenzymatic system with POX and ACK is a promising method for ATP regeneration, as it offers high yield, high turnover number, mild conditions, and renewable energy integration. The novel ATP regeneration system can be applied to other biocatalytic reactions that require ATP, such as the synthesis of terpenoids, nucleotides, or coenzymes. In the future, the system can be further optimized by improving the electrode design, enzyme immobilization, and reaction engineering

Publications:
Siedentop, R.; Prenzel, T.; Waldvogel, R.S.; Rosenthal, K.; Lütz, S. Reaction Engineering and Comparison of Electroenzymatic and Enzymatic ATP Regeneration Systems. ChemElectroChem 2023, 10, e202300332.
https://doi.org/10.1002/celc.202300332

Contacts:
regine.siedentop@tu-dortmund.de
krosenthal@constructor.university.de
stephan.luetz@tu-dortmund.de

Publications

2023

- Siedentop R.; Prenzel T.; Waldvogel S.R.; Rosenthal K.; Lütz S.
Reaction Engineering and Comparison of Electroenzymatic and Enzymatic ATP Regeneration Systems.
ChemElectroChem 10, e202300332 (2023).
https://doi.org/10.1002/celc.202300332

- Siedentop R.; Prenzel T.; Waldvogel S.R.; Rosenthal K.; Lütz S.
Reaction Engineering and Comparison of Electroenzymatic and Enzymatic ATP Regeneration Systems. (Coverprofil)
ChemElectroChem 10, e202300587 (2023).
https://doi.org/10.1002/celc.202300587

- Lindig A.; Schwarz S.; Hubmann G.; Rosenthal K.; Lütz S.
Bivariate One Strain Many Compounds Designs Expand the Secondary Metabolite Production Space in *Corallococcus coralloides*.
Microorganisms 11(10):2592 (2023).
https://doi.org/10.3390/microorganisms11102592

- Rolf J.; Handke J.; Burzinski F.; Lütz S.; Rosenthal K.
Amino acid balancing for the prediction and evaluation of protein concentrations in cell-free protein synthesis systems.
Biotechnol. Prog. 39(6):e3373 (2023).
https://aiche.onlinelibrary.wiley.com/doi/10.1002/btpr.3373

- Siedentop R.; Siska M.; Möller N.; Lanzrath H.; von Lieres E.; Lütz S.; Rosenthal K.
Bayesian Optimization for an ATP-Regenerating In Vitro Enzyme Cascade.
Catalysts 13(3):468 (2023).
https://doi.org/10.3390/catal13030468

- Siedentop R.; Dziennus M.; Lütz S.; Rosenthal K.
Debottlenecking of an In Vitro Enzyme Cascade Using a Combined Model- and Experiment-Based Approach.
Chemie Ingenieur Technik 95: 543-548 (2023).
https://doi.org/10.1002/cite.202200170

- Kruth S.; Zimmermann C.J.-M.; Kuhr K.; Hiller W.; Lütz S.; Pietruszka J.; Kaiser M.; Nett M.
Generation of Aurachin Derivatives by Whole-Cell Biotransformation and Evaluation of Their Antiprotozoal Properties.
Molecules 28(3):1066 (2023).
https://doi.org/10.3390/molecules28031066

2022

- Becker M.; Ziemińska-Stolarska A.; Markowska D.; Lütz S.; Rosenthal K.
Comparative life cycle assessment of chemical and biocatalytic 2'3'-cyclic GMP-AMP synthesis.
ChemSusChem 16, e202201629 (2022)
https://doi.org/10.1002/cssc.202201629

- Vogt J.; Rosenthal K.
Validation of Easy Fabrication Methods for PDMS-Based Microfluidic (Bio) Reactors.
Sci 4(4):36 (2022)
https://www.mdpi.com/2413-4155/4/4/36

- Steinmann A.; Schullehner K.; Kohl A.; Dickmeis C.; Finger M.; Hubmann G.; Commandeur U.; Girhard M.; Urlacher V.; Lütz S.
A targeted metabolomics method for extra- and intracellular metabolite quantification covering the complete monolignol and lignan synthesis pathway.
Metabolic Engineering Communications 15,1-12 (2022)
https://doi.org/10.1016/j.mec.2022.e00205

- Steinmann A.; Finger M.; Nowacki C.; Decembrino D.; Hubmann G.; Girhard M.; Urlacher V.; Lütz S.
Heterologous Lignan Production in Stirred-Tank Reactors—Metabolomics-Assisted Bioprocess Development for an In Vivo Enzyme Cascade.
Catalysts 12(11):1473 (2022)
https://doi.org/10.3390/catal12111473

- Menke M.; Behr A.; Rosenthal K.; Linke D.; Kockmann N.; Bornscheuer U.; Dörr M.
Development of an Ontology for Biocatalysis.
Chemie Ingenieur Technik, 94: 1827-1835 (2022)
https://doi.org/10.1002/cite.202200066

- Rosenthal K.; Bornscheuer U.; Lütz S.
Cascades of Evolved Enzymes for the Synthesis of Complex Molecules.
Angew. Chem. Int. Ed. 61, e202208358; Angew. Chem. 134, e202208358 (2022)
https://doi.org/10.1002/anie.202208358

- Rolf J.; Ngo A.; Tischler D.; Lütz S.; Rosenthal K.
Cell-free protein synthesis for the screening of novel azoreductases and their preferred electron donor.
ChemBioChem 23(15), e202200121 (2022)
https://doi.org/10.1002/cbic.202200121

- Kinner A., Nerke P.; Siedentop R.; Steinmetz T.; Claassen T.; Rosenthal K.; Nett M.; Pietruszka J.; Lütz S.
Recent Advances in Biocatalysis for Drug Synthesis
Biomedicines 10(5): 964
https://doi.org/10.3390/biomedicines10050964

- Siedentop R.; Rosenthal K.
Industrially Relevant Enzyme Cascades for Drug Synthesis and Their Ecological Assessment:
Int. J. Mol. Sci. 23(7): 3605
https://doi.org/10.3390/ijms23073605

- Grühn J.; Behr A.; Eroglu T.; Trögel V.; Rosenthal K.; Kockmann N.
From Coiled Flow Inverter to Stirred Tank Reactor – Bioprocess Development and Ontology Design.
Chemie Ingenieur Technik 94: 852-863 (2022)
https://doi.org/10.1002/cite.202100177

- Kinner A.; Lütz S.; Rosenthal, K.
Agar Plate-Based Screening Approach for the Identification of Enzyme-Catalyzed Oxidations.
Chemie Ingenieur Technik 94: 1853-1859 (2022)
https://doi.org/10.1002/cite.202200084

2021

- Bartsch T.*; Becker M.*; Rolf J.*; Rosenthal K.; Lütz S. (*contributed equally)
Biotechnological production of cyclic dinucleotides — Challenges and opportunities.
Biotechnology and Bioengineering 119, 677–684 (2021)
https://doi.org/10.1002/bit.28027

- Siedentop R.; Claaßen C.; Rother D.; Lütz S.; Rosenthal K.
Getting the Most Out of Enzyme Cascades: Strategies to Optimize In Vitro Multi-Enzymatic Reactions.
Catalysts 11(10):1183 (2021)
https://doi.org/10.3390/catal11101183

- Rolf J.; Nerke P.; Britner A.; Krick S.; Lütz S.; Rosenthal K.
From Cell-Free Protein Synthesis to Whole-Cell Biotransformation: Screening and Identification of Novel-Ketoglutarate-Dependent Dioxygenases for Preparative-Scale Synthesis of Hydroxy-L-Lysine.
Catalysts 11(9):1038 (2021)
https://doi.org/10.3390/catal11091038

- Kinner A.; Rosenthal K.; Lütz S.
Identification and Expression of New Unspecific Peroxygenases – Recent Advances, Challenges and Opportunities.
Front. Bioeng. Biotechnol. 9:705630 (2021)
https://doi.org/10.3389/fbioe.2021.705630

- Schmitz LM.; Hageneier F.; Rosenthal K.; Busche T.; Brandt D.; Kalinowski J.; Lütz S.
Recombinant Expression and Characterization of Novel P450s from Actinosynnema mirum.
Bioorganic & Medicinal Chemistry 116241 (2021)
https://doi.org/10.1016/j.bmc.2021.116241

- Becker M.; Nikel P.; Andexer JN.; Lütz S.; Rosenthal K.
A Multi-Enzyme Cascade Reaction for the Production of 2'3'-cGAMP.
Biomolecules 11(4): 590 (2021)
https://doi.org/10.3390/biom11040590

- Schmitz LM.; Kinner A.; Althoff K.; Rosenthal K.; Lütz S.
Investigation of vitamin D2 and vitamin D3 hydroxylation by Kutzneria albida.
ChemBioChem 22, 2266 (2021)
https://doi.org/10.1002/cbic.202100027

- Schwarz J.; Hubmann G.; Rosenthal K.; Lütz S.
Triaging of Culture Conditions for Enhanced Secondary Metabolite Diversity from Different Bacteria.
Biomolecules 11(2), 193 (2021)
https://doi.org/10.3390/biom11020193

- Becker M.; Lütz S.; Rosenthal K.
Environmental Assessment of Enzyme Production and Purification.
Molecules 26(3):573 (2021)
https://doi.org/10.3390/molecules26030573

Computational Bioengineering (CBE)

Tailoring Chemical Reactivity on Metal Surfaces

Quantum Mechanics (QM) meets Scanning Tunneling Microscopy (STM)

Joel Mieres-Perez, Elsa Sánchez-García

Catalysis of chemical reactions often occurs at the surface of metals. Improving our understanding of such complex processes is key to optimize such reactions and to design new catalytic routes. By combining QM calculations, organic synthesis (Sander, RUB) and scanning tunneling microscopy (Morgenstern, RUB), we characterized at the molecular level complex chemical phenomena on metal surfaces, from dimerization reactions to enantioselectivity control.

C–C bond forming reactions are essential for the chemical and pharmaceutical industry since they are critical steps in the synthesis of a large variety of pharmaceutical and agrochemical compounds. Transient carbenes are organic molecules that play a key role as intermediates in these reactions. However, in solution chemistry, the amount of carbene molecules that effectively undergoes C–C bond forming reactions is diminished by side reactions, for instance with solvent molecules. Therefore, the usability of carbene dimerization as a C–C bond forming reaction is limited. Our quantum mechanical calculations (QM), together with the experimental work of the Sander and Morgenstern groups at the Ruhr University Bochum (RUB), contributed to the development of an efficient carbene dimerization reaction by activation with a metal surface.

Diphenylcarbene (DPC), an archetypical carbene, was adsorbed on a silver surface in the presence of water to generate the C-C coupling product (Fig. 1). By using scanning tunneling microscopy and quantum mechanical calculations we were able to effectively identify and characterize single molecules of the key species involved in the reaction on the surface. In contrast to the chemistry of carbenes in solution, where the local concentration of carbenes and thus the probability for a dimerization reaction is small, on the surface the conditions for dimerization reactions are much better. The first step is a proton transfer reaction from a water molecule to the carbene, which results in the formation of a highly reactive cation. The metal surface induces an electron transfer reaction from the surface to the cation, resulting in a neutral radical species that is mobile on the surface. The lower adsorption energy of the radical compared to that of the carbene and the cation allows the radical to diffuse and react with other species on the surface, producing the C-C coupling product. This reaction only takes place if DPC is formed on the surface in the presence of water molecules. Our work thus paves the way for developing novel, efficient C-C coupling reactions with no precedent in liquid phase chemistry.
Another interesting result from our single molecule studies on metal surfaces is the control of chirality.

Contacts:
joel.mieresperez@tu-dortmund.de
professors.cbe.bci@tu-dortmund.de

Chirality is a property of molecules that is of key importance for catalysis, drug development, electronics, and nanotechnology. We studied how the chirality of single molecules of DPC bound on a metal surface can be controlled. When adsorbed on a metal surface, the rotation of the two phenyl rings of DPC connected to the central carbene carbon results in the formation of two distinct chiral species (enantiomers) on the surface. These species can be interconverted by controlling the tip-molecule distance during the scanning tunneling microscopy experiments. Quantum mechanical calculations revealed the geometry changes responsible for the stabilization of each of the enantiomers. This study delivers an important way to achieve enantioselectivity control on metal surfaces in a precise manner.

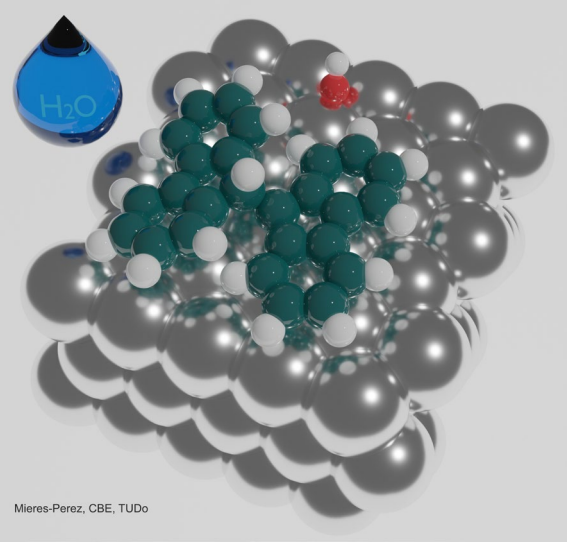


Figure 1: C-C coupling reaction product on a silver surface. The reaction only takes place if DPC is formed on the surface in the presence of water.

Publications:
Cao, Y.; Mieres-Perez, J.; Lucht, K.; Ulrich, I; Schweer, P.; Sanchez-Garcia, E., Morgenstern, K; Sander, W., C-C coupling of carbene molecules on a metal surface in the presence of water. Journal of the American Chemical Society 2023, 145, 21, 11544–11552. https://doi.org/10.1021/jacs.2c12274
Cao, Y.; Mieres-Perez, J.; Rowen, J. F.; Sanchez-Garcia, E., Sander, W.; Morgenstern, K., Chirality control of a single carbene molecule by tip-induced van der Waals interactions. Nature Communications 2023, 14, 4500. https://doi.org/10.1038/s41467-023-39870-y

Towards therapeutic alternatives targeting the chemokine receptor CXCR4

Biomolecular simulations enable the optimization of peptide ligands and the discovery of small molecules with therapeutic potential

Yasser Almeida-Hernandez and Elsa Sánchez-García

Peptides that inhibit the chemokine receptor CXCR4 have great potential as therapeutics in the treatment of cancer and HIV infection. The present study shows that biomolecular simulations aid the engineering of more effective variants of such peptides. These peptide derivatives have improved plasma stability and enable radio-theragnostics applications. Furthermore, we reported how spermine, a small molecule found in human semen, acts as inhibitor of CXCR4.

The C-X-C chemokine receptor type 4 (CXCR4) is a G-protein coupled receptor involved in key processes such as cell migration and vascularization. CXCR4 is involved in inflammation, human immunodeficiency virus-1 (HIV-1) infection and in cancer, with a large amount of reported cancer cases related to CXCR4. Therefore, CXCR4 is a very important target for the pharmaceutical industry and therapeutics targeting CXCR4 are highly sought. Due to the presence of CXCR4 in several body tissues and the lack of specificity of drug candidates, blocking CXCR4 may induce severe side effects. This represents a major obstacle to the development of anti-CXCR4 drugs. So far, the only approved antagonist of CXCR4 is Plerixafor, which has strong side effects in cancer patients.

EPI-X4 is an endogenous peptide inhibitor of CXCR4. Using biomolecular simulations and experimental assays (University of Ulm), we optimized EPI-X4-derived peptides. Our work delivered peptides with plasma stability in animal models higher than the parent compound. At the same time, these derivatives retain the binding and antagonistic activity of EPI-X4 against CXCR4. Our molecular modeling showed that, despite modifications of the N-terminal residue, the peptides preserved key interactions with CXCR4.

Radio-theragnostics approaches targeting CXCR4 are very important, since they allow both imaging and therapy of CXCR4-related tumors. Accordingly, in collaboration with experimental partners of the University of Ulm and the University of Basel, we studied EPI-X4-derived candidates modified with the ^{177}Lu-DOTA radiotracer(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-^{177}Lu). Our biomolecular modeling (Fig. 1) showed that the modification of the peptide scaffold does not affect the binding of the parent peptide to CXCR4.

As mentioned, the CXCR4 receptor is also related to HIV infections. Semen is one of the main body fluids involved in HIV transmission. Together with our experimental partners, we reported that spermine, which is a molecule found in human semen, blocks CXCR4, decreasing HIV-1 infection in cells. We studied the binding of spermine to CXCR4, through extensive biomolecular simulations. Our work showed how spermine binds to CXCR4, involving spermine's positive charges. Our computational models also indicated that other related molecules which are less (or not at all) positively charged such as putrescine, ornithine and the four-fold acetylated spermine bind less efficiently to CXCR4, and exhibit very poor to none inhibitory effect, which was experimentally corroborated.

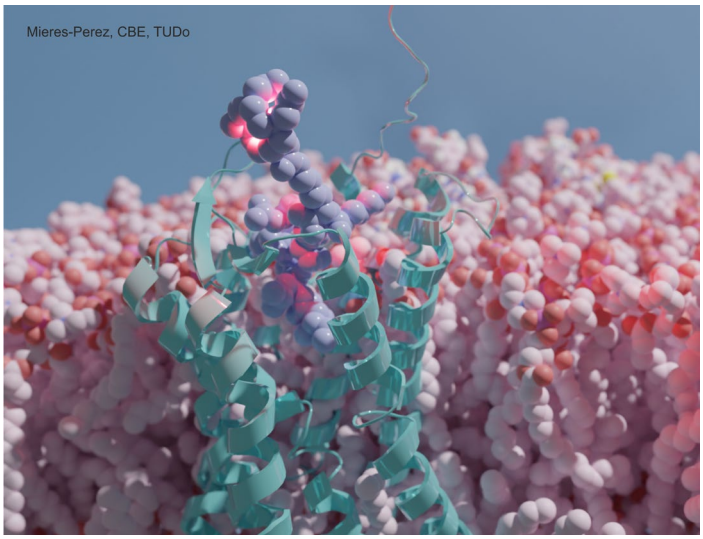


Figure 1: Depiction of our computational model of CXCR4 (partially shown, cyan), a peptide derivative of EPI-X4 (lilac) with the radiotracer (^{177}Lu-DOTA) highlighted. The model cellular membrane is shown in rose with oxygen atoms in red. Water molecules are omitted in the figure for clarity.

Our work on CXCR4 inhibitors thus opens new routes for the design and optimization of novel scaffolds for CXCR4 antagonists.

Publications:
Harms, M.; Hansson, R. F.; Gilg, A.; Almeida-Hernández, Y.; et al. Development of N-terminally modified variants of the CXCR4-antagonistic peptide EPI-X4 for enhanced plasma stability. Journal of Medicinal Chemistry 2023, 66, 22, 15189–15204. https://doi.org/10.1021/acs.jmedchem.3c01128
Gaonkar, R. H.; Schmidt, Y. T.; Mansi, R.; Almeida-Hernández, Y.; et al. Development of a new class of CXCR4 targeting radioligands based on the endogenous antagonist EPI-X4 for oncological applications. Journal of Medicinal Chemistry (Special issue "Diagnostic and Therapeutic Radiopharmaceuticals" 2023, 66, 13, 8484–8497. https://doi.org/10.1021/acs.jmedchem.3c00131
Harms, M.; Smith, N.; Han, M.; Groß, R.; et al. Spermine and spermidine bind CXCR4 and inhibit CXCR4- but not CCR5-tropic HIV-1 infection. Science Advances 2023, 9, eadf8251.

Contacts:
yasser.almeida@tu-dortmund.de
professors.cbe.bci@tu-dortmund.de

Publications

2023

Peer-reviewed Journal Articles

- M. Harms, R. F. Hansson, A. Gilg, Y. Almeida-Hernández, J. Löffler, A. Rodríguez-Alfonso, M. M. W. Habib, D. Albers, N. S. Ahmed, A.H. Abadi, G. Winter, V. Rasche, A. J. Beer, G. Weidinger, N. Preising, L. Ständker, S. Wiese, E. Sanchez-Garcia, A. N. Zelikin, J. Münch.
Development of N-terminally modified variants of the CXCR4-antagonistic peptide EPI-X4 for enhanced plasma stability.
Journal of Medicinal Chemistry, 66, 22, 15189 (2023)
https://doi.org/10.1021/acs.jmedchem.3c01128

- Y. Cao, J. Mieres-Perez, K. Lucht, I. Ulrich, P. Schweer, E. Sanchez-Garcia, K. Morgenstern, W. Sander.
C-C coupling of carbene molecules on a metal surface in the presence of water.
Journal of the American Chemical Society, 145, 21, 11544 (2023)
https://doi.org/10.1021/jacs.2c12274

- C. Kling, A. Sommer, Y. Almeida-Hernandez, A. Rodríguez, J. A Perez-Erviti, R. Bhadane, L. Ständker, S. Wiese, H. Barth, M. Pupo-Meriño, A. T Pulliainen, E. Sánchez-García, K. Ernst.
Inhibition of pertussis toxin by human-defensins-1 and-5: Differential mechanisms of action.
International Journal of Molecular Sciences (Special Issue Current Advances in Peptide Inhibitors), 24 (13), 10557 (2023)
https://doi.org/10.3390/ijms241310557

- M. Harms, N. Smith, M. Han, R. Groß, P. von Maltitz, C. Stürzel, Y. B Ruiz-Blanco, Y. Almeida-Hernández, A. Rodriguez-Alfonso, D. Cathelin, B. Caspar, B. Tahar, S. Sayettat, N. Bekaddour, K. Vanshylla, F. Kleipass, S. Wiese, L. Ständker, F. Klein, B. Lagane, A. Boonen, D. Schols, S. Benichou, E. Sanchez-Garcia, J.-P. Herbeuval, J. Münch.
Spermine and spermidine bind CXCR4 and inhibit CXCR4- but not CCR5-tropic HIV-1 infection.
Science Advances, 9, eadf8251 (2023)
https://doi.org/10.1126/sciadv.adf8251

- Y. Cao, J. Mieres-Perez, J. F. Rowen, E. Sanchez-Garcia, W. Sander, K. Morgenstern.
Chirality control of a single carbene molecule by tip-induced van der Waals interactions.
Nature Communications, 14, 4500 (2023)
https://doi.org/10.1038/s41467-023-39870-y

- J. Neblik, A. Kirupakaran, C. Beuck, J. Mieres Perez, F. C. Niemeyer, M.-H. Le, U. Telgheder, J. F. Schmuck, A. Dudziak, P. Bayer, E. Sanchez-Garcia, S. Westermann, T. Schrader.
Multivalent molecular tweezers disrupt the essential NDC80 interaction with microtubules.
Journal of the American Chemical Society, 145, 28, 15251 (2023)
https://doi.org/10.1021/jacs.3c0218

- R. H. Gaonkar, Y. T. Schmidt, R. Mansi, Y. Almeida-Hernandez, E. Sanchez-Garcia, M. Harms, J. Münch, M. Fani.
Development of a new class of CXCR4 targeting radioligands based on the endogenous antagonist EPI-X4 for oncological applications.
Journal of Medicinal Chemistry (Special issue Diagnostic and Therapeutic Radiopharmaceuticals, 66, 13, 8484 (2023)
https://doi.org/10.1021/acs.jmedchem.3c00131

- L.-R. Olari, R. Bauer, M. Gil Miró, V. Vogel, L. Cortez Rayas, R. Groß, A. Gilg, R. Klevesath, A. A. Rodríguez Alfonso, K. Kaygisiz, U. Rupp, P. Pant, J. Mierez-Perez, L. Steppe, R. Schäffer, L. Rauch-Wirth, C. Conzelmann, J. A. Müller, F. Zech, F. Gerbl, J. Bleher, N. Preising, L. Ständker, S. Wiese, D. R. Thal, C. Haupt, H. R. A. Jonker, M. Wagner, E. Sanchez-Garcia, T. Weil, S. Stenger, M. Fändrich, J. von Einem, C. Read, P. Walther, F. Kirchhoff, B. Spellerberg, J. Münch.
The C-terminal 32-mer fragment of hemoglobin alpha is an amyloidogenic peptide with antimicrobial properties.
Cellular and Molecular Life Sciences, 80, 151, (2023)
https://doi.org/10.1007/s00018-023-04795-8

- H. Shahpasand-Kroner, I. Siddique, R. Malik, G. Linares, M. Ivanova, J. Ichida, T. Weil, J. Münch, E. Sanchez-Garcia, F.-G. Klärner, T. Schrader, G. Bitan.
Molecular tweezers – supramolecular hosts with broad-spectrum biological applications.
Pharmacological Reviews, 75 (2), 263 (2023)
https://doi.org/10.1124/pharmrev.122.000654

2022

Peer-reviewed Journal Articles

- L. Wettstein, P. Immenschuh, T. Weil, C. Conzelmann, Y. Almeida-Hernández, M. Hoffmann, A. Kempf, I. Nehlmeier, R. Lotke, M. Petersen, S. Stenger, F. Kirchhoff, D. Sauter, S. Pöhlmann, E. Sanchez-Garcia, J.Münch
Native and activated antithrombin inhibits TMPRSS2 activity and SARS-CoV-2 infection
Journal of Medical Virology, 95 (1), e28124 (2022) Journal Cover
https://doi.org/10.1002/jmv.28124

- A. Rodríguez-Alfonso, A. Heck, Y. B Ruiz-Blanco, A. Gilg, L.Ständker, S. L. Kuan, T. Weil, E. Sanchez-Garcia, S. Wiese, J. Münch, M. Harms
Advanced EPI-X4 derivatives covalently bind human serum albumin resulting in prolonged plasma stability.
International Journal of Molecular Sciences, 23(23), 15029 (2022)
https://doi.org/10.3390/ijms232315029

- Y. B. Ruiz-Blanco, G. Agüero-Chapin, S. Romero-Molina, A. Antunes, L.-R. Olari, B. Spellerberg, J. Münch, E. Sanchez-Garcia
ABP-Finder: A Tool to Identify Antibacterial Peptides and the Gram-Staining Type of Targeted Bacteria.
Antibiotics, 11(12), 1708 (2022)
https://doi.org/10.3390/antibiotics11121708

- N. Samanta, Y. B. Ruiz-Blanco, Z. Fetahaj, D. Gnutt, C. Lantz, J. A. Loo, E. Sanchez-Garcia, S. Ebbinghaus
Superoxide Dismutase Folding Stability as a Target for Molecular Tweezers in SOD1-related Amyotrophic Lateral Sclerosis.
ChemBioChem, 23, e20220039 (2022)
https://doi.org/10.1002/cbic.202200396

- T. Weil, A. Kirupakaran, M.-H. Le, P. Rebmann, J. Mieres-Perez, L. Issmail, C. Conzelmann, J. A. Müller, L. Rauch, A. Gilg, L. Wettstein, R. Groß, C. Read, T. Bergner, S. A. Pålsson, N. Uhlig, V. Eberlein, H. Wöll, F.-G. Klärner, S. Stenger, B. M. Kümmerer, H. Streeck, G. Fois, M. Frick, P. Braubach, A.-L. Spetz, T. Grunwald, J. Shorter, E. Sanchez-Garcia, T. Schrader, J. Münch
Advanced Molecular Tweezers with Lipid Anchors against SARS-CoV-2 and Other Respiratory Viruses.
Journal of the American Chemical Society Au, 2(9): 2187–2202 (2022)
https://doi.org/10.1021/jacsau.2c00220

- A. Bera, S. Henkel, J. Mieres-Perez, Y. Andargie Tsegaw, E. Sanchez-Garcia, W. Sander, K. Morgenstern.
Surface Diffusion Aided by a Chirality Change of Self-Assembled Oligomers under 2D Confinement
Angewandte Chemie International Edition, 61, e202212245 (2022)
https://doi.org/10.1002/anie.202212245

- S. Romero-Molina, Y. B. Ruiz-Blanco, J. Mieres-Perez, M. Harms, J. Münch, M. Ehrmann, E. Sanchez-Garcia
PPI-Affinity: A web tool for the prediction and optimization of protein – peptide and protein – protein binding affinity.
Journal of Proteome Research, 21, 1829–1841 (2022)
https://doi.org/10.1021/acs.jproteome.2c00020

- J. Rey, M. Breiden, V. Lux, A. Bluemke, M. Steindel, K. Ripkens, B. Möllers, K. Bravo Rodriguez, P. Boisguerin, R. Volkmer, J. Mieres-Perez, T. Clausen, E. Sanchez-Garcia, M. Ehrmann
An allosteric HTRA1-calpain 2 complex with restricted activation profile.
Proceedings of the National Academy of Sciences, 119, 14, e2113520119 (2022)
https://doi.org/10.1073/pnas.2113520119

- M. Harms, R. F. Hansson, S. Carmali, Y. Almeida-Hernández, E. Sanchez-Garcia, J. Münch, A. N. Zelikin.
Dimerization of the peptide CXCR4-antagonist on macromolecular and supramolecular protraction arms affords increased potency and enhanced plasma stability.
Bioconjugate Chemistry, 33, 4, 594–607, (2022) Journal Cover
https://doi.org/10.1021/acs.bioconjchem.2c00034

- R. Kosinski, J. M. Perez, E.-C. Schöneweiß, Y. B. Ruiz-Blanco, I. Ponzo, K. Bravo-Rodriguez, M. Erkelenz, S. Schlücker, G. Uhlenbrock, E. Sanchez-Garcia, B. Saccà.
The role of DNA nanostructures in the catalytic properties of an allosterically regulated protease.
Science Advances, 8, 1, (2022)
https://doi.org/10.1126/sciadv.abk0425

- D. Aschmann, C. Vallet, S. K. Tripathi, Y. B. Ruiz-Blanco, M. Brabender, C. Schmuck, E. Sanchez-Garcia, S. K. Knauer, M. Giese.
Selective Disruption of Survivin's Protein-Protein Interactions: A Supramolecular Approach Based on Guanidiniocarbonylpyrrole.
ChemBioChem, 23, e202100618 (2022)
https://doi.org/10.1002/cbic.202100618

- K. N. Ingenbosch, J. C. Vieyto-Nuñez, Y. B. Ruiz-Blanco, C. Mayer, K. Hoffmann-Jacobsen, E. Sanchez-Garcia.
Effect of Organic Solvents on the Structure and Activity of a Minimal Lipase
The Journal of Organic Chemistry, 87 (3), 1669-1678 (2022)
https://doi.org/10.1021/acs.joc.1c01136

2021

Peer-reviewed Journal Articles

- G. König, P. Sokkar, N. Pryk, S. Heinrich, D. Möller, G. Cimicata, D. Matzov, P. Dietze, W. Thiel, A. Bashan, J. E. Bandow, J. Zuegg, A. Yonath, F. Schulz, E. Sanchez-Garcia
  Rational prioritization strategy allows the design of macrolide derivatives that overcome antibiotic resistance
  Proceedings of the National Academy of Sciences, 118, 46 (2021)
  https://doi.org/10.1073/pnas.2113632118

- P. Sokkar, M. Harms, C. Stürzel, A. Gilg, G. Kizilsavas, M. Raasholm, N. Preising, M. Wagner, F. Kirchhoff, L. Ständker, G. Weidinger, B. Mayer, J. Münch, E. Sanchez-Garcia.
  Computational modeling and experimental validation of the EPI-X4/CXCR4 complex allows rational design of small peptide antagonists
  Communications Biology, 4 (1), 1-13 (2021)
  https://doi.org/10.1038/s42003-021-02638-5

- T. Lohmiller, S. K. Sarkar, J. Tatchen, S. Henkel, T. Schleif, A. Savitsky, E. Sanchez-Garcia and W. Sander
  Sequential hydrogen tunneling in o-tolylmethylene
  Chemistry–A European Journal, 27 (71), 17873-17879 (2021)
  https://doi.org/10.1002/chem.202102010

- R. Malishev, N. Salinas, J. Gibson, A. B. Eden, J. Mieres-Perez, Y. B. Ruiz-Blanco, O. Malka, S. Kolusheva, F. G. Klarner, T. Schrader, E. Sanchez-Garcia, C. Wang, M. Landau, G. Bitan, and R. Jelinek.
  Inhibition of Staphylococcus aureus biofilm-forming functional amyloid by molecular tweezers
  Cell Chemical Biology, 28, 1–11 (2021)
  https://doi.org/10.1016/j.chembiol.2021.03.013

- M. Böhm, K. Killinger, A. Dudziak, P. Pant, K. Jänen, S. Hohoff, K. Mechtler, M. Örd, M. Loog, E. Sanchez-Garcia and S. Westermann.
  Cdc4 phospho-degrons allow differential regulation of Ame1CENP-U protein stability across the cell cycle
  eLife, 10, e67390. (2021)
  https://doi.org/10.7554/eLife.67390

- J. Mieres-Perez, K. Lucht, I. Trosien, W. Sander, E. Sanchez-Garcia, and K. Morgenstern.
  Controlling reactivity—real-space imaging of a surface metal carbene
  Journal of the American Chemical Society, 143 (12), 4653–4660 (2021)
  Journal Cover and ACS spotlight.
  https://doi.org/10.1021/jacs.0c12995

- L. Wettstein, T. Weil, C. Conzelmann, J. A. Müller, R. Groß, M. Hirschenberger, A. Seidel, S. Klute, F. Zech, C. P. Bozzo, N. Preising, G. Fois, R. Lochbaum, P. M. Knaff, V. Mailänder, L. Ständker, D. R. Thal, C. Schumann, S. Stenger, A. Kleger, G. Lochnit, B. Mayer, Y. B. Ruiz-Blanco, M. Hoffmann, K. M. J. Sparrer, S. Pöhlmann, E. Sanchez-Garcia, F. Kirchhoff, M. Frick & J. Münch.
  Alpha-1 antitrypsin inhibits TMPRSS2 protease activity and SARS-CoV-2 infection
  Nature Communications, 12, 1726 (2021)
  https://doi.org/10.1038/s41467-021-21972-0

- A. Meiners, S. Bäcker, I. Hadrović, C. Heid, C. Beuck, Y. B. Ruiz-Blanco, J. Mieres-Perez, M. Pörschke, J. N. Grad, C. Vallet, D. Hoffmann, P. Bayer, E. Sánchez- García, T. Schrader & S. K. Knauer.
  Specific inhibition of the Survivin–CRM1 interaction by peptide-modified molecular tweezers
  Nature Communications, 12, 1505 (2021)
  https://doi.org/10.1038/s41467-021-21753-9

Computational Systems Biology (CSB)

The pseudoentropy of allele frequency trajectories, the persistence of variation, and the effective population size

Nikolas Vellnow, Toni I. Gossmann, David Waxman

In order to understand biological evolution and its molecular basis it is essential to measure genetic variation and follow its change over time. Here, we derive a new measure, pseudoentropy, which concisely captures variation at individual genes or across whole genomes. We show through diffusion analysis and individual-based computer simulations that pseudoentropy generally decreases over time, but that these trajectories can change in response to the type of selection the population experiences. Finally, we show the applicability of pseudoentropy for real-world data by following its changes in a natural population of the fruit fly ***Drosophila melanogaster.*** *This analysis suggests selection acting on only isolated genes of the genome while most of the genome evolves in a neutral fashion.*

To concisely describe how genetic variation, at individual loci or across whole genomes, changes over time, and to follow transitory allelic changes, we introduce a quantity related to entropy, that we term *pseudoentropy*. This quantity emerges in a diffusion analysis of the mean time a mutation segregates in a population. For a neutral locus with an arbitrary number of alleles, the mean time of segregation is generally proportional to the pseudoentropy of initial allele frequencies. After the initial time point, pseudoentropy generally decreases (Figure 1), but other behaviours are possible, depending on the genetic diversity and selective forces present.

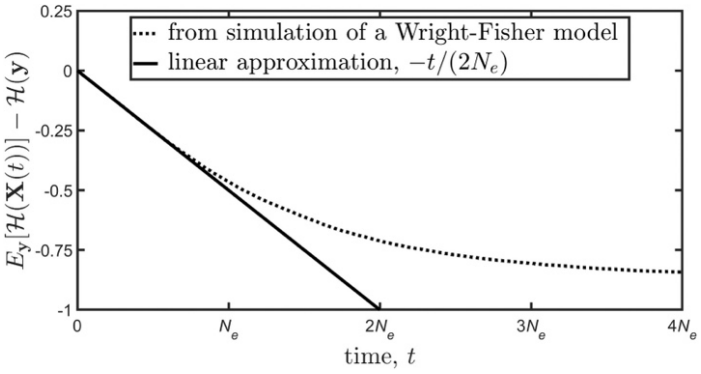


Figure 1: A plot of the pseudoentropy difference over generation time. For short time intervals it approximates a measure of the effective population size.

For a locus with two alleles, pseudoentropy and entropy coincide, but they are distinct quantities with more than two alleles. Thus for populations with multiple *biallelic* loci, the language of entropy suffices. Then entropy, combined across loci, serves as a concise description of genetic variation. We used individual-based simulations to explore how this entropy behaves under different evolutionary scenarios. In agreement with predictions, the entropy associated with unlinked neutral loci decreases over time. However, deviations from free recombination and neutrality have clear and informative effects on the entropy's behaviour over time (Figure 2).

Contacts:
nikolas.vellnow@tu-dortmund.de
toni.gossmann@tu-dortmund.de

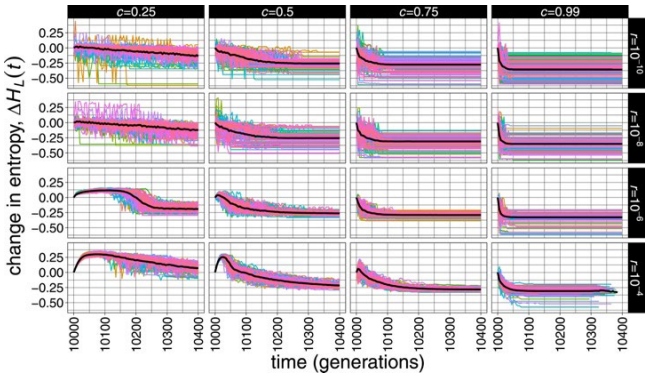


Figure 2: Change in pseudoentropy simulated for a multiple loci model under varying negative frequency dependent selection (c=0.25 to c=0.99) and varying recombination rate (r).

Analysis of publicly available data of a natural *D. melanogaster* population, that had been sampled over seven years, using a sliding-window approach, yielded considerable variation in entropy trajectories of different genomic regions. These mostly follow a pattern that suggests a substantial effective population size and a limited effect of positive selection on genome-wide diversity over short time scales (Figure 3).

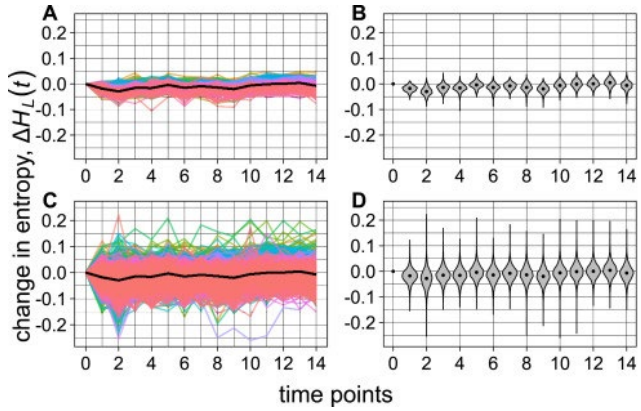


Figure 3: Little change in pseudoentropy in real-world data suggests large effective population sizes and/or the lack of selection.

Publications:
N. Vellnow, T. Goßmann, und D. Waxman, „The pseudoentropy of allele frequency trajectories, the persistence of variation, and the effective population size", Biosystems, Bd. 238, Art. Nr. 105176, März 2024, doi: 10.1016/j.biosystems.2024.105176.

Publications

2023

Peer-reviewed Journal Articles

- Ord, James, Toni I. Gossmann, and Irene Adrian-Kalchhauser.
High nucleotide diversity accompanies differential DNA methylation in naturally diverging populations.
Molecular biology and evolution 40, no. 4 (2023): msad068.
https://doi.org/10.1093/molbev/msad068

Publications (pre-print, under review)

- Chen, Yu-Chi, David LJ Vendrami, Maximilian L. Huber, Luisa EY Handel, Christopher R. Cooney, Joseph I. Hoffman, and Toni I. Gossmann.
Phylonumtomics uncovers diverse evolutionary trajectories of mitogenomic fossils buried in mammalian and avian genomes.
bioRxiv (2023): 2023-08.
https://doi.org/10.1101/2023.08.07.552327

- Kaiser, Marie I., Anton Killin, Annette KF Malsch, Anja-Kristin Abendroth, Mitja D. Back, Bernhard T. Baune, Nicola Bilstein et al.
Individualisation and Individualised Science:
Integrating Disciplinary Perspectives." (2023).
https://doi.org/10.32942/X2P016

- Muenzner, Julia, Pauline Trébulle, Federica Agostini, Christoph B. Messner, Martin Steger, Andrea Lehmann, Elodie Caudal et al.
The natural diversity of the yeast proteome reveals chromosome-wide dosage compensation in aneuploids.
BioRxiv (2022): 2022-04.
https://doi.org/10.1101/2022.04.06.487392

Solids Process Engineering (FSV)

UV/Vis spectroscopy as a real-time release tool for pharmaceutical tablets

René Brands, Jens Bartsch, Markus Thommes

Continuous manufacturing provides several advantages compared to batch manufacturing e.g., increased product quality or flexible scalability, and is gaining importance in the pharmaceutical industry. In particular, the implementation of tableting in continuous plants is an important part of current research. Therefore, the acquisition of real-time data via in-line monitoring of Critical Quality Attributes (CQA) through process analytical technology (PAT) tools is crucial. This study focuses on an UV/Vis spectroscopy approach for the quantification of the Active Pharmaceutical Ingredient (API) content in tablets. This technology is particularly advantageous here, because of a univariate data analysis based on mechanistic models without complex data processing and statistic models like Partial Least Squares Regression.

To ensure the reliability of the UV/Vis spectroscopy method, the corresponding probe was mounted at the tablet ejection position (Fig. 1). Thereby, measurements were performed on the tablet sidewall at the first moment in time at which a tablet is accessible in its final form. Experiments were conducted at two different tableting speeds (7200 and 20000 tablets per hour). The model formulation consisted of lactose monohydrate, theophylline monohydrate and magnesium stearate. The validation process followed the ICH Q2 guideline focusing on specificity, linearity, precision, accuracy, and range for pharmaceutical content uniformity.

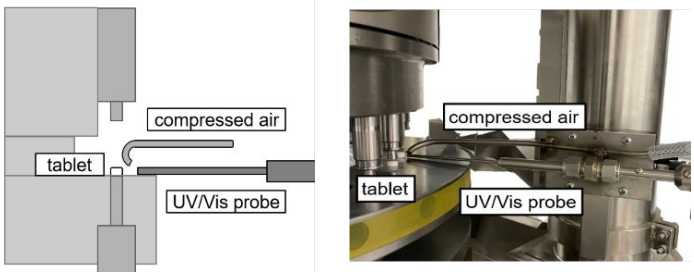


Figure 1: Schematic diagram of the new developed setup of in-line monitoring with probe and compressed air, as well as a photo of the setup.

First, a data-pretreatment was performed. In order to evaluate the diffuse reflectance spectra of solids, the Kubelka-Munk transformation was applied. Here, scattering and absorption coefficients are taken into account. However, no correlation between signal intensity and API content is recognizable after the transformation. This is due to the fact that diffuse reflectance spectra provide information on the chemical composition and are affected by scattering effects. Especially physical properties like surface roughness and porosity are important factors for the scattering behavior and therefore may disguise the information on chemical composition. In order to remove such scattering effects, standard normal variate transformation was performed. Subsequently, a linear relationship is recognizable.

The specificity for the chosen formulation was confirmed as long as the absorption maxima of the excipients and the API do not interfere with each other. Furthermore, the linearity (Fig. 2) was sufficient with a coefficient of determination of 0.9891 for the low throughput and 0.9936 for the high throughput. However, the linearity in terms of coefficient of determinations increases with increasing tableting throughput. This was attributed to the integrated tablet surface. Increasing the tableting speeds increases the integrated tablet surface and thus the measurement volume and the number of API molecules. This leads to a more accurate mean and lower confidence interval. Precision was assessed in terms of intra-laboratory variations. Here, the suitability was indicated by a coefficient of variation of 6.46% and 6.34%, respectively. Accuracy was evaluated through mean percent recovery, indicating a higher accuracy at 20,000 tablets per hour compared to 7,200 tablets per hour. These results can be attributed to the previously described effects of the tableting speed on the measured tablet surface.

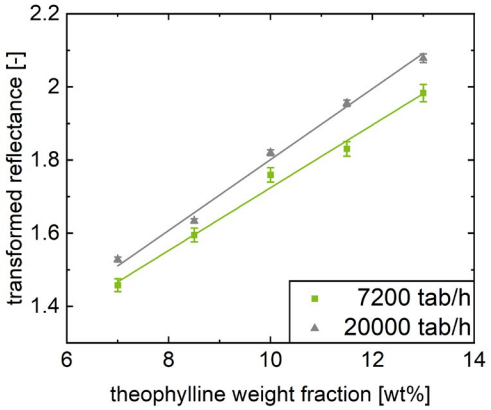


Figure 2: Linear regression for in-line determined reflectance and theophylline weight fraction of tablets.

In conclusion, UV/Vis spectroscopy appears to be a promising alternative to the commonly used NIR and Raman spectroscopy methods. The simplicity of the univariate data analysis in combination with the successful validation results highlight the potential as a reliable tool for in-line monitoring of tablet content uniformity in continuous manufacturing processes.

Contacts:
rene.brands@tu-dortmund.de
jens.bartsch@tu-dortmund.de
markus.thommes@tu-dortmund.de

Publications:
Brands, R.; Bartsch, J.; Thommes, M., UV/Vis spectroscopy as an in-line monitoring tool for tablet content uniformity. Journal of Pharmaceutical and Biomedical Analysis 2023, S. 115721, DOI: 10.1016/j.jpba.2023.115721.

Predicting Key Process Parameters in Pharmaceutical Hot Melt Extrusion

Steven Meyer, Tobias Gottschalk, Judith Winck, Markus Thommes

A significant number of drug candidates for future use show poor solubility in aqueous media. The solubility and dissolution rate of the active pharmaceutical ingredients (APIs) can be increased by formulating them as amorphous solid dispersions (ASDs). In this case, the API is molecularly dispersed in the amorphous form in a polymer matrix. This means that no energy is required to break the crystal lattice and higher apparent solubilities as well as faster dissolution can be achieved resulting in higher bioavailability. Hot melt extrusion is a manufacturing technique that is frequently used in the pharmaceutical industry to produce ASDs. Thereby, the dissolution of the API in the polymer is highly dependent on the process conditions. A better understanding and the ability to predict these process parameters can give advantages in process control and reduce experimental effort during product design. Therefore, models were developed to predict key process parameters.

The dissolution of the API in the polymer during hot melt extrusion depends on the temperature and residence time. If these parameters are set too low, the API may not be fully dissolved so that no ASD is formed. However, if temperature and residence time are set too high, the risk of degradation of the polymer and/or the API is increased. In this study, three pharmaceutical polymers frequently used in industrial HME were processed in autogenous extrusion mode, which means that no heat is actively removed or added externally, but heat losses through the extruder walls occurred. During the experiments, the throughput was varied at a constant ratio of throughput to screw speed (specific feed load, SFL) and the impact on temperature and residence time was investigated. Prediction models were then derived based on the results.

For the temperature prediction, a material-independent correlation was found between the screw speed and the die viscosity. This means that although the melt temperature differs between the materials at the same screw speed, the viscosity is the same. Only one experimentally determined, extruder-dependent parameter is required to characterize the correlation. Using the Carreau-Arrhenius approach, which describes the relationship between viscosity and temperature, the melt temperature at the die can be predicted for any material. The models were validated by predicting the material-specific temperature with the set of parameters of the two other used materials. To determine the residence time distribution, the two-compartment model, which combines the residence time behavior of a pipe and a continuously mixing tank, was used to represent the experimental data. The model uses three parameters to characterize the residence time distribution, whereby these were used as response variables in a variance analysis with the melt temperature, the polymer type and the SFL as influencing factors. The resulting model parameters were used to calculate the residence time distribution for all experiments performed and compared with the experimental observations, whereby no systematic deviations were found.

Finally, design spaces were developed to provide a simple visualization of the complex mathematical models. These are shown in Fig. 1 and can be used intuitively to find the appropriate operating points for the desired residence time or temperature. With this approach, the experimental effort required to set optimal process parameters during melt extrusion can be greatly reduced.

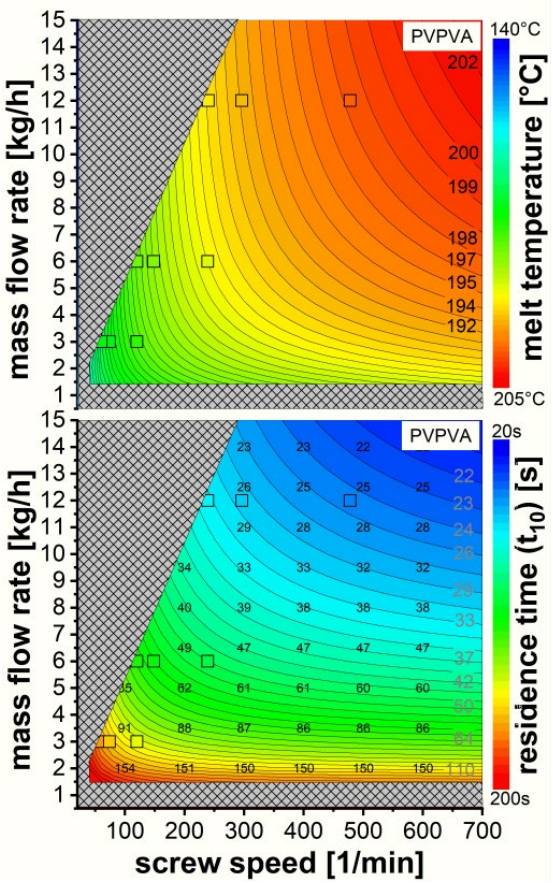


Figure 1: Melt temperature (top) and residence time (bottom) as functions of mass flow rate and screw speed for the polymer PVPVA. The color scale is melt temperature (top) or the 10 % quantile of the residence time distribution based on the models.

Publications:
Winck, J.; Gottschalk, T.; Thommes, M., Predicting Residence Time and Melt Temperature in Pharmaceutical Hot Melt Extrusion. Pharmaceutics 2023, 15, 1417. https://doi.org/10.3390/pharmaceutics15051417

Contacts:
steven.meyer@tu-dortmund.de
judith.winck@tu-dortmund.de
markus.thommes@tu-dortmund.de

Increased Drug Dissolution by Embedding of Micro-Particles

Anna Justen, Alina Faye Weltersbach, Gerhard Schaldach, Markus Thommes

High dissolution rates of poor water-soluble active pharmaceutical ingredients are essential for the application of these substances into the human body. This is achieved by a low drug particle size and the embedding of these particles in a high water soluble matrix. Therefore, a new continuous process for the production of submicron particles (0.1-1 µm) and the in situ implementation in a molten sugar was developed. The in vitro dissolution of drug particles shows an extraordinary high dissolution rate.

The new concept combines the generation of submicron particles by spray drying and their continuous embedding in a water-soluble matrix. For the generation of dry particles in the desired size range droplets with diameters of about 2 µm are required. An ultrasonic nebulizer based on a piezo crystal with a particularly high resonance frequency of 3.2 MHz was utilized. Due to the high resonance frequency exceptionally small droplets with a narrow size distribution were generated. These were carried by a carbon dioxide gas stream into the drying unit and were deposited in the precipitation unit.
The electrostatic precipitator (Fig.1) was built of stainless steel for particle embedding into the molten sugar alcohol xylitol, which has a melting temperature of 96 °C. Therefore, the collecting electrode was heated throughout the process.

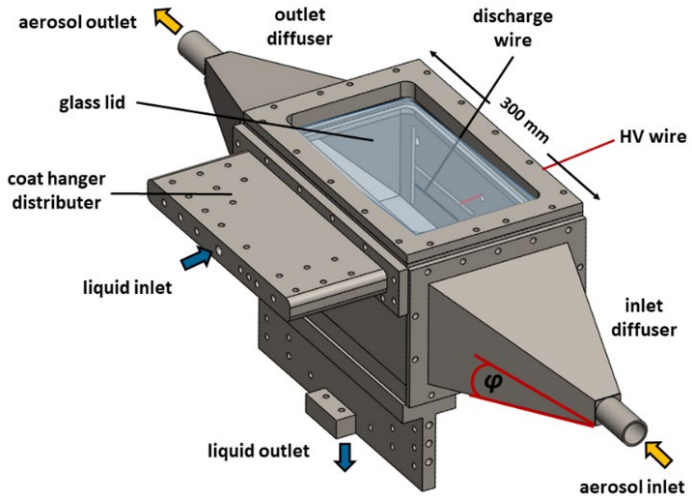


Figure 1: Technical drawing of electrostatic precipitator, completely assembled with glass lid, diffuser opening angle φ.

A wall film of molten xylitol served as collecting electrode. In order to create a laminar, waveless wall film a die was designed based on the concept of flat slit extrusion dies, which consists of a manifold or flow channel and a land area. The design of a coat hanger die was chosen as it provides a more stable, uniform melt distribution. The melt was pumped in a loop with a gear pump and celecoxib particles were continuously deposited into the xylitol melt. Therefore the discharge and collecting electrode had a distance of 50 mm and a high voltage generator was used applying negative potential of up to 20 kV.
Drug particles (celecoxib) were deposited over a period of 8 h in a heated wall film of molten xylitol, which was pumped in circulate.

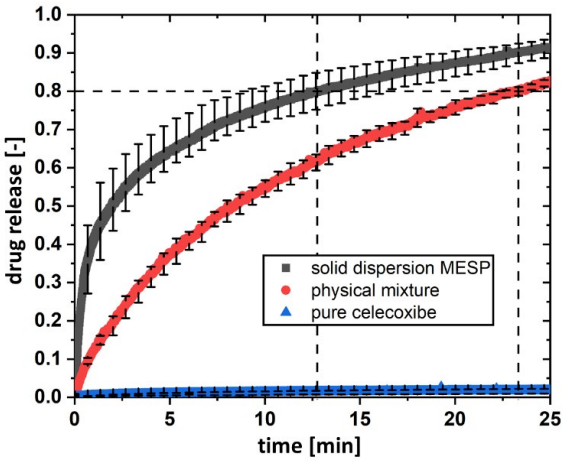


Figure 2: In vitro dissolution of celecoxib conducted in a flow through cell with purified water at 37 °C, (av ± min/max, n=3).

The drug laden solid product was characterized regarding its dissolution behavior with the USP apparatus 4 (flow through cell), according to the procedure described in the European Pharmacopoeia (Fig.2). Next to the solid dispersion, obtained with the melt electrostatic precipitator, a physical mixture with comparable drug content (0.5 wt.%) was investigated. This product showed a two-time higher dissolution rate (t_{80}) in comparison to a physical mixture of both components.
The presented method was found to be suitable for the manufacturing of solid dispersions, which show a particularly fast drug dissolution. The knowledge gained from this study can be applied to improve other electrostatic precipitator designs.

Contacts:
anna.justen@tu-dortmund.de
gerhard.schaldach@tu-dortmund.de
markus.thommes@tu-dortmund.de

Publications:
Justen, A.; Weltersbach, A.F.; Schaldach, G.; Thommes, M., Design and Characterization of a Melt Electrostatic Precipitator for Advanced Drug Formulations. Processes 2024, 12 (100). https://doi.org/10.3390/pr12010100

Evolutionary Optimization of Filter Media

Kevin Hoppe, Felix Giesa, Gerhard Schaldach, Markus Thommes, Damian Pieloth

Manufacturers of filter media are faced with increasingly stringent requirements for separation performance and energy efficiency. The development of filter media tailored to specific applications currently requires considerable experimental effort. Due to the complex structure of filter media and the multitude of influencing variables, the application of optimization strategies is limited. To generate optimized filter structures with improved properties, a conceptual framework has been developed based on the integration of evolutionary optimization and 1D simulation of the filter gradient structure. The resulting filter media exhibit significantly lower increases in pressure drops compared to reference geometries.

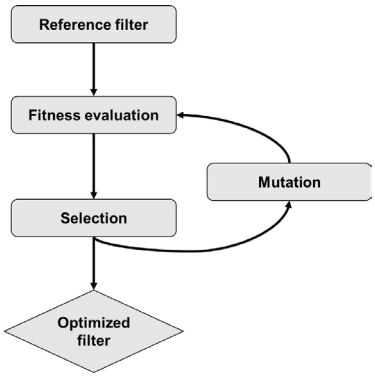


Figure 1: Simplified principle of evolutionary optimization of filter media.

The developed strategy for optimizing filter media is rooted in the principles of Darwin's theory of evolution, as observed in nature, involving the mutation and selection of the best-adapted individuals (see Figure 1).

The assessment of fitness is based on the separation efficiency of filters in their initial state and the increase in pressure drop during the storage of solid particles within the filter. The driving force behind this optimization strategy lies in generating as many descendants as possible and inducing mutations. To facilitate this, a previously developed 1D model with low computational complexity is employed, enabling the calculation of a high number of filter structures concerning their filtration efficiency and pressure drop. An optimization study was conducted based on optimizing the porosity gradient.

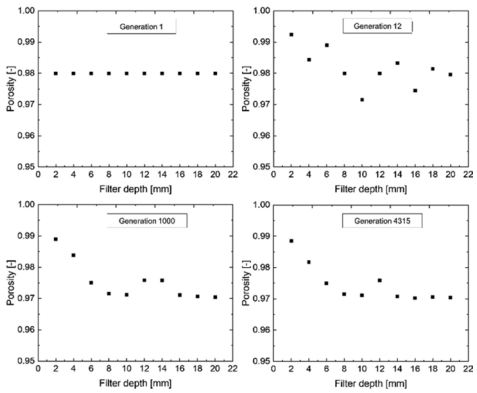


Figure 2: Evolution of filter porosity during the optimization process.

A constant porosity across the filter thickness is considered as a reference (generation 1), and the optimization process was tracked over approximately 10,000 generations. The evolution of the porosity gradient is depicted for different generations in Figure 2. This illustrates the initial random mutation of the structure, which leads to a two-stage structure with increasing generations. Calculations showed that a significantly more uniform storage of particles within the filter could be achieved. This improved utilization of the filter surface also significantly and reduced the increase in pressure drop, as shown in Figure 3. Filtration efficiency could even be increased, highlighting the unique potential of this strategy for managing conflicting requirements.

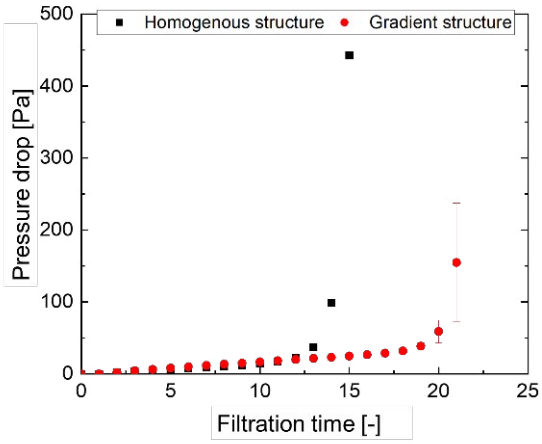


Figure 3: Pressure drops of reference and optimized filter as a function of the filter loading.

The strategy is versatile, capable of taking any structural parameter of the filter medium into account. With the ability to conduct an optimization over 10,000 generations on a standard PC within 12 hours, this approach becomes accessible to a broad user base, facilitating the personalized selection and design of filter materials.

Publications:
Hoppe, K; Wischemann, L; Schaldach, G; Zielke, R; Tillmann, W; Thommes, M; Pieloth, D, Filtration Kinetics of Depth Filters-Modeling and Comparison with Tomographic Data of Particle Depositions, Atmosphere 2023, 14-4 (640)
Hoppe, K; Giesa, F; Schaldach, G; Thommes, M; Pieloth, D, Optimization of Filter Structures by Evolutionary Strategies Materials Today Communications, 2024, accepted.

Contacts:
kevin.hoppe@tu-dortmund.de
damian.pieloth@tu-dortmund.de
markus.thommes@tu-dortmund.de

Publications

2023

- Brands, R.; Tebart, N.; Thommes, M.
UV/Vis spectroscopy as an in-line monitoring tool for tablet content uniformity.
Journal of Pharmaceutical and Biomedical Analysis, 236 (2023).
https://doi.org/10.1016/j.jpba.2023.115721

- Mansuri, A.; Völkel, M.; Mihiranga, D.; Feuerbach, T.; Winck, J.; Vermeer, A. W. P.; Hoheisel, W.; Thommes, M.
Predicting self-diffusion coefficients in semi-crystalline and amorphous solid dispersions using free volume theory.
European Journal of Pharmaceutics and Biopharmaceutica, 190, 107-120 (2023).
https://doi.org/10.1016/j.ejpb.2023.07.001

- Nesges, D.; Lang, T.; Birr, Th.; Thommes, M.; Bartsch, J.
Planetary roller melt granulation (PRMG) – A new continuous method for powder processing.
Powder Technology, 427 (2023).
https://doi.org/10.1016/j.powtec.2023.118728

- Lang, T.; Bramböck, A.; Thommes, M.; Bartsch, J.
Material Transport Characteristics in Planetary Roller Melt Granulation.
Pharmaceutics, 15, 8 (2023).
https://doi.org/10.3390/pharmaceutics15082039

- Winck, J.; Gottschalk, T.; Thommes, M.
Predicting Residence Time and Melt Temperature in Pharmaceutical Hot Melt Extrusion.
Pharmaceutics 15 (5), 1417 (2023).
https://doi.org/10.3390/pharmaceutics15051417

- Mansuri, A.; Völkel, M.; Feuerbach, T.; Winck, J.; Vermeer, A. W. P.; Hoheisel, W.; Thommes, M.
Modified Free Volume Theory for Self-Diffusion of Small Molecules in Amorphous Polymers.
Macromolecules, 56 (8), 3224-3237 (2023).
https://doi.org/10.1021/acs.macromol.2c02451

- Mansuri, A.; Münzner, Ph.; Heermant, A.; Hänsch, S.; Feuerbach, T.; Fischer, B.; Winck, J.; Vermeer, A. W.P.; Hoheisel, W.; Böhmer, R.; Gainaru, C.; Thommes, M.
Characterizing Phase Separation of Amorphous Solid Dispersions Containing Imidacloprid.
Molecular Pharmaceutics, 20 (4), 2080-2093 (2023).
https://doi.org/10.1021/acs.molpharmaceut.2c01043

- Mansuri, A.; Münzner, Ph.; Heermant, A.; Patzina, F.; Feuerbach, T.; Winck, J.; Vermeer, A. W. P.; Hoheisel, W.; Böhmer, R.; Gainaru, C.; Thommes, M.
Molecular Dynamics and Diffusion in Amorphous Solid Dispersions Containing Imidacloprid.
Molecular Pharmaceutics, 20 (4), 2067-2079 (2023).
https://doi.org/10.1021/acs.molpharmaceut.2c01042

- Justen, A.; Kurth, Ch.; Schaldach, G.; Thommes, M.
Preparation of Micron and Submicron Particles via Spray Drying and Electrostatic Precipitation.
Chemical Engineering and Technology, 46 (2), 343–349 (2023).
https://doi.org/10.1002/ceat.202200357

- Zimmermann, M.; Michel, F.; Bartsch, J.; Thommes, M.
A novel approach of external lubrication in a rotary tablet press using electrostatics.
Drug Development and Industrial Pharmacy, 48, 737-744 (2023).
https://doi.org/10.1080/03639045.2023.2165662

- Pieloth, D.; Rodeck, M.; Schaldach, G.; Thommes, M.
Categorization of Sprays by Image Analysis with Convolutional Neuronal Networks.
Chemical Engineering Technology, 46 (2), 264-269 (2023).
https://doi.org/10.1002/ceat.202200356

- Hoppe, K.; Wischemann, L.; Schaldach, G.; Zielke, R.; Tillmann, W.; Thommes, M.; Pieloth, D.
Filtration Kinetrics of Depth Filters-Modeling and Comparison with Tomographic Data of Particle Depositions
Atmosphere, 14 (4), 640 (2023).
https://doi.org/10.3390/atmos14040640

- Lauscher, C.; Licau, A.; Schaldach, G.; Thommes, M.
Characterization of Sprays Generated by the Expansion of Emulsions with Liquid Carbon Dioxide
Chemical Engineering and Technology (2023).
https://doi.org/10.1002/ceat.202300261

2022

- Sleziona, D.; Ely, D. R.; Thommes, M.
  Modeling of Particle Dissolution Behavior Using a Geometrical Phase-Field Approach.
  Molecular Pharmaceutics, 19 (11), 3749–3756 (2022).
  https://doi.org/10.1021/acs.molpharmaceut.2c00214

- Gottschalk, T.; Özbay, C.; Feuerbach, T.; Thommes, M.
  Predicting Throughput and Melt Temperature in Pharmaceutical Hot Melt Extrusion.
  Pharmaceutics, 14 (9), 1757 (2022).
  https://doi.org/10.3390/pharmaceutics14091757

- Lauscher, C.; Schaldach, G.; Thommes, M.
  Particle Generation with Liquid Carbon Dioxide Emulsions.
  Chemical Engineering and Technology, 45 (9), 1631–1636 (2022).
  https://doi.org/10.1002/ceat.202200176

- Evers, M.; Weis, D.; Antonyuk, S.; Thommes, M.
  Particle movement in the spheronizer – Experimental investigations with respect to the toroidal and poloidal direction.
  Powder Technology, 404, 117452 (2022).
  https://doi.org/10.1016/j.powtec.2022.117452

- Zimmermann, M.; Raffel, C.; Bartsch, J.; Thommes, M.
  Simulation of Powder Flow Behavior in an Artificial Feed Frame Using an Euler-Euler Model.
  Chemical Engineering and Technology, 45 (5), 853–859 (2022).
  https://doi.org/10.1002/ceat.202100580

- Wolbert, F.; Fahrig, I.-K.; Gottschalk, T.; Luebbert, C.; Thommes, M.; Sadowski, G.
  Factors Influencing the Crystallization-Onset Time of Metastable ASDs.
  Pharmaceutics, 14 (2), 269 (2022).
  https://doi.org/10.3390/pharmaceutics14020269

- Lauscher, C.; Schaldach, G.; Thommes, M.
  An Approach for Small Droplet Production: Nebulization by Expansion of Water/Liquid Carbon Dioxide Emulsion.
  Atomization and Sprays, 32 (4), 77–93 (2022).
  https://doi.org/10.1615/AtomizSpr.2022039582

- Gottschalk, T.; Grönniger, B.; Ludwig, E.; Wolbert, F.; Feuerbach, T.; Sadowski, G.; Thommes, M.
  Influence of process temperature and residence time on the manufacturing of amorphous solid dispersions in hot melt extrusion.
  Pharmaceutical Development and Technology, 27 (3), 313–318 (2022).
  https://doi.org/10.1080/10837450.2022.2051549

- da Igreja, P.; Klump, D.; Bartsch, J.; Thommes, M.
  Reduction of submicron particle agglomeration via melt foaming in solid crystalline suspension.
  Journal of Dispersion Science and Technology
  https://doi.org/10.1080/01932691.2022.2146707

- Winck, J.; Daalmann, M.; Berghaus, A.; Thommes, M.
  In-line-monitoring of solid dispersion preparation in smale scale extrusion based on UV-vis spectroscopy.
  Journal of Pharmaceutical Development and Technology
  https://doi.org/10.1080/10837450.2022.2144887

Books & Book Chapters

- Bauer-Brandl, A.; Ritschel, W. A.; Thommes, M.; Warnke, G.
  Die Tablette, Handbuch der Entwicklung, Herstellung und Qualitätssicherung.
  Editio Cantor Verlag, ISBN 978-3-87193-487-2, 4. Auflage (2022).

2021

- Mansuri, A.; Münzner, P.; Feuerbach, T.; Vermeer, A. W. P.; Hoheisel, W.; Böhmer, R.; Thommes, M.; Gainaru, C.
  The relaxation behavior of supercooled and glassy imidacloprid.
  Journal of Chemical Physics 155, 174502 (2021).
  https://doi.org/10.1063/5.0067404

- Evers, M.; Mattusch, A.; Weis, D.; Garcia, E.; Antonyuk, S.; Thommes, M.
  Elucidation of mass transfer mechanisms in pellet formation by spheronization.
  European Journal of Pharmaceutics and Biopharmaceutics 160, 92-99 (2021).
  https://doi.org/10.1016/j.ejpb.2021.01.013

- Flügel, K.; Schmidt, K.; Mareczek, L.; Gäbe, M.; Hennig, R.; Thommes, M.
  Impact of incorporated drugs on material properties of amorphous solid dispersions.
  European Journal of Pharmaceutics and Biopharmaceutics 159, 88-98 (2021).
  https://doi.org/10.1016/j.ejpb.2020.12.017

- Feuerbach, T.; Thommes, M.
  Design and Characterization of a Screw Extrusion Hot-End for Fused Deposition Modeling.
  Molecules 26 (3), 590 (2021).
  https://doi.org/10.3390%2Fmolecules26030590

- Weis, D.; Grohn, P.; Evers, M.; Thommes, M.; García, E.; Antonyuk, S.
  Implementation of formation mechanisms in DEM simulation of the spheronization process of pharmaceutical pellets.
  Powder Technology 378, Part A, 667-679 (2021).
  https://doi.org/10.1016/j.powtec.2020.09.013

- Zimmermann, M.; Thommes, M.
  Residence time and mixing capacity of a rotary tablet press feed frame.
  Drug Development and Industrial Pharmacy 47 (5), 790–798 (2021).
  https://doi.org/10.1080/03639045.2021.1934871

- da Igreja, P.; Erve, A.; Thommes, M.
  Melt milling as manufacturing method for solid crystalline suspensions.
  European Journal of Pharmaceutics and Biopharmaceutics 158, 245-253 (2021).
  https://doi.org/10.1016/j.ejpb.2020.11.020

- Sleziona, D.; Mattusch, A.; Schaldach, G.; Ely, D.R.; Sadowski, G.; Thommes, M.
  Determination of Inherent Dissolution Performance of Drug Substances.
  Pharmaceutics 13 (2), 146 (2021).
  https://doi.org/10.3390/pharmaceutics13020146

Fluid Separations (FVT)

Recent Developments in Rotating Packed Bed Technology

Nico-Joel Greven, Tobias Pyka, Rouven Loll, Christoph Held, Gerhard Schembecker

Recent advances in rotating packed bed (RPB) technology have revolutionized mass transfer efficiency and separation performance. Still, one open question is how to efficiently feed the liquid into the RPB. A pivotal development lies in a novel liquid distribution system, the rotating baffle distributor (RBD). This innovative distributor, leveraging rotor rotational speed (n_{rot}), ensures uniform liquid distribution across the rotors, a feature previously unattainable with traditional methods. Additionally, pioneering γ-ray computed tomography (CT) techniques have been employed to scrutinize the intricate fluid dynamics within RPBs, shedding light on liquid distribution phenomena, including the behavior of structured Zickzack packings (ZZ packings) under varying operational conditions.

Beneficial liquid distribution is of major importance in separation equipment, and mal-distribution must be avoided. The effectiveness of the RBD in achieving uniform fluid distribution was investigated in detail using high-speed camera analyses and CT scans. The results emphasized the ability of the RBD to achieve axial and circumferential liquid distribution, even at high rotational speeds of more than 600 rpm. Distillation experiments with RBDs showed superior separation efficiency compared to conventional methods, especially at rotation speeds of more than 900 rpm, highlighting the operational advantages. These results are shown schematically in Figure 1, as well as the RBD design.

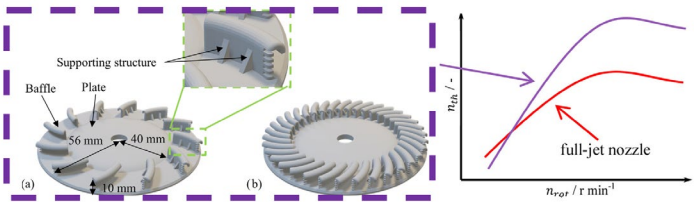


Figure 1: CAD drawings of the RBD with (a) 12 baffle plates and (b) 36 baffle plates and schematic illustration of the theoretical stages of the rotational speed during the distillation of ethanol water of the RBD 36 and a full-jet nozzle.

Investigations of the influence of different liquid distributors on liquid hold-up distribution within RPBs elucidated critical factors impacting separation performance. γ-ray CT imaging enabled non-invasive visualization of liquid accumulation phenomena, revealing the propensity for mal-distribution with conventional single-point full-jet nozzles. In contrast, RBDs demonstrated enhanced liquid distribution uniformity, mitigating the risk of mal-distribution and optimizing mass transfer efficiency. A comparison of the 12-baffle RBD, 36-baffle RBD, and single-point full-jet (SPFJ) nozzle is illustrated in Figure 2.

Furthermore, as depicted in Figure 3, analyses of flow patterns within structured ZZ packings using γ-ray CT imaging provided insights into the interplay between rotational speed and liquid distribution uniformity. Observations highlighted the critical role of operational parameters in maintaining homogeneous liquid distribution, emphasizing the importance of optimizing parameters to maximize mass transfer efficiency within RPBs.

These advances highlight the transformative potential of novel liquid distribution concepts and analytical techniques to improve the performance and scalability of RPBs and open a new era of efficiency and sustainability of separation processes in various industrial applications.

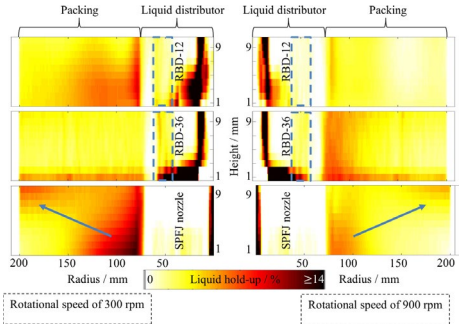


Figure 2: Comparison of axial liquid hold-up distributions using RBD-12, RBD-36, and SPFJ nozzle as liquid distributors for a packing height of 9 mm using different n_{rot} = 300 rpm and n_{rot} = 900 rpm, V_L = 60 l h^{-1}, and F_G = 2.3 Pa$^{0.5}$.

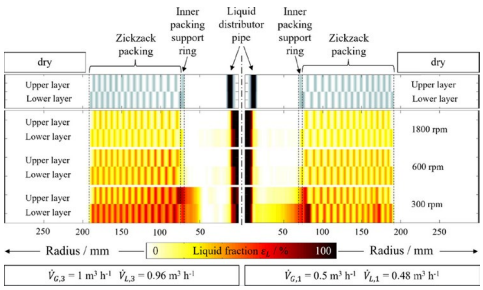


Figure 3: Summary of axial and radial distributions of dry rotor elements and corresponding liquid fractions in unstacked ZZ packing at rotational speeds from 300 to 1800 rpm, with air and tap water flow rates of $\dot{V}_{G,1}$ = 0.5 m^3/h and $\dot{V}_{L,1}$ = 0.48 m^3/h, and $\dot{V}_{G,3}$ = 1 m^3/h^{-1} and $\dot{V}_{L,3}$ = 0.96 m^3/h^{-1}.

Contact:
nico.greven@tu-dortmund.de
christoph.held@tu-dortmund.de
gerhard.schembecker@tu-dortmund.de

Publications:
Pyka, T.; Bieberle, A.; Loll, R.; Held, C.; Schubert, M.; Schembecker, G.: Distributor Effects on Liquid Hold-Up in Rotating Packed Beds. Ind. Eng. Chem. Res. 2024, 63 (4), 2000-2010. https://doi.org/10.1021/acs.iecr.3c03996
Loll, R.; Nordhausen, L.; Bieberle, A.; Schubert, M.; Pyka, T.; Koop, J.; Held, C.; Schembecker, G.: Analysis of Flow Patterns in Structured Zickzack Packings for Rotating Packed Beds Using Y-Ray Computed Tomography. Ind. Eng. Chem. Res. 2023, 62 (38), 15625-15634. https://doi.org/10.1021/acs.iecr.3c02252

Publications

2023

- Pyka, T.; Backhaus, V.; Held, C.; Schembecker, G.
Impact of number of rotors in rotating packed beds on separation performance in distillation.
Ind. Eng. Chem. Res. 62 (46), 19855-19861 (2023).
https://doi.org/10.1021/acs.iecr.3c03173

- Hubach, T.; Pillath, M.; Knaup, C.; Schlüter, S.; Held, C.
Li+ Separation from Multi-Ionic Mixtures by Nanofiltration Membranes: Experiments and Modeling.
Modelling 4 (3), 408-425 (2023).
https://doi.org/10.3390/modelling4030024

- Loll, R.; Nordhausen, L.; Bieberle, A.; Schubert, M.; Pyka, T.; Koop, J.; Held, C.; Schembecker, G.
Analysis of flow patterns in structured zickzack packings for rotating packed beds using γ -ray computed tomography.
Ind. Eng. Chem. Res. 62 (38), 15625-15634 (2023).
https://doi.org/10.1021/acs.iecr.3c02252

- Koop, J.; Bera, N.; Quickert, E.; Schmitt, M.; Schlüter, M.; Held, C.; Schembecker, G.
Separation of Volatile Organic Compounds from Viscous Liquids with RPB Technology.
Ind. Eng. Chem. Res. 62 (34), 13637-13645 (2023).
https://doi.org/10.1021/acs.iecr.3c01597

- Pyka, T.; Ressemann, A.; Held, C.; Schembecker, G.; Repke, J. U.
Impact of vapor bypasses on separation performance of rotating packed beds in distillation.
Ind. Eng. Chem. Res. 62 (33), 13274-13279 (2023).
https://doi.org/10.1021/acs.iecr.3c01947

- Hubach, T.; Schlüter, S.; Held, C.
Model-Based Optimization of Multi-Stage Nanofiltration Using the Solution-Diffusion–Electromigration Model.
Processes 11 (8), 2355 (2023).
https://doi.org/10.3390/pr11082355

- Pyka, T.; Brunert, M.; Koop, J.; Bieberle, A.; Held, C.; Schembecker, G.
Novel Liquid Distributor Concept for Rotating Packed Beds.
Ind. Eng. Chem. Res. 62 (14), 5984-5994 (2023).
https://doi.org/10.1021/acs.iecr.3c00248

- Kruber, K. F.; Kroll, M.; Held, C.; Skiborowski, M.
Evaluation of the potential of a deep eutectic solvent for liquid-liquid extraction of furfural using optimization-based process design.
Computer Aided Chemical Engineering 52, 955-960 (2023).
https://doi.org/10.1016/B978-0-443-15274-0.50152-9

- Schlüter, M.; Bhutani, S.; Bahr, J.; Wohlgemuth, K. Held, C.
Measurement and PC-SAFT Modeling of the Solubility of the BHET Monomer, the BHET Dimer, and PET in Single Solvents.
Journal of Chemical & Engineering Data (2023).
https://doi.org/10.1021/acs.jced.3c00627

- Zawadzki, D.; Blatkiewicz, M.; Jaskulski, M.; Piątkowski, M.; Koop, J.; Loll, R.; Górak, A.
Design and Optimisation of Structural Packings for Rotating Bed Absorbers Using Computational Fluid Dynamics Simulation.
Chemical Engineering Research and Design 195, 508-525 (2023).
http://dx.doi.org/10.2139/ssrn.4222640

2022

- Peterwitz, M.; Jodwirschat, J.; Loll, R.; Schembecker, G.
Tracking raw material flow through a continuous direct compression line Part I of II: Residence time distribution modeling and sensitivity analysis enabling increased process yield.
Int. J. Pharm. 614, 121467 (2022).
https://doi.org/10.1016/j.ijpharm.2022.121467

- Schlüter, S.; Huxoll, F.; Grenningloh, K.; Sadowski, G.; Petzold, M.; Böhm, L.; Kraume, M.; Skiborowski, M.
Unraveling the influence of dissolved gases on permeate flux in organic solvent nanofiltration – Experimental analysis.
Separation and Purification Technology 295, 121265 (2022).
https://doi.org/10.1016/j.seppur.2022.121265

- Pyka, T.
Characterization of the Operating Limits of a Two-Rotor Rotating Packed Bed.
Conference proceeding The 12th international conference Distillation & Absorption (2022)
https://doi.org/10.1016/j.cherd.2022.10.005

- Pyka, T.; Koop, J.; Held, C.; Schembecker, G.
Dry Pressure Drop in Two-Rotor Rotating Packed Bed.
Ind. Eng. Chem. Res. 61, 17156–17165 (2022).
https://doi.org/10.1021/acs.iecr.2c02500

- Loll, R.; Runge, L.; Koop, L.; Held, C.; Schembecker, G.
Zickzack Packings for Deaeration in Rotating Packed Beds γ Improved Rotor Design to Counter Bypass Flows.
Ind. Eng. Chem. Res. 61, 11934–11946 (2022).
https://doi.org/10.1021/acs.iecr.2c01443

- Ascani, M.; Held, C.
Thermodynamics for reactive separations.
Book Chapter in "Process Intensification by By Reactive and Membrane-assisted Separations" by Skiborowski and Górak
Berlin, Boston: De Gruyter (2022).
https://doi.org/10.1515/9783110720464

- Schlüter, S.; Franke, P.
OSN-assisted reaction and separation processes.
Book Chapter in "Process Intensification by By Reactive and Membrane-assisted Separations" by Skiborowski and Górak
Berlin, Boston: De Gruyter (2022).
https://doi.org/10.1515/9783110720464

- Holtbrügge, J.; Pela, J. P.
Pervaporation and vapor permeation– assisted reactive separation processes.
Book Chapter in "Process Intensification by By Reactive and Membrane-assisted Separations" by Skiborowski and Górak
Berlin, Boston: De Gruyter (2022).
https://doi.org/10.1515/9783110720464

- Pyka, T.; Koop, J.
Rotating packed beds in distillation: rotor configurations.
Book Chapter in "Process Intensification by By Rotating Packed Beds" by Skiborowski and Górak
Berlin, Boston: De Gruyter (2022).
https://doi.org/10.1515/9783110720464

- Loll, R.; Koop, J.
3D printed packings for rotating packed beds.
Book Chapter in "Process Intensification by By Rotating Packed Beds" by Skiborowski and Górak
Berlin, Boston: De Gruyter (2022).
https://doi.org/10.1515/9783110720464

2021

- Vondran, J.; Pela, J.; Palczewski, D.; Skiborowski, M.; Seidensticker, T.
Curse and Blessing–The Role of Water in the Homogeneously Ru-Catalyzed Epoxidation of Technical Grade Methyl Oleate.
ACS Sustainable Chem. Eng., 34, 11469 (2021).
https://doi.org/10.1021/acssuschemeng.1c03573

- Schlüter, S.; Künnemann, K.; Freis, M.; Roth, T.; Vogt, D.; Dreimann, J.; Skiborowski, M.
Continuous co-product separation by organic solvent nanofiltration for the hydroaminomethylation in a thermomorphic multiphase system.
Chem. Eng. Journal 409, 128219 (2021).
https://doi.org/10.1016/j.cej.2020.128219

- Huxoll, F.; Schlüter, S.; Budde, R.; Skiborowski, M.; Petzold, M.; Böhm, L.; Kraume, M.; Sadowski, G.
Phase Equilibria for the Hydroaminomethylation of 1-Decene.
Journal of Chem. & Eng. Data, 66, 4484 (2021).
https://doi.org/10.1021/acs.jced.1c00561

- Scharzec, B; Merschhoff, D.; Henrichs, J.; Kappert, E. J.; Skiborowski, M.
Evaluation of membrane-assisted hybrid processes for the separation of a tetrahydrofuran-methanol-water mixture.
Chem Eng Proc 167, 108545 (2021).
https://doi.org/10.1016/j.cep.2021.108545

- Kruber, K. F.; Grueters, T.; Skiborowski, M.
Advanced hybrid optimization methods for the design of complex separation processes.
Computers & Chemical Engineering 147, 107257 (2021).
https://doi.org/10.1016/j.compchemeng.2021.107257

- Lukin, I.; Gładyszewski, K.; Skiborowski, M.; Górak, A.; Schembecker, G.
Aroma absorption in a rotating packed bed with a tailor-made archimedean spiral packing.
Chemical Engineering Science 231, 116334 (2021).
https://doi.org/10.1016/j.ces.2020.116334

- Gładyszewski, K.; Groß, K.; Bieberle, A.; Schubert, M.; Hild, M.; Górak, A.; Skiborowski, M.
Evaluation of performance improvements through application of anisotropic foam packings in rotating packed beds.
Chemical Engineering Science 230, 116176 (2021).
https://doi.org/10.1016/j.ces.2020.116176

- Scharzec, B.; Kruber, K. F.; Skiborowski, M.
Model-based evaluation of a membrane-assisted hybrid extraction-distillation process for energy and cost-efficient purification of diluted aqueous streams.
Chem Eng Sci, 116650 (2021).
https://doi.org/10.1016/j.ces.2021.116650

Process Automation Systems (PAS)

Improving the control performance of a model predictive controller with reinforcement learning for chemical processes

Dean Brandner, Torben Talis, Erik Esche, Jens-Uwe Repke, Sergio Lucia

Model predictive control (MPC) is an advanced control scheme that can optimally control nonlinear systems with multiple inputs under consideration of constraints. However, it requires the online solution of an optimal control problem, which can render the application intractable for real-world scenarios as it is time consuming. To solve this issue, simpler models can be used in the optimal control problem at the expense of model accuracy leading to a worse control performance. In this work, we apply reinforcement learning ideas to an MPC that uses a simple surrogate model based on data to recover the optimal control performance which would be achieved when using a rigorous complex system model. We show that the trained MPC outperforms the untrained MPC with respect to closed loop cost, and achieves a similar performance than a benchmark MPC that uses the rigorous system model while having a significantly smaller computational cost.

Model predictive control (MPC) is a widely adopted control scheme as it can deal with nonlinear systems with multiple inputs and constraints. However, for its application, an optimal control problem must be solved at each sampling time, which can be time consuming, rendering the application of MPC to a real-world system intractable. Instead of using a full rigorous model, simpler potentially data-driven surrogate models can be used to simplify the obtained optimization problem. Although being faster, this may cause a worse control performance due to the less accurate system model.

Recent results in machine learning show that ideas from reinforcement learning can be used to train an optimized controller (also known as agent). Without having to rely on an accurate system model in the solution process of an optimal control problem, the agent learns the optimal control inputs by direct interaction with the real system or a high-fidelity simulation. For most classical cases, these agents are neural networks. However, due to their lack of structure, and due to the inherent nature of most reinforcement learning algorithms, the training often turns out to be extremely data inefficient, which can be prohibitive if simulations are expensive as well.

We propose to combine methods from reinforcement learning and optimal control and consider an MPC as the agent instead of neural networks. In contrast to neural networks, MPC typically provides a good initial policy, which may lie close to an optimal policy. As a result, it is likely that less data is needed in the training process. Simultaneously, the structure of an optimization problem allows rigorous consideration of constraints, which is not the case for neural networks.

We investigate Q-learning as a reinforcement learning algorithm to train a MPC for a setpoint tracking example applied to a flash separation unit. Firstly, data is generated to train neural network as a data-driven surrogate model, which is used inside the MPC. This MPC is then trained using Q-learning by adapting the weights of the terminal cost inside the MPC's objective function. The trained controller is compared with its untrained counterpart and a benchmark MPC, which uses the rigorous model instead of the surrogate model. All controllers are compared with respect to its closed-loop cost and the computation time. Figure 1 shows the state and input trajectories (left and right respectively) when using the mentioned controllers. It is shown that Q-learning updates the MPC such that the initially deviating control policy converges to the benchmark policy especially when approaching the steady state. This also results in lower closed loop cost. Additionally, the computation time decreases from 0.414±0.081 s (benchmark) to 0.015±0.003 s (trained).

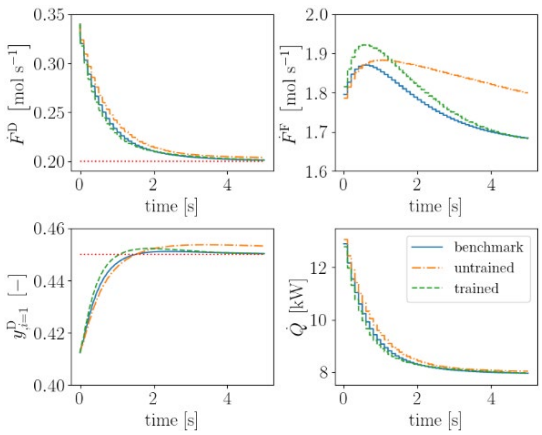


Figure 1: Comparison of the control performance of the benchmark, untrained and trained MPC. The dotted lines are the setpoints.

To summarize, we showed that training an MPC with Q-learning can be used to improve an inaccurate MPC controller and approaching the benchmark controller, while reducing the computation time by more than an order of magnitude.

Contacts:
dean.brandner@tu-dortmund.de
sergio.lucia@tu-dortmund.de

Publication:
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https://doi.org/10.1016/B978-0-443-15274-0.50094-9

Sobolev Training for Data-efficient Approximate Nonlinear MPC

Lukas Lüken, Dean Brandner, Sergio Lucia

Model predictive control (MPC) is a powerful method for control of complex systems. It allows the explicit consideration of constraints, nonlinear dynamics or economic objective functions and is also suitable for systems with multiple input and output variables, which makes it especially interesting for process control. However, since the application of MPC requires the solution of a nonlinear optimization problem (NLP), the real-time capability of this method poses a considerable challenge. One possible approach to solve this problem is to leverage deep learning to approximate the control law based on offline sampled data. This can significantly reduce the online evaluation time. To improve the data efficiency of this learning algorithm, we combine the so-called Sobolev training with the parametric NLP sensitivities, i.e. the changes of the optimal solution with respect to the problems parameters.

The real-time capability of MPC poses a challenge due to the need for solving nonlinear optimization problems (NLP) in real-time. To circumvent this problem, the control law can be approximated using general function approximators such as neural networks. In an offline phase, the NLP is solved for different initial states to gather data, with which a neural network can be trained. In the online application of this approximate MPC, only one neural network then needs to be evaluated, which can be carried out very quickly even on limited hardware. While this approach is able to reduce the computation time by up to multiple orders of magnitude, approximation errors can significantly affect the performance of the controller. Therefore, a precise approximation is necessary, which, however, requires a sufficient amount of training data. Obtaining such data for complex systems can be challenging, even in the offline phase, motivating an efficient use of the data.

To this end, we propose to combine the so-called Sobolev training of neural networks with parametric sensitivities of the underlying NLP of the MPC, to increase data efficiency and achieve a higher approximation accuracy with the same amount of data. The parametric sensitivities describe the local derivative of the full solution of the NLP with respect to its parameters, including the initial states. This information is obtained in the offline phase at negligible cost by applying the implicit function theorem to the first-order optimality conditions (KKT conditions). Sobolev training for neural networks involves a cost function that reduces the deviation of the derivative of the output of the approximate MPC from the corresponding parametric sensitivities with respect to the initial states in addition to the classical regression of the predicted control actions with respect to the data:

$$\mathcal{L}_{\text{sob}}\left(\mathbf{x}_0, \mathbf{u}_0, \frac{\partial \mathbf{u}_0}{\partial \mathbf{x}_0}; \boldsymbol{\Theta}\right) = \frac{1}{N_s}\sum_{i=1}^{N_s} \| \mathbf{u}_0^i - \hat{\mathbf{u}}_0^i \|_2^2 + \gamma \cdot \frac{1}{N_s}\sum_{i=1}^{N_s} \left\| \left(\frac{\partial \mathbf{u}_0}{\partial \mathbf{x}_0}\right)^i - \left(\frac{\partial \hat{\mathbf{u}}_0}{\partial \mathbf{x}_0}\right)^i \right\|_2^2$$

To illustrate this approach, a simulation study of an MPC for a nonlinear continuous stirred tank reactor is presented. The results indicate that Sobolev training with the parametric sensitivities can significantly improve the approximation accuracy of the approximate MPC, especially with a limited amount of training data.

Furthermore, the proposed approach also provides higher degrees of accuracy compared to other methods. Figure 1 shows the approximation accuracy for a different number of data points used for training. Our proposed method (Sobolev) obtains a better approximation for the same number of data points in all cases when compared to a standard training (nominal) or other state of the art data augmentation techniques. Thus, by combining Sobolev training and parametric sensitivities, an effective utilization of the available data is achieved, leading to an improved performance of the approximate MPC and enabling the use of approximate MPC for larger problems.

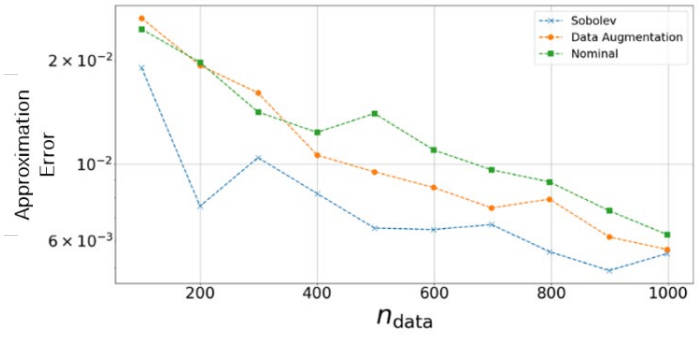


Figure 1: Comparison of Sobolev training with sensitivity-based data augmentation and nominal neural network for approximate MPC of the CSTR. The figure shows the mean absolute prediction error over the different training data sets of increasing size.

Contacts:
lukas.lueken@tu-dortmund.de
dean.brandner@tu-dortmund.de
sergio.lucia@tu-dortmund.de

Publications:
Dean Brandner, and Sergio Lucia. "Sobolev Training for Data-efficient Approximate Nonlinear MPC." IFAC-PapersOnLine 56.2 (2023): 5765-5772

Publications

2023

Peer-reviewed Journal Articles

- Brandner, D., Esche, E., Lucia, S., Renke, JU., Talis, T.
Reinforcement learning combined with model predictive control to optimally operate a flash separation unit
Computer Aided Chemical Engineering Volume 52, 595-600 (2023)
https://doi.org/10.1016/B978-0-443-15274-0.50094-9

- Fiedler, F., Lucia, S.
Improved uncertainty quantification for neural networks with Bayesian last layer
IEEE Access, Volume 11, 123149 (2023)arXiv preprint arXiv:2302.10975 (2023)
https://doi.org/10.1109/ACCESS.2023.3329685

- Aizpuru, J., Barz, T., Bournazou, MNC., Kim, JW., Krausch, N., Lucia, S., Neubauer, P.
Model predictive control and moving horizon estimation for adaptive optimal bolus feeding in high-throughput cultivation of *E. coli*
Computers & Chemical Engineering Volume 172, 108158 (2023)
https://doi.org/10.1016/j.compchemeng.2023.108158

- Alamo, T., Carnerero, AD., Lucia, S., Ramirez DR.
Prediction regions based on dissimilarity functions
ISA transactions, Volume 139, 49-59 (2023)
https://doi.org/10.1016/j.isatra.2023.03.048

- Castelletti, A., Cominola, A., De Schutter, B., Ficchì, A., Giuliani, M., Lucia, S., Maestre, JM., Ocampo-Martinez, C., Segovia, P.
Model Predictive Control of water resources systems: A review and research agenda
Annual Reviews in Control, Volume 55, 442-465 (2023)
https://doi.org/10.1016/j.arcontrol.2023.03.013

- Fiedler, F., Lucia, S.
Probabilistic multi-step identification with implicit state estimation for stochastic MPC
IEEE Access (2023) Volume 11, 117018
https://doi.org/10.1109/ACCESS.2023.3326344

- Brabender, F., Brandner, D., Fiedler, F., Heinlein, M., Karg, B., Lucia, S., Lüken, L.
do-mpc: Towards FAIR nonlinear and robust model predictive control
Control Engineering Practice Volume 140, 105676 (2023)
https://doi.org/10.1016/j.conengprac.2023.105676

- Engell, S., Lucia, S., Ozkan, DM.
Optimal Facility Location and Sizing for Waste Upcycling Systems
Chemical Engineering Transactions Volume 105, 325-330 (2023)
https://doi.org/10.3303/CET23105055

Peer-reviewed Conference Papers

- Brandner, D., Lucia, S., Lüken, L.
Sobolev Training for Data-efficient Approximate Nonlinear MPC
IFAC-PapersOnLine Volume 56 Issue (2), 5765-5772 (2023)
https://doi.org/10.1016/j.ifacol.2023.10.545

- Adamek, J., Lucia, S.
Approximate Model Predictive Control Based on Neural Networks in a Cloud-Based Environment
2023 9th International Conference on Control, Decision and Information Technologies (CoDIT),567-572 (2023)
https://doi.org/10.1109/CoDIT58514.2023.10284471

2022

Peer-reviewed Journal Papers

- Barz, T., Cruz Bournazou, MN., Groß, S., Huber, MC., Kim, JW., Krausch, N., Lucia, S., Neubauer, P., Schiller, SM.
High-throughput screening of optimal process conditions using model predictive control
Biotechnology and Bioengineering Volume 119, Issue 12, 3584-3595 (2022)
https://doi.org/10.1002/bit.28236

- Döpmann, C., Fiedler, F., Lucia, S., Tschorsch, F.
Optimization-Based Predictive Congestion Control for the Tor Network: Opportunities and Challenges
ACM Transactions on Internet Technology 22 (4), 1-30 (2022)
https://doi.org/10.1145/3520440

- Harasic, M., Kovatsch, M., Lucia, S., Mattern, D., Mazza, F., Paschke, A., Xu, J.
A Review on AI for Smart Manufacturing: Deep Learning Challenges and Solutions
Applied Sciences, Volume 12, Issue 16, 8239 (2022)
https://doi.org/10.3390/app12168239

- Albrecht, S., Braun, S., Lucia,
Adaptively robust nonlinear model predictive control based on attack identification
at-Automatisierungstechnik, Volume 70, Issue 4, 367-377 (2022)
https://doi.org/10.1515/auto-2021-0109

- Lucia, S., Paulen, R., Sand, G.
Special issue in honor of Sebastian Engell
Computers & Chemical Engineering, Volume 160, 107743 (2022)
https://doi.org/10.1016/j.compchemeng.2022.107743

- Braatz, RD., Findeisen, R., Lucia, S., Shen, DE., Wan, Y.
A Polynomial Chaos Approach to Robust Static Output-Feedback Control With Bounded Truncation Error
IEEE Transactions on Automatic Control, Volume 68, Issue 1, 470-477 (2022)
https://doi.org/10.1109/TAC.2022.3140275

Peer-reviewed Conference Papers

- Karg, B., Lucia, S.
Guaranteed safe control of systems with parametric uncertainties via neural network controllers
2022 IEEE 61st Conference on Decision and Control (CDC), 7302-7308 (2022)
https://doi.org/10.1109/CDC51059.2022.9992923

- Heinlein, M., Lucia, S., Molnar, M., Subramanian, S.
Robust MPC approaches for monotone systems*
2022 IEEE 61st Conference on Decision and Control (CDC), 2354-2360 (2022)
https://doi.org/10.1109/CDC51059.2022.9992502

- Karg, B., Lucia, S., Meske, C., Utama, C.
Explainable artificial intelligence for deep learning-based model predictive controllers
2022 26th International Conference on System Theory, Control and Computing (ICSTCC), 464-471 (2022)
https://doi.org/10.1109/ICSTCC55426.2022.9931794

- Fiedler, F., Lucia, S.
Model predictive control with neural network system model and Bayesian last layer trust regions
2022 IEEE 17th International Conference on Control & Automation (ICCA), 141-147 (2022)
https://doi.org/10.1109/ICCA54724.2022.9831975

- Fiedler, F., Guillén, P., Lucía, O., Lucía, S., Sarnago, H.
Deep Learning Implementation of Model Predictive Control for Multioutput Resonant Converters
IEEE Access Volume 10, 65228-65237 (2022)
https://doi.org/10.1109/ACCESS.2022.3183746

2021

Proceedings & Book Chapters

- Karg, B., Lucia, S.
Approximate moving horizon estimation and robust nonlinear model predictive control via deep learning
Computers & Chemical Engineering, Volume 148, 107266 (2021)
https://doi.org/10.1016/j.compchemeng.2021.107266

- Albrecht, S., Braun, S., Lucia, S.
Attack Identification for Nonlinear Systems Based on Sparse Optimization
IEEE Transactions on Automatic Control, Volume 67, Issue 12 (2021)
https://doi.org/10.1109/TAC.2021.3131433

- Engell, S., Lucia, S., Paulen, R., Subramanian, S.
Tube-enhanced multi-stage model predictive control for flexible robust control of constrained linear systems with additive and parametric uncertainties
International Journal of Robust and Nonlinear Control, Volume 31, Issue 9, 4458-4487 (2021)
https://doi.org/10.1002/rnc.5486

- Abdelsalam, Y., Engell, S., Lucia, S., Subramanian, S.
Robust Tube-Enhanced Multi-Stage NMPC With Stability Guarantees
IEEE Control Systems Letters Volume 6, 1112-1117 (2021)
https://doi.org/10.1109/LCSYS.2021.3089502

- Alamo, T., Karg, B., Lucia, S.
Probabilistic performance validation of deep learning-based robust NMPC controllers
International Journal of Robust and Nonlinear Control, Volume 31, Issue 18, 8855-8876 (2021)
https://doi.org/10.1002/rnc.5696

- Braatz, RD., Findeisen, R., Lucia, S., Shen, DE., Wan, Y.
Polynomial chaos-based H2 output-feedback control of systems with probabilistic parametric uncertainties
Automatica, Volume 131, 109743 (2021)
https://doi.org/10.1016/j.automatica.2021.109743

- Karg, B., Lucia, S.
Model Predictive Control for the Internet of Things
Recent Advances in Model Predictive Control, 165-189 (2021)
https://doi.org/10.1007/978-3-030-63281-6_7

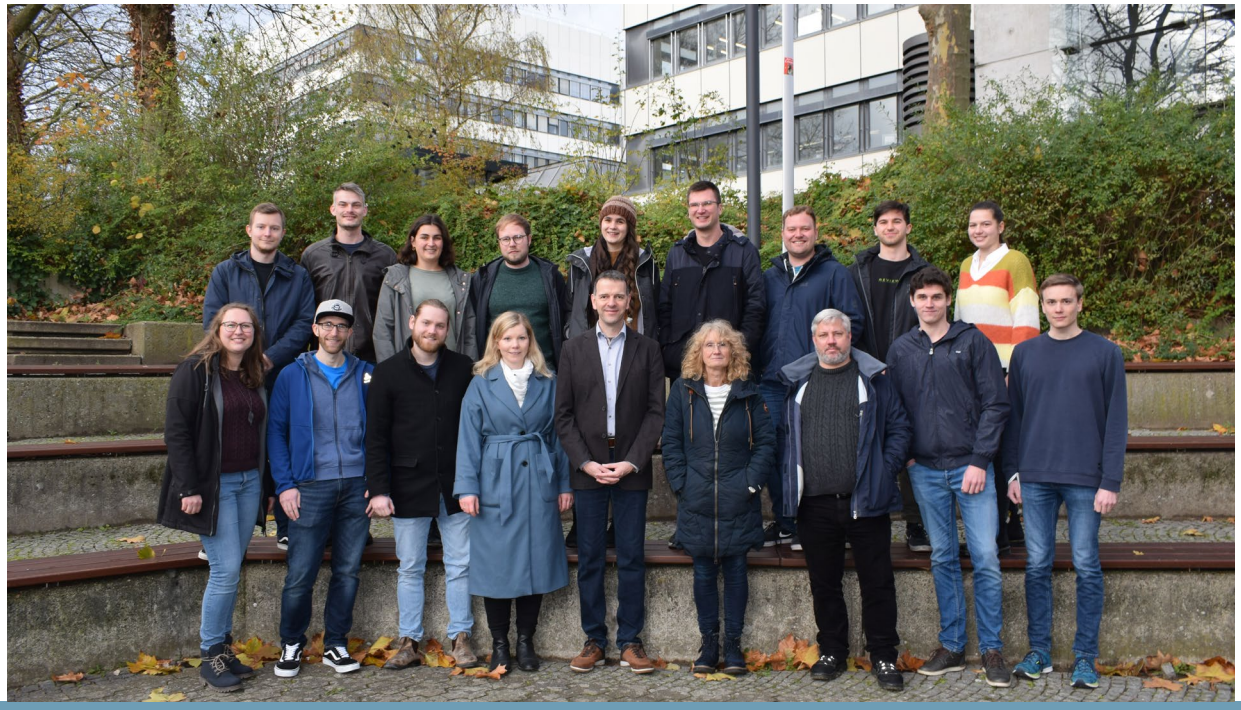
Peer-reviewed Conference Papers

- Darup, MS., Faulwasser, T., Lucia, S., Mönnigmann, M.
Teaching MPC: Which Way to the Promised Land?
IFAC-PapersOnLine, Volume 54, Issue 6, 238-243 (2021)
https://doi.org/10.1016/j.ifacol.2021.08.551

- Lucia, S., Yang, Y.
Multi-step Greedy Reinforcement Learning Based on Model Predictive Control
IFAC-PapersOnLine, Volume 54, Issue 3, 699-705 (2021) (Keynote paper)
https://doi.org/10.1016/j.ifacol.2021.08.323

- Karg, B., Lucia, S.
Reinforced approximate robust nonlinear model predictive control
23rd International Conference on Process Control, 149-156 (2021) (Best Paper by Young Author Award)
https://doi.org/10.1109/PC52310.2021.9447448

- Fiedler, F., Lucia, S.
  On the relationship between data-enabled predictive control and subspace predictive control
  European Control Conference (ECC), 222-229 (2021)
  https://doi.org/10.23919/ECC54610.2021.9654975
- Kovatsch, M. Lucia, S., Xu, J.
  Open Set Recognition for Machinery Fault Diagnosis
  IEEE 19th International Conference on Industrial Informatics (INDIN), 1-7 (2021)
  https://doi.org/10.1109/INDIN45523.2021.9557572
- Döpmann, C., Fiedler, F., Lucia, S., Tschorsch, F.
  Towards Optimization-Based Predictive Congestion Control for the Tor Network
  Electronic Communications of the EASST, Volume 80 (2021)
  http://dx.doi.org/10.14279/tuj.eceasst.80.1128
- Bermbach, D., Handziski, V., Lucia, S., Wolisz, A.
  Towards grassroots peering at the edge
  Proc. of the 8th International Workshop on Middleware and Applications for the Internet of Things, 14-17 (2021)
  https://doi.org/10.1145/3493369.3493602



Reaction Engineering and Catalysis (REC)

Flow characterization of additively manufacturable periodic open cellular structures in the context of heterogeneous catalysis

Diamond unit cell-based interpenetrating periodic open cellular structures

Sebastian Trunk, Lisa Eckendörfer, Andreas Brix, Hannsjörg Freund

Additively manufactured lattice-like catalyst support structures, known as Periodic Open Cellular Structures (POCS), serve as an innovative alternative to traditional randomly packed beds of catalyst pellets in heterogeneous catalysis. The conventional packed bed technology suffers from high pressure drop and inefficient radial heat transfer due to minimal contact points among the pellets. In contrast, POCS offer a continuous solid matrix as well as substantial voids. This design ensures efficient radial heat and mass transfer, along with reduced pressure drop. The adaptability inherent to additive manufacturing allows for the precise tailoring of these structures to meet specific reactor requirements of a chemical process. However, to fine-tune and optimize the design and its performance, a thorough understanding is essential. High potential is attributed to interPOCS, a subset of POCS, with the ability to in-operando adjust the position of a second interwoven structure.

The periodic unit cell formed by characteristically arranged solid struts is the basis of POCS. The POCS lattice is created by repeating the underlying unit cell, e.g. the diamond unit cell, in all three spatial directions. In interpenetrating POCS (interPOCS), two of these lattices are interwoven in such a way that a relative displacement of the two independently movable structures is possible. The offset of the interPOCS is a quantitative measure of the relative shift. It is defined as the ratio of the distance between the two structures and the unit cell size as a measure of the maximum distance (see Fig. 1). For a shift of 50%, one structure is placed exactly in the center of the other. As one structure is moved further away from the other, the value of the offset increases.

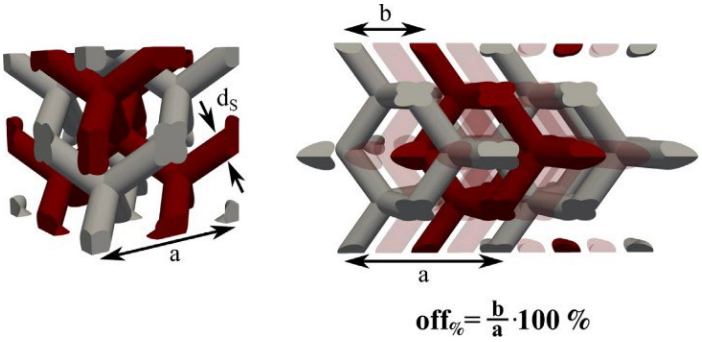


Figure 1: Schematic visualization of the diamond unit cell (left) and the calculation of the offset (right) for an interPOCS with fixed structure in grey and moveable structure in red.

We investigated the pressure drop and flow field characteristics of interPOCS as function of the offset position using computational fluid dynamics (CFD) simulations and our in-house particle tracking tool. Based on this detailed analysis, the pressure drop results of µCT-based digital duplicates show good agreement with previous experiments on 3D printed interPOCS and a notable dependence of the pressure drop on the offset position could be confirmed.

Contact:
lisa.eckendoerfer @tu-dortmund.de
andreas.brix@tu-dortmund.de
hannsjoerg.freund@tu-dortmund.de

The local flow field is strongly influenced by the offset. The flow path evolves from a double helix to a single helix like flow with increasing offset (Fig. 2). As a result, the mean tortuosity and especially the frequency distribution of the tortuosity can be adjusted in-operando via the offset (Fig. 3). This illustrates the high potential of interPOCS to alter relevant transport properties in chemical reactors in-operando. This feature is particularly expected to enable dynamic reactor operation playing an increasingly important role, e.g., in modern Power-to-X processes.

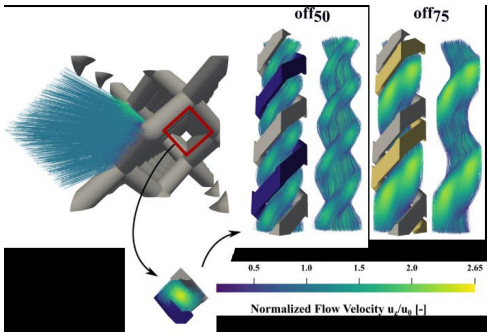


Figure 2: Helix shaped flow path through an interPOCS channel for an offset of 50% (double helix) and 75% (single helix).

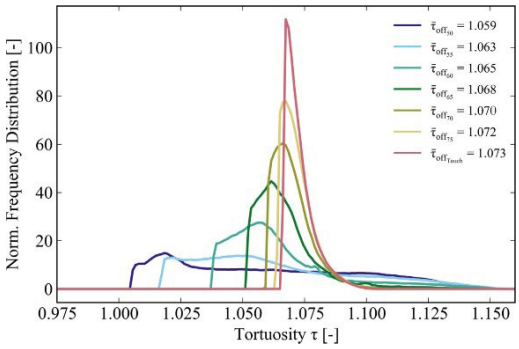


Figure 3: Normalized frequency distribution of the tortuosity for various offsets.

Publications:
Trunk, S.; Freund, H., Chem. Eng. Process. Process Intensif. 2024, 195, 109617. https://doi.org/10.1016/j.cep.2023.109617.
Ferroni, C.; Bracconi M.; Ambrosetti M.; Groppi G.; Maestri M.; Freund, H.; Tronconi E., Chem. Eng. Process. Process Intensif. 2024, 195, 109613. https://doi.org/10.1016/j.cep.2023.109613.

Dynamically Operated Fixed Bed Reactors for CO_2 Methanation

Strategies to Mitigate Catalyst Deactivation

David Kellermann, Moritz Langer, Hannsjörg Freund

Due to the fluctuating power generation from renewable sources, reactors within the power-to-X process concepts such as, e.g., the CO_2 methanation are confronted with partly strongly fluctuating feed flows. Dynamic reactor operation, however, can lead to temporally critical hot spots or unfavorable gas phase conditions, which increase the deactivation rate of the catalyst and shortens its lifetime. To investigate these effects we developed a kinetic model for the methanation reaction that describes the reaction kinetics as well as the catalyst deactivation based on experiments conducted in a gradientless Berty-type reactor. Based on these results, we are able to model and design a load-flexible industrial-scale fixed-bed reactor and describe catalyst deactivation in dynamic operation. This in turn provides a basis for the derivation of adapted policies for dynamic operation to extend the catalyst service life.

The transition of the energy sector from fossil fuels to renewable energies is currently of great interest to researchers. In this context, Power-to-X (PtX) technologies such as methanation are considered to play a crucial role. The methane produced can be easily stored, distributed, and used as a natural gas substitute by utilizing existing natural gas infrastructure. In this scenario, hydrogen is provided on site by water electrolysis, which can follow the fluctuations of renewable energy generation comparatively easily. However, fluctuations in the reactant supply of PtX plants pose challenges for the operation of the catalytic reactors, particularly because of the exothermic nature of the methanation reaction. We developed a kinetic model based on a Langmuir-Hinshelwood-Hougen-Watson approach for an industrial Ni on AlOX catalyst, which is capable of describing both, catalytic activity over a broad operation range as well as catalyst deactivation according to the given conditions. For this, we used a lab-scale plant comprising a Berty-type reactor, which allows kinetic measurements in the absence of mass and heat transfer limitations and provides gradientless reaction conditions. The deactivation behavior was investigated by long-term experiments of up to 120 h time on stream, varying in temperature, pressure and the volume flow to catalyst mass ratio. We developed a reactor design optimized simultaneously for multiple steady-state operating points within a desired load range. This leads to a high load flexibility while ensuring the required product gas quality for all scenarios. Using this obtained reactor design, we investigated three different operation scenarios for a year of operation under fluctuating inlet conditions. In case 1, inlet volume flow and composition are constant (H_2/CO_2 = 4/1), in case 2, the flow rate is fluctuating while the composition is constant (see Fig. 1) and in case 3, the inlet flow rate fluctuates as well as the H_2 to CO_2 ratio. The simulation results show a significantly accelerated deactivation of the catalyst at over-stoichiometric CO_2 concentrations in the feed (see Fig. 2). Consequently, such operating conditions should be avoided by reducing the CO_2 supply at insufficient hydrogen production rates in PtX-plants.

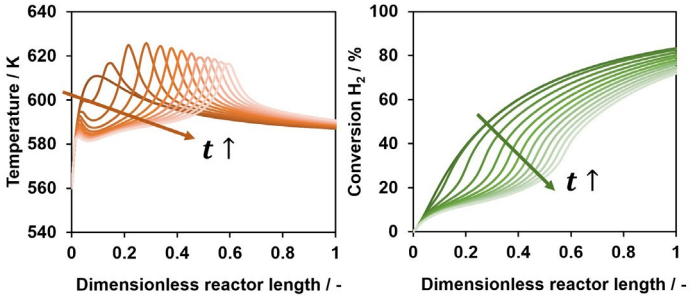


Figure 1: Development of the temperature and the hydrogen conversion in the reactor over the simulated time span of one year under fluctuating inlet volume flow (case 2). An activity front moves through the reactor and results in a significant decrease in product quality at breakthrough.

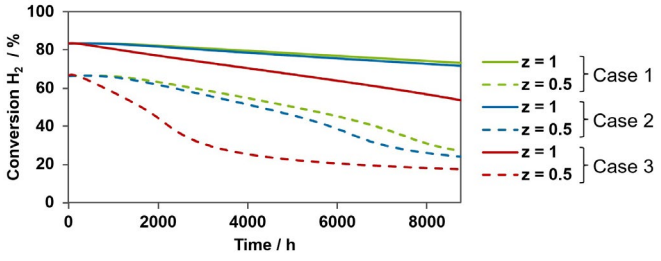


Figure 2: Comparison of the H_2 conversion for all scenarios at different dimensionless reactor lengths z. Case 1 and 2 show similar deactivation characteristics, whereas in case 3, it is significantly accelerated because of high CO_2 feed concentrations.

Publications:
D. Kellermann, M. Langer, H. Freund, Annual Meeting on Reaction Engineering, Frankfurt, Germany (2023).
D. Kellermann, M. Langer, H. Freund, International Symposium on Chemical Reaction Engineering, Québec, Canada (2023).
M. Langer, D. Kellermann, H. Freund, Kinetic modeling of dynamically operated heterogeneously catalyzed reactions: Microkinetic model reduction and semi-mechanistic approach on the example of the CO2 methanation. Chem. Eng. J., 467, 143217, 2023. https://doi.org/10.1016/j.cej.2023.143217

Contacts:
david.kellermann@tu-dortmund.de
hannsjoerg.freund@tu-dortmund.de

Process Intensification of Gas-Liquid Reactors

Identification of Mass Transfer Limitations by Kinetic Modeling of a Large-Scale Trickle Bed Reactor for Viscous Aromatics Hydrogenation

Hendrik Held, Hannsjörg Freund

Trickle bed reactors (TBRs) play a pivotal role in the refinement of over 1.6 gigatons of chemical products annually, establishing them as the predominant reactor type for heterogeneously catalyzed reactions involving liquids and dissolved gases. Common fields of application are hydrodesulfurization, hydrogenation, and oxidation reactions. TBRs face challenges related to mass transfer due to the low gas solubility and slow diffusion in the liquid phase. The significance of mass transfer in TBRs needs to be considered in catalyst selection and reactor design, as inadequate supply of reactants to the catalyst may lead to diminished reaction rates and increased side product formation. Addressing these mass transfer challenges is crucial for process intensification of TBRs in various chemical processes.

We developed a reactor model for elucidating the interplay between mass transfer and reaction kinetics within TBRs based on extensive experimental data. The hydrogenation of high-molecular weight aromatics under high pressure (7-9 MPa) and moderate temperature (90-120 °C) was chosen as model reaction system. An industrial-standard egg-shell catalyst was used for the investigations and compared to reference catalyst systems. A miniplant-scale trickle bed loop reactor (TBLR) was designed enabling the measurement of a packed bed system free of external mass transfer influences. It was proven that the TBLR operates as a differential reactor with a per pass conversion below 2%, enabling the calculation as an ideally backmixed differential reactor due to the high external recycle flow rate. Analytical techniques, including GC-FID, UV–Vis, and NMR, were employed for thorough analysis. This combination allows for precise examination of aromatic concentration within a mixture containing isomeric species.

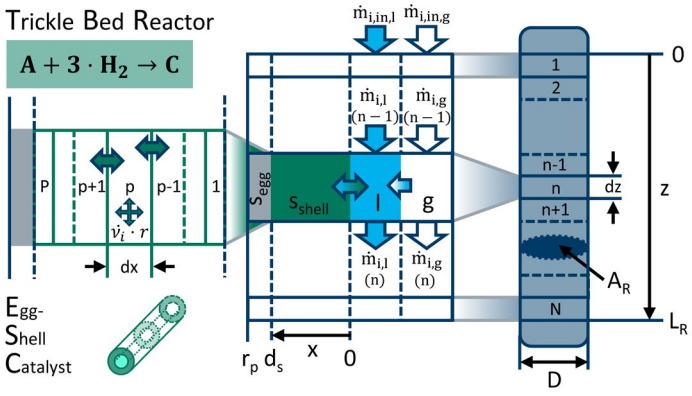


Figure 1: 1D + 1D domain for kinetic modeling of a trickle bed reactor.

The study introduces a simplified method for estimating the activation energy. Utilizing the kinetic Langmuir-Hinshelwood-Hougen-Watson (LHHW) approach, the adsorption of cyclohexane species was shown to not significantly impact the reaction rate, whereas aromatic species exhibit moderate affinity for adsorption at active sites. The developed Plug Flow Reactor (PFR) model, incorporating a discretized pore diffusion model (1D + 1D), see Fig. 1, and a neural network approach for mass transfer estimation, provides detailed insights into concentration profiles within the reactor, encompassing the catalyst pore network. The method identified hydrogen pore diffusion limitations for an industrial-standard catalyst under process conditions, even with the use of an eggshell catalyst featuring a 200 µm shell (Fig. 2). The average pore effectiveness was estimated to 11-24 % within the specified operation range.

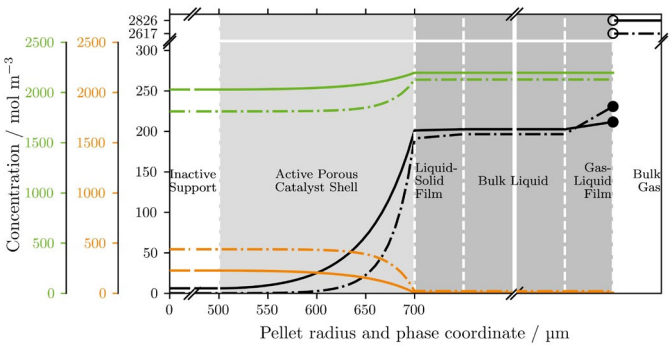


Figure 2: Concentration profiles for g-, l- and s-phase for a fixed bed length of 0.75 m. Green: educt, orange: product, black: H_2, solid line: T = 90 °C, dash-dotted line: T = 120 °C.

In contrast to reaction systems with components of low molecular mass, where gas-liquid mass transfer is typically the primary resistance, differing mass transfer relations were observed for the investigated viscous component system with slow hydrogenation rates. The presented findings advance the understanding of mass transfer phenomena in complex gas-liquid systems, particularly those involving high-viscosity components undergoing hydrogenation. The developed model enables identification of mass transfer limitations in TBRs, thereby establishing the foundation for effective process intensification.

Contacts:
hannsjoerg.freund@tu-dortmund.de

Publications:
Held, H., Freund, H., Identification of Mass Transfer Limitations by Kinetic Modeling of a Technical-Scale Trickle Bed Reactor for the Hydrogenation of Viscous Aromatics. Ind. Eng. Chem. Res. 2024, 63 (1), 147-162. https://doi.org/10.1021/acs.iecr.3c03273

Publications

2023

Journal Articles (with peer review)

- Engl, T.; Langer, M.; Freund, H.; Rubin, M.; Dittmeyer, R.
  Tap Reactor for Temporally and Spatially Resolved Analysis of the CO2 Methanation Reaction
  Chem.-Ing.-Tech. 95(5), 658-667 (2023)
  https://doi.org/10.1002/cite.202200204

- Freund, H.; Sauer, J.; Wachsen, O.
  „Digitalisierung der Reaktionstechnik“: Ein Themenfeld mit vielen Facetten!
  Editorial, Chem.-Ing.-Tech. 95(5), 619 (2023)
  https://doi.org/10.1002/cite.202370502

- *Langer, M.; Kellermann, D.; Freund, H.*
  Kinetic modeling of dynamically operated heterogeneously catalyzed reactions: Microkinetic model reduction and semi-mechanistisc approach on the example of the CO2 methanation
  Chemical Engineering Journal 467, 143217 (2023)
  https://doi.org/10.1016/j.cej.2023.143217

- Ferroni, C.; Bracconi, M.; Ambrosetti, M.; Groppi, G.; Maestri, M.; Freund, H.; Tronconi, E.
  Process Intensification in Mass-Transfer Limited Catalytic Reactors Through Anisotropic Periodic Open Cellular Structures
  Chem. Eng. Process. 195, 109613 (2024)

2022

Journal Articles (with peer review)

- Wehinger, G. D.; Ambrosetti, M.; Cheula, R.; Ding, Z.; Isoz, M.; Kreitz, B.; Kuhlmann, K.; Kutscherauer, M.; Niyogi, K.; Poissonnier, J.; Réocreux, R.; Rudolf, D.; Wagner, J.; Zimmermann, R.; Bracconi, M.; Freund, H.; Krewer, U.; Maestri, M.
  Quo Vadis Multiscale Modeling in Reaction Engineering? – A Perspective
  Chemical Engineering Research and Design, 184, 39-58 (2022)
  https://doi.org/10.1016/j.cherd.2022.05.030

- Worgul, B.; Aguilera, A. F.; Vergat-Lemercier, C.; Eränen, K.; Simakova, O.; Held, H.; Freund, H.; Murzin, D. Y.; Salmi, T.
  Sugar Acid Production on Gold Nanoparticles in Slurry Reactor: Kinetics, Solubility and Modelling
  Chemical Engineering Science 260, 117948 (2022)
  https://doi.org/10.1016/j.ces.2022.117948

- Freund, H.; Sauer, J.; Wachsen, O.
  Wie verändert sich die Reaktions- und Reaktortechnik durch die Elektrifizierung chemischer Prozesse?
  Editorial, Chemie Ingenieur Technik 94(5), 615 (2022)
  https://doi.org/10.1002/cite.202270502

2021

Journal Articles (with peer review)

- Fischer, K. L.; Freund, H.
  Intensification of Load Flexible Fixed Bed Reactors by Optimal Design of Staged Reactor Setups
  Chemical Engineering and Processing 159, 108183 (2021)
  https://doi.org/10.1016/j.cep.2020.108183

- Littwin, G.; Röder, S.; Freund, H.
  Systematic Experimental Investigations and Modeling of the Heat Transfer in Additively Manufactured Periodic Open Cellular Structures with Diamond Unit Cell
  Industrial & Engineering Chemistry Research, 60(18), 6753-6766 (2021)
  https://doi.org/10.1021/acs.iecr.0c06210

- Moioli, E.; Schmid, L.; Wasserscheid, P.; Freund, H.
  Kinetic Modelling of Reactions for the Synthesis of 2-Methyl-5-Ethyl-Pyridine
  Reaction Chemistry & Engineering, 6, 1254-1264 (2021)
  https://doi.org/10.1039/D1RE00085C

- Trunk, S.; Brix, A.; Freund, H.
  Development and Evaluation of a New Particle Tracking Solver for Hydrodynamic and Mass Transport Characterization of Porous Media – A Case Study on Periodic Open Cellular Structures
  Chemical Engineering Science 244, 116768 (2021)
  https://doi.org/10.1016/j.ces.2021.116768

- Littwin, G.; von Beyer, M.; Freund, H.
  Detailed Investigation of Liquid Distribution and Holdup in Periodic Open Cellular Structures Using Computed Tomography
  Chemical Engineering and Processing 168, 108579 (2021)
  https://doi.org/10.1016/j.cep.2021.108579

- Freund, H.; Sauer, J.; Wachsen, O.
  “Circular Economy” – ein neues und zugleich altes Arbeitsgebiet der Reaktionstechnik
  Editorial, Chemie Ingenieur Technik 93(5), 735 (2021)
  https://doi.org/10.1002/cite.202170502

Technical Biochemistry (TB)

Improving CBCA synthase activity through rational protein design

Fabian Thomas & Oliver Kayser

Global interest for the minor cannabinoid cannabichromene (CBC) is growing steadily, as potential pharmaceutical applications continue to emerge. Due to low-yielding and unspecific extraction processes from its plant host Cannabis sativa, a biotechnological production is desirable. The complete heterologous biosynthesis of several other cannabinoids has recently been demonstrated as an accessible platform. However, the enzyme involved in the biosynthesis of CBC precursor cannabichromenic acid (CBCA) suffers from comparatively low catalytic efficiency, has not been crystallized, and remains poorly characterized.

Terpenophenolic cannabinoids are the most prominent secondary metabolites in the annual herb Cannabis sativa L. Rare cannabinoids received slightly less public and scientific attention, but cannabichromene (CBC-C5) as the most abundant among them is nonetheless subject to several clinical studies for its anti-inflammatory, immunoprotective, anti-bacterial, and anti-fungal propertie

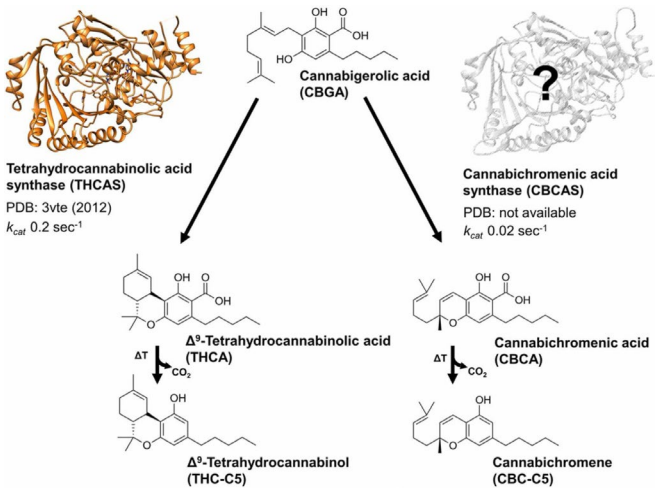


Figure 1: Biosynthesis of Δ9-tetrahydrocannabinolic acid (THCA) and cannabichromenic acid (CBCA) by their respective enzymes in Cannabis sativa. In an oxidative cyclization the common precursor cannabigerolic acid is converted to THCA or CBCA, which can be transformed to the bioactive neutral cannabinoids Δ9-tetrahydrocannabinol (THC-C5) or cannabichromene (CBC-C5) by heat decarboxylation.

Cannabinoids are produced by specialized berberine bridge-like oxidoreductases through an oxidative cyclization of the linear isoprenoid precursor cannabigerolic acid (CBGA-C5, Fig. 1). While THCA synthase and CBDA synthase have been studied thoroughly since their first characterization 20 years ago, research concerning CBCA synthase is in its infancy. The gene encoding CBCAS was identified recently, and the CBCA activity of the corresponding protein, expressed in Komagataella phaffii, was confirmed.
For the analysis, the wild type sequence and the respective CBCAS variants were expressed from single-copy genomic integrations in Komagataella phaffii cells. For all subsequent expression cultures biological triplicates were used by cultivating three different clones from each integration plate. In vitro cell lysate conversion assays were performed at enzyme optimum conditions by addition of the substrate CBGA. After protein precipitation and centrifugation, the assay supernatant was analyzed on an HPLC-UV system to detect the newly formed CBCA.

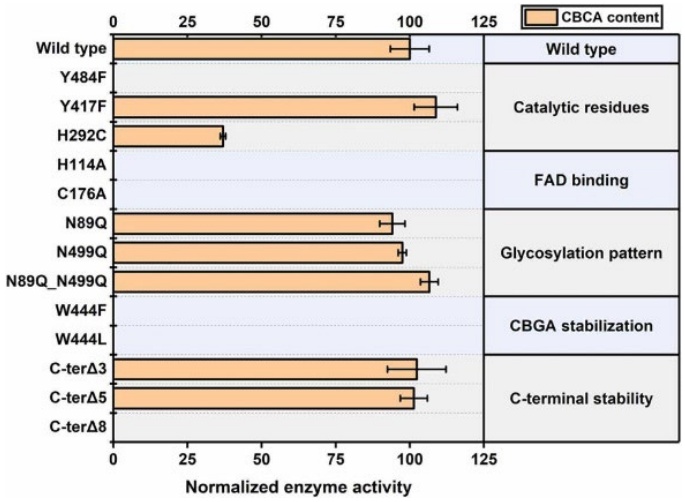


Figure 2: Enzyme activity of variants assessing structure-function relationships of CBCA synthase. CBCA content detected by HPLC-UV at 255 nm after 1 h CBGA bioconversion assays at pH 4.85, normalized to wild type enzyme content. The analysis confirms that Y484, H114, C176 and W444 are essential residues for CBCAS, like was shown previously for THCAS. Much different are results for residues Y417 and H292, as well as for certain N-glycosylation sites, where CBCAS, in contrast to THCAS, was much less affected.

Some variants, however, performed differently for both enzymes and thus hint towards a divergent binding mode of the common precursor cannabigerolic acid (CBGA) within the active site. Besides structure-function considerations, the other aspect of this research was sophisticated enzyme engineering towards facilitated CBCA activity. For the lysate containing variant C244W, a 22-fold increase in CBCA activity was confirmed, far exceeding the expectations. A total of five positions within CBCAS were identified where amino acid substitution resulted in a significant elevation of CBCA activity in cell lysates of the corresponding variants.

Contact:
oliver.kayser@tu-dortmund.de

Publications:
Thomas, F.; Kayser, O.: Improving CBCA synthase activity through rational protein design. J Biotechnol Feb 10:363:40-49.
doi: 10.1016/j.jbiotec.2023.01.004.

Generation of Cannabigerolic Acid Derivatives and Their Precursors by Using the Promiscuity of the Aromatic Prenyltransferase NphB

Saskia Spitzer, Jasmin Wloka, Jörg Pietruszka, Oliver Kayser

NphB is an aromatic prenyltransferase with high promiscuity for phenolics including flavonoids, isoflavonoids, and plant polyketides. It has been demonstrated that cannabigerolic acid is successfully formed by the reaction catalysed by NphB using geranyl diphosphate and olivetolic acid as substrates. In this study, the substrate specificity of NphB was further determined by using olivetolic acid derivatives as potential substrates for the formation of new synthetic cannabinoids. The derivatives differ in the hydrocarbon chain attached to C6 of the core structure.

NphB, a protein isolated from Streptomyces sp. strain CL190, belongs to the enzyme class of aromatic prenyltransferases and the ABBA superfamily. The natural prenyl donor substrate is GPP, but the donor substrate specificity depends on the acceptor substrate. The enzyme catalyzes a C-prenylation at the ortho- or para-position of a hydroxy group, but O-prenylation has also been observed on single hydroxy groups of flavonoids. Because NphB, like CsPT4, can catalyze the reaction to CBGA-C5, we extrapolated this fact to cannabinoid production.

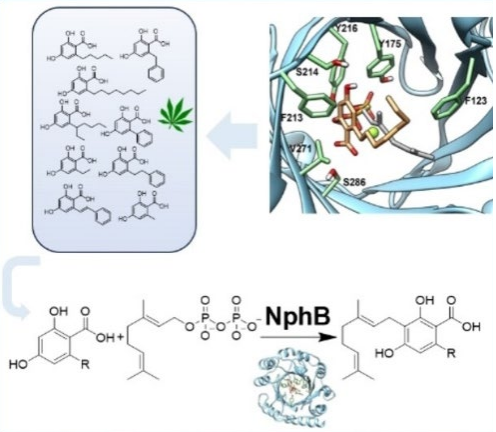


Figure 1: The conversion of novel olivetolic acid derivatives with the highly promiscuous prenyltransferase NphB is analyzed as a tool for the creation of synthetic cannabinoid libraries.

In this study, the substrate specificity of NphB is further evaluated concerning the conversion of various olivetolic acid derivatives. Novel substrates were synthesized by modifying the pentyl chain with different hydrocarbon moieties. In silico experiments were performed to generate a diversified substrate library. This substrate library was evaluated with in vitro assays regarding their conversion with NphB towards CBGA-derivatives.

The NphB wild type primarily catalyzes the formation of 2-O-GOA, and the variant G286S/Y288A predominantly forms CBGA-C5 using olivetolic acid and GPP as substrates. The resorcylate core is shifted towards the π-chamber by exchanging tyrosine at position 288 to a alanine and introducing a polar amino acid side chain with serine at position 286. Two different hydrogen bond networks stabilize when comparing the two proteins. For the NphB G286S/Y288A variant, a construct consisting of two hydrogen bonds between Ser214 and OH4 and between Ser286 and the carboxyl group was identified. For NphB wild type, this network consists of Ser214 and the carboxyl group, and Tyr288 and OH4 (Figure 1). A shift in the proximity between substrate and reaction partner GPP explains the different prenylation pattern of the variant compared to the wild type.

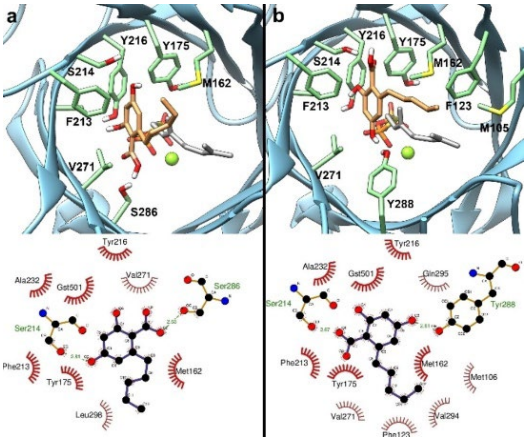


Figure 2: Hydrolysis of the PBI esters shown in Fig. 1 in different aqueous buffer solutions. The MICS.aureus values of the partially hydrolyzed polymers were determined and the respective values are marked as areas (alternating grey/white) in the diagrams.

Novel compounds containing the olivetolic acid resorcylate core and structural elements beyond the natural pentyl group have been synthesized and evaluated as potential substrates for NphB. Alkyl chain modifications up to an octyl group attached to the core are accepted as substrates and show similar conversion to olivetolic acid. A further analysis of the prenylation pattern was carried out for the most promising molecules. In an organism, like *S. cerevisiae*, NphB expression and feeding of olivetolic acid derivatives could lead to the formation of CBGA derivatives

Publications:
Spitzer, S.; Wloka,J.; Pietruszka, J.; Kayser, O.
Generation of Cannabigerolic Acid Derivatives and Their Precursors by Using the Promiscuity of the Aromatic Prenyltransferase NphB. ChemBioChem 2023, 24 (22): e202300441
https:// doi: 10.1002/cbic.202300441

Contacts:
saskia.spitzer@tu-dortmund.de
oliver.kayser@tu-dortmund.de

Publications

2023

Peer-Reviewed Journal Articles

- Erin Noel Jordan, Christina Schmidt, Oliver Kayser
  Foldseek reveals a CBGA prenylating enzyme GlyMa_02G168000 from Glycine max
  Biochem Biophys Res Commun Feb 12:696:149471 (2024)
  DOI: 10.1016/j.bbrc.2024.149471

- Saskia Spitzer, Jasmin Wloka, Jörg Pietruszka, Oliver Kayser
  Generation of Cannabigerolic Acid Derivatives and Their Precursors by Using the Promiscuity of the Aromatic Prenyltransferase NphB
  Chembiochem Nov 16;24(22):e202300441 (2023)
  DOI: 10.1002/cbic.202300441

- Fabian Thomas, Oliver Kayser
  Improving CBCA synthase activity through rational protein design
  J Biotechnol Feb 10:363:40-49 (2023)
  DOI: 10.1016/j.jbiotec.2023.01.004

2022

Peer-reviewed Journal Articles

- Erin Jordan, Gia-Nam Nguyen, Alexander Piechot, Oliver Kayser
  Cannabinoids as New Drug Candidates for the Treatment of Glaucoma
  Planta Med Nov;88(14):1267-1274 (2022)
  DOI: 10.1055/a-1665-3100

- Thanet Pitakbut, Gia-Nam Nguyen, Oliver Kayser
  Activity of THC, CBD, and CBN on Human ACE2 and SARS-CoV1/2 Main Protease to Understand Antiviral Defense Mechanism
  Planta Med Oct;88(12):1047-1059 (2022)
  DOI: 10.1055/a-1581-3707

- Gia-Nam Nguyen, Erin Noel Jordan, Oliver Kayser
  Synthetic Strategies for Rare Cannabinoids Derived from Cannabis sativa
  J Nat Prod Jun 24;85(6):1555-1568 (2022)
  DOI: 10.1021/acs.jnatprod.2c00155

- Thanet Pitakbut, Michael Spiteller, Oliver Kayser
  Genome Mining and Gene Expression Reveal Maytansine Biosynthetic Genes from Endophytic Communities Living inside Gymnosporia heterophylla (Eckl. and Zeyh.) Loes. and the Relationship with the Plant Biosynthetic Gene, Friedelin Synthase
  Plants (Basel) Jan 25;11(3):321 (2022)
  DOI: 10.3390/plants11030321

2021

Peer-reviewed Journal Articles

- Tajammul Hussain, Ganga Jeena, Thanet Pitakbut, Nikolay Vasilev, Oliver Kayser
  Cannabis sativa research trends, challenges, and new-age perspectives
  iScience Nov 1;24(12):103391 (2021).
  DOI: 10.1016/j.isci.2021.103391

- Leonie Hillebrands, Marc Lamshoeft , Andreas Lagojda, Andreas Stork, Oliver Kayser
  In vitro metabolism of tebuconazole, flurtamone, fenhexamid, metalaxyl-M and spirodiclofen in Cannabis sativa L. (hemp) callus cultures
  Pest Manag Sci Dec;77(12):5356-5366 (2021)
  DOI: 10.1002/ps.6575

- Thanet Pitakbut , Michael Spiteller , Oliver Kayser
  In Vitro Production and Exudation of 20-Hydroxymaytenin from Gymnosporia heterophylla (Eckl. and Zeyh.) Loes. Cell Culture
  Plants (Basel) Jul 21;10(8):1493 (2021)
  DOI: 10.3390/plants10081493

Technical Biology (TBL)

New Antiparasitic Drugs by Whole-Cell Biotransformation

Conversion of Quinolone Precursor Molecules into Aurachin Antibiotics

Sebastian Kruth, Cindy J.-M. Zimmermann, Stephan Lütz, Jörg Pietruszka, Marcel Kaiser, Markus Nett

The natural product aurachin D is a farnesylated quinolone alkaloid, which is known to possess activity against the causative agent of malaria, Plasmodium falciparum. *Using a previously constructed* Escherichia coli *strain that is capable of aurachin biosynthesis, we now generated nine structural derivatives of this antibiotic by whole-cell biotransformation. Bioactivity testing confirmed the antimalarial properties of aurachins and further revealed some of these compounds as extremely potent antileishmanial agent with IC_{50} values in the lower micromolar or even nanomolar range.*

Aurachin D (**1**) belongs to a family of bacterial quinolone antibiotics that are highly active against parasitic protozoa causing malaria. Previously we had described a scalable process for the biocatalytic production of **1** from the commercially available precursor molecule 2-methyl-1*H*-quinolin-4-one using a recombinant *E. coli* strain.

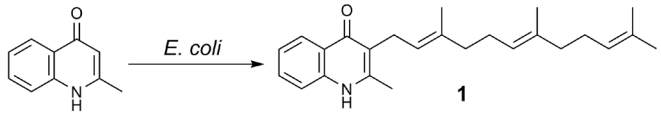


Figure 1: The same strain was now used for the conversion of synthetically prepared analogues of 2-methyl-1*H*-quinolin-4-one into aurachin derivatives.

The substrate analogues were produced in a two-step sequence from ethyl acetoacetate and substituted aniline derivatives. Following their purification and structural verification, these compounds were added to growing cultures of the recombinant *E. coli* strain. Overall, we observed satisfactory conversion rates and a broad substrate tolerance. Nine out of twelve tested precursor analogues were successfully converted into aurachin derivatives. Only substrates featuring bulky substituents on the aromatic ring system (e.g., nitro or hexyl groups) were not processed.

Consistent with previous literature reports, **1** showed potent antiplasmodial effects with an IC_{50} value of 0.012 µM against the malaria parasite *Plasmodium falciparum* (Table 1). In addition, we observed significant trypanocidal activities. The IC_{50} values of **1** against the causative agents of sleeping sickness *(Trypanosoma brucei rhodesiense)* and Chagas disease *(Trypanosoma cruzi)* were in the lower micromolar range, i.e., 4.5 µM and 1.3 µM, respectively. In the case of *Leishmania donovani*, which causes visceral leishmaniasis, **1** was even active at nanomolar concentrations (IC_{50} 0.044 µM). The bioactivity testing revealed further that the antiprotozoal properties of aurachin D can be significantly altered by furnishing its quinolone backbone with different functional groups. Although none of the generated derivatives showed increased activities against the tested protozoa in comparison to **1**, the lack of consistent structure-activity relationship trends suggests that the aurachins exert their effects via different targets in the tested protozoa and also in mammalian cells.

Table 1: Activities of aurachin D and the generated derivatives against parasitic protozoa and mammalian cells. IC_{50} values are given in µM. The antileishmanial selectivity index (S.I) was determined as IC_{50} (L6)/IC_{50} (*L. donovani*).

Test Compound	IC_{50} *Plasmodium falciparum* NF54	IC_{50} *Trypanosoma brucei rhodesiense* STIB 900	IC_{50} *Trypanosoma cruzi* Tulahuen C4	IC_{50} *Leishmania donovani* MHOM-ET-67/L82	IC_{50} Rat Myoblast L6 Cells	Antileishmanial S.I.
aurachin D	0.012	4.5	1.3	0.044	130.7	2969.5
2-desmethyl aurachin D	0.006	9.5	2.4	1.5	20.4	13.2
6-methyl aurachin D	0.514	43.2	7.6	4.3	18.6	4.3
7-methyl aurachin D	0.007	163.8	45.7	9.1	65.3	7.2
6-methoxy aurachin D	0.866	40.3	19.3	7.3	118.3	16.2
7-methoxy aurachin D	0.089	44.8	21.9	17.1	80.8	4.7
6-fluoro aurachin D	0.061	37.2	1.8	0.617	125.8	203.9
6-chloro aurachin D	0.021	37.4	11.2	6.2	117.5	18.9
7-chloro aurachin D	0.070	104.9	41.8	9.2	54.7	5.9
6-bromo aurachin D	0.119	40.2	22.6	13.9	107.7	7.7

Contact:
markus.nett@tu-dortmund.de

Publications:
Kruth, S.; Zimmermann, C. J.-M.; Kuhr, K.; Hiller, W.; Lütz, S.; Pietruszka, J.; Kaiser, M.; Nett, M., Generation of Aurachin Derivatives by Whole-Cell Biotransformation and Evaluation of Their Antiprotozoal Properties. Molecules 2023, 28, 1066. https://doi.org/10.3390/molecules28031066.

Biocatalytic Flow Synthesis of Heterocycles

Design of an Immobilized Enzyme Reactor for the Condensing Amidohydrolase MxcM

Lea Winand, Stefanie Theisen, Stephan Lütz, Katrin Rosenthal, Markus Nett

Heterocycles are important structural elements in pharmaceuticals and agrochemicals. In 2022, 83% of the 200 top-selling small molecule pharmaceuticals featured at least one heterocyclic motif. The chemical synthesis of heterocycles typically requires harsh reaction conditions and the use of hazardous agents. Because of these deficiencies, the synthetic utility of enzymes in heterocyclic chemistry is increasingly explored. Of particular interest in this context are condensing amidohydrolases due to their tolerance towards organic solvents and their independence of cosubstrates. An example for such an enzyme is the imidazoline-forming amidohydrolase MxcM, which has now been integrated into an immobilized enzyme reactor (IMER) that can be operated under flow conditions.

In 2018, the amidohydrolase MxcM was discovered in the marine bacterium *Pseudoalteromonas piscicida*. This enzyme was found to convert monoacylated 1,2-diamines into imidazoline residues. A biochemical characterization of MxcM revealed that this enzyme exhibits high stability and tolerance towards organic solvents. Furthermore, it does not require cosubstrates for its catalytic activity. For these reasons, MxcM is a promising biocatalyst for integration into chemical process synthesis of heterocyclic compounds. To further evaluate the synthetic utility of this enzyme, we first developed a concept for the immobilization of MxcM. Immobilization is generally known to increase the operational stability of enzymes and makes them re-usable. A hexahistidine tag was used for fixation on a solid, porous carrier. Our immobilization protocol leads to immobilization yields of ~75% and enzyme loadings between 7 and 8 wt%. In buffer, the remaining activity of the immobilized MxcM amounted to 30–40% compared to the free enzyme. Since immobilization can influence the solvent tolerance of enzymes, we also analyzed the activity of the immobilized MxcM in different solvent systems (Figure 1).

We observed that the immobilization improved the tolerance of MxcM to all tested organic solvents. Due to the good solvent and storage stability, we further probed the performance of immobilized MxcM for biocatalysis in flow. For that purpose, packed bed-reactors were designed and installed into an HPLC system (Figure 2).

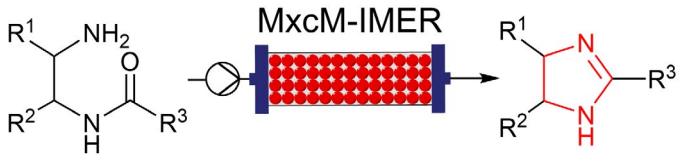


Figure 2: Schematic representation of immobilized enzyme reactor (MxcM-IMER) used for biocatalytic flow synthesis of imidazoline heterocycles.

Interestingly, the composition of the mobile phase greatly influenced the conversion, while the residence time and the temperature had only minor impact under the tested conditions. The MxcM-IMER features a good operational stability, indicating that no significant leaching events occurred, and that the enzyme remains stable under operation in flow. In future, the presented HPLC-coupled flow system can be used to screen the substrate scope of the amidohydrolase MxcM for synthesis of imidazoline-containing, heterocyclic compounds.

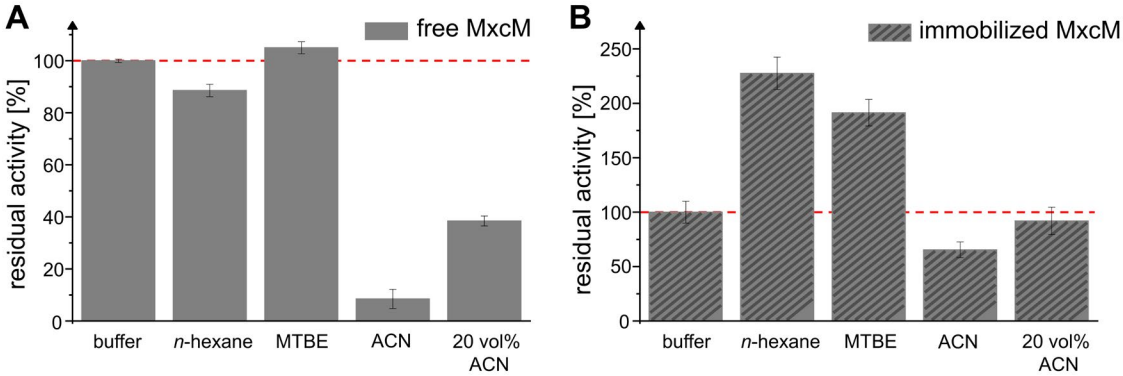


Figure 1: Residual activity of free (A) and immobilized MxcM (B) in phosphate buffer, *n*-hexane, MTBE, acetonitrile (ACN), and buffer with 20 vol% ACN.

Publications:
Winand, L.; Theisen, S.; Lütz, S.; Rosenthal, K.; Nett, M., Immobilization of the Amidohydrolase MxcM and Its Application for Biocatalytic Flow Synthesis of Pseudochelin A. Catalysts. 2023, 13(2), 229. https://doi.org/10.3390/catal13020229

Contact:
lea.winand@tu-dortmund.de

Publications

2023

Peer-reviewed Journal Articles

- Winand, L.; Lernoud, L.; Meyners, S. A.; Kuhr, K.; Hiller, W.; Nett, M.
Myxococcus xanthus as Host for the Production of Benzoxazoles
ChemBioChem, 24, e202200635 (2023)
https://doi.org/10.1002/cbic.202200635

- Winand, L.; Theisen, S.; Lütz, S.; Rosenthal, K.; Nett, M.
Immobilization of the Amidohydrolase MxcM and Its Application for Biocatalytic Flow Synthesis of Pseudochelin A
Catalysts, 13, 229 (2023)
https://doi.org/10.3390/catal13020229

- Kruth, S.; Zimmermann, C. J.-M.; Kuhr, K.; Hiller, W.; Lütz, S.; Pietruszka, J.; Kaiser, M.; Nett, M.
Generation of Aurachin Derivatives by Whole-Cell Biotransformation and Evaluation of Their Antiprotozoal Properties
Molecules, 28, 1066 (2023)
https://doi.org/10.3390/molecules28031066

- Kruth, S.; Nett, M.
Aurachins, Bacterial Antibiotics Interfering with Electron Transport Processes
Antibiotics, 12, 1067 (2023)
https://doi.org/10.3390/antibiotics12061067

- Steinmetz, T.; Lombe, B. K.; Nett, M.
Intermediates and Shunt Products of Massiliachelin Biosynthesis in _Massilia_ sp. NR 4-1
Beilstein Journal of Organic Chemistry, 19, 909-917 (2023)
https://doi.org/10.3762/bjoc.19.69

2022

Peer-reviewed Journal Articles

- Kinner, A.; Nerke, P.; Siedentop, R.; Steinmetz, T.; Classen, T.; Rosenthal, K.; Nett, M.; Pietruszka, J.; Lütz, S.
Recent Advances in Biocatalysis for Drug Synthesis
Biomedicines, 10, 964 (2022)
https://doi.org/10.3390/biomedicines10050964

- Lombe, B. K.; Winand, L.; Diettrich, J.; Töbermann, M.; Hiller, W.; Kaiser, M.; Nett, M.
Discovery, Biosynthetic Origin, and Heterologous Production of Massinidine, an Antiplasmodial Alkaloid
Organic Letters, 24, 2935-2939 (2022)
https://doi.org/10.1021/acs.orglett.2c00963

- Vollmann, D. J.; Winand, L.; Nett, M.
Emerging Concepts in the Semisynthetic and Mutasynthetic Production of Natural Products
Current Opinion in Biotechnology, 77, 102761 (2022)
https://doi.org/10.1016/j.copbio.2022.102761

- Kruth, S.; Schibajew, L.; Nett, M.
Biocatalytic Production of the Antibiotic Aurachin D in _Escherichia coli_
AMB Express, 12, 138 (2022)
https://doi.org/10.1186/s13568-022-01478-8

- Steinmetz, T.; Hiller, W.; Nett, M.
Amamistatins Isolated from _Nocardia altamirensis_
Beilstein Journal of Organic Chemistry, 18, 360-367 (2022)
https://doi.org/10.3762/bjoc.18.40.

2021

Peer-reviewed Journal Articles

- Tippelt, A.; Nett, M.
Saccharomyces cerevisiae as Host for the Recombinant Production of Polyketides and Nonribosomal Peptides
Microbial Cell Factories, 20, 161 (2021)
https://doi.org/10.1186/s12934-021-01650-y

- Vollmann, D. J.; Busche, T.; Rückert, C.; Nett, M.
Complete Genome Sequence of the Nonmotile _Myxococcus xanthus_ Strain NM
Microbiology Resource Announcements, 10, e00989-21 (2021)
https://doi.org/10.1128/MRA.00989-21

- Winand, L.; Sester, A.; Nett, M.
Bioengineering of anti-inflammatory natural products
ChemMedChem, 16, 767-776 (2021)
https://doi.org/10.1002/cmdc.202000771

- Winand, L.; Vollmann, D. J.; Hentschel, J.; Nett, M.
Characterization of a Solvent-Tolerant Amidohydrolase Involved in Natural Product Heterocycle Formation
Catalysts, 11, 892 (2021)
https://doi.org/10.3390/catal11080892

- Winand, L.; Schneider, P.; Kruth, S.; Greven, N.-J.; Hiller, W.; Kaiser, M.; Pietruszka, J.; Nett, M.
Mutasynthesis of Physostigmines in _Myxococcus xanthus_
Organic Letters, 23, 6563–6567 (2021)
https://doi.org/10.1021/acs.orglett.1c02374

Industrial Chemistry (TC)

Polymer-Grade Bio-Monomers from Oleochemicals by Combining Homogeneous Catalysis and Selective Product Crystallization in an Integrated Process

Astrid Ina Seifert, Hannes Wegener, Katharina Brühl, Thomas Seidensticker, and Kerstin Wohlgemuth

As part of the global shift towards a sustainable chemical industry, it is essential to develop new chemical processes based on renewable resources as an alternative to increasingly scarce fossil reserves. Oleo-chemicals, which are produced from natural fats and oils, can be modified to have properties suitable for bio-based monomers for polymer production. They have exceptionally high potential as drop-in solutions for conventional petrochemical monomers. Simultaneously, it is essential to separate the catalyst and product phases downstream. This is necessary to meet purity requirements since transition metals are often toxic. Additionally, it enables the recycling of expensive catalysts, making these processes more economically viable. In this study, we combined a highly selective reaction with an innovative cooling crystallization procedure to produce polymer-grade bio-monomers.

For the preparation of bio-based monomers, the substrate methyl 10-undecenoate (C11-ME) is converted to the bifunctional 1,12-dimethyl dodecanedioate (l-C12-DME) via palladium-catalyzed methoxycarbonylation (see Figure 1). A cooling crystallization strategy was developed and implemented to obtain the monomer product in high purity after the reaction step and to recycle the catalyst.

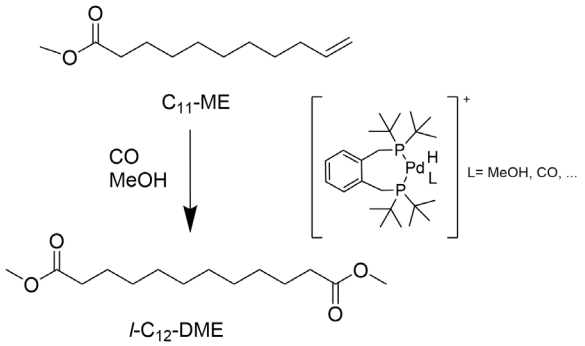
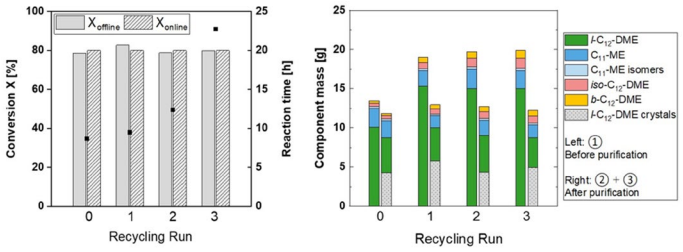


Figure 1: Reaction scheme of the homogeneously catalyzed methoxycarbonylation of methyl 10-undecenoate (C11-ME) to linear 1,12-dimethyl dodecanedioate (l-C12-DME).

Previous studies have demonstrated the recyclability of the catalyst and the excellent crystallization properties of the desired product. However, these studies were developed separately. Therefore, a combination of the individual steps resulted in a reaction-crystallization setup that enabled highly inert and effective coupling of the reaction, crystallization, separation, and recycling steps. This setup provides an excellent starting position for further optimization. Crystallization is a delicate process that is sensitive to minor changes in the composition of the reaction solution. This change occurs over the course of several recycling runs. Maintaining consistent product purity is a significant challenge due to the accumulation of side products and a decrease in substrate conversion. To address this challenge, a non-invasive reaction monitoring system was implemented to track the reaction's conversion progress via CO gas consumption. By utilizing this setup, it was possible to transition from a time-dependent reaction procedure to a conversion-dependent one. Figure 2 displays the results of a recycling experiment, where 80 % conversion were set and achieved in each run, prolonging the reaction time accordingly to reach this goal. This consistency resulted in a nearly constant composition of the reaction solution, enabling optimal crystallization conditions



Recycling series	Run [-]	t [h]	$X_{offline}$ [%]	X_{online} [%]	Purity [%]
X = 80 %	0	8.69	79	80	99.97
	1	9.49	83	80	> 99.99
	2	12.37	79	80	99.98
	3	22.76	80	80	99.96

Figure 2: Results of recycling with constant conversion (X = 80%) (left) Conversion measured offline and online, and (right) composition of organic components in the mixture before (left bars) and after (right bars) purification in the respective recycling steps.

These optimized conditions resulted in product purities > 99.9 %, making them applicable in polymer synthesis.
The developed concepts and their combination resulted in a setup that produces polymer-grade bio-monomers, improving existing works and setting new grounds for further studies.

Contact:
hannes.wegener@tu-dortmund.de
thomas.seidensticker@tu-dortmund.de
kerstin.wohlgemuth@tu-dortmund.de

Publications:
Seifert, A. I., Wegener, H. W., Brühl, K., Seidensticker, T., Wohlgemuth, K., (2023) "Polymer-Grade Bio-Monomers from Oleochemicals by Combining Homogeneous Catalysis and Selective Product Crystallization in an Integrated Process" Processes, 11(10), 2861; DOI: 10.3390/pr11102861

Development of Eco-Friendly and Sustainable PET Glycolysis Using Sodium Alkoxides as Catalyst

Saqib Javed and Dieter Vogt

The mounting environmental burden of postconsumer polyethylene terephthalate (PET) waste needs a more effective recycling approach to combat global pollution and foster a circular economy. PET glycolysis offers a promising approach by transforming PET into the valuable monomer bis(2-hydroxyethyl)terephthalate (BHET). However, conventional methods rely on water-intensive processes, hindering catalyst stability and solvent reuse. Here, we introduced a "green" glycolysis technique using sodium alkoxides and eliminating the need for an anti-solvent. Through response surface methodology, we optimized reaction parameters to achieve high PET conversion and ethylene glycol (EG) recycling. Our approach also demonstrates catalyst tolerance for colored and mixed PET waste, with sodium methoxide (MeONa) exhibiting superior performance. Thus, the potential of BHET precipitation without the need for water, subsequent reuse of EG, and catalyst tolerance in mixed PET waste provide a viable strategy to meet the future demands of waste recycling.

Most of the literature reported on PET glycolysis (homogeneously catalyzed) indicates the use of water as a precipitating agent to separate the BHET (the main product of depolymerization via glycolysis). Water, on one hand, serves as a precipitating agent (anti-solvent), while it also dilutes the glycolysis mixture, making it easier to let the reaction mixture flow out of the reaction vessel. However, this added water needs to be evaporated in later steps. Furthermore, water destroys the sodium alkoxides, the glycolysis catalysts. From an industrial point of view, if no water is added to EG, this solvent can be reused in the depolymerization, and the catalyst will also be saved from water destruction, leading to the maximum utility of all resources. According to the experimental setup depicted in Figure 1, BHET is directly precipitated from the EG solution without adding water after the reaction.

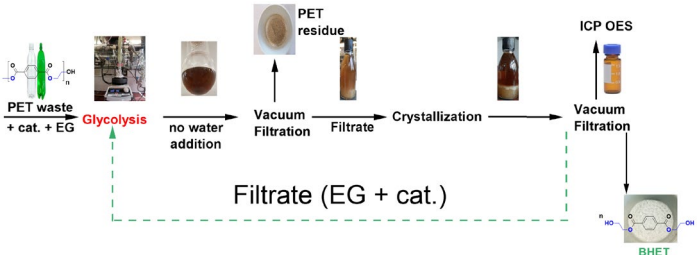


Figure 1: Experimental setup for green glycolysis.

However, this method required the use of a large excess of EG to PET, which was optimized via the design of the experiment (DoE).

Afterwards, we implemented the optimum recipe for recycling the EG in the presence of sodium ethoxide (EtONa) and sodium methoxide (MeONa), and the results are presented in Figure 2. Under similar reaction conditions, MeONa has better conversion than EtONa due to its better catalytic activity. ICP measurements indicated the presence of Na+ in the filtrate of various samples. To confirm the catalytic activity, EG was recycled two times (R1 and R2) and the results are comparable to the initial run for both catalysts. The optimum recipe was also implemented on green-colored PET waste and results showed that both catalysts can also depolymerize colored PET waste. Furthermore, GR1 results show that both filtrates from colored PET waste were successfully recycled to get PET conversion up to 95%. We have also implemented the optimized glycolysis procedure to mixed PET waste resulting in substantial PET conversion signifying the potential of both catalysts to recycle mixed PET waste.

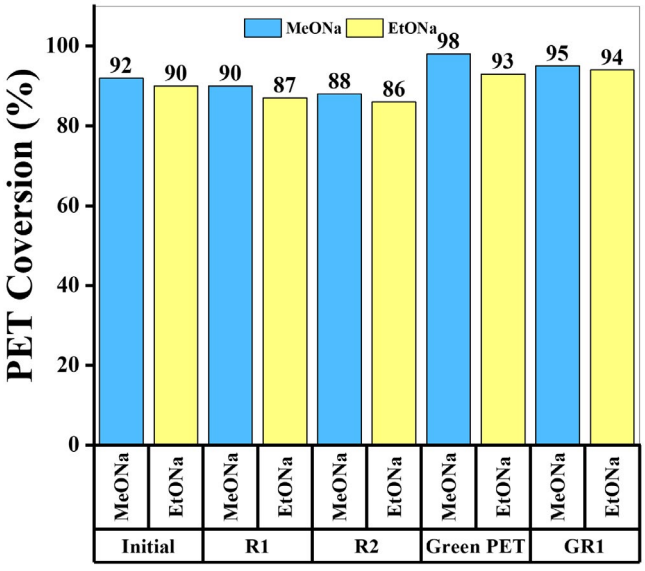


Figure 2 Recycling of EG under optimized conditions.

From an industrial standpoint, if no water is added, EG can be recycled without further processing. Additionally, it will reduce the requirement for unit operations that involve heating water first, followed by filtration and evaporation. As a result, these characteristics make the PET depolymerization procedure more efficient and affordable.

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Contact:
saqib.javed@tu-dortmund.de
dieter.vogt@tu-dortmund.de

Stable and Continuous Production of Amines via Reductive Amination in a Green Switchable Solvent System with Efficient Water Removal

Tim Benjamin Riemer, Philipp Lapac, Dieter Vogt, Thomas Seidensticker

Homogeneous catalysis is central to sustainable chemistry since its high catalytic activity and selectivity allow efficient reactant conversion into desired products. However, recycling the active catalyst complex poses significant challenges. At the same time, it is often a crucial requirement for bringing new and potentially more sustainable processes from research into application. An efficient way to achieve this is the utilization of thermomorphic multiphase systems (TMS). At reaction temperature, the solution is monophasic, allowing reaction without transport limitation. Cooling after reaction reduces the miscibility gap, and two phases are formed. One phase ideally contains the product, and the second phase contains the catalyst, which, therefore, can be recycled through simple decantation. This work stands out with its comprehensive approach, highlighting TMS's potential as a catalyst recycling method for continuous chemical processes by demonstrating exceptional performance in its critical areas, such as reaction yields, catalyst stability/retention, and co-product removal.

In this study, a novel continuous process for the homogeneously catalyzed reductive amination to aliphatic amines in a green methanol-based TMS with simultaneous removal of the co-product water is presented.

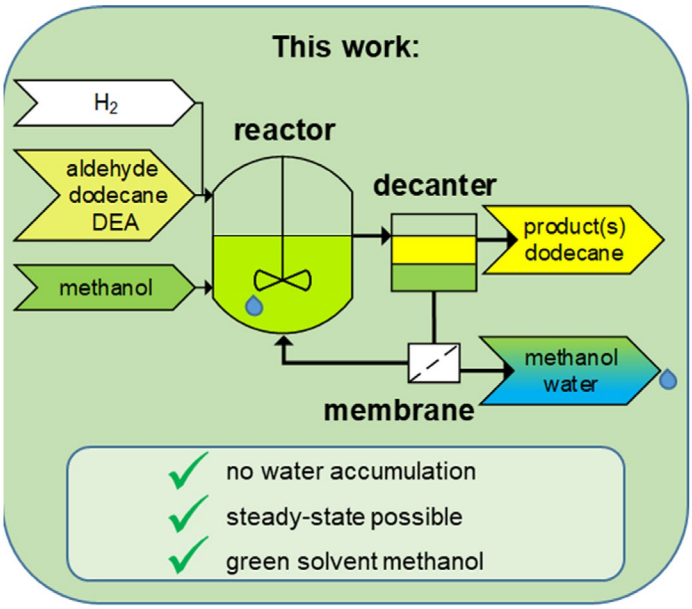

Figure 1: Concept of the continuous TMS process with water removal.

The importance of continuous miniplant experiments is emphasized as they allow for identifying and counteracting potential adverse effects of accumulating components early on. Despite this TMS already being applied in hydroaminomethylation, unexpected challenges were encountered in adapting the TMS to reductive amination due to the formation of high amounts of the undesired alcohol. Here, water accumulation in the recycle phase was identified as a critical and enhancing factor for alcohol formation. Subsequent batch experiments revealed the addition of carbon monoxide to the gas phase as the most effective measure against alcohol formation, even in the presence of water. By transferring these results to the miniplant operation, over the entire operation period of over 90 hours, high yields of over 90% to the tertiary product amine were achieved by controlling the CO content in the gas phase. In addition to the high amine selectivities of up to 96.5%, an outstanding stable and efficient membrane operation was performed, leading to a steady-state water concentration of less than 3.1 wt.%. In addition to water removal via the membrane, the stability of the process is largely dependent on the amount of catalyst loss, which can occur both via the permeate stream of the membrane and the product phase stream. In total, only 0.6 mg of rhodium per kg product amine was lost over the miniplant operation. Since membrane rejections of over 99.7% of the valuable catalyst were maintained, only 0.9 wt% of the initial rhodium mass was lost over the membrane. Despite the excellent membrane performance, its catalyst loss was still outperformed by the TMS, with only 33 ppb rhodium in the product phase and <0.2 mg rhodium per kg of produced product amine. This way, a leaching rate of only 0.003 %/h of the initial rhodium mass over the product phase was achieved. To our knowledge, this is the lowest recorded leaching in continuous thermomorphic multiphase systems. For evaluation of the overall process performance, the reaction yields, the catalyst stability, and retention, the water discharge over the OSN membrane, and the stability of the membrane operation must be taken into account. Here, for the first time, excellent performance in each of those areas has been demonstrated, which gives an optimistic outlook for the potential of the proposed green TMS in chemical processes.

Contact:
tim.riemer@tu-dortmund.de
dieter.vogt@tu-dortmund.de
thomas.seidensticker@tu-dortmund.de

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Continuous production of amines directly from alkenes via cyclodextrin-mediated hydroaminomethylation using only water as the solvent

Thomas Roth, Rebecca Evertz, Niklas Kopplin, Sébastien Tilloy, Eric Monflier, Dieter Vogt and Thomas Seidensticker

Homogeneous transition metal catalysts offer many strengths, including high catalyst activity and selectivity even at comparatively mild operating conditions. Despite these advantages, homogeneous catalysts are not used in most large-scale industrial processes, as separation is complex and therefore cost-intensive. Since recycling of the transition metals is indispensable for the economic and ecological sustainability of processes using homogeneous catalysts, the development of efficient separation and recycling concepts is required to make use of their strengths. The immobilization of the catalyst in multiphase systems offers a promising approach in this respect, as the catalyst phase can be separated and recycled with relatively low effort. However, this approach also poses certain challenges, such as mass transport limitations across the phase interface, which makes the use of intensification strategies imperative. Various intensification strategies are discussed in the literature, but are usually not evaluated under scale-up and continuous conditions. Therefore, a particularly promising intensification strategy for continuous processes using aqueous multiphase systems for homogeneously catalyzed carbonylation reactions is investigated and optimized in this research work.

Hydroaminomethylation (HAM), a tandem reaction of hydroformylation and reductive amination, is an atom-economic route for the efficient production of amines in a single reaction step, starting from basic chemicals such as alkenes (Figure 1). Herein we present the first successful establishment of a continuous process for HAM in an aqueous multiphase system.

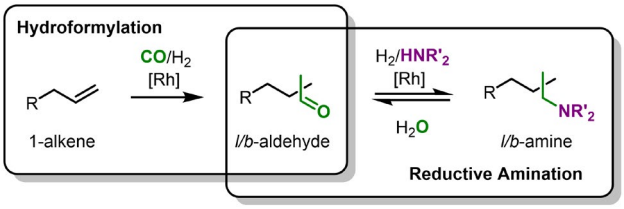

Figure 1: General scheme of the hydroaminomethylation based on a 1-alkene and a secondary amine.

The green mass transfer agents randomly methylated-ß-cyclodextrins (CD) enabled the catalytic system consisting of rhodium/sulfoXantphos to achieve high yields of up to 70% with selectivities of up to 80% in several continuous experiments with a total run time of more than 220 h. The key here is that water and products have large polarity differences, but the reaction still proceeds effectively due to the addition of cyclodextrin (Figure 2), which made the application of further organic solvents obsolete.

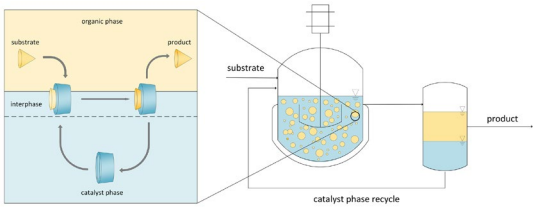

Figure 2: Proposed mechanism for cyclodextrin-mediated reaction systems (left). Basic process design for the recycling of homogeneous catalysts using aqueous biphasic reaction systems (right).

The main achievements in this way were the investigation of the influence of the randomly methylated-ß-cyclodextrin concentration on the reaction rate and the selectivity in batch studies. In continuous experiments, various operating conditions such as reaction and separation temperature, residence time, stirrer speed and different substrate ratios were optimized on-stream (Figure 3). In a final experiment it was shown that high yields of >70% can be achieved while the catalyst loss in the product phase is enormously small at 0.003% h–1 of the initial mass, which is the lowest ever reported value for the HAM on this scale. Within a run time of 78 hours, 2.87 kg of tertiary amine were produced using only 0.2 g of transition metal, while the loss of rhodium per kg of product produced was mostly around 0.15 mg kg–1, suggesting possible economical applicability.

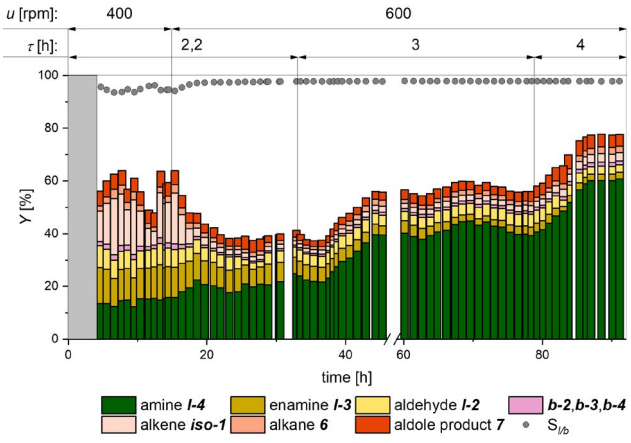

Figure 3: Yields for continuously operated hydroaminomethylation of 1-octene with diethylamine during parameter optimization on stream.

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Contact:
thomas2.roth@tu-dortmund.de
dieter.vogt@tu-dortmund.de
thomas.seidensticker@tu-dortmund.de

Publications

2023

Journal Articles

- Seifert, A. I., Wegener, H. W., Brühl, K., Seidensticker, T., Wohlgemuth, K.
Polymer-Grade Bio-Monomers from Oleochemicals by Combining Homogeneous Catalysis and Selective Product Crystallization in an Integrated Process
Processes, 11 (10), 2861 (2023)
https://doi.org/10.3390/pr11102861

- Riemer, T. B., P. Lapac, P., Vogt, D., Seidensticker, T.
Stable and Continuous Production of Amines via Reductive Amination in a Green Switchable Solvent System with Efficient Water Removal
ACS Sustainable Chem. Eng., 11, 12959–12966 (2023)
https://doi.org/10.1021/acssuschemeng.3c02320

- Javed, S., Ropel, D., Vogt, D.
Sodium ethoxide as an environmentally benign and cost-effective catalyst for chemical depolymerization of post-consumer PET waste,
Green Chem., 25, 1442-1452 (2023)
https://doi.org/10.1039/D2GC04548F

- Javed, S., Vogt, D.
Development of Eco-Friendly and Sustainable PET Glycolysis Using Sodium Alkoxides as Catalysts
ACS Sustainable Chem. Eng., 11, 31, 11541–11547 (2023)
https://doi.org/10.1021/acssuschemeng.3c01872

- Vondran, J., Moeschke, R., Deysenroth, T., Seidensticker, T.
Pushing Boundaries—Selective Cooling Crystallization as Tool for Selectivity Compensation and Product Purification Using a Recyclable Pd/Xantphos Catalyst in the Methoxycarbonylation of Methyl 10-Undecenoate
Eur. J. Lipid Sci. Technol., 125, 2200126 (2023)
https://doi.org/10.1002/ejlt.202200126

- Heider, C., Menk, M., Terhorst, M., Vogt, D., Seidensticker, T.
Synthesis of Tertiary Fatty Amines in Water: The Dual Role of Dimethylamine as Reagent and Phase Mediator in the Homogeneously Catalyzed Fatty Alcohol Amination
ACS Sustainable Chem. Eng. 11, 31, 11359–11363 (2023)
https://doi.org/10.1021/acssuschemeng.3c02764

- Diekamp, J., Seidensticker, T.
Synthesis Strategies towards Tagged Homogeneous Catalysts To Improve Their Separation
Angew. Chem. Int. Ed. , e202304223 (2023)
DOI: 10.1002/anie.202304223

- Roth, T., Evertz, R., Kopplin, N., Tilloy, S., Monflier, E., Vogt, D., Seidensticker, T
Continuous production of amines directly from alkenes via cyclodextrin-mediated hydroaminomethylation using only water as the solvent
Green Chem., 25, 3680-3691(2023)
https://doi.org/10.1039/D2GC04847G

- Kampwerth, A., Terhorst, M., Kampling, N., Vogt, D., Seidensticker, T.
Synthesis of biobased amines via Pd-catalysed telomerisation of the renewable β-myrcene in a water/ethanol multiphase system: catalyst recycling enabled by a self-separating product phase
Green Chem. 25, 6345-6354, (2023)
https://doi.org/10.1039/D3GC00453H

- Heider, C., Winter, A., Voß, V., Vogt, D., Seidensticker, T.
Homogeneous Catalysis at its Edge: High-Temperature Ru-Catalysed Amination of Alcohols under Continuous Flow Conditions
ChemCatChem, 15 (5), e202201307 (2023)
https://doi.org/10.1002/cctc.202201307

- Metzger, J. O., Biermann, U., Seidensticker, T.
Fats and Oils as Renewable Feedstock for the Chemical Industry
Eur. J. Lipid Sci. Technol. 125 (5), 2300038 (2023)
https://doi.org/10.1002/ejlt.202300038

- Javed, S., Vogt, D.
Kinetic Investigation for Chemical Depolymerization of Post-Consumer PET Waste Using Sodium Ethoxide
Ind. Eng. Chem. Res. 62(10), 4328–4336 (2023)
https://doi.org/10.1021/acs.iecr.2c04308

- von Vietinghoff, N., Immken, A., Seidensticker, T., de Caro, P., Thiebaud Roux, S., Agar, D. W.
Gas Introduction by Permeation into Long Fluorinated Ethylene Propylene Capillaries with Slug Flow
Chem Eng Technol, 46 (5), 1047-1051 (2023)
https://doi.org/10.1002/ceat.202200557

- Javed, S., Fisse, J., Vogt, D.
Optimization and Kinetic Evaluation for Glycolytic Depolymerization of Post-Consumer PET Waste with Sodium Methoxide
Polymers 15 (3), 687 (2023)
DOI: 10.3390/polym15030687

2022

- Hares, K., Vogelsang, D., Wernsdörfer, C.S., Panke, D., Vogt, D., Seidensticker, T.
Palladium-catalyzed synthesis of mixed anhydrides via carbonylative telomerization
Catal. Sci. Technol., 12, 3992-4000 (2022)
https://doi.org/10.1039/D2CY00486K

- Vondran, J., Benninghoff, T., Emminghaus, A.I., Seidensticker, T.
Catalytic Synthesis of Methyl 9,10-dihydroxystearate from Technical Feedstocks in Continuous Flow via Epoxidation and Hydrolysis
Eur. J. Lipid Sci. Technol. 124(7), 2200041 (2022)
https://doi.org/10.1002/ejlt.202200041

- Huxoll, F., Kampwerth, A., Seidensticker, T., Vogt, D., Sadowski, G.
Predicting Solvent Effects on Homogeneity and Kinetics of the Hydroaminomethylation: A Thermodynamic Approach Using PC-SAFT
Ind. Eng. Chem. Res. 61, 5, 2323–2332 (2022)
https://doi.org/10.1021/acs.iecr.1c03891

- Vondran, J., Seifert, A.I., Schäfer, K., Laudanski, A., Deysen, T., Wohlgemuth, K., Seidensticker, T.
Progressing the Crystal Way to Sustainability: Strategy for Developing an Integrated Recycling Process of Homogeneous Catalysts by Selective Product Crystallization
Ind. Eng. Chem. Res. 61(27), 9621–9631 (2022)
https://doi.org/10.1021/acs.iecr.2c00476

- Heider, C., Pietschmann, D., Vogt, D., Seidensticker, T.
Selective Synthesis of Primary Amines by Kinetic-based Optimization of the Ruthenium-Xantphos Catalysed Amination of Alcohols with Ammonia
ChemCatChem, 14 (18), e202200788 (2022)
DOI: 10.1002/cctc.202200788

- Vondran, J., Peters, M., Schnettger, A,. Sichelschmidt, C., Seidensticker, T.
From tandem to catalysis – organic solvent nanofiltration for catalyst separation in the homogeneously W-catalyzed oxidative cleavage of renewable methyl 9,10-dihydroxystearate
Catal. Sci. Technol., 12, 3622-3633 (2022)
https://doi.org/10.1039/D1CY02317A

2021

- Söderholm, V., Esteban, J., Vogt, D.
Synthesis of a H-Sulfo-POSS catalyst and application in the acetalization of glycerol with 2-butanone to yield a biofuel additive
Catal. Sci. Technol. 11, 4529-4538 (2021)
https://doi.org/10.1039/D1CY00344E

- Vondran, J., Pela, J., Palczewski, D., Skiborowski, M., Seidensticker, T.
Curse and Blessing–The Role of Water in the Homogeneously Ru-Catalyzed Epoxidation of Technical Grade Methyl Oleate
ACS Sustainable Chem. Eng. 9 (34), 11469–11478 (2021)
https://doi.org/10.1021/acssuschemeng.1c03573

- Vondran, J., Furst, M.R.L., Eastham, G.E., Seidensticker, T., Cole-Hamilton, D.J.
Magic of Alpha: The Chemistry of a Remarkable Bidentate Phosphine, 1,2-Bis(di-tert-butylphosphinomethyl)benzene
Chem. Rev. 121(11) 6610–6653, (2021)
https://doi.org/10.1021/acs.chemrev.0c01254

- Künnemann, K. U., Weber, D., Becquet, C., Tilloy, S., Monflier, E., Seidensticker, T., Vogt, D.
Aqueous Biphasic Hydroaminomethylation Enabled by Methylated Cyclodextrins: Sensitivity Analysis for Transfer into a Continuous Process
ACS Sustainable Chem. Eng., 9, 273–283 (2021)
https://doi.org/10.1021/acssuschemeng.0c07125

- Huxoll, F., Jameel, F., Bianga, J., Seidensticker, T., Stein, M., Sadowski, G., Vogt, D.
Solvent Selection in Homogeneous Catalysis – Optimization of Kinetics and Reaction Performance
ACS Catal., 11, 590–594, (2021)
https://doi.org/10.1021/acscatal.0c04431

- Schlüter, S., Künnemann, K. U., Freis, M., Roth, T., Vogt, D., Dreimann, J. M., Skiborowski, M.
Continuous co-product separation by organic solvent nanofiltration for the hydroaminomethylation in a thermomorphic multiphase system
Chem. Eng. J., 409, 128219 (2021)
https://doi.org/10.1016/j.cej.2020.128219

Thermodynamics (TH)

Continuous Non-Centrifugal Phase Separation in Biphasic Whole-Cell Biocatalysis

Applied Catastrophic Phase Inversion on a Lab-Scale Prototype.

Lisa Janssen, Gabriele Sadowski, Christoph Brandenbusch

Within several chemical and biotechnological processes, the presence of particles (e.g. as catalyst) in a biphasic reaction system (oil/water) often leads to the formation of stable Pickering type emulsions, hindering cost-efficient and effective downstream processing. State-of-the-art-concepts for phase separation fail or include inefficient and costly strategies (centrifugation / de-emulsifiers). Using the phenomenon of catastrophic phase inversion (CPI), efficient phase separation can be achieved by addition of dispersed phase. Based on a patent filed at TU Dortmund, a process concept (termed: Applied Catastrophic Phase Inversion; ACPI) was developed, enabling continuous phase separation of stable emulsion by using the CPI phenomenon. A fully automated pilot-scale prototype was planned and constructed and applicability of the concept to different biocatalysts and aqueous/organic systems confirmed.

Depending on their wettability, cells / particles will either stabilize oil in water, or water in oil emulsions. Wettability is thereby characterized by the three-phase contact angle $_{ow}$ measured through the aqueous phase (see Fig. 1). The particle stabilized, also termed Pickering-type emulsions, can undergo a phenomenon called catastrophic phase inversion, being the sudden switch of emulsion types from an oil/water to a water/oil emulsion (or vice versa). This inversion is achieved by addition of dispersed phase exceeding a critical volumetric threshold. This catastrophic phase inversion (CPI) is accompanied by a complete destabilization of the emulsion.

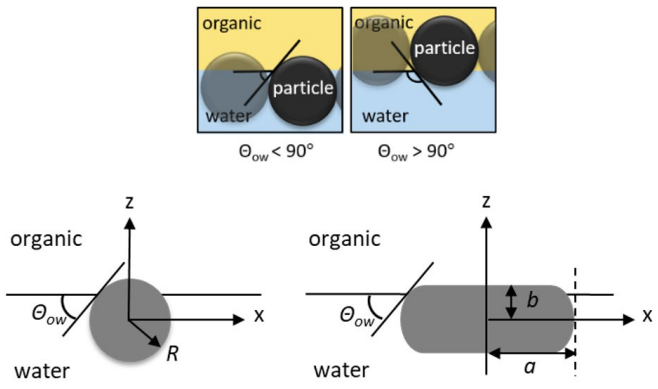


Figure 1: Attachment of particles with three-phase contact angle $_{ow}$ to a planar organic/water interface. (Left) Spherical particles with radius R. (Right) Non-spherical, rod-shape, particles / cells with rod length a, and rod radius b.

Within this work, we designed and constructed a fully automated lab-scale prototype (see Fig. 2) for continuous phase separation adhering to the CPI principle. We demonstrate the applicability of the concept for various long-term stable bioprocess-derived Pickering-type emulsions, investigating the influence of both, different organic solvents (n-heptane, ethyl oleate and 1-octanol) as well as biocatalysts (*Escherichia coli* JM101 and *Pseudomonas putida* KT2440). The critical volumetric phase ratio of organic to water phase (V_o:V_w) which has to be applied to achieve phase inversion, was calculated based on the guideline developed in our previous work.

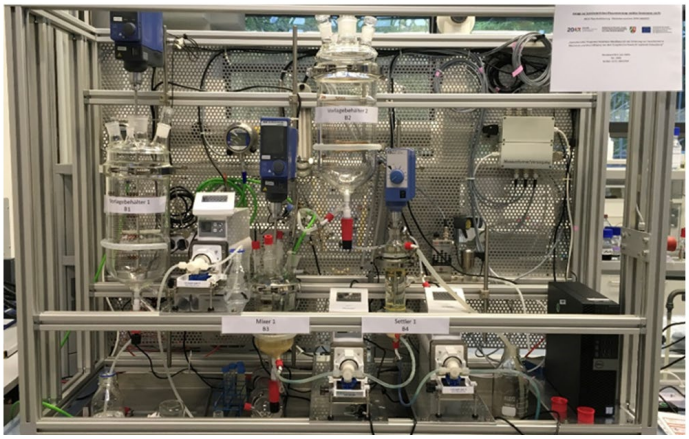


Figure 2: Picture of the lab-scale ACPI prototype as constructed within this work.

A process window that allowed for reliable operating conditions was defined. We investigated the influence of process parameters (e.g., flow rates) on stability and success of the (continuous) phase separation. Furthermore, we investigated the robustness towards perturbations (e.g., fluctuation in water/organic phase ratio of the feed emulsion).
A phase separation efficiency of over 96 % could be achieved for all emulsions considered within this work.
ACPI thus is an innovative and universal tool, overcoming the limitations of the drawbacks in classical downstream processing concepts used in state-of-the-art processing of bioprocess-derived Pickering-type emulsions.

Contacts:
lisa2.janssen@tu-dortmund.de
christoph.brandenbusch@tu-dortmund.de
gabriele.sadowski@tu-dortmund.de

Publications:
Janssen, L.; Sadowski, G.; Brandenbusch, C. Continuous Phase Separation of Stable Emulsions from Biphasic Whole-cell Biocatalysis by Catastrophic Phase Inversion. Biotechnology journal 2023, 18 (6). https://doi.org/10.1002/biot.202200489

Effects of solvent and of catalyst on the acid-catalyzed esterification of levulinic acid via activity-based models

Marcel Klinksiek, Sindi Baco, Christoph Held

This study focuses on understanding the kinetics and thermodynamics of the esterification of levulinic acid with ethanol. So far, thermodynamic models have been used to predict solvent influences on reaction rates and reaction yields. The idea of this work was to also consider the catalyst activity in the kinetic model. Accessing catalyst activity with the model ePC-SAFT allowed the first time to precisely predict the catalyst effects on reaction rates.

When considering the transition from a fossil-fuel based economy to a sustainable one, biomass valorization represents a promising strategy. Increasing the knowledge in the catalyst-kinetics-thermodynamics relation allows understanding and improving the efficiency of biomass conversion, e.g. into levulinic acid (LA) or ethyl levulinate (ELA). In general, ELA is synthesized via an acid-catalyzed esterification reaction of LA with an excess amount of ethanol (Eqs. 1 & 2).

$$\mathrm{LA + EtOH \rightleftharpoons ELA + H_2O} \quad (1)$$

$$\mathrm{H_2SO_4 + H_2O \rightleftharpoons HSO_4^- + H_3O^+} \quad (2)$$

The solvent influences H_2SO_4 dissociation, reaction kinetics, catalyst activity and reaction equilibrium. We studied the influence of the green solvent GVL (γ-valerolactone) and of the H_2SO_4 concentration on reaction kinetics of (1) (see Figure 1).

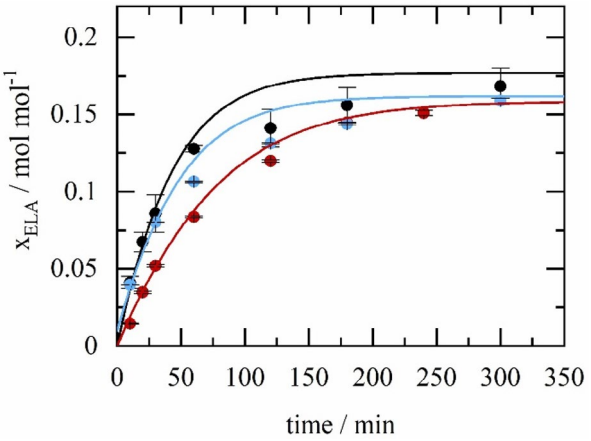


Figure 1: Ethyl levulinate mole fraction during the esterification reaction without cosolvent (black, "ref"), with GVL cosolvent (blue, "3"), with GVL cosolvent and reduced catalyst concentration (red, "4") at 333 K. Symbols: Exp. data, lines: ePC-SAFT predictions. Exact conditions: See publications.

The kinetics of LA esterification in the cosolvent-free system (black) appears to be the fastest, followed by the reaction under GVL addition. Decreased amount of catalyst reduces the reaction kinetics. This behavior has been confirmed by an ePC-SAFT prediction. For the latter, we developed an activity-based model to account for the catalyst interactions with the reaction components. The resulting equation describes the reaction rate r by

$$\frac{r}{a_{H_3O^+}} = k_1 \cdot \gamma_{LA} x_{LA} \cdot \gamma_{EtOH}\, x_{EtOH} \cdot - \frac{k_1}{K_{th}} \cdot \gamma_{ELA} x_{ELA} \cdot \gamma_{H_2O} x_{H_2O}$$

where x, γ and K_{th} describe the mole fractions, the activity coefficients and the thermodynamic equilibrium constant, respectively. This approach incorporates the dissociation of H_2SO_4 in the reaction mixture, which we solved in order to predict proton activity (aH_3O^+) along the reaction coordinate using ePC-SAFT.

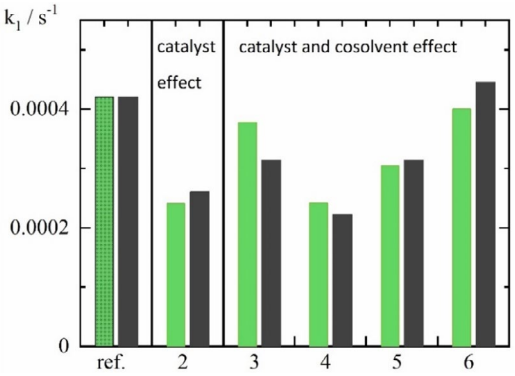


Figure 2: Rate constants k_1 for selected conditions at 333 K. Green: exp. data, Black: ePC-SAFT prediction using one experiment as reference (shaded, "ref"). Exact conditions: See publication.

Figure 2 compares experimental and predicted rate constants k_1 at various experimental conditions (see figure caption of Figure 1). The results show that the activity-based model is capable of predicting the catalyst effect on the reaction rate. Only one reference experimental k_1 ("ref.") was required to predict the influence of catalyst and cosolvent on the kinetics. This was possible at the different conditions (2-6) concerning the cosolvent or catalyst concentration. To conclude, we were able to predict kinetics in an arbitrarily chosen reaction environment concerning solvent, catalyst, and any concentration by combining proton activity, dissociation equilibria and reactant activities from ePC-SAFT into a reaction kinetics approach.

Publications:
Klinksiek, M.; Baco, S; Leveneur, S.; Legros, J.; Held, C., Activity-based models to predict kinetics of levulinic acid esterification, ChemPhysChem 2023, 24, e202200729
https://doi.org/10.1002/cphc.202200729

Contact:
christoph.held@tu-dortmund.de

Modeling the impact of tablet surface layers on the dissolution rate in water

Stefanie Dohrn, Gabriele Sadowski

This study utilized thermodynamic modeling to understand the behavior of amorphous solid dispersion (ASD) tablets during dissolution when exposed to water. It emphasizes the importance of the interfacial surface layers formed during dissolution and predicts drug load (DL)-dependent loss of release (LoR) that often prevents the complete dissolution of the tablet in water. The reasons for this are crystallization and/or liquid-liquid phase separation (LLPS) at the tablet surface. To this end, the phase behavior and glass transition of tablets composed of the drugs naproxen or venetoclax and of poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA64) in contact with water were predicted using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) and the Gordon-Taylor equation. The modeling results were found to be in perfect agreement with (non)dissolution experiments.

According to the concept depicted in Figure 1, the behavior of tablets in contact with water is influenced by water sorption, LLPS, crystallization, and the viscosity of the gel layer formed, impacting the dissolution performance. Phase changes can lead to surface passivation. The LoR mechanisms were categorized into two types, depending on whether the passivation is primarily driven by drug crystallization (LoR Type I) or LLPS (LoR Type II).

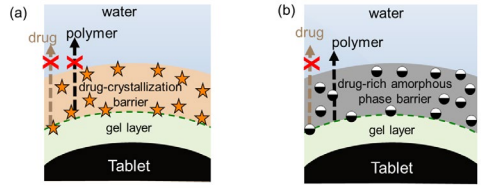


Figure 1: Schematic tablet/water surface of (a) LoR Type I and (b) Type II.

The DL-dependent release mechanisms for PVPVA64-based naproxen (LoR Type I) and venetoclax (LoR Type II) ASDs were predicted and experimentally investigated (Figures 2 and 3).

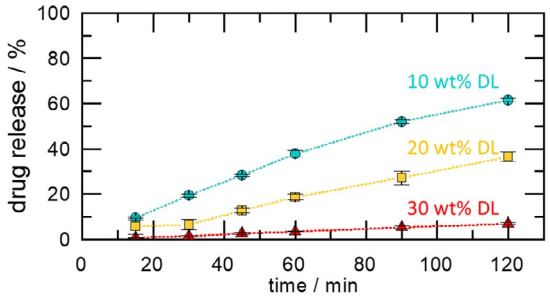


Figure 2: Release profile of naproxen at 37 °C from a naproxen/PVPVA64 ASD, with DLs of 10 wt % (blue circles), 20 wt % (yellow squares), and 30 wt % (red triangles).

The predictions were in excellent agreement with experimentally observed layer formation and its impact on the dissolution. It turned out that the drug-release levels strongly decreased with increasing DL. While the 10 wt % DL tablets released 60% of the naproxen, the 30 wt% DL tablets released only 10% of the naproxen at the same time (Figure 2). The predicted tablet/water phase behavior (Figures 3a and 3b) and DL-dependent phase transition at the tablet/water surface could experimentally be validated via microscopy images (Figures 3c-h).

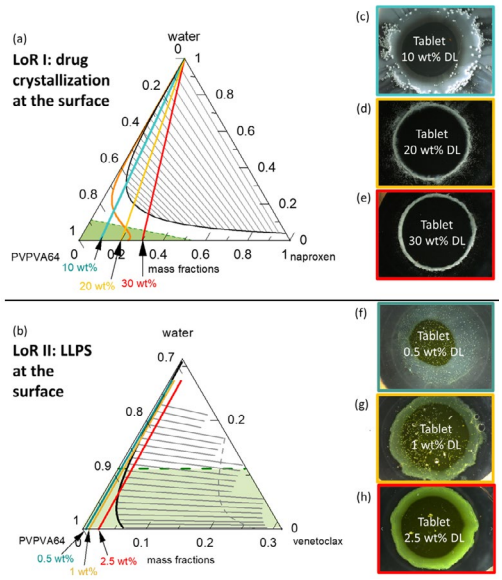


Figure 3: Ternary phase diagrams at 37 °C of (a) LoR Type I system: naproxen/PVPVA64/water and (b) LoR type II system: venetoclax/ PVPVA64/water. The green dashed lines represent the glass transition; the orange lines represent the solubility lines; the black lines represent the LLPS boundaries with gray tie lines; and the blue, yellow, and red straight lines represent the hydration pathways for different DLs. Tablet images after 40 min dissolution for DLs (c) 10 wt%, (d) 20 wt%, and (e) 30 wt% naproxen and (f) 0.5 wt%, (g) 1 wt%, and (h) 2.5 wt% venetoclax.

The presented modeling approach supports the understanding of a tablet release mechanism during dissolution and helps to identify the maximum DL of a tablet, which allows high drug release without undergoing phase changes during dissolution.

Contacts:
stefanie.walter@abbvie.com
gabriele.sadowski@tu-dortmund.de

Publication:
Dohrn S.; Kyeremateng S.O.; Bochmann E.; Sobich E.; Wahl A.; Liepold B.; Sadowski G.; Degenhardt. M., Thermodynamic Modeling of the Amorphous Solid Dispersion-Water Interfacial Layer and Its Impact on the Release Mechanism, Mol. Pharmaceutics 2023, 15 (5), 1539. doi:10.3390/pharmaceutics15051539

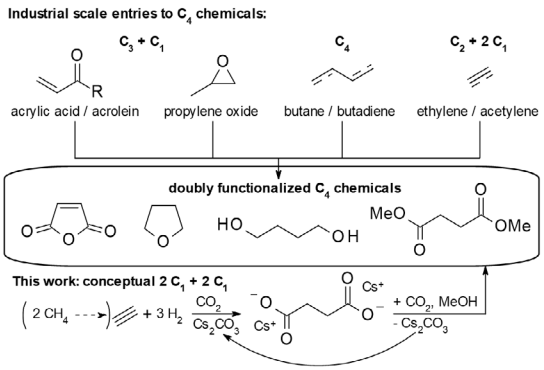
Carboxylation of Acetylene without Salt Waste: Using thermodynamic predictions to optimize the catalyst and the reaction solvent

Christoph Held, Daniel Schick, Tim van Lingen, Lukas Gooßen, Gabriele Sadowski

The utilization of CO_2 as C1 building block is a key towards a sustainable industrial synthesis of base chemicals. In this work, we developed a circular process for the production of the C4 chemical dimethyl succinate from CO_2 and acetylene, i.e. a C-H carboxylation reaction. The inherent formation of salt waste in such C-H carboxylations has so far been a major challenge. This was resolved in this work by esterification of the carboxylate product using methanol. The challenge of enabling a one-pot synthesis in such a reaction sequence is to find reaction conditions that are efficient for all reaction steps. Here, we applied ePC-SAFT to screen the reaction solvent and the base salt for the reaction to reach high solubility of both the salt base and the reactants.

Conventionally, C4 chemicals are synthesized from acrylic acid, propylene oxide, butane or ethylene, i.e. by coupling building blocks C3 + C1, C2 + C1 or directly using C4 units. In contrast, we were aiming at a route that uses CO_2 as a building block. However, it is known that it is very hard to activate CO_2 due to its thermodynamic low energetic level. Thus, a very common way to activate CO_2 is using molecular hydrogen to produce formic acid. In contrast, in this work we used CO_2 as a building block for a carboxylation reaction. A concept has been developed (c.f. Fig. 1) over the last years to carboxylate an alkyne, and we chose the example of acetylene carboxylation, yielding the C4- based chemical dimethyl succinate.

Figure 1: Synthetic entries to difunctionalized C4-commodities.



Our concept for sustainable C4 synthesis was as follows: At moderate CO_2 pressures, acetylene is doubly carboxylated, which requires basic conditions. The subsequent esterification of the succinate salt with methanol allowed regenerating the base salt. Realizing a one-pot synthesis of this concept requires a solvent that is efficient for all reaction steps. This solvent must provide high solubility of the salt base and the reactants acetylene and CO_2. Without fitting parameters, ePC-SAFT identified N-methyl-2-pyrrolidone (NMP) as most efficient solvent, c.f. Fig. 2. NMP provides high solubility for CO_2 and for acetylene, outperforming the other solvents (water, methanol, acetonitrile, THF). ePC-SAFT predicted that Cs_2CO_3 had the highest solubility in NMP among the considered carbonate bases.

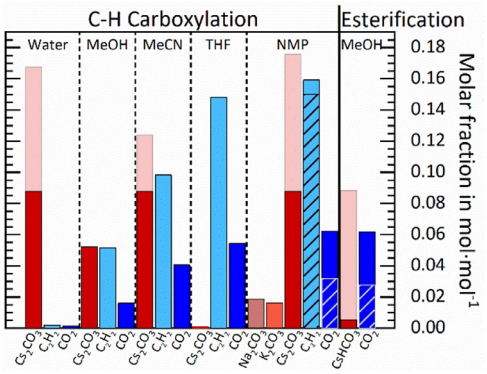


Figure 2: ePC-SAFT predicted solubility of gases at carboxylation conditions (T = 100 °C; p = 10 bar) and esterification conditions (T = 200 °C; p = 72 bar) and solubility of salts (T = 25°C). Solid bars represent solubilities in pure solvents. Striped bars is gas solubility in solvent + Cs_2C_{03}. Whenever the experimental amount of added salt (dark red bar) is lower than its solubility, the dark red bar is extended with a light red bar which represents the maximum solubility.

Summing up, our concept shown in Fig. 1 provides the proof of concept for a salt-free route to C4 chemicals based on CO_2 as C1 building block, and could potentially be used to valorize biogas (CH_4/CO_2).
ePC-SAFT proved to be efficient for optimizing the reaction medium of the one-pot synthesis of the C4 chemical from CO_2 by suggesting the optimal reaction solvent NMP and the optimal base Cs_2CO_3.

Publication:
Van Lingen, T.; Bragoni, V.; Dyga, M.; Exner, B.; Schick, D.; Held, C.; Sadowski, G.; Goossen, L., Carboxylation of Acetylene without Salt Waste: Green Synthesis of C4 Chemicals Enabled by a CO_2-Pressure Induced Acidity Switch. Angewandte Chemie I.E. e202303882, doi.org/10.1002/anie.202303882

Contacts:
christoph.held@tu-dortmund.de
gabriele.sadowski@tu-dortmund.de

Direct Generation of Compressed Air from Waste Heat by Cascaded Thermocompressors with Self-Excited Overdriven Free Displacers

Analytical and Numerical Analysis

Fabian Fischer, Sebastian Peveling, Hans-Detlev Kühl

Compressed air is a widely used but expensive and inefficient industrial energy source. At the same time, large amounts of waste heat remain unused. In order to exploit and utilize this waste heat potential at low production and operating costs, a novel concept based on reciprocating thermocompressors has been developed. It focusses on maximum constructional simplicity by arranging a cascade of identical stages, and on the application of self-excited, overdriven free displacers, the frequencies of which may adapt independently of the pressure to ensure optimum operation of all stages, while largely maintaining or even exceeding thermal similarity to the first stage. In order to prove the feasibility of such a system, it has been investigated by means of an analytical and a numerical analysis.

The basic layout of a reciprocating thermocompressor shows similarities to a β- or γ-type Stirling engine, in which a pair of check valves replaces the power piston. Thus, the air to be compressed simultaneously acts as the working fluid of an open cycle. Figure 1 shows the schematic arrangement of two consecutive stages k and k+1 within a cascade. Their reciprocating displacers periodically relocate the air between the hot and cold cylinder volumes via a duct consisting of a cooler, a regenerator and a heater. During the downward motion, the pressure is raised due to isochoric heating, until it reaches the outlet pressure. From then on, it remains constant, since the outlet valves open and discharge the air into the upward buffer volume. At the end of stroke, the displacers hit elastic limit stops, so that their motion is reversed, preserving their kinetic energy in the ideal case. The outlet valves close, and the pressure drops due to cooling, until the inlet valves open and air from the downward buffer enters the cycle volume. At the lower end of stroke, the displacers once again bounce back elastically, and the cycle is closed. As the displacer rod periodically plunges into the cold cylinder, the overall cycle volume varies, and p,V-work is generated. When properly designed, this work compensates any friction losses, thus eliminating the need for external actuation.

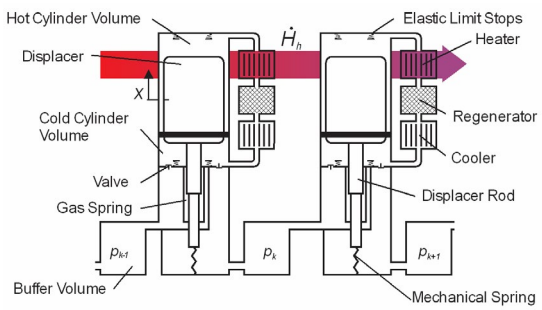


Figure 1: Schematic drawing of two stages of a cascade of identical overdriven free-displacer thermocompressors.

All relevant operating parameters, such as the conveyed mass of air, the heat absorbed and the exergy gain of the compressed air flow, depend on the stage pressure ratio in such a way that a self-controlled steady-state operation can be expected. The results obtained with an analytical model indicate that such stable operating points exist above a critical stage pressure ratio.

To further investigate the operating characteristics, a three-stage cascade was modelled in Simulink® with its extension SimscapeTM. Figure 2 exemplarily shows the exergy gain of the compressed air flow as a function of the total pressure ratio for the single stages k and for the entire cascade. The simulation results confirm the expected stable operation of all stages for a wide range of total pressure ratios as well as the existence of lower stability limits, where the lowest operating stage stops.

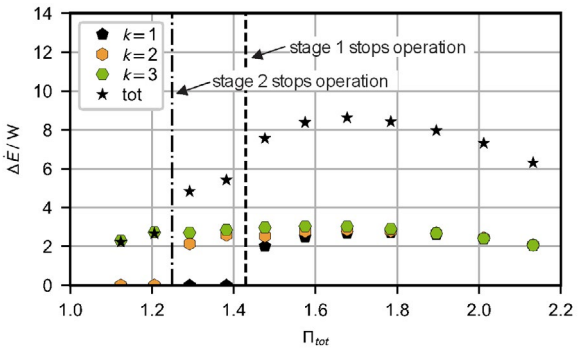


Figure 2: Exergy gain ΔĖ of the compressed air flow (total and for each stage k of the three-stage cascade) vs. total pressure ratio Πtot.

The results demonstrate that the presented concept is a promising approach to generate compressed air from waste heat in a both economically and ecologically advantageous way, and therefore strongly suggest further experimental investigations as the next step.

Contacts:
fabian2.fischer@tu-dortmund.de
sebastian.peveling@tu-dortmund.de
hans-detlev.kuehl@tu-dortmund.de

Publication:
Fischer, F.; Peveling, S.; Kühl, H.-D., Simulation and stability analysis of a thermocompressor cascade with overdriven free displacers. Thermal Science and Engineering Progress 2023, 44, 102037. https://doi.org/10.1016/j.tsep.2023.102037

Publications

2023

- Kroll, P.; Exner, L.; Brandenbusch, C.; Sadowski, G.
Influence of Hydrophobic and Hydrophilic Chain Length of CiEj Surfactants on the Solubilization of Active Pharmaceutical Ingredients.
Molecular pharmaceutics 2023, 20 (2), 1296-1306.
https://doi.org/10.1021/acs.molpharmaceut.2c00941

- Klinksiek, M.; Baco, S.; Leveneur, S.; Legros, J.; Held, C.
Activity-based Models to Predict Kinetics of Levulinic Acid Esterification.
ChemPhysChem 2023, 24 (4).
https://doi.org/10.1002/cphc.202200729

- Ascani, M.; Sadowski, G.; Held, C.
Simultaneous Predictions of Chemical and Phase Equilibria in Systems with an Esterification Reaction Using PC-SAFT.
Molecules 2023, 28.
https://doi.org/10.3390/molecules28041768

- Anjum, F.; Wessner, M.; Sadowski, G.
Membrane-Based Solvent Exchange Process for Purification of API Crystal Suspensions.
Membranes 2023, 13 (3), 263.
https://doi.org/10.3390/membranes13030263

- Grönniger, B.; Fritschka, E.; Fahrig, I.; Danzer, A.; Sadowski, G.
Water Sorption in Rubbery and Glassy Polymers, Nifedipine, and Their ASDs.
Molecular pharmaceutics 2023, 20 (4), 2194–2206.
https://doi.org/10.1021/acs.molpharmaceut.3c00006

- Yu, G.; Gajardo-Parra, N. F.; Chen, M.; Chen, B.; Sadowski, G.; Held, C.
Aromatic Volatile Organic Compounds Absorption with Phenyl-based Deep Eutectic Solvents: A Molecular Thermodynamics and Dynamics Study.
AIChE journal / American Institute of Chemical Engineers 2023, 69 (5).
https://doi.org/10.1002/aic.18053

- Cordier, A.; Klinksiek, M.; Held, C.; Legros, J.; Leveneur, S.
Biocatalyst and Continuous Microfluidic Reactor for an Intensified Production of N-Butyl Levulinate : Kinetic Model Assessment.
Chemical engineering journal 2023, 451.
https://doi.org/10.1016/j.cej.2022.138541

- Grönniger, B.; Danzer, A.; Kimpe, K.; Singh, A.; Sadowski, G.
Viscoelastic Behavior of Supercooled and Glassy ASDs at Humid Conditions Can Be Predicted.
Molecular pharmaceutics 2023, 20 (5), 2568–2578.
https://doi.org/10.1021/acs.molpharmaceut.3c00008

- Krummnow, A.; Danzer, A.; Voges, K.; Kyeremateng, S. O.; Degenhardt, M.; Sadowski, G.
Kinetics of Water-Induced Amorphous Phase Separation in Amorphous Solid Dispersions via Raman Mapping.
Pharmaceutics 2023, 15 (5).
https://doi.org/10.3390/pharmaceutics15051395

- Janssen, L.; Sadowski, G.; Brandenbusch, C.
Continuous Phase Separation of Stable Emulsions from Biphasic Whole-cell Biocatalysis by Catastrophic Phase Inversion.
Biotechnology journal 2023, 18 (6).
https://doi.org/10.1002/biot.202200489

- Habicht, J.; Brandenbusch, C.; Sadowski, G.
Predicting PC-SAFT Pure-Component Parameters by Machine Learning Using a Molecular Fingerprint as Key Input.
Fluid phase equilibria 2023, 565.
https://doi.org/10.1016/j.fluid.2022.113657

- Dohrn, S.; Kyeremateng, S. O.; Bochmann, E.; Sobich, E.; Wahl, A.; Liepold, B.; Sadowski, G.; Degenhardt, M.
Thermodynamic Modeling of the Amorphous Solid Dispersion-Water Interfacial Layer and Its Impact on the Release Mechanism.
Pharmaceutics 2023, 15 (5).
https://doi.org/10.3390/pharmaceutics15051539

- Lingen, T. van; Bragoni, V.; Dyga, M.; Exner, B.; Schick, D.; Held, C.; Sadowski, G.; Gooßen, L. J.
Carboxylation of Acetylene without Salt Waste: Green Synthesis of C4 Chemicals Enabled by a CO_2-pressure Induced Acidity Switch.
Angewandte Chemie International edition 2023, 62 (27).
https://doi.org/10.1002/anie.202303882

- Hubach, T.; Schlüter, S.; Held, C.
Model-Based Optimization of Multi-Stage Nanofiltration Using the Solution-Diffusion–Electromigration Model.
Processes 2023, 11 (8).
https://doi.org/10.17877/de290r-23911

- Loll, R.; Nordhausen, L.; Bieberle, A.; Schubert, M.; Pyka, T.; Koop, J. Held, C.; Schembecker, G.
Analysis of Flow Patterns in Structured Zickzack Packings for Rotating Packed Beds Using γ-Ray Computed Tomography.
Industrial & engineering chemistry research 2023, 62 (38), 15625–15634.
https://doi.org/10.1021/acs.iecr.3c02252

- Gajardo-Parra, N. F.; Rodríguez, G.; Arroyo-Avirama, A. F.; Veliju, A.; Happe, T.; Canales, R. I.; Sadowski, G.; Held, C.
Impact of Deep Eutectic Solvents on Kinetics and Folding Stability of Formate Dehydrogenase.
Processes 2023, 11 (10).
https://doi.org/10.3390/pr11102815

- Hubach, T.; Pillath, M.; Knaup, C.; Schlüter, S.; Held, C.
Li+ Separation from Multi-Ionic Mixtures by Nanofiltration Membranes: Experiments and Modeling.
Modelling 2023, 4 (3), 408–425.
https://doi.org/10.3390/modelling4030024

- Fischer, F.; Peveling, S.; Kühl, H.-D.
Simulation and Stability Analysis of a Thermocompressor Cascade with Overdriven Free Displacers.
Thermal science and engineering progress 2023, 44.
https://doi.org/10.1016/j.tsep.2023.102037

- Zäh, M.; Brandenbusch, C.; Winter, G.; Sadowski, G.
Predicting the Amorphous-Phase Composition during Lyophilization.
International journal of pharmaceutics 2023, 636.
https://doi.org/10.1016/j.ijpharm.2023.122836

- Ostermeier, L.; Ascani, M.; Gajardo Parra, N. F.; Sadowski, G.; Held, C.; Winter, R.
Leveraging Liquid-Liquid Phase Separation and Volume Modulation to Regulate the Enzymatic Activity of Formate Dehydrogenase.
Biophysical chemistry 2023, 304.
https://doi.org/10.1016/j.bpc.2023.107128

- Held, C.; Liang, X.
100 Years from the Debye-Hückel Theory and Beyond.
Fluid phase equilibria; Elsevier: Amsterdam, 2023; Vol. 575.
https://doi.org/10.1016/j.fluid.2023.113931

- Aravena, P.; Cea-Klapp, E.; Gajardo Parra, N. F.; Held, C.; Garrido, J. M.; Canales, R. I.
Effect of Water and Hydrogen Bond Acceptor on the Density and Viscosity of Glycol-Based Eutectic Solvents.
Journal of molecular liquids 2023, 389.
https://doi.org/10.1016/j.molliq.2023.122856

- Pyka, T.; Ressemann, A.; Held, C.; Schembecker, G.; Repke, J.-U.
Impact of Vapor Bypasses on Separation Performance of Rotating Packed Beds in Distillation.
Industrial & engineering chemistry research 2023, 62 (33), 13274–13279.
https://doi.org/10.1021/acs.iecr.3c01947

- Meneses, L.; Gajardo Parra, N. F.; Cea-Klapp, E.; Garrido, J. M.; Held, C.; Duarte, A. R.; Paiva, A.
Improving the Activity of Horseradish Peroxidase in Betaine-Based Natural Deep Eutectic Systems.
RSC sustainability 2023, 1 (4), 886–897.
https://doi.org/10.1039/d2su00127f

- Arroyo-Avirama, A. F.; Carreño-Guzmán, S.; Lorenzo-Llanes, J.; Gajardo Parra, N. F.; Santiago, R.; Held, C.; Palomar, J.; Canales, R. I.
In Situ Product Recovery of β-Ionone from a Fermentation Broth: Computational Solvent Selection and Process Design of Its Extraction and Purification.
ACS sustainable chemistry & engineering 2023, 11 (24), 9065–9076.
https://doi.org/10.1021/acssuschemeng.3c01739

- Martinez, F.; Held, C.; Siepmann, J. I.
Introducing JCED Associate Editor Fleming Martinez and Topic Editor Christoph Held - Some Remarks on Reporting on the Solubility of Organic Compounds and of Electrolytes.
Journal of chemical & engineering data; ACS Publ.: Washington, DC, 2023; 68, 1265–1266.
https://doi.org/10.1021/acs.jced.3c00278

- Schick, D.; Arrad, M.; Sadowski, G.; Figiel, P.; Held, C.
Modeling the Temperature-Dependent Solubility of Salts in Organic Solvents.
Fluid phase equilibria 2023, 572.
https://doi.org/10.1016/j.fluid.2023.113828

- Pyka, T.; Brunert, M.; Koop, J.; Bieberle, A.; Held, C.; Schembecker, G.
Novel Liquid Distributor Concept for Rotating Packed Beds.
Industrial & engineering chemistry research 2023, 62 (14), 5984–5994.
https://doi.org/10.1021/acs.iecr.3c00248

- Schick, D.; Bierhaus, L.; Strangmann, A.; Figiel, P.; Sadowski, G.; Held, C.
Predicting CO_2 Solubility in Aqueous and Organic Electrolyte Solutions with EPC-SAFT Advanced.
Fluid phase equilibria 2023, 567.
https://doi.org/10.1016/j.fluid.2022.113714

- Delgado, J.; Vásquez Salcedo, W. N.; Devouge-Boyer, C.; Hebert, J.-P.; Legros, J.; Renou, B.; Held, C.; Grenman, H.; Leveneur, S.
Reaction Enthalpies for the Hydrogenation of Alkyl Levulinates and Levulinic Acid on Ru/C– Influence of Experimental Conditions and Alkyl Chain Length.
Process safety and environmental protection 2023, 171, 289–298.
https://doi.org/10.1016/j.psep.2023.01.025

- Espinoza-Cartagena, F.; Ormazábal-Latorre, S.; Pazo-Carballo, C.; Gajardo Parra, N. F.; Núñez, G. A.; Garrido, J. M.; Cea-Klapp, E.; Santiago, R.; Held, C.; Canales, R. I.
Separation of Isoeugenol from Methylcyclohexane as a Model Mixture of Biojet Fuel Purification: Solvent Selection and Liquid–Liquid Equilibrium.
Industrial & engineering chemistry research 2023, 62 (30), 12006–12020.
https://doi.org/10.1021/acs.iecr.3c01440

- Koop, J.; Bera, N.; Quickert, E.; Schmitt, M.; Schlüter, M.; Held, C.; Schembecker, G.
Separation of Volatile Organic Compounds from Viscous Liquids with RPB Technology.
Industrial & engineering chemistry research 2023, 62 (334), 13637–13645.
https://doi.org/10.1021/acs.iecr.3c01597

- Cea-Klapp, E.; Arroyo-Avirama, A. F.; Ormazábal-Latorre, S.; Gajardo-Parra, N. F.; Gajardo Parra, N. F.; Pazo-Carballo, C.; Quinteros-Lama, H.; Marzialetti, T.; Held, C.; Canales, R. I.; Garrido, J. M.
Separation of Furfuryl Alcohol from Water Using Hydrophobic Deep Eutectic Solvents.
Journal of molecular liquids 2023, 384.
https://doi.org/10.1016/j.molliq.2023.122232

- Tsurko, E. N.; Held, C.; Kunz, W.
Thermodynamic Modeling of Aqueous Guanidinium Chloride/Sodium l-Aspartate (Na-l-Asp) Mixtures.
Journal of solution chemistry 2023, 52 (10), 1157–1175.
https://doi.org/10.1007/s10953-023-01306-y

- Chen, Q.; Weng, J.; Sadowski, G.; Ji, Y.
Influence Mechanism of Polymeric Excipients on Drug Crystallization: Experimental Investigation and Chemical Potential Gradient Model Analysis and Prediction.
Crystal growth & design 2023, 23 (5), 3862–3872.
https://doi.org/10.1021/acs.cgd.3c00314

- Ge, K.; Paus, R.; Penner, V.; Sadowski, G.; Ji, Y.
A Novel Theoretical Strategy for Predicting Dissolution Kinetics and Mechanisms of Pharmaceuticals in Complex Biorelevant Media.
International journal of pharmaceutics 2023, 648.
https://doi.org/10.1016/j.ijpharm.2023.123594

- Wolbert, F.; Luebbert, C.; Sadowski, G.
The Shelf Life of ASDs: 2. Predicting the Shelf Life at Storage Conditions.
International journal of pharmaceutics: X 2023, 6.
https://doi.org/10.1016/j.ijpx.2023.100207

- Kloc, A. P.; Danzer, A.; Sadowski, G.
Solubility of Naproxen and Indomethacin in Supercritical Carbon Dioxide/Ethyl Acetate Mixtures.
The journal of supercritical fluids 2023, 200.
https://doi.org/10.1016/j.supflu.2023.105990

- Pyka, T.; Backhaus, V.; Held, C.; Schembecker, G.
Impact of Number of Rotors in Rotating Packed Beds on Separation Performance in Distillation.
Industrial & engineering chemistry research 2023, 62 (46), 19855–19861.
https://doi.org/10.1021/acs.iecr.3c03173

- Lingen, T. van; Bragoni, V.; Dyga, M.; Exner, B.; Schick, D.; Held, C.; Sadowski, G.; Gooßen, L. J.
Salzabfall-freie Carboxylierung von Acetylen: grüne Synthese von C4-Chemikalien durch einen CO_2-Druck-induzierten Aciditätsswitch.
Angewandte Chemie 2023, 135 (27).
https://doi.org/10.1002/ange.202303882

2022

- Sauer, J.; Kühl, H.-D.
Performance Improvements in Stirling Cycle Machines by a Modified Appendix Gap Geometry.
International journal of energy research 2022, 46 (2), 1180–1197.
https://doi.org/10.1002/er.7237

- Wolbert, F.; Fahrig, I.-K.; Gottschalk, T.; Lübbert, C.; Thommes, M.; Sadowski, G.
Factors Influencing the Crystallization-Onset Time of Metastable ASDs.
Pharmaceutics 2022, 14 (2).
https://doi.org/10.3390/pharmaceutics14020269

- Chua, Y. Z.; Do, H. T. J.; Kumar, A.; Hallermann, M.; Zaitsau, D.; Schick, C.; Held, C.
The Melting Properties of D-α-Glucose, D-β-Fructose, D-Sucrose, D-α-Galactose, and D-α-Xylose and Their Solubility in Water: A Revision.
Food biophysics 2022, 17 (2), 181–197.
https://doi.org/10.1007/s11483-021-09707-6

- Borrmann, D.; Danzer, A.; Sadowski, G.
Water Sorption in Glassy Polyvinylpyrrolidone-Based Polymers.
Membranes 2022, 12 (4).
https://doi.org/10.3390/membranes12040434

- Borrmann, D.; Danzer, A.; Sadowski, G.
Measuring and Modeling Water Sorption in Amorphous Indomethacin and Ritonavir.
Molecular pharmaceutics 2022, 19 (3), 998–1007.
https://doi.org/10.1021/acs.molpharmaceut.1c00984

- Kroll, P.; Benke, J.; Enders, S.; Brandenbusch, C.; Sadowski, G.
Influence of Temperature and Concentration on the Self-Assembly of Nonionic CiEj Surfactants: A Light Scattering Study.
ACS omega 2022, 7 (8), 7057–7065.
https://doi.org/10.1021/acsomega.1c06766

- Ascani, M.; Sadowski, G.; Held, C.
Calculation of Multiphase Equilibria Containing Mixed Solvents and Mixed Electrolytes: General Formulation and Case Studies.
Journal of chemical & engineering data 2022, 67 (8), 1972–1984.
https://doi.org/10.1021/acs.jced.1c00866

- Pabsch, D.; Figiel, P.; Sadowski, G.; Held, C.
Solubility of Electrolytes in Organic Solvents: Solvent-Specific Effects and Ion-Specific Effects.
Journal of chemical & engineering data 2022, 67 (9), 2706–2718.
https://doi.org/10.1021/acs.jced.2c00203

- Ascani, M.; Pabsch, D.; Klinksiek, M.; Gajardo-Parra, N.; Sadowski, G.; Held, C.
Prediction of PH in Multiphase Multicomponent Systems with EPC-SAFT Advanced.
Chemical communications 2022, 58 (60), 8436–8439.
https://doi.org/10.1039/d2cc02943j

- Krummnow, A.; Danzer, A.; Voges, K.; Dohrn, S.; Kyeremateng, S. O.; Degenhardt, M.; Sadowski, G.
Explaining the Release Mechanism of Ritonavir/PVPVA Amorphous Solid Dispersions.
Pharmaceutics 2022, 14 (9).
https://doi.org/10.3390/pharmaceutics14091904

- Borrmann, D.; Danzer, A.; Sadowski, G.
Anomalous Water-Sorption Kinetics in ASDs.
Pharmaceutics 2022, 14 (9).
https://doi.org/10.3390/pharmaceutics14091897

- Kroll, P.; Sadowski, G.; Brandenbusch, C.
Solubilization of Aldehydes and Amines in Aqueous CiEj Surfactant Aggregates: Solubilization Capacity and Aggregate Properties.
Langmuir 2022, 38 (32), 10022–10031.
https://doi.org/10.1021/acs.langmuir.2c01463

- Wolbert, F.; Nikoleit, K.; Steinbrink, M.; Lübbert, C.; Sadowski, G.
The Shelf Life of ASDs: 1. Measuring the Crystallization Kinetics at Humid Conditions.
Molecular pharmaceutics 2022, 19 (7), 2483–2494.
https://doi.org/10.1021/acs.molpharmaceut.2c00188

- Borrmann, D.; Danzer, A.; Sadowski, G.
Predicting the Water Sorption in ASDs.
Pharmaceutics 2022, 14 (6).
https://doi.org/10.3390/pharmaceutics14061181

- Huxoll, F.; Kampwerth, A.; Seidensticker, T.; Vogt, D.; Sadowski, G.
Predicting Solvent Effects on Homogeneity and Kinetics of the Hydroaminomethylation: A Thermodynamic Approach Using PC-SAFT.
Industrial & engineering chemistry research 2022, 61 (5), 2323–2332.
https://doi.org/10.1021/acs.iecr.1c03891

- Siepmann, J. I.; Gardas, R.; Kofke, D. A.; Nieto de Castro, C.; Paulechka, E.; Pini, R.; Sadowski, G.; Schwarz, C. E.
The Journal of Chemical & Engineering Data: Introduction of Topical Sections and Updates from the Editorial Team.
Journal of chemical & engineering data 2022, 67 (1), 1–2.
https://doi.org/10.1021/acs.jced.1c00969

- Gajardo-Parra, N. F.; Akrofi-Mantey, H.; Ascani, M.; Cea-Klapp, E.; Garrido, J. M.; Sadowski, G.; Held, C.
Osmolyte Effect on Enzymatic Stability and Reaction Equilibrium of Formate Dehydrogenase.
Physical chemistry, chemical physics 2022, 24 (45), 27930–27939.
https://doi.org/10.1039/d2cp04011e

- Loll, R.; Runge, L.; Koop, J.; Held, C.; Schembecker, G.
Zickzack Packings for Deaeration in Rotating Packed Beds: Improved Rotor Design to Counter Bypass Flows.
Industrial & engineering chemistry research 2022, 61 (32), 11934–11946.
https://doi.org/10.1021/acs.iecr.2c01443

- Arroyo-Avirama, A. F.; Gajardo-Parra, N. F.; Espinoza-Carmona, V.; Garrido, J. M.; Held, C.; Canales, R. I.
Solvent Selection for the Extraction of 2-Phenylethanol from Aqueous Phases: Density and Viscosity Studies.
Journal of chemical & engineering data 2022, 67 (8), 1893–1904.
https://doi.org/10.1021/acs.jced.1c00975

- Arroyo-Avirama, A. F.; Ormazábal-Latorre, S.; Jogi, R.; Gajardo-Parra, N. F.; Pazo-Carballo, C.; Ascani, M.; Virtanen, P.; Garrido, J. M.; Held, C.; Mäki-Arvela, P.; Canales, R. I.
Improving the Separation of Guaiacol from N-Hexane by Adding Choline Chloride to Glycol Extracting Agents.
Journal of molecular liquids 2022, 355.
https://doi.org/10.1016/j.molliq.2022.118936

- Baco, S.; Klinksiek, M.; Ismail Bedawi Zakaria, R.; Antonia Garcia-Hernandez, E.; Mignot, M.; Legros, J.; Held, C.; Casson Moreno, V.; Leveneur, S.
Solvent Effect Investigation on the Acid-Catalyzed Esterification of Levulinic Acid by Ethanol Aided by a Linear Solvation Energy Relationship.
Chemical engineering science 2022, 260.
https://doi.org/10.1016/j.ces.2022.117928

- Cea-Klapp, E.; Gajardo-Parra, N.; Aravena, P.; Quinteros-Lama, H.; Held, C.; Canales, R. I.; Garrido, J. M.
Interfacial Properties of Deep Eutectic Solvents by Density Gradient Theory.
Industrial & engineering chemistry research 2022, 61 (6), 2580–2591.
https://doi.org/10.1021/acs.iecr.1c03817

- Delgado, J.; Vasquez Salcedo, W. N.; Bronzetti, G.; Casson Moreno, V.; Mignot, M.; Legros, J.; Held, C.; Grénman, H.; Leveneur, S.
Kinetic Model Assessment for the Synthesis of γ-Valerolactone from n-Butyl Levulinate and Levulinic Acid Hydrogenation over the Synergy Effect of Dual Catalysts Ru/C and Amberlite IR-120.
Chemical engineering journal 2022, 430.
https://doi.org/10.1016/j.cej.2021.133053

- Janssen, L.; Sadowski, G.; Brandenbusch, C.
Long-Term Stable Bioprocess-Derived Pickering-Type Emulsions: Identification of Key Parameters for Emulsion Stability Based on Cell Interaction at Interface.
Chemical engineering science 2022, 264.
https://doi.org/10.1016/j.ces.2022.118164

- Nolte, L.; Brandenbusch, C.
Monitoring and Investigating Reactive Extraction of (Di–)Carboxylic Acids Using Online FTIR – Part II: Reaction Equilibria, Reaction Kinetics and Competition within the Complex Formation between Itaconic Acid and Several Amine Extractants.
Journal of molecular liquids 2022, 366.
https://doi.org/10.1016/j.molliq.2022.120223

- Stolzke, T.; Krieg, F.; Peng, T.; Zhang, H.; Häusler, O.; Brandenbusch, C.
Hydroxylpropyl-β-Cyclodextrin as Potential Excipient to Prevent Stress-Induced Aggregation in Liquid Protein Formulations.
Molecules 2022, 27 (16).
https://doi.org/10.3390/molecules27165094

- Stolzke, T.; Brandenbusch, C.
Simplified Choice of Suitable Excipients within Biologics Formulation Design Using Protein-Protein Interaction- and Water Activity-Maps.
European journal of pharmaceutics and biopharmaceutics 2022, 176, 153–167.
https://doi.org/10.1016/j.ejpb.2022.05.017

- Nolte, L.; Nowaczyk, M.; Brandenbusch, C.
Monitoring and Investigating Reactive Extraction of (Di–)Carboxylic Acids Using Online FTIR – Part I: Characterization of the Complex Formed between Itaconic Acid and Tri-n-Octylamine.
Journal of molecular liquids 2022, 352.
https://doi.org/10.1016/j.molliq.2022.118721

- Aliyeva, M.; Brandão, P.; Gomes, J. R. B.; Coutinho, J. A. P.; Held, C.; Ferreira, O.; Pinho, S. P.
Salt Effects on the Solubility of Aromatic and Dicarboxylic Amino Acids in Water.
The journal of chemical thermodynamics 2022, 177.
https://doi.org/10.1016/j.jct.2022.106929

- Gajardo Parra, N. F.; Meneses, L.; Duarte, A. R. C.; Paiva, A.; Held, C.
Assessing the Influence of Betaine-Based Natural Deep Eutectic Systems on Horseradish Peroxidase.
ACS sustainable chemistry & engineering 2022, 10 (38), 12873–12881.
https://doi.org/10.1021/acssuschemeng.2c04045

- Pyka, T.; Koop, J.; Held, C.; Schembecker, G.
Dry Pressure Drop in a Two-Rotor Rotating Packed Bed.
Industrial & engineering chemistry research 2022, 61 (46), 17156–17165.
https://doi.org/10.1021/acs.iecr.2c02500

- Schick, D.; Lindfeld, J.; Schwalm, J.; Strangmann, A.; Figiel, P.; Sadowski, G.; Held, C.
Influence of Solvent and Salt on Kinetics and Equilibrium of Esterification Reactions.
Chemical engineering science 2022, 263.
https://doi.org/10.1016/j.ces.2022.118046

- Keppler, M.; Moser, S.; Jessen, H. J.; Held, C.; Andexer, J. N.
Make or Break: The Thermodynamic Equilibrium of Polyphosphate Kinase-Catalysed Reactions.
Beilstein journal of organic chemistry 2022, 18, 1278–1288.
https://doi.org/10.3762/bjoc.18.134

- Ge, K.; Paus, R.; Penner, V.; Sadowski, G.; Ji, Y.
Theoretical Modeling and Prediction of Biorelevant Solubility of Poorly Soluble Pharmaceuticals.
Chemical engineering journal 2022, 444.
https://doi.org/10.1016/j.cej.2022.136678

- Schlüter, S.; Huxoll, F.; Grenningloh, K.; Sadowski, G.; Petzold, M.; Böhm, L.; Kraume, M.; Skiborowski, M.
Unraveling the Influence of Dissolved Gases on Permeate Flux in Organic Solvent Nanofiltration – Experimental Analysis.
Separation and purification technology 2022, 295.
https://doi.org/10.1016/j.seppur.2022.121265

- Gottschalk, T.; Grönniger, B.; Ludwig, E.; Wolbert, F.; Feuerbach, T.; Sadowski, G.; Thommes, M.
Influence of Process Temperature and Residence Time on the Manufacturing of Amorphous Solid Dispersions in Hot Melt Extrusion.
Pharmaceutical development and technology an official journal of the American Association of Pharmaceutical Scientists 2022, 27 (3), 313–318.
https://doi.org/10.1080/10837450.2022.2051549

2021

- Bülow, M.; Greive, M.; Zaitsau, D. H.; Verevkin, S. P.; Held, C.
Extremely Low Vapor-pressure Data as Access to PCγ SAFT Parameter Estimation for Ionic Liquids and Modeling of Precursor Solubility in Ionic Liquids.
ChemistryOpen 2021, 10 (2), 216–226.
https://doi.org/10.1002/open.202000258

- Sleziona, D.; Mattusch, A.; Schaldach, G.; Ely, D. R.; Sadowski, G.; Thommes, M.
Determination of Inherent Dissolution Performance of Drug Substances.
Pharmaceutics 2021, 13 (2), 146.
https://doi.org/10.17877/de290r-21914

- Greinert, T.; Vogel, K.; Maskow, T.; Held, C.
New Thermodynamic Activity-Based Approach Allows Predicting the Feasibility of Glycolysis.
Scientific reports 2021, 11.
https://doi.org/10.1038/s41598-021-85594-8

- Ascani, M.; Held, C.
Prediction of Salting-out in Liquid-Liquid Two-Phase Systems with EPC-SAFT: Effect of the Born Term and of a Concentration-Dependent Dielectric Constant.
Zeitschrift für anorganische und allgemeine Chemie 2021, 647 (12), 1305–1314.
https://doi.org/10.1002/zaac.202100032

- Do, H. T.; Franke, P.; Volpert, S.; Klinksiek, M.; Thome, M.; Held, C.
Measurement and Modelling Solubility of Amino Acids and Peptides in Aqueous 2-Propanol Solutions.
Physical chemistry, chemical physics 2021, 23 (18), 10852–10863.
https://doi.org/10.1039/d1cp00005e

- Huxoll, F.; Jameel, F.; Bianga, J.; Seidensticker, T.; Stein, M.; Sadowski, G.; Vogt, D.
Solvent Selection in Homogeneous Catalysis - Optimization of Kinetics and Reaction Performance.
ACS catalysis 2021, 11 (2), 590–594.
https://doi.org/10.1021/acscatal.0c04431

- Jaworek, M.; Gajardo-Parra, N. F.; Sadowski, G.; Winter, R.; Held, C.
Boosting the Kinetic Efficiency of Formate Dehydrogenase by Combining the Effects of Temperature, High Pressure and Co-Solvent Mixtures.
Colloids and surfaces / B B, Biointerfaces 2021, 208.
https://doi.org/10.1016/j.colsurfb.2021.112127

- Gajardo-Parra, N. F.; Do, H. T. J.; Yang, M.; Pérez-Correa, J. R.; Garrido, J. M.; Sadowski, G.; Held, C.; Canales, R. I.
Impact of Deep Eutectic Solvents and Their Constituents on the Aqueous Solubility of Phloroglucinol Dihydrate.
Journal of molecular liquids 2021, 344.
https://doi.org/10.1016/j.molliq.2021.117932

- Huxoll, F.; Schlüter, S.; Budde, R.; Skiborowski, M.; Petzold, M.; Böhm, L.; Kraume, M.; Sadowski, G.
Phase Equilibria for the Hydroaminomethylation of 1-Decene.
Journal of chemical & engineering data 2021, 66 (12), 4484–4495.
https://doi.org/10.1021/acs.jced.1c00561

- Borrmann, D.; Danzer, A.; Sadowski, G.
Generalized Diffusion–Relaxation Model for Solvent Sorption in Polymers.
Industrial & engineering chemistry research 2021, 60 (43), 15766–15781.
https://doi.org/10.1021/acs.iecr.1c02359

- Veith, H.; Lübbert, C.; Rodríguez-Hornedo, N.; Sadowski, G.
Co-Crystal Screening by Vapor Sorption of Organic Solvents.
Crystal growth & design 2021, 21 (8), 4445–4455.
https://doi.org/10.1021/acs.cgd.1c00355

- Huxoll, F.; Heyng, M.; Andreeva, I. V.; Verevkin, S. P.; Sadowski, G.
Thermodynamic Properties of Biogenic Amines and Their Solutions.
Journal of chemical & engineering data 2021, 66 (7), 2822–2831.
https://doi.org/10.1021/acs.jced.1c00202

- Jastram, A.; Lindner, T.; Lübbert, C.; Sadowski, G.; Kragl, U.
Swelling and Diffusion in Polymerized Ionic Liquids-Based Hydrogels.
Polymers 2021, 13 (11).
https://doi.org/10.3390/polym13111834

- Veith, H.; Lübbert, C.; Sadowski, G.
Predicting Deliquescence Relative Humidities of Crystals and Crystal Mixtures.
Molecules 2021, 26 (11).
https://doi.org/10.3390/molecules26113176

- Bülow, M. R.; Gerek Ince, N.; Hirohama, S.; Sadowski, G.; Held, C.
Predicting Vapor–Liquid Equilibria for Sour-Gas Absorption in Aqueous Mixtures of Chemical and Physical Solvents or Ionic Liquids with EPC-SAFT.
Industrial & engineering chemistry research 2021, 60 (17), 6327–6336.
https://doi.org/10.1021/acs.iecr.1c00176

- Gardas, R. L.; Kofke, D. A.; Pini, R.; Sadowski, G.; Schwarz, C. E.; Siepmann, J. I.; Wu, J.
Historical Perspective of the Journal of Chemical & Engineering Data's Published Topics, 1956–2020.
Journal of chemical & engineering data 2021, 66 (4), 1555–1556.
https://doi.org/10.1021/acs.jced.1c00193

- Brinkmann, J.; Exner, L.; Verevkin, S. P.; Lübbert, C.; Sadowski, G.
PC-SAFT Modeling of Phase Equilibria Relevant for Lipid-Based Drug Delivery Systems.
Journal of chemical & engineering data 2021, 66 (3), 1280–1289.
https://doi.org/10.1021/acs.jced.0c00912

- Siepmann, J. I.; Gardas, R. L.; Kofke, D. A.; Pini, R.; Sadowski, G.; Schwarz, C. E.; Wu, J.
Journal of Chemical & Engineering Data: Why Change the Cover Page?
Journal of chemical & engineering data; ACS Publ.: Washington, DC, 2021; Vol. 66, pp 859–860.
https://doi.org/10.1021/acs.jced.1c00048

- Sepúlveda-Orellana, B.; Gajardo-Parra, N. F.; Do, H. T.; Pérez-Correa, J. R.; Held, C.; Sadowski, G.; Canales, R. I.
Measurement and PC-SAFT Modeling of the Solubility of Gallic Acid in Aqueous Mixtures of Deep Eutectic Solvents.
Journal of chemical & engineering data 2021, 66 (2), 958–967.
https://doi.org/10.1021/acs.jced.0c00784

- Sosa, A.; Ortega, J.; Fernández, L.; Haarmann, N.; Sadowski, G.
Methodology Based on the Theory of Information to Describe the Representation Ability of the DMC + Alkane Behavior.
Industrial & engineering chemistry research 2021, 60 (2), 1036–1054.
https://doi.org/10.1021/acs.iecr.0c05301

- Siepmann, J. I.; Gardas, R. L.; Kofke, D. A.; Pini, R.; Sadowski, G.; Schwarz, C.; Wu, J.
Journal of Chemical & Engineering Data: An Update from the Editorial Team.
Journal of chemical & engineering data 2021, 66 (1), 1–2.
https://doi.org/10.1021/acs.jced.0c01080

- Kühl, H.-D.; Sauer, J.
Appendix Gap Losses in Stirling Engines: Review of Recent Findings.
19th International Stirling Engine Conference (ISEC 2021); EDP Sciences: London, 2021; Vol. 313.
https://doi.org/10.1051/e3sconf/202131303001

- Fischer, F.; Kühl, H.-D.
Generation of Compressed Air by Cascaded Thermocompressors – Project Status.
19th International Stirling Engine Conference (ISEC 2021); EDP Sciences: London, 2021; Vol. 313.
https://doi.org/10.1051/e3sconf/202131304003

- Dohrn, S.; Rawal, P.; Lübbert, C.; Lehmkemper, K.; Kyeremateng, S. O.; Degenhardt, M.; Sadowski, G.
Predicting Process Design Spaces for Spray Drying Amorphous Solid Dispersions.
International journal of pharmaceutics: X 2021, 3.
https://doi.org/10.1016/j.ijpx.2021.100072

- Bueno, A.; Lübbert, C.; Enders, S.; Sadowski, G.; Smirnova, I.
Production of Polylactic Acid Aerogels via Phase Separation and Supercritical CO2 Drying: Thermodynamic Analysis of the Gelation and Drying Process.
Journal of materials science 2021, 56 (34), 18926–18945.
https://doi.org/10.1007/s10853-021-06501-0

- Ji, Y.; Hao, D.; Lübbert, C.; Sadowski, G.
Insights into Influence Mechanism of Polymeric Excipients on Dissolution of Drug Formulations: A Molecular Interaction-based Theoretical Model Analysis and Prediction.
AIChE journal / American Institute of Chemical Engineers 2021, 67 (11).
https://doi.org/10.1002/aic.17372

- Dohrn, S.; Lübbert, C.; Lehmkemper, K.; Kyeremateng, S. O.; Degenhardt, M.; Sadowski, G.
Solvent Mixtures in Pharmaceutical Development: Maximizing the API Solubility and Avoiding Phase Separation.
Fluid phase equilibria 2021, 548.
https://doi.org/10.1016/j.fluid.2021.113200

- Veith, H.; Zaeh, M.; Lübbert, C.; Rodríguez-Hornedo, N.; Sadowski, G.
Stability of Pharmaceutical Co-Crystals at Humid Conditions Can Be Predicted.
Pharmaceutics 2021, 13 (3).
https://doi.org/10.3390/pharmaceutics13030433

- Brinkmann, J.; Becker, I.; Kroll, P.; Lübbert, C.; Sadowski, G.
Predicting the API Partitioning between Lipid-Based Drug Delivery Systems and Water.
International Journal of Pharmaceutics 2021, 595.
https://doi.org/10.1016/j.ijpharm.2021.120266

- Prell, C.; Busche, T.; Rückert, C.; Nolte, L.; Brandenbusch, C.; Wendisch, V. F.
Adaptive Laboratory Evolution Accelerated Glutarate Production by Corynebacterium Glutamicum.
Microbial cell factories 2021, 20.
https://doi.org/10.1186/s12934-021-01586-3

- Wessner, M.; Meier, M.; Bommarius, B.; Bommarius, A. S.; Brandenbusch, C.
Intensifying Aqueous Two-Phase Extraction by Adding Decisive Excipients for Enhancement of Stability and Solubility of Biomolecules.
Chemical engineering and processing 2021, 167.
https://doi.org/10.1016/j.cep.2021.108534

- Do, H. T. J.; Chua, Y. Z.; Habicht, J.; Klinksiek, M.; Volpert, S.; Hallermann, M.; Thome, M.; Pabsch, D.; Schick, D.; Zaitsau, D.; Schick, C.; Held, C.
Melting Properties of Peptides and Their Solubility in Water. Part 2: Di- and Tripeptides Based on Glycine, Alanine, Leucine, Proline, and Serine.
Industrial & engineering chemistry research 2021, 60 (12), 4693–4704.
https://doi.org/10.1021/acs.iecr.0c05652

- Sun, Y.; Zuo, Z.; Shen, G.; Held, C.; Lu, X.; Ji, X.
Modeling Interfacial Properties of Ionic Liquids with EPC-SAFT Combined with Density Gradient Theory.
Fluid phase equilibria 2021, 536.
https://doi.org/10.1016/j.fluid.2021.112984

- Do, H. T. J.; Chakrabarty, S.; Held, C.
Modeling Solubility of Amino Acids and Peptides in Water and in Water+2-Propanol Mixtures: PC-SAFT vs. GE Models.
Fluid phase equilibria 2021, 542–543.
https://doi.org/10.1016/j.fluid.2021.113087

- Roda, A.; Santos, F.; Chua, Y. Z.; Kumar, A.; Do, H. T. J.; Paiva, A.; Duarte, A. R. C.; Held, C.
Unravelling the Nature of Citric Acid:l-Arginine:Water Mixtures: The Bifunctional Role of Water.
Physical chemistry, chemical physics 2021, 23 (2), 1706–1717.
https://doi.org/10.1039/d0cp04992a

- Bülow, M. R.; Ascani, M.; Held, C.
EPC-SAFT Advanced - Part I: Physical Meaning of Including a Concentration-Dependent Dielectric Constant in the Born Term and in the Debye-Hückel Theory.
Fluid phase equilibria 2021, 535.
https://doi.org/10.1016/j.fluid.2021.112967

- Bülow, M. R.; Ascani, M.; Held, C.
EPC-SAFT Advanced – Part II: Application to Salt Solubility in Ionic and Organic Solvents and the Impact of Ion Pairing.
Fluid phase equilibria 2021, 537.
https://doi.org/10.1016/j.fluid.2021.112989

- Wysoczanska, K.; Nierhauve, B.; Sadowski, G.; Macedo, E. A.; Held, C.
Solubility of DNP-Amino Acids and Their Partitioning in Biodegradable ATPS: Experimental and EPC-SAFT Modeling.
Fluid phase equilibria 2021, 527.
https://doi.org/10.1016/j.fluid.2020.112830

Transport Processes (TP)

Publications

2023

Publications Alba Diéguez Alonso

- A. Dieguez-Alonso, T.-L.E. Vu-Han, H. Almuina-Villar, J.J. Rico Fuentes, L. Hilfert, A. Dernbecher, J.M. de la Rosa, F. Behrendt
  Tailored production and application of biochar for tar removal
  Fuel 2023, 348, 128306.
  https://doi.org/10.1016/j.fuel.2023.128306

- D.D. Attanayake, F. Sewerin, S. Kulkarni, A. Dernbecher, A. Dieguez-Alonso, B. van Wachem
  Review of modelling of pyrolysis processes with CFD-DEM
  Flow, Turbulence and Combustion 2023, 111 (2), 355-408.
  https://doi.org/10.1007/s10494-023-00436-z

- J.J. Rico, R. Pérez-Orozco, J. Porteiro, D. Patiño
  Effect of air staging and porous inert material on the emission of volatile organic compounds in solid biomass combustion
  Fuel 2023, 351, 128907.
  https://doi.org/10.1016/j.fuel.2023.128907

- G.F. García Sánchez, J.L. Chacón Velasco, D.A. Fuentes Díaz, Y.J. Rueda-Ordóñez, D. Patiño, J.J. Rico, J.R. Martínez Morales
  Biomass Combustion Modeling Using OpenFOAM: Development of a Simple Computational Model and Study of the Combustion Performance of Lippia origanoides Bagasse
  Energies 2023, 16(6), 2932.
  https://doi.org/10.3390/en16062932

2022

- L. Wang, M. N. Olsen, C. Moni, A. Dieguez-Alonso, J. M. de la Rosa, M. Stenrød, X. Liu, and L. Mao.
  Comparison of properties of biochar produced from different types of lignocellulosic biomass by slow pyrolysis at 600 °C
  Applications in Energy and Combustion Science 2022, 12, 100090.
  https://doi.org/10.1016/j.jaecs.2022.100090

- A. Anca-Couce, L. von Berg, G. Pongratz, R. Scharler, C. Hochenauer, M. Geusebroek, J. Kuipers, C. Mourao Vilela, T. Kraia, K. Panopoulos, I. Funcia, A. Dieguez-Alonso, H. Almuina-Villar, T. Tsiotsias, N. Kienzl, and S. Martini.
  Assessment of measurement methods to characterize the producer gas from biomass gasification with steam in a fluidized bed
  Biomass and Bioenergy 2022, 163, 106527.
  https://doi.org/10.1016/j.biombioe.2022.106527

- A. Dernbecher and A. Dieguez-Alonso.
  Advanced porous particle model in biomass pyrolysis
  Chemical Engineering Transactions 2022, 92, 685–690, 2022.
  https://doi.org/10.3303/CET2292115

- S. M. Weldon, B. van der Veen, E. Farkas, N. Kocatürk-Schumacher, A. Dieguez-Alonso, A. Budai, and D. P. Rasse
  A re-analysis of NH_4+ sorption on biochar: have expectation been been too high?
  Chemosphere 2022, 301, 134662, 2022.
  https://doi.org/10.1016/j.chemosphere.2022.134662

- H. Khodaei, C. Olson, D. Patiño, J.J. Rico, Q. Jin, A. Boateng
  Multi-objective utilization of wood waste recycled from construction and demolition (C&D): Products and characterization
  Waste Maganement 2022, 149, 228-238.
  https://doi.org/10.1016/j.wasman.2022.06.021

- J.J. Rico, R. Pérez-Orozco, D. Patiño Vilas, J. Porteiro,
  TG/DSC and kinetic parametrization of the combustion of agricultural and forestry residues
  Biomass and Bioenergy 2022, 162, 106485.
  https://doi.org/10.1016/j.biombioe.2022.106485

2021

- J.L. Míguez, J. Porteiro, F. Behrendt, D. Blanco, D. Patiño, and A. Dieguez-Alonso.
  Review of the use of additives to mitigate operational problems associated with the combustion of biomass with high content in ash-forming species
  Renewable and Sustainable Energy Reviews 2021, 141, 110502.
  https://doi.org/10.1016/j.rser.2020.110502

- P. Maziarka, C. Wurzer, P. J. Arauzo, A. Dieguez-Alonso, O. Mašek, and F. Ronsse.
  Do you BET on routine? The reliability of N2 physisorption for the quantitative assessment of biochar's surface area
  Chemical Engineering Journal 2021, 418, 129234.
  https://doi.org/10.1016/j.cej.2021.129234

- A. Dernbecher and A. Dieguez-Alonso.
  Advanced porous particle model in biomass pyrolysis
  Chemical Engineering Transactions 2022, 92, 685–690, 2022.
  https://doi.org/10.3303/CET2292115

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