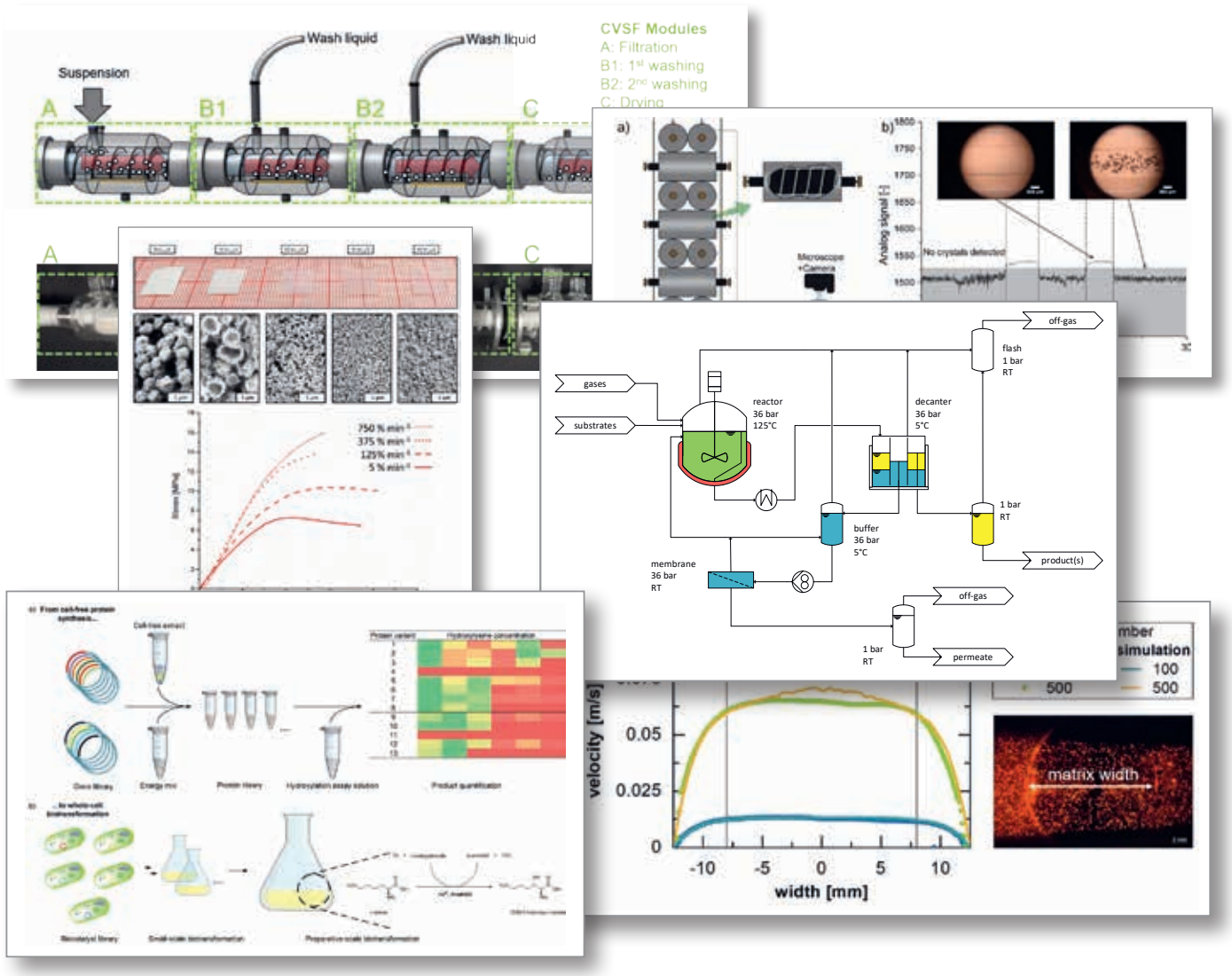
technische universität
dortmund

2021

SCIENTIFIC HIGHLIGHTS

Annual Report

SCIENTIFIC HIGHLIGHTS 2021



Fakultät Bio- und
Chemieingenieurwesen

Content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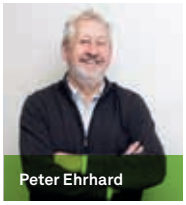
Peter Ehrhard


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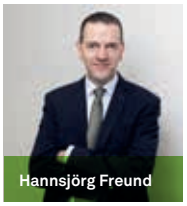
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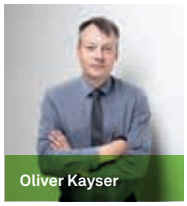
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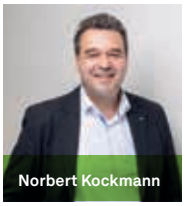
Norbert Kockmann


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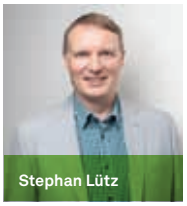
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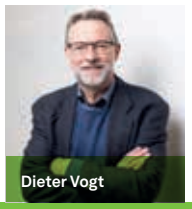
Gerhard Schembecker


Markus Thommes


Jörg C. Tiller


Dieter Vogt

Department of BCI

Preface

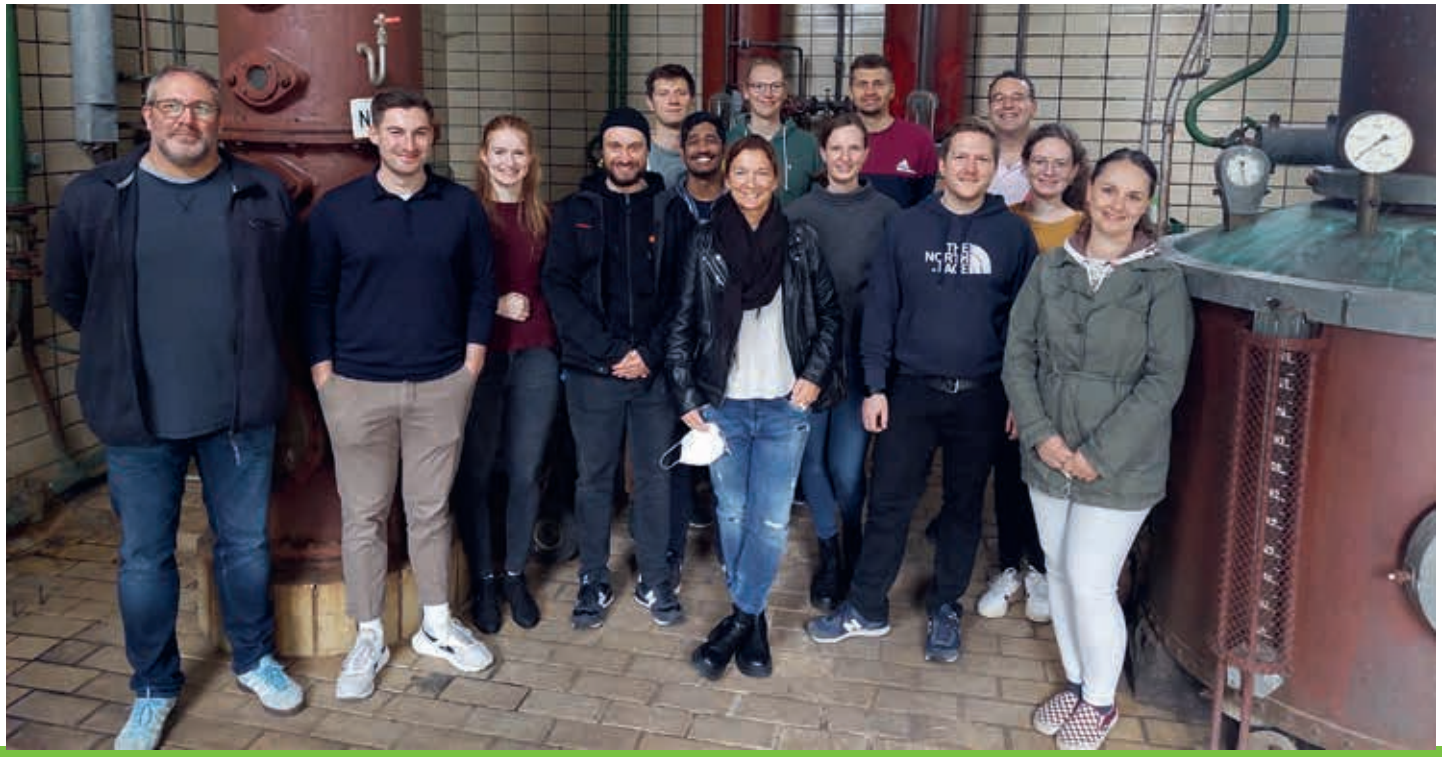
Dear Reader,

I proudly present the Scientific Highlights 2021 of the Department of Bio- and Chemical Engineering of the TU Dortmund to you. We all experienced another challenging year of the pandemic, but were not only able to keep up our teaching, but managed to realize numerous important scientific achievements, which are presented in this publication. These Highlights of engineering and natural sciences are also testament of the creativity of our students, our PhD candidates and our Postdocs. Without their ideas and their engagement almost no scientific work would be possible at a university. Thank you! Further, we welcome two new colleagues in our faculty: Natalie Germann is heading the group of fluid mechanics and Hannsjörg Freund has taken the chair of reaction engineering and catalysis. I am convinced that both will greatly contribute to the scientific achievements of our research efforts.

As always, I encourage the readers of these Scientific Highlights – may they be from academia or industry – to stay or become partners of our research activities, because such partnerships are the cornerstones for even greater achievements in the future.

Enjoy the reading,

Joerg C. Tiller



Equipment Design (AD)

Characterization of a Lab-scale Coiled Tubular Cooling Crystallizer

3D imaging of laminar mixing and diffusion in helically coiled capillaries

Julia Schuler, Norbert Kockmann

Microfluidic devices and capillary reactors, in particular, contribute to process intensification as high surface-to-volume ratios prevail and diffusion lengths are reduced. Secondary flow patterns can be induced by coiling the capillary around a cylinder leading to high selectivity and reaction performance due to improved radial mixing and narrow residence time distribution. To increase the understanding of transport phenomena in helically coiled capillaries micro-computed tomography (CT) is applied as a 3D, non-invasive imaging approach providing high spatial resolutions.

The transport phenomena in helically coiled capillaries were studied by applying X-ray-based micro CT for the visualization of cross-sectional concentration fields (Figure 1). These radial concentration fields emerging due to the dispersion of iodide were directly evaluated. The effect of torsion and curvature on the radial concentration profiles was identified through the variation of the dimensionless Dean number *Dn* and the modified torsion parameter *T**. The iodide concentration was recorded at angular positions of 0°, 360°, and 540° for different total volumetric flow rates and pitches (Figure 2). A T-junction was used to contact pure water and water containing 15 w% potassium iodide (KI) resulting in a parallel flow of both phases. For 3D reconstruction, X-ray projection images of the helically coiled capillary were acquired at different angular positions resulting in a stack of cross-sectional slices after segmentation. The reconstructed CT volume is used to extract the qualitative separation areas between iodide-rich, intermediate, and iodide-poor regions. It was found that an increasing Dean number leads to the formation of a characteristic concentration profile normal to the main flow direction and in consequence, enhanced radial mixing, while at the same time increasing the pitch of the coils reduces radial mixing due to Dean vortices only slightly.

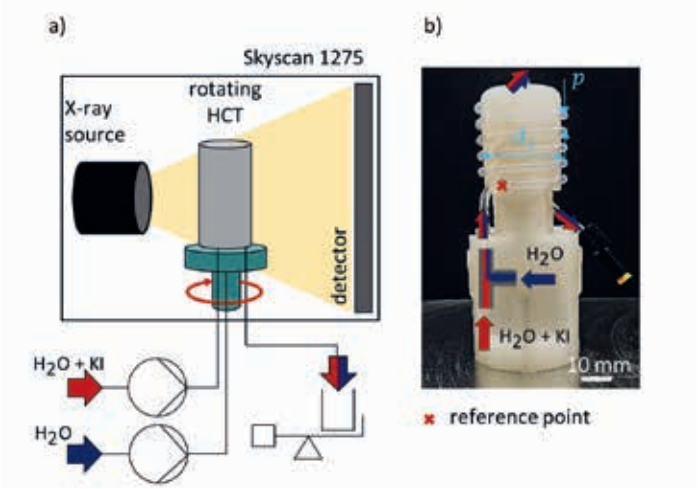


Figure 1: Schematic of the experimental setup. (a) Pure deionized water and deionized water enriched with potassium iodide are contacted in the helically coiled tube, that is mounted into the CT scanner. (b) Photograph of the helically coiled tube and schematic of the liquid-liquid contacting device.

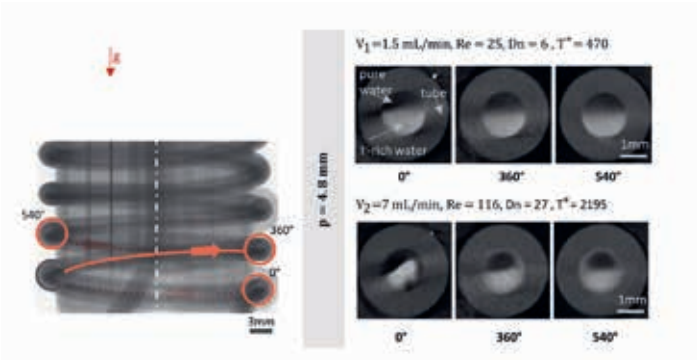


Figure 2: Projection image (1944 x 1382 pixels) for a helically coiled tube with the pitch p = 4.8 mm. The orange line indicates the main flow direction. Related cross-sectional views (180 x 180 voxels) of the capillary with radial concentration field are given on the right. Bright voxels indicate I^--rich liquid, dark voxels indicate pure water. Present forces are emphasized and the experimental conditions are shown in the figure.

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Publications:
[1] J. Schuler, J. Herath, N. Kockmann, J Flow Chem 11(3), 217-222 (2021).

Gas-Liquid Mass Transfer in Microstructured Devices

Investigations on mass transfer intensification and digital image processing

Julia Grühn, Felix Reichmann, Norbert Kockmann

Gas-liquid reactions are of great importance in the chemical and biochemical industry and therefore subject of current research. The mass transfer of a gaseous component into the liquid phase is the rate-limiting step. Micro reactors are characterized by a large specific surface area, which leads to an enhanced heat and mass transfer. A colorimetric method is used in order to visualize and quantify mass transfer during the refinement of two-phase flow using micro nozzles. When investigating mass transfer phenomena within micro reactors the implementation of traditional sensors is a drawback since they disturb the flow. This works presents digital image processing as a suitable tool for investigations on gas-liquid reactions.

A colorimetric method based on the oxygen sensitive dye resazurin is used in order to visualize and quantify mass transfer for slug flow through micro nozzles, bubble deformation (Figure 1), laminar bubble breakup, and turbulent bubble breakup. The gas-liquid mass transfer is quantified for these regimes concerning volumetric mass transfer coefficient k_{la} and benchmarked against mass transport in a straight reference microchannel. Furthermore, two nozzle designs are evaluated. The work presents micro nozzles in combination with millichannels as a great opportunity to enhance gas-liquid mass transfer.

For the evaluation of hydrodynamic phenomena in micro and millichannels digital image processing (DIP) suits very well because it does not disturb the flow due to its non-invasive principle. An already existing DIP method is extended and further optimized for the analysis of bio-catalytic gas-liquid reactions in capillary reactor designs. The new DIP method has been adjusted to new capillary geometries, reaction systems, and colors. Considering mixtures of two different species with different colors, the new method is able to determine the concentration of each specie in this mixture.

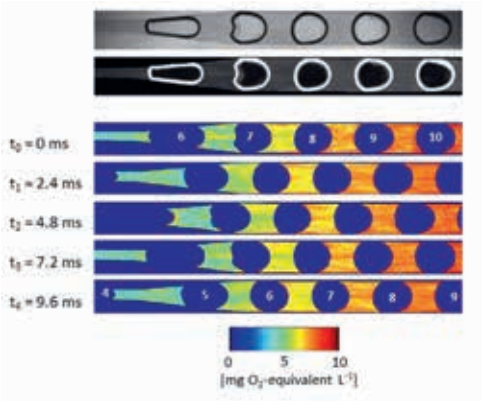

Figure 1: Image series of heat maps for bubble deformation behind a micro nozzle with respective local concentration profiles downstream of the nozzle.

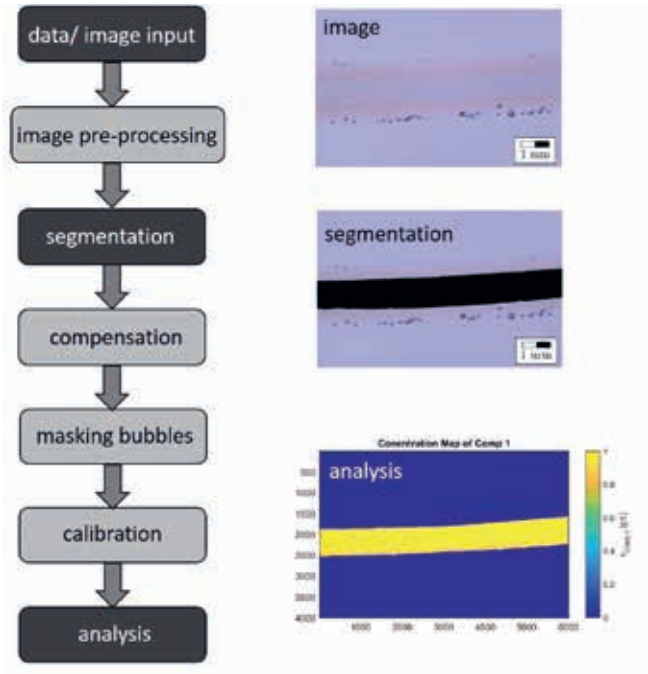

Figure 2: Left: Single steps for digital image processing (DIP). Right: Examples for the original image input, segmentation, and analysis of ABTS (c_{ABTS}= 0.9 g L–1) in a capillary with an inner diameter of 1.6 mm. The images were captured with a Nikon D5300.

Publications:
F. Reichmann, J. Herath, L. Mensing, N. Kockmann, J. Flow Chem., 11, 429-444 (2021).
J. Grühn, M. Vogel, N. Kockmann, Chem. Ing. Technik, 93(5), 825-829 (2021).

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Software-guided Microscale Flow Calorimeter based on Thermoelectric Elements

Investigation of a continuous-flow reaction calorimeter cell with commercially available microreactors

Timothy Aljoscha Frede, Inga Burke, Marlene Dietz, Norbert Kockmann

Fast chemical process development is inevitably linked to an optimized determination of thermokinetic data of chemical reactions. Thus, the interest in the development of continuous flow calorimeter increases constantly. Moreover, the miniaturization of calorimetry enables the investigation of fast and even highly exothermic reactions under safe conditions due to the superior temperature control when compared to standard batch equipment. Therefore, an automated microscale flow calorimeter and a methodology to determine optimal experimental settings for its calorimetric measurements is developed.

The calorimeter's setup and its peripheral equipment have been described in previous works of Reichmann et al. In this work, a commercial lab automation system (LabManager®, HiTec Zang GmbH, Germany) has been added to the experimental setup to automate the execution of calibration and experiments. The current calorimeter setup is adapted to commercially available plate microreactors made of glass (HTM-series, Little Things Factory GmbH, Germany). The complete experimental setup is shown in Figure 1. Prior to calorimetric measurements, optimal experimental settings are evaluated using a methodology that includes computational fluid dynamics (CFD) simulations and short-cut estimations. The systematical use of simulation tools such as CFD is essential to overcome challenges related to experimental measurements and to optimize real processes. Thus, information regarding transient flow behavior, velocity, pressure and concentration fields is gained and can be used to reduce the number of experiments. The acid-base reaction of hydrochloric acid and sodium hydroxide is used to demonstrate the calorimeter's and methodology's functionality.

The overall experimental design space was halved by the methodology (Figure 2 a). The reaction enthalpy of the neutralization reaction was determined at the previously determined experimental settings and compared to the literature value. Good agreement of measured reaction enthalpy with the literature value was obtained (Figure 2 b). These results confirmed the applicability of the methodology and the calorimeter's performance.

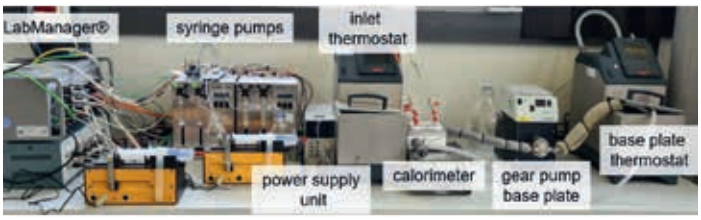

Figure 1: Experimental setup of microfluidic reaction calorimeter.

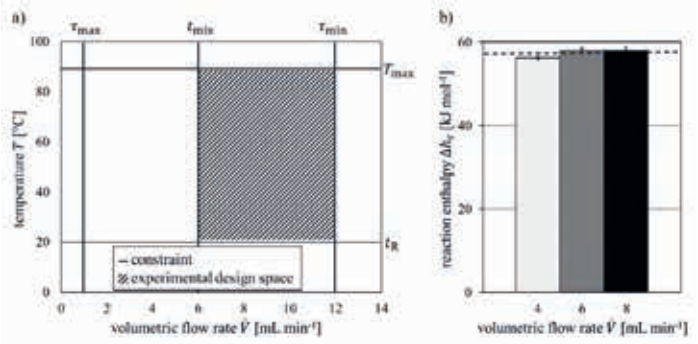

Figure 2: a) Quantitative representation of the experimental design space for calorimetric measurements. b) Measured neutralization enthalpies for varying volumetric flow rates and comparison to literature value (dotted line at 57.6 kJ/mol). All measurements were performed in triplicate and the bars are the standard deviation.

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Publications:
T.A. Frede, I. Burke, N. Kockmann, Chem. Ing. Tech. 93(5), 802-808 (2021).
T.A. Frede, M. Dietz, N. Kockmann, J. Flow Chem. 11(3), 321-332 (2021).

Small-scale Laboratory Columns for Solvent Extraction and Distillation

Investigation of the stirred-pulsed solvent extraction measurement cell and the spinning band distillation column

Piriyanth Sakthithasan, Lukas Bittorf, Norbert Kockmann

Small-scale columns are promising concepts in investigating downstream processes on a laboratory scale. They allow the development of new separation methods at relatively low costs and give great insights into the process. Another advantage is the low consumption of resources, making these small-scale devices interesting for the pharmaceutical & fine chemical industry. The miniaturized stirred-pulsed extraction and the spinning band distillation column are presented in these contributions. Both devices are based on well-known downstream processes and are modified to allow high separation efficiencies.

The miniaturized stirred-pulsed extraction column combines counter-current flow with high separation performance. A pulsation system has been investigated, particularly the influence of asymmetric pulsation patterns. It utilizes a rapid upward stroke for a system with a lighter dispersed phase combined with a slow return. The ratio between these stroke times (time ratio) and its influence on flooding, holdup, and separation performance has been investigated for a standard EFCE test system in an extraction measurement cell. The measurement cell with an active extraction height of 136 mm and six stirred compartments has been used. The most promising results were the increasing flooding limit and higher holdup for an increased time ratio. The separation performance increased from approx. 20 theoretical stages per meter to a value of nearly 30 with an increasing time ratio.

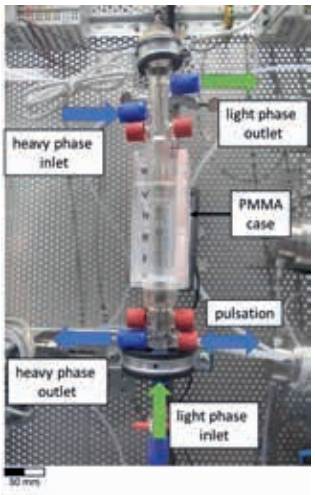

Figure 1: Extraction measurement cell with connected inlet and outlet streams and pulsation unit (middle).

A modular continuously operated spinning-band distillation column for small product amounts is presented and characterized regarding operating window and separation efficiency. The column can be used for first product amounts within a small-scale production or as feasibility studies for distillation in a scale-up context with small resources, energy, and time. Another small-scale column is the spinning-band distillation column. This column can be operated almost fully automatically and integrated quickly to higher automation structures such as a process orchestration layer by introducing the modular automation concept and a certain degree of automation structures. The spinning-band distillation column with a total spinning band length of 670.6 mm has been used to investigate two chemical systems. With the implementation of a vacuum unit, the HETP value, hence the separation efficiency, could be improved from 5 and 8 cm to 4 cm.

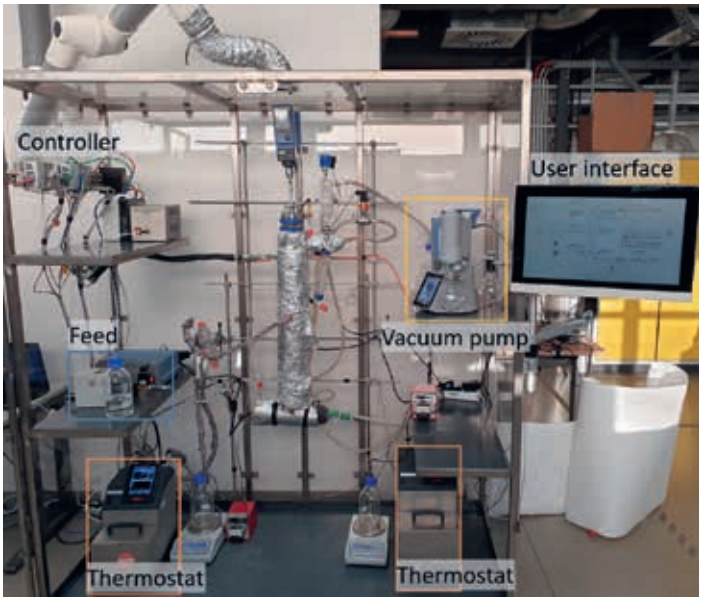

Figure 2: Set-up of the whole plant with spinning band column in the middle, vacuum unit (top right), thermostats for heating (bottom left) and cooling (bottom right), and feeding unit (middle left).

Publications:
P. Sakthithasan, N. Gerdes, M. Venhuis, N. Kockmann, Chem. Eng. Process., 108757 (2021).
M. Schmalenberg, T.A. Frede, C. Mathias, N. Kockmann, Chem. Ing. Technik, 93(3), 466-472 (2021).
L. Bittorf, N. Böttger, D. Neumann, A. Winter, N. Kockmann, Chem. Eng. & Technol., 44(9), 1660-1667 (2021).
L. Bittorf, K. Pathak, N. Kockmann, Ind. Eng. Chem. Res., 60(30), 10854–10862 (2021).

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Continuous Cooling Crystallization in Tubular and Stirred Equipment

Tool box for process development

Mira Schmalenberg, Norbert Kockmann

Cooling crystallization often occurs in chemical synthesis to gain or purify solid product out of a solution or reaction mixture. Coiled Flow Inverter Crystallizer Technology as tubular devices as well as a miniaturized Draft Tube Baffle Crystallizer as stirred device were developed and characterized for aqueous solutions. Particular emphasis was put on continuous flow nucleation by sonocrystallization for Coiled Capillary Crystallizers, where stable operation was possible for certain flow rates and supersaturation. The continuous miniaturized Draft Tube Baffle Crystallizer was equipped with a particle screw at the bottom outlet for suspension discharge support. Further operation modes such as reactive precipitation or evaporative crystallization will be investigated in the future.

The continuous operation of small-scale equipment is of utmost importance for accelerated process development, particularly for particle generation and solid handling processes. In tubular devices for crystallization, spontaneous nucleation will lead to unstable operation conditions and frequent blockages. Seeding or controlled nucleation by sonification of the incoming solution are successful strategies to stable and robust operation. The feed solution is lead through a coiled tube in the sonication bath, see Fig. 1B, and seed crystals are generated for cooling crystallization in the succeeding coiled flow crystallizer with double tube counter-current cooling. The cooling crystallization results is monitored in a flow cell under the microscope (Fig. 1F and G).

The draft tube baffle (DTB) crystallizer is often used in industrial processes and was miniaturized to approx. 2 L content for continuous lab-scale cooling crystallization. After characterization of heat transfer and hydrodynamics for particle classification the continuous product discharge was identified as major bottleneck in the continuous operation. The developed and investigated particle screw is a novel device for continuous supportive suspension discharge for DTB operation. The detected abrasive effects are negligible, and the first residence time investigations with different particle sizes suggest that the screw transports the bigger crystals while the fluid flow transports the smaller crystals if the particle screw is implemented in vertical orientation. With this observation, the screw could even be used to influence the residence time of different crystal sizes and not just support the outlet, but therefore a possible influence of the inclination of the particle screw should be investigated on the residence time behavior of the solid phase.

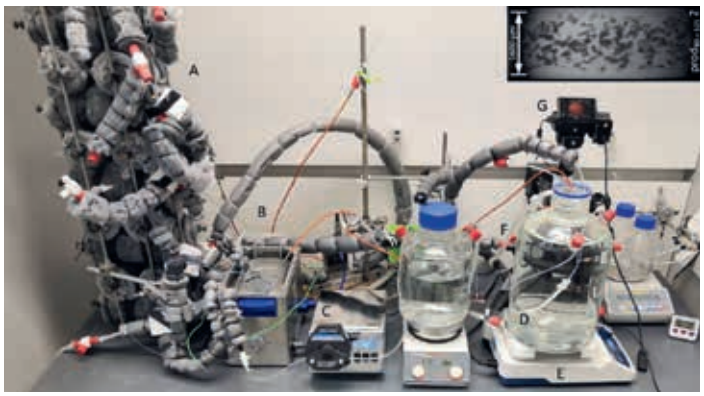

Figure 1: Coiled-flow Inverter Crystallizer (A) with ultrasonic seeding unit (B), solution feed pump (C), collection vessel, and feed solution vessel (D) on heated plate with magnetic stirring (E). Particle image analysis flow cell (F) under a microscope with digital camera (G) is hidden behind the feed vessel. Top left box shows typical analyzed crystals.

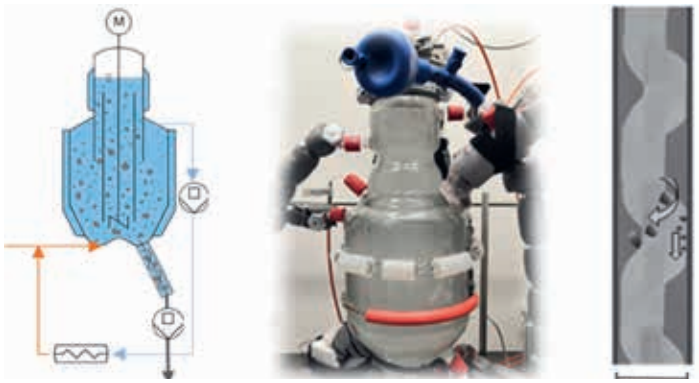

Figure 2: Left: Schematic Draft Tube Baffle DTB Crystallizer with recirculation pumps and discharge screw; Right: DTB for hydrodynamic studies of residence time and classification of crystals with different diameter.

Publications:
M. Schmalenberg, L. Mensing, S. Lindemann, T. Krell, N. Kockmann, Chem. Eng. R&D, online first, Dec. 2021, doi.org/10.1016/j.cherd.2021.12.024.
M. Schmalenberg, T. Krell, C. Mathias, N. Kockmann, Ind. Eng. Chem. Res, online first, Dec 2021, https://doi.org/10.1021/acs.iecr.1c03748.
M. Schmalenberg, L. Weick, N. Kockmann, J. Flow Chem, 11(3), 303-319, 2021, doi.org/10.1007/s41981-020-00138-x.
M. Schmalenberg, S. Kreis, L. Weick, C. Haas, F. Sallamon, N. Kockmann, Processes, 9, 1537, 2021, doi.org/10.3390/pr9091537.

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Multi-Purpose Sensors for Measurements in Capillary Flow

Open-source equipment for quantitative analytics, qualitative analytics and lab automation

Stefan Höving, Norbert Kockmann

Limited applicability and scarce availability of analytical equipment for micro- and millifluidic applications, which are of high interest in research and development, complicate process development, control, and monitoring. The low-cost sensor presented here is a modular, fast, non-invasive, multi-purpose, and easy to apply solution for detecting phase changes and concentrations of optically absorbing substances in single and multi-phase capillary flow. It aims at generating deeper insight into existing processes in fields of (bio-)chemical and reaction engineering, e.g. for residence time measurements in a heat exchanger, for concentration measurements in a tubular reactor, for suspension detection in a tubular crystallizer, and assisting a pipetting robot for flow automation purposes.

The presented optical sensor and its working principle for the analysis of capillary single and multi-phase flow phenomena are an interesting choice compared to common analytical methods such as spectrometer and conductivity meter as well as camera setups that generate information from images. By detecting differences in light absorption of samples or process streams the presented sensor provides reliable online process information with a simple electrical setup. Its capabilities with regards to solid phase detection, process automation, process monitoring for biochemical reactions, and determination of RTD characteristics have been demonstrated in a quantitative or qualitative way. The installed program making the data accessible is easy to understand for non-professionals and adaptable for specific needs. Further applications would allow for parallelized systems with more than two sensors connected to one microcontroller recording the intensity of several wavelengths at once, achieving more specific results of a sample. Skipping the microcontroller is possible, while connecting the sensor directly to an existing process control system. There is a wide variety of possible applications within the field of flow chemistry. Straightforward software and hardware design enable for the integration of both into already existing processes constituting an attractive possibility to increase process knowledge and automation.

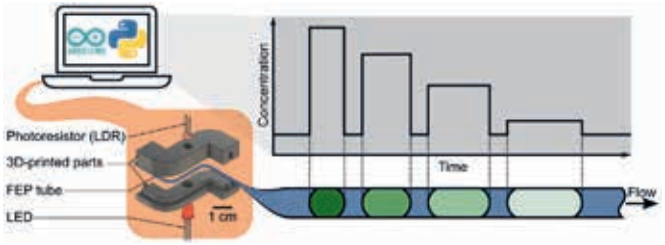

Figure 1: Concept of the open-source and 3D-printed sensor for concentration and slug length measurements.

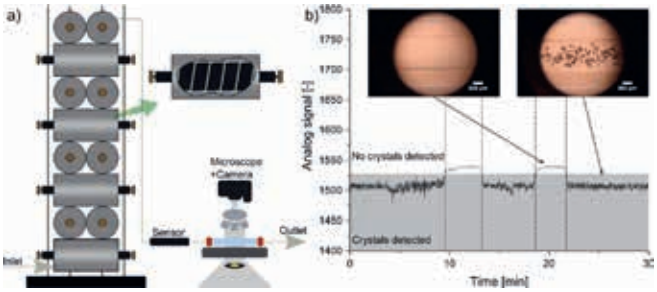

Figure 2: a) Schematic setup of a CFI crystallizer with a camera setup at the suspension outlet. The multi-purpose sensor installed close to the microscope delivers the analog signal shown in b). Here the grey box depicts the static threshold used for the evaluation of crystal presence. The images are exemplary for both states.

Publications:
S. Höving, J. Bobers, N. Kockmann, J. Flow Chem., published paper, December (2021).
V. Fath, P. Lau, C. Greve, P. Weller, N. Kockmann, T. Röder, J. Flow Chem., 11(3), 285 – 302, (2021).
T. Klement, S. Hanf, N. Kockmann, F. Wolff, S.A. Schunk, T. Röder, Reac. Chem. Eng., 6, 1023-1030, (2021).
T. Klement, N. Kockmann, C. Schwede, T. Röder, Ind. Eng. Chem. Res, 60(11), 4240-4250, (2021).

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Artificial Intelligence AI Tools in Process Industry

Machine Learning and Deep Learning implementation in process engineering and control

Jonas Oeing, Laura Neuendorf, Norbert Kockmann

As part of the Industry 4.0, the engineering workflows in the process industry are becoming more and more digitalized. In this context artificial intelligence (AI) with Machine Learning (ML) and Deep Learning (DL) algorithms finds its way in different applications from process development, such as ML-based suggestions of separation units, to supervisor systems forecasting critical process behavior, like a DL-based flooding detection in liquid-liquid extraction columns. However, the potential of AI also offers major challenges, such as standardized and efficient structuring of data.

The successful use of AI tools requires a clean and well-structured data basis. In concrete terms, this can be illustrated by an example. The development of chemical and biotechnological plants takes place in many different development steps, such as simulations and mass or heat balances in basic engineering or the development of P&ID flowsheets, equipment lists and safety considerations in detail engineering. Within the KEEN project, ways have been identified how it is possible to systematically harmonize data with existing data standards in order to make information from the process industry available for AI applications, particularly in machine-interpretable file formats such as piping & instrumentation diagrams in DEXPI format (Data Exchange in Process Industry).

Algorithms such as random forest or decision trees are thus particularly suitable for obtaining suggestions for separation units based on existing information from simulation. Figure 1 shows the results of ML-classification in a confusion matrix. The diagonal line shows how many separation units of each class will be correctly predicted by the classification. With the use of a programming interface, the developed models can be easily integrated into existing process simulators.

Another important step is the linkage between AI and modular plants. AI models will be encapsulated in add-ons and mapped to existing OPC UA server variables of modular systems with automation according to the MTP concept (Module Type Package), see Figure 2. Here, ML algorithms are able to predict the flooding behavior of distillation plants by analyzing the pressure curve and its influencing parameters. In addition, AI-based image classification with DL algorithms enables real time process monitoring in liquid/liquid extraction columns (Figure 3.) and allows for operating closer to its optimum.

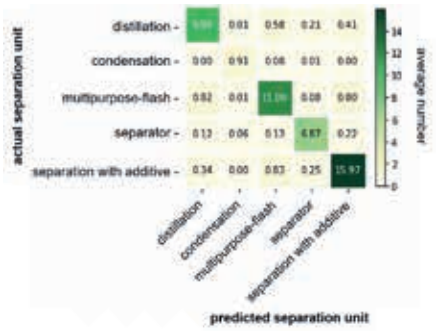

Figure 1: Average confusion matrix of classification results for a cross-validation.

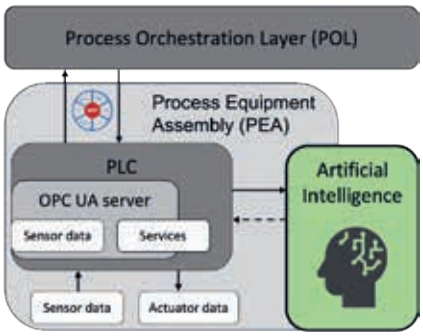

Figure 2: AI-Addon to interface an MTP-automated modular plant.

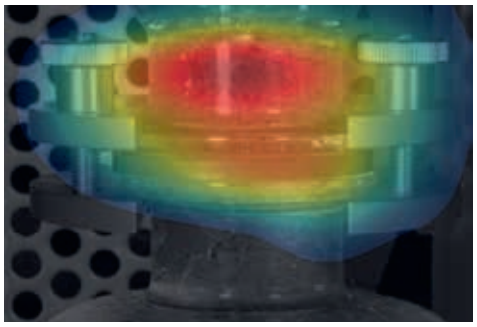

Figure 3: Droplet size distribution detected by deep neural networks.

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Data Handling in Catalytical and Process Engineering Sciences

From ontologies to meta data standards guided by FAIR principles

Alexander Behr, Norbert Kockmann

Catalysis is viewed as one of the core technologies to solve pressing challenges posed by e.g. climate change, green energy and more. The National Research Data Infrastructure for Catalysis-Related Sciences (NFDI4Cat) aims to advance the digitalization of all scientific research data in accordance with the FAIR (Findable, Accessible, Interoperable, Reusable) principles for data. In order to obtain FAIR data, it is crucial to communicate in shared vocabularies, defining and using same names for the same concepts. This is helped by ontologies which provide a formal explicit definition of a conceptualisation to derive meta data standards.

Modern research methods produce large amounts of scientifically valuable data. Tools to process and analyze such data have advanced rapidly. Yet, access to large amounts of high-quality data remains limited in many fields, including catalysis research. Implementing the concept of FAIR data (Findable, Accessible, Interoperable, Reusable) in the catalysis community would improve this situation dramatically, thus enabling better research. Starting out from the current state, research needs are identified. A vision for a integrating all research data along the catalysis value chain, with its challenges, is illustrated in Fig. 1.

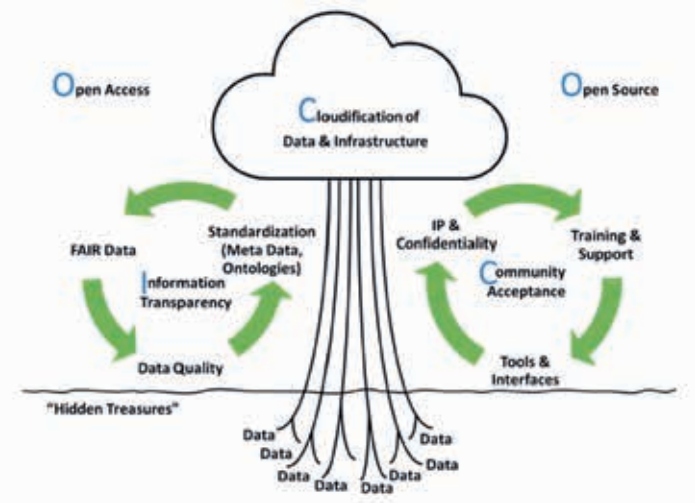

Figure 1: Illustration of the core principles and elements of NFDI4Cat.

The data value chain in catalysis research is analysed, and architecture and interoperability requirements are identified by conducting user interviews, collecting competency questions, and exploring the landscape of semantic artefacts. Methods from agile software development are employed to collect, organize, and present the collected requirements; workflows are annotated on the basis of metadata standards for research data provenance, by which requirements for domain ontologies in catalysis are deduced. Fig. 2 shows interconsortial interfaces as well as semantic artefacts and domain ontologies relevant to the data value chain of catalysis.

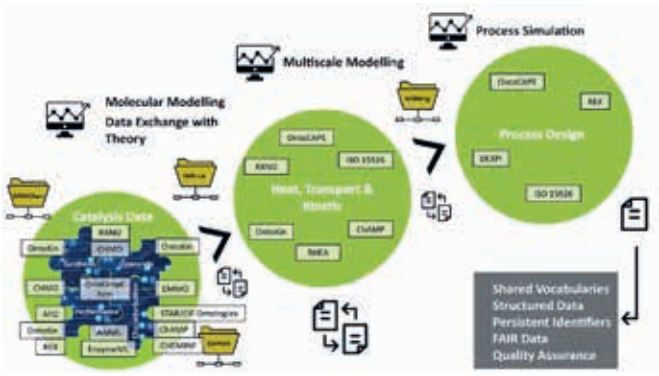

Figure 2: Landscape of semantic artefacts relevant to the data value chain of catalysis.

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Plant and Process Design (APT)

Relation between Molecular Protein Properties and the Macroscopic Effects of Surface Activity

Jörg Koop, Juliane Merz, Gerhard Schembecker

Surface activity, i.e., the ability to adsorb at and stabilize interfaces, is an intrinsic protein property leading to foam formation from gassed aqueous solutions. Predicting that surface activity based on known protein properties like their amino acid sequence or polarity is desirable for many industrial processes, especially in biotechnology. From the biotechnologist's point of view, the formation of foam is, in most cases, seen as a tedious thing but it can be utilized for selective separation of the surface-active molecules. However, with a better understanding of protein's surface activity, that knowledge could be used for sophisticated downstream processes. Thus, we experimentally determined the surface activity of model proteins via foaming experiments and analyzed their structure on molecular level to find correlations to their macroscopically determined surface activity.

Proteins are fascinating molecules with various properties making them desirable products for food, (bio)chemical, and pharmaceutical industries. One of their intrinsic properties is the so-called surface activity, i.e., their ability to adsorb at surfaces and thereby stabilize them. In the case of surfaces between gas and liquid, then called gas-liquid-interfaces, the surface activity of proteins leads to the formation of, more or less, stable foam from gassed aqueous solutions. In biotechnology the formation of foam, for instance, during fermentation in aerated bioreactors, is an undesired effect in most cases. Thus, antifoaming agents are frequently used to prohibit foam formation. However, utilizing the foam for selective separation of surface-active molecules might be an elegant way of process intensification. Since the surface-active molecules are adsorbed in the foam, by separating the foam from the remaining liquid, a depleted liquid phase and an enriched foam are received. To use the somewhat imprecise property "surface-activity" for downstream process synthesis effectively, it is highly desirable to predict it based on known protein properties like their amino acid sequence, amino acid polarity, or amphilicity of protein parts. Amphiphilic means, that a section of the protein is polar on one side and non-polar on the other, thus behaving like an artificial surfactant with a polar (water-attracting) and a non-polar (water-repelling) part. With the macroscopic surface activity being predictable, one would not be dependent on experiments or far fewer experiments would be required for process synthesis. Thus, we performed foaming experiments with model proteins and determined the surface activity based on carefully selected key performance indicators derived from the experiments. Furthermore, the structure of the proteins was analyzed on molecular level to find correlations between structural features and the macroscopically determined surface activity (see Figure 1). The surface activity decreased in the order α lactalbumin > β-lactoglobulin > trypsinogen > papain. For the theoretical analysis, the database was extended by including 2 hydrophobins in the investigation, since they are known to exhibit an outstanding surface activity.

Surprisingly, no relation to the macroscopic behavior was found considering the hydrophobicity alone. In addition, no relations were found considering the amphilicity of the secondary structure elements. Some proteins had special features that either increased or decreased surface activity. Those features were related to their flexibility or the accessibility of non-polar structures. Thus, by considering the tertiary protein structure, we found that for most of the proteins investigated the presence of exposed amphiphilic secondary structure elements in combination with a certain amount of flexibility correlates with the surface activity.

However, since the amount of flexibility was derived from experimental results, prediction of protein's surface activity based on theoretical data only remains a challenging task.

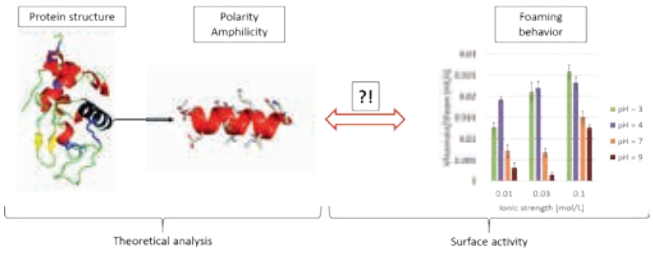

Figure 1: Procedure used to find correlations between known protein properties and their macroscopic surface activity.

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Continuous Particle Isolation using Modular Continuous Vacuum Screw Filter (CVSF)

Design and characterization of an innovative, patented, and modular apparatus for small-scale filtration, washing, and drying

Claas Steenweg and Kerstin Wohlgemuth

Integrated continuous manufacturing processes of active pharmaceutical ingredients (APIs) and fine chemicals provide key benefits concerning product quality control, scale-up capability, and a reduced time-to-market. Thereby, the crystallization step, which is used in approximately 90 % of all small molecular API manufacturing processes, mainly defines the final API properties. The crystal process chain consists of the process steps of crystallization, followed by filtration, washing, and drying to harvest the final dried product particles. We have invented an innovative modular apparatus, which is uniquely able to combine all the steps after crystallization in it, so that free-flowing particles of the highest quality leave the apparatus.

Within the scope of this research, the concept of the modular continuous vacuum screw filter (CVSF) was invented, the prototype designed, built and characterized, and the idea patented in 2021. The overall goal is to obtain dried and free-flowing product particles continuously from the feed suspension, by means of integrated solid-liquid separation, washing, and drying in a flexible and modular set-up. The apparatus is designed to cope with high standards in small-scale production of APIs relating to a defined and constant product quality, especially with regard to maintaining the particle properties across the entire purification and isolation process. The CVSF consists of two basic elements: a tubular body, in case of filtration or washing with a porous filter frit in the lower half of the inner jacket and a rotating screw for the axial transport of the particles. To enable visibility of the transport phenomena inside the apparatus, the CVSF body was manufactured from borosilicate glass at the TU Dortmund University glass blowing workshop. The general set-up of the modular CVSF is shown in Figure 1. It is designed for a typical API production scale of 250 – 1000 kg per year, which can be transferred to suspension volume flow rates of 10 – 100 mL min^{-1}.

A model system (L-alanine/water) with comparable particulate properties as higher-priced APIs was used for the fundamental process and apparatus characterization. The CVSF ensures fully continuous particle isolation, preservation of particle size distribution, and reduction of residual moisture to free-flowing products. Also for higher aspect ratio particles, e.g. needles, the preservation of product quality and prevention of attrition, breakage, and agglomeration was possible (see Figure 2). The targeted residual moisture below 1% was achieved for spherical-like particles after two-stage washing. For needles this could be achieved by adding a drying module (T_{dry} = 60 °C) to the CVSF, which highlights the great advantage of the flexible adaptation of the CVSF based on its modular design.

In addition to its modularity, the CVSF exhibits a rapid start-up behavior, offering unique features and representing a promising concept for small-scale continuous particle isolation to remove the main obstacles for integrated continuous manufacturing processes of APIs and fine chemicals.

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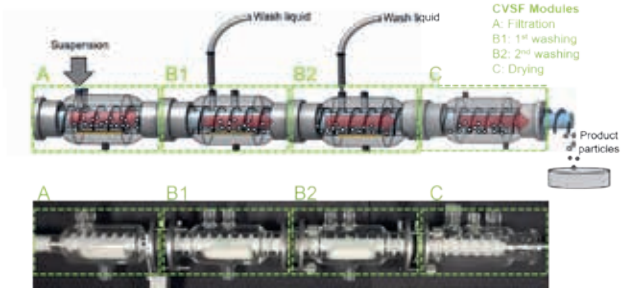

Figure 1: Schematic drawing (upper half) and photograph (lower half) of the modular CVSF.

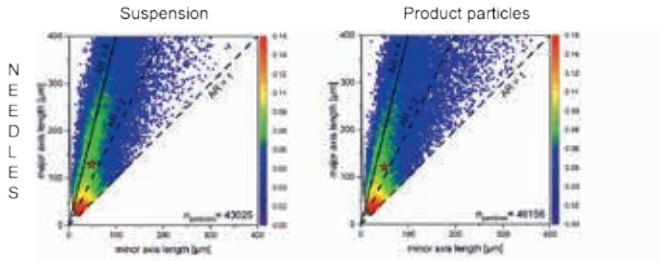

Figure 2: Axis length distribution of the inlet suspension (left) and washed product particles after drying (right).

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Biomaterials and Polymer Science (BMP)

Novel, Ultrastiff Hydrogels formed as Mimics of Corals

Controlling of interphasic forces towards highly stiff and tough hydrogel materials

Marko Milovanovic, Lydia Mihailowitsch, Mathusiha Santhirasegaran, Volker Brandt, Joerg C. Tiller

Corals have the unique ability to use amorphous $CaCO_3$ (ACC) in order to stabilize their structure. In order to mimic this behavior for the first time, we have previously found that ACC is stabilized by glyphosate in hydrogels. Although high amounts of ACC could be formed in the hydrogel the resulting composite showed no improved mechanical properties. In the present study, we solved this problem by introducing groups into the hydrogel that form reversible bonds between organic and inorganic phase. This way the first ultrastiff and tough hydrogel based on ACC could be designed.

Urease-mediated mineralization of hydrogel networks leads to highly filled composites containing $CaCO_3$ of various morphologies. The control over the modifications formed within the network are subject to the presence of substances that can influence or inhibit crystallization. Recently *N*-(phosphonomethyl)glycine, also known as glyphosate, was identified as a compound for crystallization inhibition and stabilization of amorphous calcium carbonate (ACC) nanoparticles. However, while accumulation of ACC results in highly filled composites, the mechanical properties of the water-swollen material is not improved, which is due to the missing percolation of the inorganic component in the composite and the weak interactions between organic and inorganic phase. It was found that the incorporation of carboxyl groups in the polymer network controls the morphology of the ACC agglomerates formed, which results in the onset of percolation and a significant improvement in the mechanical properties of the composite with the formation of organic-inorganic double networks (O-I-DN, Figure 1).

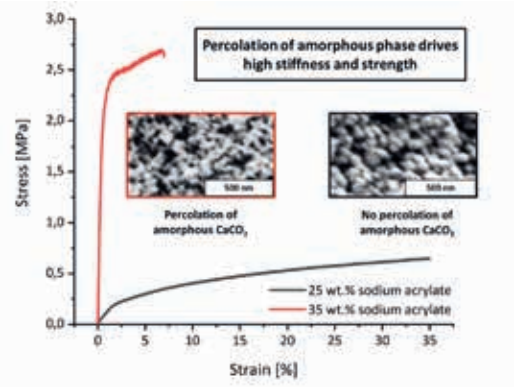

Figure 1: Stress-Strain curves of two mineralized polymer networks with precipitated and stabilized amorphous calcium carbonate. SEM-images reveal visible percolation of the nanometer-sized particles, which leads to the formation of a continuous second inorganic network, once a sufficient amount of sodium acrylate is copolymerized in the network.

The interaction between organic and inorganic phase via reversible bonds, combined with the controlled growth and percolation of the inorganic agglomerates (Figure 2) led to water-swollen O-I-DN hydrogels with a 1000-fold increased Young's modulus (455 MPa) compared to unmineralized networks, remarkable tensile strength (3.4 MPa) and fracture toughness (1100 J m^{-2}), which are higher than the previously reported, amorphous calcium phosphate (ACP) based DN, while being synthesized significantly faster (7 hours instead of 7 days).

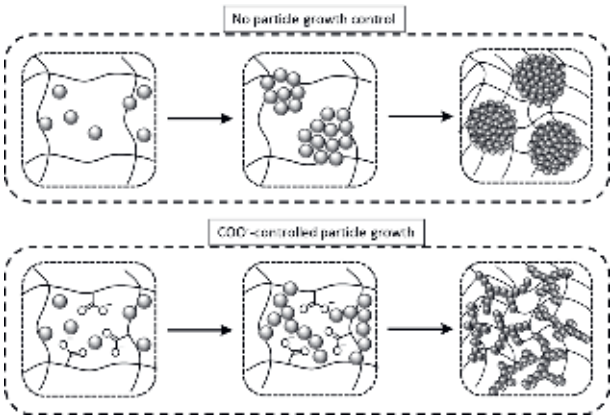

Figure 2: Schematic presentation of the mineralization process with and without particle growth control, leading to different morphologies of the precipitated inorganic phase.

This work emphasizes the synthesis of O-I-DN based on amorphous inorganic minerals and organic hydrogel networks as a general method for strengthening of polymer networks. Homogenous, ultrastiff, strong and tough composite hydrogel networks are not limited to ACP and the approach of enzyme-induced mineralization is transferable to composite materials based on a variety of components.

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Strengthening the Stiffest Hydrogel of the World

Improving the strength of a mineralized hydrogel by double enforcement

Marko Milovanovic, Nicola Isselbaecher, Volker Brandt, Joerg C. Tiller

Ultrastiff hydrogels are of great importance in biomedical and membrane applications. We have previously reported on enzyme-induced mineralized calcium phosphate-filled hydrogels that have the highest stiffness known in this area due to the percolated inorganic phase. Due to combination of the percolated inorganic phase with an ionically cross-linked polymer network, the strength of this still highly stiff hydrogel could be improved by more than an order of magnitude. This renders the mineralized hydrogel to one of the strongest existing hydrogels.

Swollen double networks (DN) are hydrogels with greatly improved mechanical properties compared to classical hydrogels. The highest stiffness is achieved for organic-inorganic (O-I) DN hydrogels, however, these show with 1 MPa a significantly lower tensile strength than that observed for the strongest known DN hydrogel systems (~10 MPa). It was presumed that this is due to an insufficient reversible bond formation between inorganic and organic phase, thus we investigated the influence of inserted carboxylate groups that form reversible bonds between these two phases on the example of amorphous calcium phosphate-based O-I-DN. After alkaline phosphatase (ALP)-induced mineralization of *N, N*-dimethylacrylamide-based hydrogels copolymerized with acrylic acid (AA), we found that the structure of the formed inorganic phase became smaller and more homogeneous with increasing AA content (Figure 1, top).

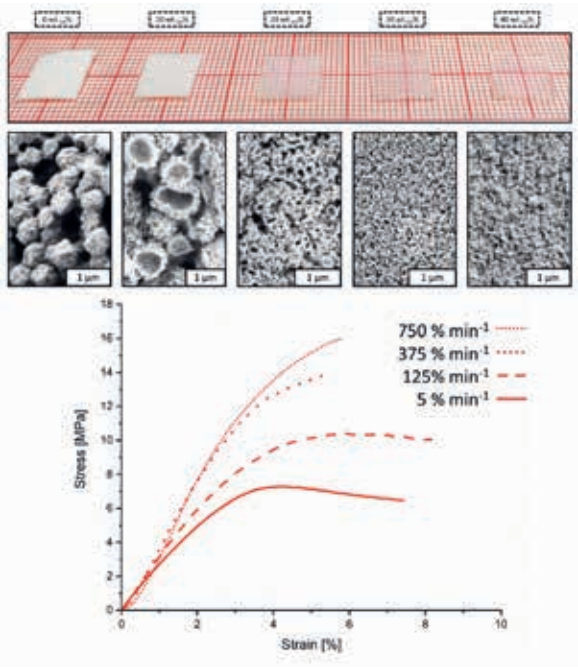

Figure 1: Top: Photographs and SEM images of ALP-induced mineralized hydrogels with varying content of acrylic acid as copolymer. Bottom: Stress-Strain curves of O-I-DN with copolymerized acrylic acid (40 wt%), carried out at different strain rates (5, 125, 375 and 750 % min^{-1}).

The mineralized hydrogel with 40 wt.% copolymerized AA results in a significant improvement in terms of strength (>7 MPa, compared 0.4 MPa without AA) of the formed ultrastiff DN hydrogels. The fracture toughness of the optically transparent DN, which are among the stiffest and strongest existing hydrogels ever reported, improved as well, with up to 2000 J m^{-2}.

Stress-strain curves at different strain rates revealed that the Young´s modulus of ~300 MPa is constant in all cases, while the tensile strength dynamically increases to ~17 MPa at higher strain rates (Figure 1, bottom).

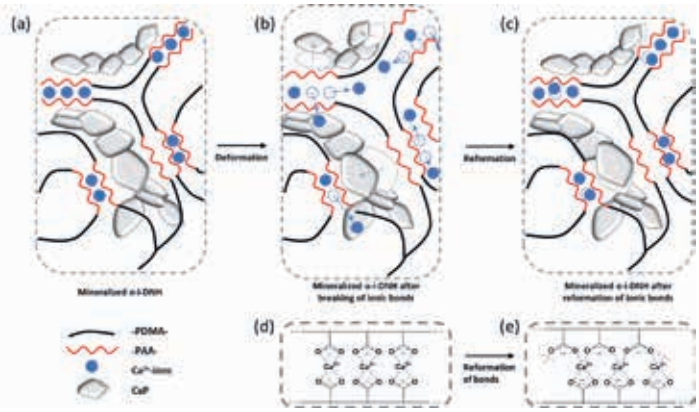

Figure 2: Illustration of the deformation-induced breaking of ionic bonds (b) of mineralized O-I-DNH (a) and it´s respective reformation (c-e).

IR-investigations indicated the presence of ionic bridges formed by the acrylate groups and calcium ions within the O-I-DN. Thus, the inorganic phase is connected to the polymer matrix via copolymerized carboxylate groups, and the hydrogel itself is cross-linked via Ca^{2+}-ions, forming calcium ion bridges. This double enforcement lends the material an additional increase in strength and fracture toughness and dynamically enhances the O-I-DN (Figure 2).

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Morphology Tailoring of Crosslinked Polyethylenes towards Improved HVDC Materials Properties

Influence of orientation on injection and trapping of space charges

Michail Maricanov, Dominik Segiet, Frank Katzenberg

The energy system is in the midst of a very significant transformation. High-voltage-direct-current (HVDC) power transmission will play a key role in meeting the increasing global energy demand and reaching climate goals in the future. Offering benefits such as low-loss energy transmission over long distances, HVDC also places new demands on the polymeric insulation used in the entire network equipment chain. The main issue is injection and trapping of space charges into insulation materials under DC-fields, which leads to an increase of field strength and limits lifetime. Now we found that tailoring the morphology of a polymer offers great potential to influence the injection and accumulation and of space charges in crosslinked low density polyethylene (XLPE), the most common insulator with a high number of operating hours rated up to 400 kV in high-voltage-alternate-current (HVAC) systems.

The objective of this study – a cooperation with the group of Jenau from the Institute of High Voltage Engineering, Faculty of Electrical Engineering & Information Technology of the TU Dortmund – was to increase knowledge of the interplay between morphology and material performance of XLPE under HVDC by tailoring its morphology beyond the capabilities of "common crystallization kinetics". Since XLPE is an elastomer above its melting temperature, it was possible to crystallize it constrained at elongations λ up to 10 (Fig. 1).

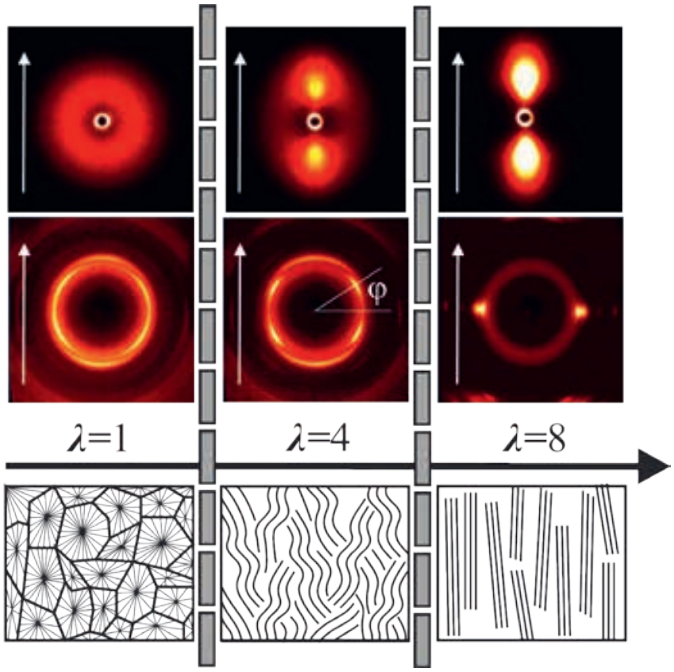

Figure 1: Small- (top), wide-angle X-ray-Scattering (middle) and schemes of the deduced morphology (bottom) of XLPE crystallized at different elongations λ (arrows indicate strain direction during crystallization).

Upon pulsed electro acoustic (PEA) measurements it was found that the tailored oriented morphology causes reduction of the space charge density and influences the energetic depth of traps (Fig.2). Moreover, the optimized oriented morphology leads to a significant reduction of field enhancement for field strengths $E_{Laplace} \geq 20$ kV mm^{-1} compared to unoriented XLPEs with spherulitic morphology. It is shown that this way of morphology tailoring results in a considerable, material dependent reduction of field exposure by a factor of 4, which promises a significant improvement in the electrical life time of polymeric insulation material.

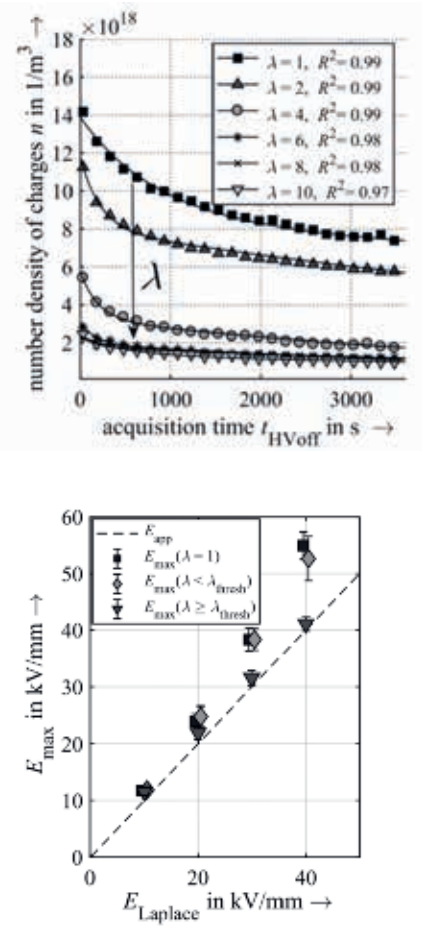

Figure 2: Number density of trapped charges over time and maximum electric field enhancement under DC field conditions.

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The Secret of Contact Lenses

X-ray scattering experiments reveal the nanostructural integrity during solvent uptake of amphiphilic polymer conetworks (APCNs)

Sascha A. Wilhelm, Michail Maricanov, Volker Brandt, Frank Katzenberg, Joerg C. Tiller

Contact lenses have the unique properties to be highly permeable for water and oxygen, which is required for keeping the cornea alive. The material that enables this is an amphiphilic polymer conetwork, which contains two interconnected co-continuous polymer nanophases. One of these nanophases is permeable for water and the other for oxygen. The interconnectivity required for this could be destroyed upon swelling. The present study has shown for the first time that the morphology changes in APCNs upon swelling are dependent on the chemical nature of the hydrophilic phase. The material of soft contact lenses prevents such changes, which is the reason, why they work.

Two novel APCN families were synthesized based on the new macromonomeric hydrophobic cross-linker DMAP-MAA-PEPOx$_{32}$-DMAP-MAA and copolymerized with a hydrophilic proton-donor monomer, 2-hydroxyethyl acrylate (HEA), and a hydrophilic proton-acceptor monomer *N,N*-dimethylacrylamide (DMA), respectively (see Figure 1). The proportion of the hydrophobic component was varied between 30 and 90 wt% to study the influence of the respective network composition on the topology and swelling behavior.

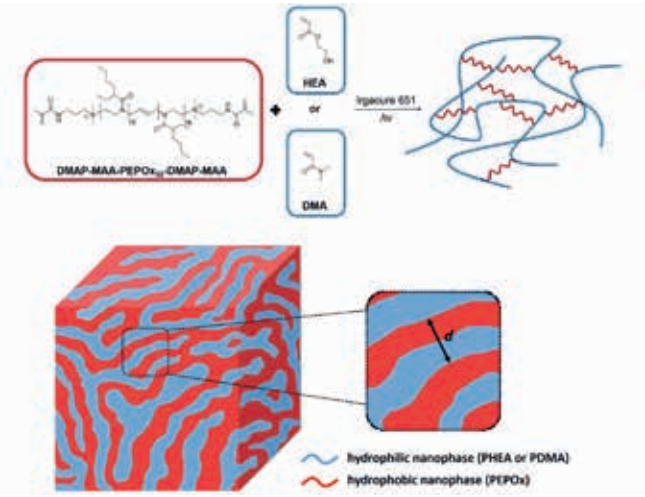

Figure 1: Schematic depiction of the co-continuous APCN nanostructure confirmed by AFM measurements with exemplary illustration of long-period *d*.

The influence of the respective, structural changes upon swelling in selective solvents (water, toluene and *n*-heptane) was explored using small angle X-ray scattering (SAXS). This analytical method revealed the different nanophasic changes upon solvent uptake between the two APCN families. The DMA-based APCN showed significant changes in its nanostructure upon swelling. This would be expected, because a change of the volume ratios of the polymer phases will most likely result in a change in the nanostructure as well. These morphology changes result in isolated structures of the hydrophobic phase. This would prevent any diffusion processes through the hydrophobic phase of this material in water-swollen state. Thus, a contact lens would not be permeable for oxygen. On the other hand, the APCN PHEA-*l*-PEPOx did not show significant nanostructural changes upon swelling in all applied phase-selective solvents (see Figure 2). This is the first example of an APCN which was reported with such an ideal swelling behavior. In contrast to the other investigated APCNs, this network contains hydrogen bridges within the PHEA-phase as well as between the PHEA and the PEPOx phase, possibly stabilizing the nanophases of the dry state.

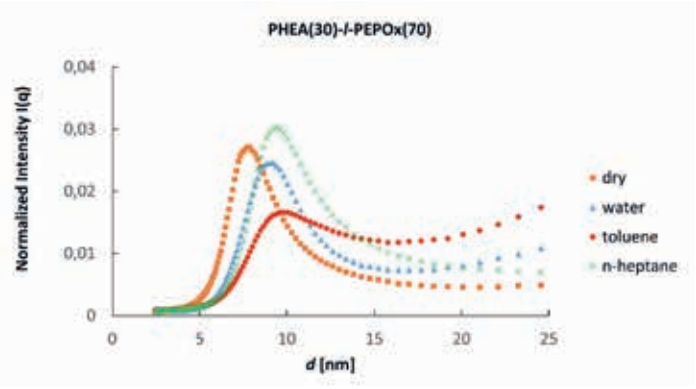

Figure 2: SAXS profiles received from PHEA(30)-*l*-PEPOx(70) conetwork samples under dry and swollen conditions with long-period *d* calculated using $d = 2\pi/q$. Measurements of dry samples were carried out for 1 h and of swollen samples for 8 h.

Since soft contact lenses contain PHEA as hydrophilic phase, the stabilizing effect of hydrogen bridges on the morphology changes of this polymer is most likely the reason, why this APCN is permeable for oxygen even in the water-swollen state.

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Amphiphilic Polymer-Antibiotic Conjugates are Active against CIP-Resistant Bacteria

Conjugates of ciprofloxacin and amphiphilic block copoly(2-alkyl-2-oxazoline)s overcome efflux pumps

Alina Romanovska, Johanna Keil, Jonas Tophoven, Murat Furkan Oruc, Martin Schmidt, Marina Breisch, Christina Sengstock, Daniela Weidlich, Dagmar Klostermeier, and Joerg C. Tiller

In the 21st century, one of humankind's biggest challenges is the mitigation of bacterial infections caused by multiresistant bacteria. One solution for this problem could be the formulation and derivatization of existing antimicrobial agents. Conjugation of antibiotics with polymers is an emerging strategy to improve the performance of these important drugs. This study has revealed that conjugation of the antibiotic ciprofloxacin (CIP) with amphiphilic block copolymers makes the antibiotic in some cases even more active than CIP alone provides the antibiotic with the new function to use efflux pumps as entrance in the bacterial cells. This makes these conjugates active against bacteria that are fully resistant against CIP.

The antibiotic ciprofloxacin (CIP) was conjugated with amphiphilic poly(2-oxazoline) (POx) block copolymers. The resulting polymer–antibiotic conjugates (PACs) are an order of magnitude more active against the bacterial strain *Staphylococcus aureus* than CIP and show high activities against numerous pathogenic bacterial strains. Due to their dependence of the MIC value on the molar mass the PACs with the shortest polymer chain ($PMOx_{19}$-*b*-$PHeptOx_4$-EDA-xCIP) are the most efficient.

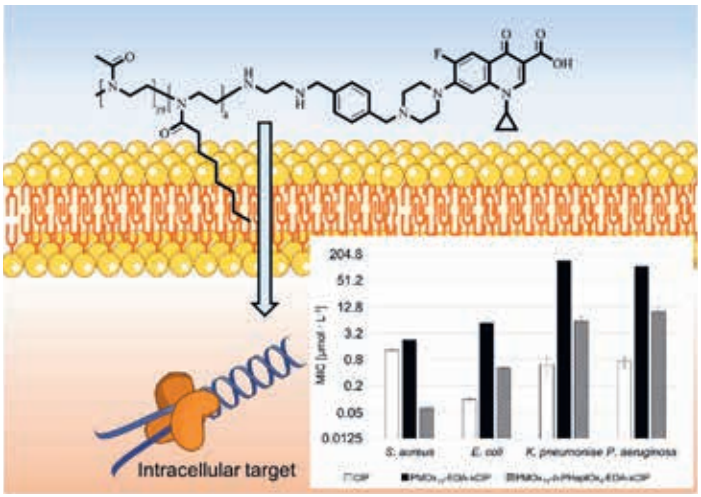

Figure 1: Schematic representation of the mechanism of action of amphiphilic polymer-antibiotic conjugates. The diagram shows the antimicrobial effect of CIP (white), of $PMOx_{30}$-EDA-xCIP (black) and of $PMOx_{19}$-b-$PHeptOx_4$-EDA-xCIP (striped).

Their high activity depends also on an optimal hydrophobic/hydrophilic balance (HHB) of the POx tail. Mechanistic studies revealed that the derivatization of CIP required for the polymer conjugation lowers the affinity of the antibiotic to its target topoisomerase IV. However, the amphiphilic PACs are most likely concentrated within the bacterial cytoplasm, which overcompensates the loss of affinity and results in high antibacterial activity. In addition, the development of resistance in *Staphylococcus aureus* and *Escherichia coli* is slowed down. The results show that even after 15 days, hardly any resistance has developed in the amphiphilic PACs. In contrast, both CIP and a conjugate based on the homopolymer poly(2-methyl-2-oxazoline) show a significant increase in resistance.

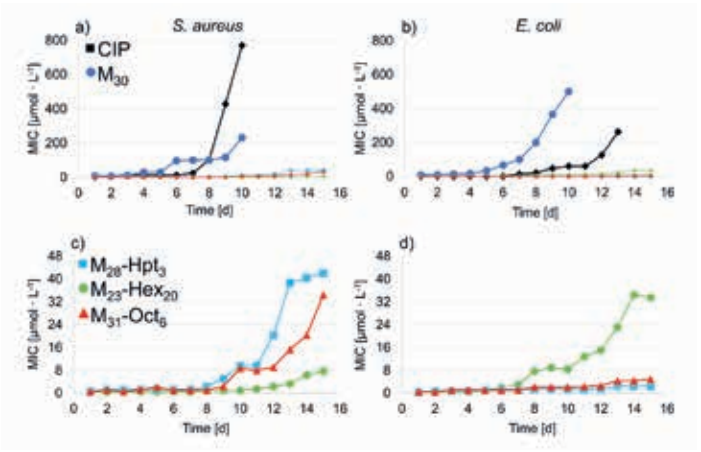

Figure 2: Resistance test for the compounds CIP (black), $PMOx_{30}$-EDA-xCIP (dark blue), $PMOx_{23}$-b-$PHexOx_{20}$-EDA-xCIP (green, HHR = 1.15, M_{23}-Hex_{20}), $PMOx_{28}$-b-$PHeptOx_3$-EDA-xCIP (light blue, HHR = 9.3, M_{28}-Hpt_3), $PMOx_{31}$-b-$POctOx_6$-EDA-xCIP (red, HHR = 5.2, M_{31}-Oct_6) for a), c) S. aureus and b), d) E. coli, respectively. c) and d) are showing the data for the last three PACs in higher magnification. The whole study was reproduced once.

More importantly, the amphiphilic PACs are active against CIP-resistant *S. aureus* and *E. coli.* The PACs probably use the efflux pumps of the mutant bacteria, which makes their membranes more permeable to enter the cell. PACs owe these antimicrobial properties to the amphiphilic character of the polymers. It seems reasonable that the amphiphilic polymer rather sticks to the membrane than become enriched in the cytoplasm. In addition, the PACs with the highest activity are not cytotoxic toward human stem cells and do not lyse blood cells in saturated solution.

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Bioprocess Engineering (BPT)

From Cell-Free Protein Synthesis to Whole-Cell Biotransformation

Novel dioxygenases for the preparative synthesis of hydroxy-L-lysine

Jascha Rolf, Philipp Nerke, Annette Britner, Sebastian Krick, Stephan Lütz and Katrin Rosenthal

Reliable and fast screening of novel enzymes is of high importance for future industrial processes. Conventional protein production can be very laborious and time-consuming. In this study, we demonstrated the suitability of cell-free protein synthesis (CFPS) for the screening of novel non-heme Fe^{2+}/α-ketoglutarate-dependent dioxygenases for the production of hydroxy-L-lysine. The screening led to the identification of several new lysine dioxygenases (KDOs), which were successfully employed in whole-cell biotransformations. A newly identified KDO from Photorhabdus luminescens was used in a preparative-scale biotransformation producing almost 5 g L^{-1} product without prior optimization.

Non-heme Fe^{2+}/α-ketoglutarate-dependent dioxygenases represent exceptional biocatalysts for the selective activation of C-H-bonds catalyzing mainly hydroxylations. Thus, the discovery of new enzymes with suitable reactivity for biotechnological applications is of high interest. To accelerate enzyme screening, cell-free protein synthesis (CFPS) can be performed (Figure 1a). We executed the synthesis of known KDOs and yet undescribed homologs with an *E. coli*-based CFPS system. Remarkably, four of six novel enzymes were confirmed as KDOs. Moreover, we tested chaperone-enriched CFPS systems for the synthesis of KDOs, which led to a higher fraction of soluble enzyme and thereby doubled hydroxylation activity for two of the selected enzymes. The chaperone-assisted CFPS is thus a good tool for the rapid screening of putative enzymes and suitable chaperones. In a next step, the different KDOs were applied in *E. coli*-based whole-cell biocatalysts to confirm the CFPS results in small-scale biotransformations (Figure 1b). The whole-cell biocatalyst expressing the gene coding for the KDO from *Photorhabdus luminescens* showed the highest specific activity of 8.6 ± 0.6 U g_{CDW}^{-1} and was selected for the preparative synthesis of hydroxy-L-lysine. Multi-gram scale product concentrations were achieved providing a good starting point for further bioprocess development.

To conclude, a systematic approach was established to screen and identify novel Fe^{2+}/α-ketoglutarate-dependent dioxygenases, covering the entire pathway from gene to product, which contributes to accelerating the development of bioprocesses for the production of value-added chemicals.

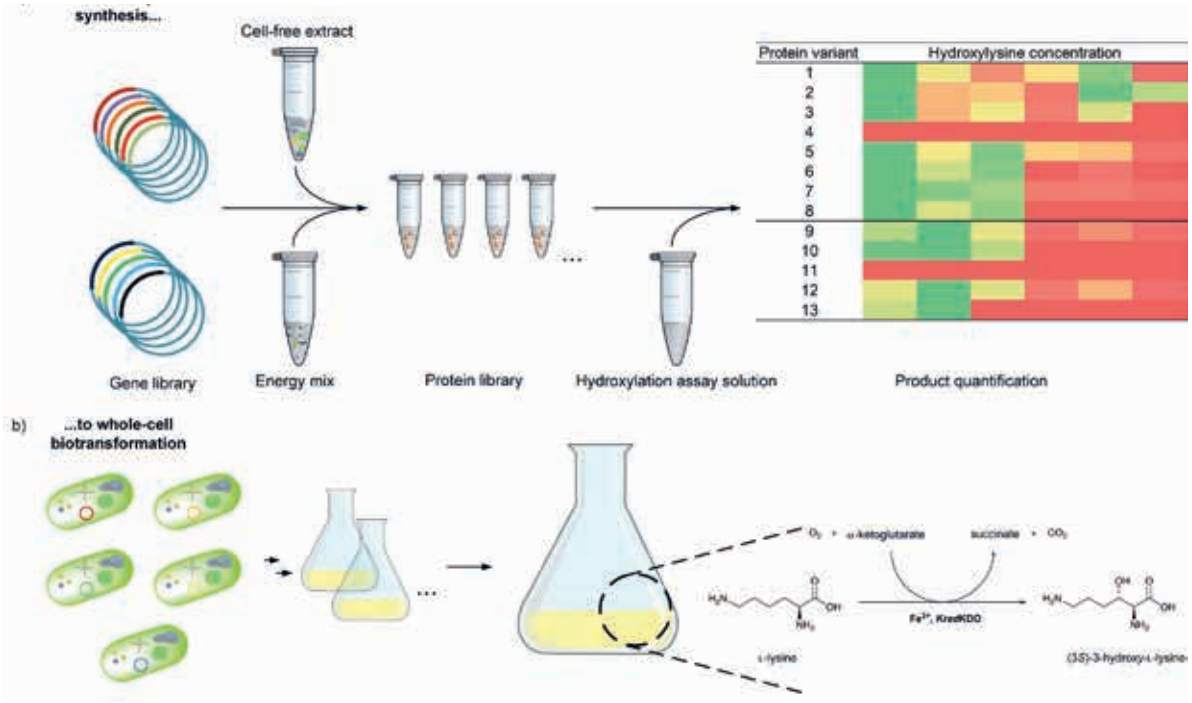

Figure 1: Schematic representation of the study. a) Suitable enzymes were identified by means of cell-free protein synthesis with subsequent assay reactions. b) Selected enzymes were employed in whole-cell biotransformations in small and preparative scale.

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Publications:
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A Multi-Enzyme Cascade Reaction for the Production of 2'3'-cGAMP

Optimization of a cascade of four enzymes

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Multi-enzyme cascades enable the synthesis of complex molecules without purification of intermediates. This facilitates the handling of unstable intermediates and unfavorable thermodynamics due to coupled equilibria. In this study, a four-enzyme cascade was successfully developed consisting of three kinases for ATP synthesis coupled to the cyclic GMP-AMP synthase (cGAS) that catalyzes 2'3'-cyclic GMP-AMP (2'3'-cGAMP) formation. 2'3'-cGAMP is of particular interest in medical research because it induces the synthesis of type I interferons. The established enzyme cascade was iteratively optimized for 2'3'-cGAMP synthesis from GTP and inexpensive adenosine as well as polyphosphate in a one-pot reaction, demonstrating the potential of multi-enzyme cascades.

The four enzymes were synthesized with recombinant *E. coli* and subsequently purified. First, specific activities of the kinases *Sc*ADK, *Aj*PPK2, and *Sm*PPK2 were determined (Figure 1a). Subsequently, the multi-enzyme cascade was prepared and enzyme and substrate concentrations were adjusted to achieve high overall reaction rates and product yields (Figure 1b). Three different enzyme ratios and substrate concentrations were examined with *in vitro* assays and analyzed by HPLC measurements. Yields of up to 0.08 mole of 2'3'-cGAMP per mole of adenosine were achieved. Even though the product yield can certainly be improved, it is a promising starting point for further optimization. It should be emphasized that the value is already comparable to the chemical synthesis of 2'3'-cGAMP with a yield of 5 % within 3 days. The achieved synthesis rate of 2'3'-cGAMP synthesis was 52 mU mg_{cGAS}^{-1}. The specific rate refers to the enzyme cGAS used in the last reaction step. This value is close to the intrinsic specific activity of cGAS indicating that the cGAS-catalyzed reaction proceeded near its optimum. Simultaneously, this last reaction step also represents the rate-limiting step of the cascade.

To sum up, the established multi-enzyme cascade enabled 2'3'-cGAMP synthesis from GTP and inexpensive adenosine as well as polyphosphate. Through iterative optimization, adequate production performance was achieved, demonstrating the potential of multi-enzyme cascades for the synthesis of pharmaceutically relevant products.

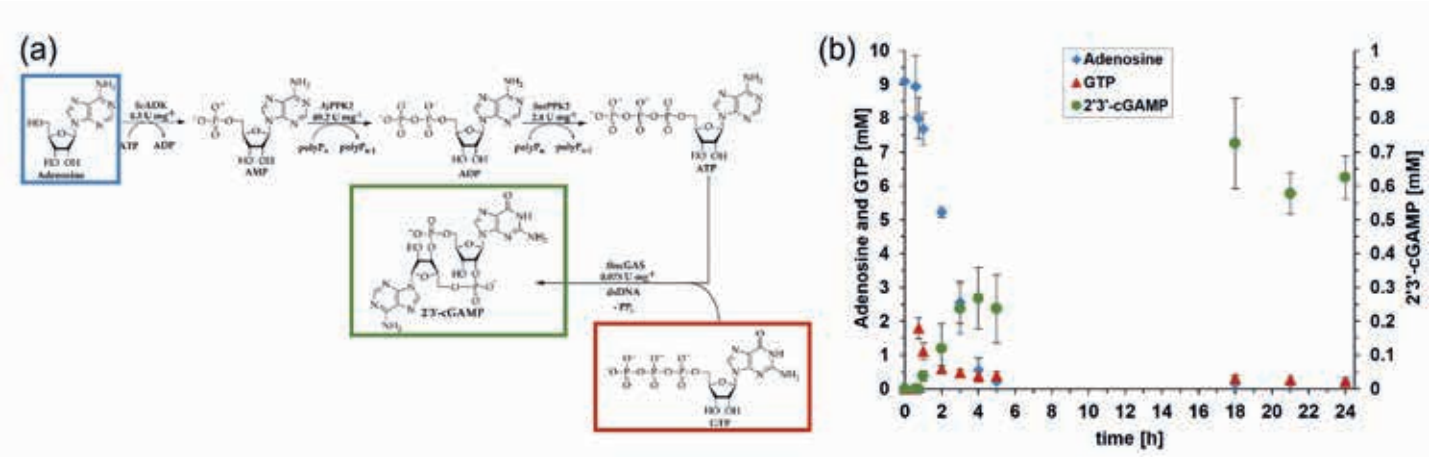

Figure 1: 2'3'-cGAMP synthesis with a multi-enzyme cascade reaction: (a) Scheme of 2'3'-cGAMP synthesis by the enzymes *Sc*ADK, *Aj*PPK2, *Sm*PPK2, and cGAS from adenosine, polyphosphate, and GTP; (b) Mean ATP, GTP, and 2'3'-cGAMP concentrations of enzyme reaction cascade for 2'3'-cGAMP synthesis (used enzyme concentrations: 50 mg L^{-1} *Sc*ADK, 5 mg L^{-1} *Aj*PPK2, 50 mg L^{-1} *Sm*PPK2 and 120 mg L^{-1} cGAS; substrate concentrations: 10 mM adenosine, 1 mM AMP, and 30 mM polyphosphate).

Publications:
M. Becker, P. Nikel, J.N. Andexer, S. Lütz, K. Rosenthal, Biomolecules 2021, 11(4), 590, doi:10.3390/biom11040590.

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Publications 2019 – 2021

2021

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  Biotechnological production of cyclic dinucleotides — Challenges and opportunities
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  Environmental Assessment of Enzyme Production and Purification
  Molecules 26(3), 573 (2021)

Presentations & Poster

- Rosenthal K., Rolf J., Becker M., Siedentop R., Lütz S.
  Towards accelerated bioprocess development: Using cell-free protein synthesis to screen for promising biocatalysts
  6th BioProScale Berlin (2021)

- Siedentop R., Dziennus M., Lütz S., Rosenthal K. (Best poster award, selected for Poster Flash Talk)
  Identification of Optimization Parameters in Cell-free Enzyme Cascades by Computer Modelling and Experimental Validation
  5th Multistep Enzyme Catalyzed Processes Conference (MECP2020+1) (2021)

- Steinmann A., Krey M., Schullehner K., Lütz S.
  Impact of Copper Supplementation on Monolignol Production in Recombinant *Escherichia coli*
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- Becker M., Nikel P., Andexer J. N., Lütz S., Rosenthal K.
  A Multi-Enzyme Cascade Reaction for the Synthesis of 2'3'-cGAMP
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- Lindig A, Hubmann G, Lütz S.
  Secondary metabolite discovery in *Streptomyces griseocromogenes* is influenced by culture systems and sample preparation
  4th European Conference on Natural Products (2021)

- Rosenthal K., Becker M., Rolf J., Siedentop R., and Lütz S. (selected for Poster Pitch Talk)
  Single-step reaction and enzyme cascade – Biocatalytic synthesis routes for novel cyclic dinucleotides
  15th International Symposium on Biocatalysis and Biotransformations (Biotrans) (2021)

- Rolf J., Nerke P., Britner A., Krick S., Lütz S., Rosenthal K.
  Chaperone assisted cell-free protein synthesis for screening of novel enzymes
  15th International Symposium on Biocatalysis and Biotransformations (Biotrans) (2021)

- Rosenthal K., Grühn J., Behr A., Eroglu T., Trögel V., Kockmann N. (Best poster award)
  Biocatalytic Reaction and Process Development using a Coiled Flow Inverter –From Reactor Concept to Ontology Design
  13th European Congress of Chemical Engineering and 6th European Congress of Applied Biotechnology (ECCE/ECAB) (2021)

- Kinner A., Rosenthal K., Lütz S.
  Identification of novel unspecific peroxygenases by genome mining
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- Schmitz L.M., Schäper J., Hageneier F., Rosenthal K., Busche T., Brandt D., Kalinowski J., Lütz S.
  Combining genome mining and activity screening: Novel biocatalysts for hydroxylation reactions
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- Nerke P., Rolf J., Rosenthal K., Lütz S..
  Identification of novel Fe2+/α-ketoglutarate-dependent dioxygenases for the preparative synthesis of hydroxy-L-lysine.
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- K. Rosenthal, M. Becker, J. Rolf, R. Siedentop, M. Hillen, M. Nett, S. Lütz
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  ChemBioChem, 21(22), 3225-3228 (2020)

- S. Lütz, A. Liese
  30 Jahre sichere Gentechnik in Deutschland
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- J. Schwarz, K. Rosenthal, R. Snajdrova, M. Kittelmann, S. Lütz
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  A Gram-Scale Limonene Production Process with Engineered *Escherichia coli*
  Molecules, 2020, 25(8), 1881 (2020)

- A. Sester, K. Stüer-Patowsky, W. Hiller, F. Kloss, S. Lütz, M. Nett
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  ChemBioChem 21(16), 2268-2273 (2020)

Presentations & Poster

- K. Rosenthal, J. Rolf, M. Becker, R. Siedentop, S. Lütz
  Cell-free synthesis of enzymes for the production of pharmaceutically relevant molecules
  ProcessNet-Jahrestagung, 21. – 24. September 2020, online

- K. Rosenthal
  Microbioreactors for Biotransformations and Whole Cell Biocatalysis (invited lecture)
  µTAS 2020 (24th International Conference on miniaturized Systems for Chemistry and Life Science), 3. – 4. October 2020, online

2019

Journal Papers

- L.M. Schmitz, J. Schäper, K. Rosenthal, S. Lütz
  Accessing the biocatalytic potential for C-H-activation by targeted genome mining and screening
  ChemCatChem 11, 5766-5777 (2019)

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- J. Rolf, K. Rosenthal, S. Lütz
  Application of Cell-Free Protein Synthesis for Faster Biocatalyst Development
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Presentations & Poster

- K. Rosenthal, M. Becker, M. Nett, S. Lütz
  Enzymatic synthesis of cyclic dinucleotides – Exploiting a human enzyme with broad substrate scope
  GDCh-Wissenschaftsforum Chemie, 15 – 18 September 2019, Aachen, Germany

- K. Rosenthal, M. Becker, J. Rolf, M. Nett, S. Lütz
  Enzymatic synthesis of cyclic dinucleotides – Exploring the catalytic potential of human cGAS
  (Best poster award) Trends in Enzymology and Biocatalysis, 27 – 31 May 2019, Rome, Italy

- L.M. Schmitz, J. Schäper, S. Lütz
  Genome mining combined with high throughput screening revealed novel biocatalysts for hydroxylation reactions
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- J. Rolf, K. Hildebrand, K. Rosenthal, S. Lütz
  Protein synthesis without cells: Engineering a high-throughput platform for enzyme screening
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  Identification of novel microbial P450s as drug-metabolizing enzymes
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- J. Schwarz, S. Lütz
  Targeting the potential for new bioactive molecules
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Chemical Reaction Engineering (CVT)

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- Becker, T.; Keuchel, F.; Agar, D. W.
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- Drechsler, C.; Agar, D. W.
  Characteristics of DAC operation within integrated PtG concepts
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- Schwarz, Ch.A.; Mendalawi, M.; Agar, D.W.
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  Chemie-Ingenieur-Technik 94(4), 594-598 (2021)

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- Arsenjuk, L., Asshoff, M., Kleinheider, J. , Agar, D.W.
  “A device for continuous and flexible adjustment of liquid-liquid slug size in micro-channels”
  Flow Chem., 10:409–422 (2020)

- Arsenjuk, L., Wiesehahn, M., Morales Zimmermann, M., Katschan, W., Agar, D.W.
  “Capacitive determination of wall-film thickness in liquid-liquid slug flow and its application as a non-invasive microfluidic viscosity sensor”
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- Drechsler, C., Agar, D.W.
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- Drechsler, C., Agar, D.W.
  “Intensified integrated direct air capture - power-to-gas process based on H_2O and CO_2 from ambient air”
  Applied Energy, 273:115076 (2020)

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- von Vietinghoff, N., Lungrin, W., Schulzke, R., Tilly, J., Agar, D.W.
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  Simulation and optimization of a novel moving belt adsorber concept for the direct air capture of carbon dioxide
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  Bubble Behavior in Marine Applications of Bubble Columns: Case of Ellipsoidal Bubbles in Slanted and Rolling Columns
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Process Dynamics and Operations (DYN)

Accelerating the design of new chemical processes by combining superstructure optimization under uncertainties and optimal design of experiments

Stefanie Kaiser, Sebastian Engell

The early stage of the design of new processes is a critical phase as it largely determines the final production costs. Due to shorter product cycles in the chemical industry, the pressure to reduce the development time is also increasing. The traditional approach of subsequently performing extensive laboratory experiments for detailed kinetic and thermodynamic modelling, process simulation and manual investigation of possible configurations is time consuming. A novel methodology is presented here that determines the effect of uncertain parameters on the design and helps to focus the experimental work on the determination of those parameters that significantly influence the production cost.

Process design is understood here as the decision on the process structure, i.e. the choice and the connections of the process units, and their sizing, heat integration, and operating conditions. When the set of suitable unit operations is known, these decisions can be represented by a superstructure and the best process design can be determined by mathematical optimization.

The prerequisite of superstructure optimization are models of all process units. Especially for innovative processes and products, these models will initially have significant errors, as the amount of data is limited. This uncertainty can make a decision on the best process structure impossible, as for different model parameters, different solutions result. Then the model uncertainty has to be reduced by additional experiments, but experiments are time consuming and costly, so the number of experiments should be as small as possible. We developed a methodology that helps to focus the experiments on the determination of those model parameters that are the most relevant ones for the decision on the process structure.

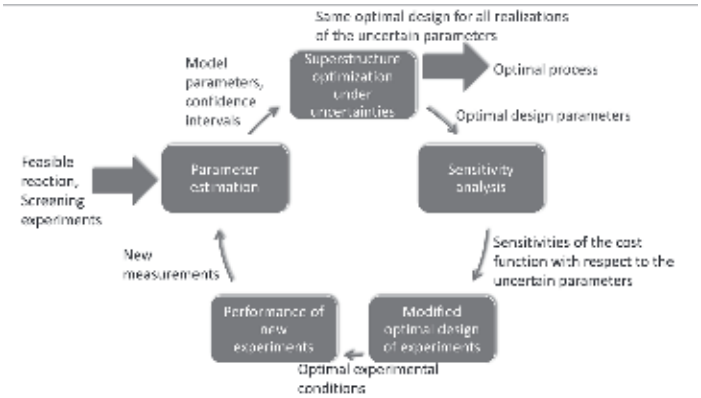

Figure 1: Schematic representation of the main elements of the integrated process design methodology.

The methodology is depicted in Figure 1. Starting with first screening experiments, models are set up and their parameters and the uncertainties of the parameters are estimated from the experimental data. The models are used in superstructure optimization under uncertainty, as proposed in Steimel & Engell (2015). If, due to the uncertainties, not one design alternative can be identified as optimal, the sensitivity of the design decision to the model parameters is identified and used in a model-based optimal design of experiments to plan experiments that are focused on determining the critical parameters. After new experiments have been performed, the procedure is repeated until the uncertainties are small enough such that they do not influence the ranking of the design alternatives.

As an example, the hydroaminomethylation of 1-decene is considered. The superstructure of the process is presented in Figure 2. It includes the alternatives of a tandem reaction in one reactor or a sequence of hydroformylation and reductive amination in two reactors, and the feeding of the solvent dodecane in the reaction step or only in the decanters. In a simulation study, it was shown that when the new approach is applied to the design of the hydroaminomethylation process, it can reduce the number of required experiments to 8 in addition to the screening experiments. A full-factorial design with 16 additional experiments in contrast does not lead to a sufficient reduction of the uncertainty to select one design alternative.

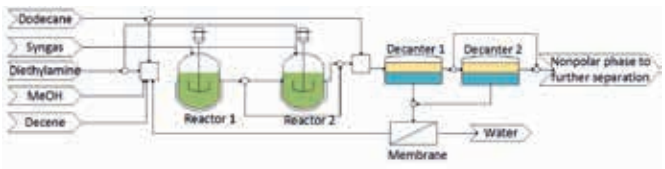

Figure 2: Superstructure for the hydroaminomethylation process.

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Publications:
S. Kaiser, K. H. G. Rätze, F. Huxoll, G. Sadowski, K. Sundmacher, S. Engell. In Integrated Chemical Processes in Liquid Multiphase Systems - From chemical reaction to process design. De Gruyter (2022) To be published.
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Simulation-based Scheduling of Large-scale Industrial Processing Plants Combining Discrete-Event Simulation and Genetic Algorithms

Christian Klanke, Dominik Bleidorn, Christian Koslowski, Christian Sonntag, Sebastian Engell

Improvements in the scheduling of industrial processing plants can lead to a significant increase of their production capacity without investments in new equipment. For industrial use of a scheduling system, it is crucial that the computed schedules can be executed at the plant without further adaptations, otherwise the operators will not accept the system. This requires a detailed representation of many elements of the production, including the availability of personnel, storage capacities, internal transport operations, etc. On the other hand, rigorous optimization methods cannot handle such very detailed models for problems of realistic size. Therefore, we developed an optimization-simulation approach based on a commercial discrete-event simulator and a Genetic Algorithm.

Discrete Event Simulation (DES) is a versatile simulation paradigm to execute computer models of production processes that are dominated by discrete changes of the state of the system, e.g. starting and stopping of the execution of a phase of a batch process or of a transport operation. For an event to take place, complex conditions can be formulated so that an accurate representation of the constraints in the real plant is possible. Discrete Event Simulators such as the software from INOSIM often also include scheduling heuristics which however do not provide optimal schedules if many choices for the allocation of operations to units and their sequencing exist. Therefore, in our work a Genetic Algorithm (GA) is used to optimize the schedules. A GA is a stochastic optimization algorithm, inspired by Darwinian evolution.

The proposed optimization approach is used to schedule an industrial two-stage formulation and filling production process with optional buffer tanks and a transfer panel for flexible routing of intermediates (see Fig. 1). Sequence-dependent changeover times, unit- and product-dependent processing times, limited intermediate storage, a semi-continuous filling stage, and operator shift constraints are represented in the simulation model.

The GA proposes sets of scheduling decisions i.e. the sequences of the production orders and their allocations to the formulation and filling equipment. The effects of the decisions are then evaluated by the simulator. It reports back whether the schedule can be executed and, if so, the values of the objective functions. From the proposed solutions, in each generation a set of survivors is selected of which a subset is selected as parents. From the parent solutions, offspring are generated by recombination and mutation. The newly created solutions are evaluated again and the cycle repeats. The best found solution upon termination of the algorithm is then applied to the real production process. Typically a few thousand evaluations of schedules are needed to obtain a near-optimal schedule which poses a challenge for the efficiency of the simulation.

It was shown in Klanke et al., 2021 that the proposed approach yields reproducible results of high-quality which far outperform the heuristics applied in practice and the non-optimized schedules generated by the INOSIM DES.

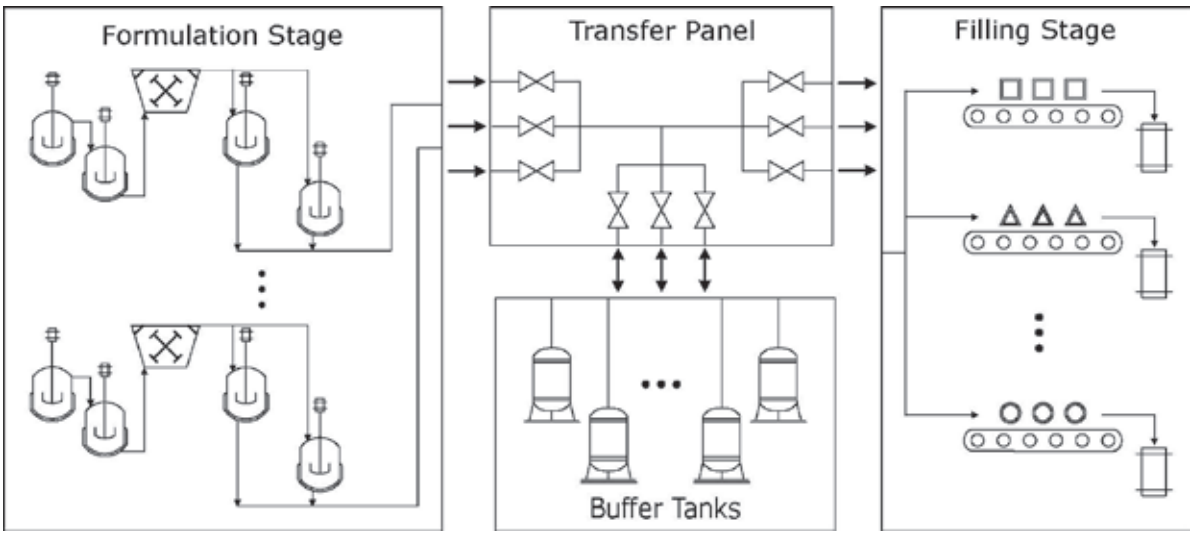

Figure 1: Schematic representation of an industrial formulation plant.

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Dominik Bleidorn, Christian Koslowski and Christian Sonntag are affiliated with INOSIM GmbH.

Modelling and optimization of reactive twin-screw extrusion processes

Continuous production of rheological paint additives

Maximilian Cegla, Sebastian Engell

Twin-screw extruders are a commonly applied processing equipment for polymer formulation. Their application as chemical reactors is still quite rare, despite the fact that they offer the benefits of being able to process solid feedstock, can process highly viscous material, have a high surface to volume ratio for heat supply or removal, and can combine reaction and formulation into one equipment. One reason for not using twin-screw extruders as reactors is that their design and sizing is challenging. The processing conditions are commonly determined experimentally by time consuming experiments, and the structural decisions such as the screw design or the positioning of the feeds are based on the experience of engineers and often suboptimal. To overcome this problem, we suggest a model based optimization approach to the development and optimization of reactive extrusion processes.

Specifically, we are focusing on the production of paint additives for which the transition from batch production to continuous production by reactive extrusion is economically promising. The employed twin-screw extruder model is based upon a mechanistic model where the extruder is discretized into finite volumes. This model was extended to take into account the effects coming along with reactive extrusion. Depending on the geometry of the screw at a certain position, different types of flows between the discrete volumes occur. The flow rates are a function of the local viscosity, the filling level, the pressure difference between the elements as well as of the rotation speed of the screw. To improve the description of the internal flows and the mixing effects, we suggest the use of additional information about the residence times of the screw elements. This information is used to update the internal flows by introducing contributions both in forward as well as in backward direction for each element. To compute the ratio between these two flows, the computation routines of the backflow cell model are used. This leads to a precise description of the mixing characteristics in the extruder. The pressure within the extruder is included as a differential state by using a singular perturbation approach instead of the solution of a linear system of equations. This enables the use of efficient nonlinear solvers. The extruder model in combination with a reaction model is then used for the optimization of the geometry by a memetic algorithm. The discrete design decisions such as the feeding positions and the screw geometry are determined by an evolutionary algorithm and the continuous decisions such as throughput, ratios of the reactants, rotation speed and temperatures are optimized by local continuous optimization for each individual of the population.

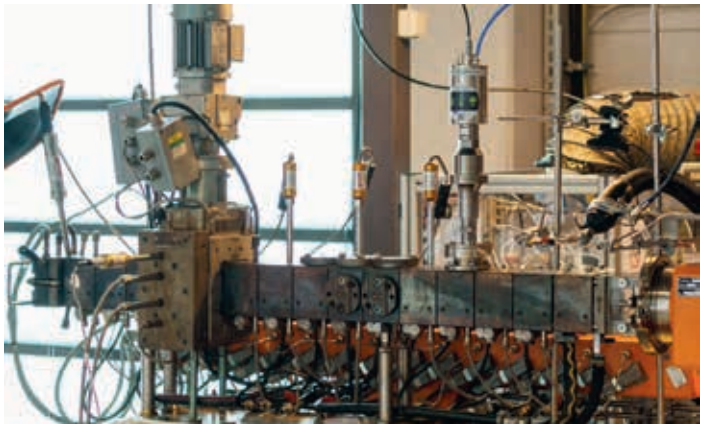

Figure 1: Picture of the reactive extrusion setup with measurement equipment realized at the project partner Fraunhofer ICT. ©Fraunhofer ICT.

The optimization results were validated experimentally in a technical scale on the 18 mm Leistritz Maxx extruder that is shown in Figure 1 at the facilities of the project partner Fraunhofer ICT in Pfinztal.

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Column-specific online state and parameter estimation in SMB processes

Continuous chromatography for an amino acid separation

Stefanie Gerlich, Sebastian Engell

Chromatography is an important separation technology in the production of fine chemicals, pharmaceuticals and biotechnological products. Often it is the method of choice for separation due to its high selectivity, comparatively low operating temperatures, and suitability for the handling of aqueous solutions. The standard chromatographic separation technique is batch chromatography, but by switching to a continuous operation by using the simulated moving bed (SMB) process, solvent consumption can be reduced and throughput can be increased. Due to its switched dynamics that lead to discontinuities and sharp moving concentration fronts, the stable and at the same time optimal SMB process operation is challenging, as the optimal operation is close to the specified limits of the product purities. It has been shown in previous work that the performance of SMB chromatography can be improved by applying model-based optimizing control scheme. However, in this work, it was assumed that all columns in the process exhibit the same behavior which is not true in reality. We therefore have developed a strategy to estimate key parameters of the individual columns for process monitoring and online optimization based on more precise models. The successful experimental application of the strategy has been demonstrated for the continuous separation of two amino acids on an SMB pilot plant taking into account extra-column equipment.

The SMB process is a multi-column chromatographic process that establishes a counter-current flow between the stationary phase and the mobile phase by periodically switching the inlet and outlet ports. Figure 1 illustrates the widely used 4-zone SMB process with two columns per zone. As the columns are not identically packed with adsorbent, the columns do not show the same behavior which should be considered in the computation of an optimal operating point. To estimate individual column parameters is a challenge, as only scarce measurement information, the concentration profiles at the product ports, is available. The strategy used here for individual state and parameter estimation exploits the switching nature of the SMB process. In the parameter estimation, the parameters of the Langmuir isotherm are estimated as various effects of columns parameters can be lumped into isotherm parameters.

When applying online process monitoring schemes to real SMB processes, especially at small scale the influence of extra-column equipment such as pumps, pipes, valves and detectors cannot be ignored as it causes back-mixing and delays. SMB experiments at our lab-scale pilot plant (see Figure 2) revealed that the delay that is observed between the switching of the valve and the corresponding jump in the concentration profile is approximately the same for all columns and switching states. The observed delay is approximately 20 % of the duration of one period while the ratio between all dead volumes in the plant and the volume of all columns is only 5 %. We therefore lump all time-delays caused by extra-column equipment into one plug flow element at each outlet. With this extension of the model, the state and parameter estimation scheme is capable of correcting large plant-model mismatches and of capturing the effects of disturbances that occur during operation. This provides the basis for the real-time monitoring of the plant and for reliable online optimization.

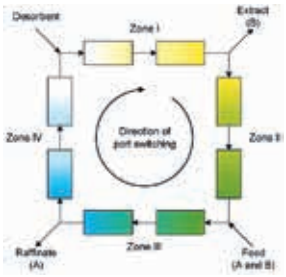

Figure 1: Schematic representation of a 4-zone SMB process with 2 columns per zone. The stronger retained component (B) is collected at the extract port, while the less retained component (A) is withdrawn at the raffinate port.

Figure 2: Photo of the Knauer SMB pilot plant in the lab of the Process Dynamics and Operations group.

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- S. Engell
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Fluid Mechanics (FM)

Thermal phase change and bacterial inactivation in a superheated steam dishwasher using CFD simulations

L. Abu-Farah and N. Germann

The use of superheated steam in dishwashers as a means of reducing water consumption and cleaning time without the use of chemical cleaning agents has great future potential for the restaurants, hotels, and hospitals. In these sectors in particular, hygienic safety is an important concern in addition to the removal of food residues. The present study demonstrates how superheated steam effectively kills bacterial cells in a dishwasher.

The heat transfer and phase change characteristics of superheated steam associated with bacterial inactivation were investigated in an idealized three-dimensional dishwasher with a nozzle and a plate (Fig. 1) a temperature of 180 °C and a pressure of 10 bar.

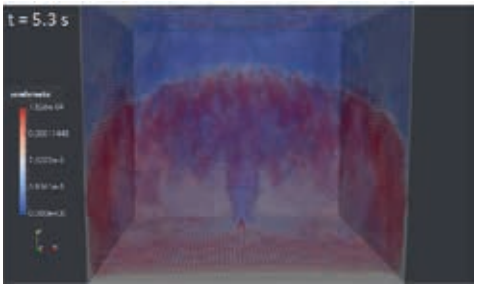

Figure 1: The simulation shows, among others, how the superheated steam rises out of the nozzles at the bottom of the dishwasher and condenses on the sides.

Transient OpenFOAM simulations were performed using an interThermalPhaseChangeFoam solver. The k-omega shear stress transport turbulence model was used to capture the turbulent flow conditions. Bacteria inactivation was described using first-order Arrhenius kinetics. The flow pattern of the steam jet and the shape of the steam plume, the steam condensate, and the separation of the boundary layer are affected by the structure of the shock interaction, and vortices occurred near the nozzle exit, around the perimeter of the plate, and on the side walls of the dishwasher Fig. 2).

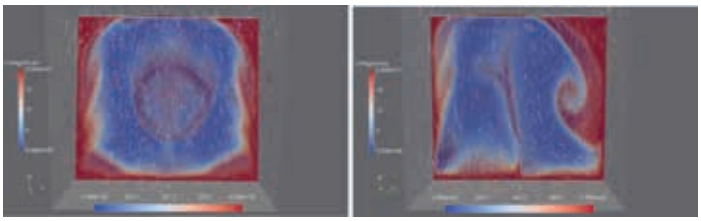

Figure 2: The simulation shows the flow of steam (arrows) and the temperature in the superheated steam dishwasher. It is hotter near the sides and on the surface of the plate (red) than in the empty space (blue).

Strong steam shocks result in a temperature increase, higher steam condensation rate, and lower bacterial concentration on the plate surface. The bacteria on the plate surface are killed within a short time of 25 seconds (Fig. 3), proving the effectiveness of superheated steam in dishwasher cleaning. This study provides a basis for future development and optimization of next-generation superheated steam dishwashers

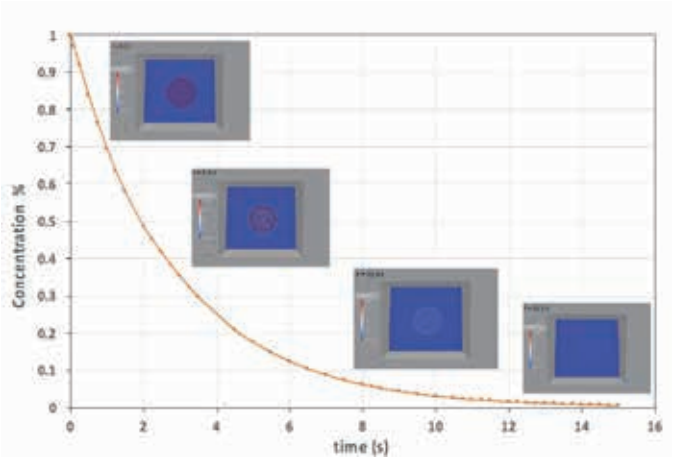

Figure 3: The superheated steam kills off the bacteria on the plate in 25 seconds.

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- A. Moeini, S. Mayer, M. Tallawi, I. De Luca, A. Calarco, N. Reinhardt, L.A. Gray, K. Drechsler, and N. Germann
  Antimicrobial and physicochemical characterization of 2,3 dialdehyde cellulose-based wound dressing systems
  International online conference on Macromolecules: Synthesis, Morphology, Processing, Structure, Properties and Applications, Kottayam, India, September 10–12, 2021. Invited Talk

- L. Abu-Farah and N. Germann
  Thermal phase change and bacterial inactivation in a superheated steam application using CFD
  74th Annual Meeting of the APS Division of Fluid Dynamics Phoenix, Arizona, USA, November 21–24, 2021

Solids Process Engineering (FSV)

A Novel Spraying Process for Droplets in the Small Micrometer Size Range

Clara Lauscher, Gerhard Schaldach, Markus Thommes

Droplets in the small micrometer size range (< 10 µm) are essential in a variety of fields. For example, they can be used for the production of submicron particles in the pharmaceutical industry or can be beneficial in the mass transfer in chemical reactions. However, the preparation of droplets in the small micrometer size range with conventional atomizers is rather challenging.

The aim of this work is to develop a novel process for the generation of droplets in the desired size range. As shown in Figure 1, the process includes the generation of an emulsion with liquid carbon dioxide and a subsequent expansion process of the emulsion through an orifice. The small length-to-diameter ratio of the orifice leads to a rapid pressure drop of the emulsion, which causes an evaporation of the carbon dioxide. Thus, a symmetrical spray cone of the droplets in gaseous carbon dioxide is formed (Figure 2).

The process was studied with water as the disperse phase of the emulsion. The emulsion was generated by dispersing the water into the liquid carbon dioxide through an emulsification nozzle with a diameter of 100 or 200 µm. In addition to the emulsification nozzle, the influence of the mass load of the disperse phase was investigated in the range between 0.01 and 0.08. The resulting droplet sizes in the aerosol are shown in Figure 3. The median droplet diameter in the aerosol increases with increasing water mass load. This can be explained by the decreasing specific energy of the expanding carbon dioxide, which is responsible for the droplet breakup, with increasing water mass load. A smaller diameter of the emulsification nozzle leads to decreasing droplet diameters in the emulsion and consequently to smaller droplets in the final aerosol.

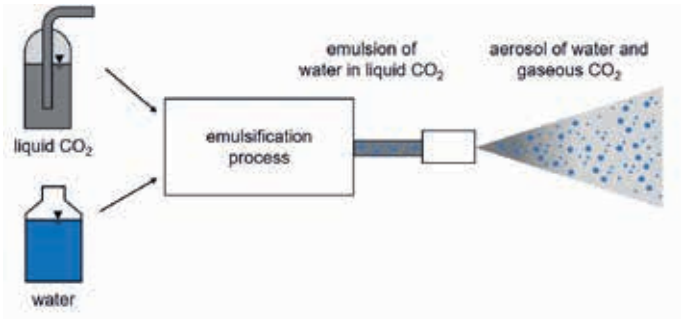

Figure 1: Novel approach for the production of droplets in the small micrometer size range.

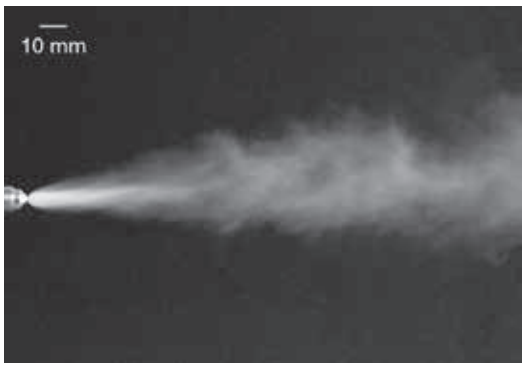

Figure 2: Expanding carbon dioxide emulsion.

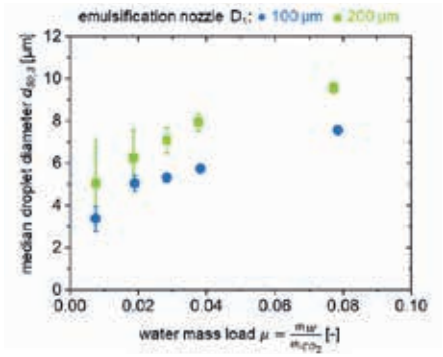

Figure 3: Median droplet diameter in dependence of the water mass load at a distance to the nozzle of 350 mm (av. ± s_m; n ≥ 3).

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Characterizing Molecular Mobility in Amorphous Active Ingredients

An experimental toolbox

Ali Mansuri, Markus Thommes

Molecular mobility of active ingredients (AI) reflected in their relaxation dynamics is regarded as a central parameter in the design of amorphous life science products. Long-lasting insecticide-treated mosquito nets as well as amorphous pharmaceutical formulations constitute examples, where quantifying and adjusting the kinetics of the corresponding systems is subject to contemporary research efforts. In the former case of the mosquito nets, which eliminate vectors such as that of Malaria upon the controlled release of an insecticide within the net, it is critical to ensure the availability of the AI on the surface of the net especially after washing. In the latter case of pharmaceutical formulations, the adverse effect of the drug's high molecular mobility on its physical stability is the kinetic challenge to be addressed. Here we provide an experimental platform encompassing distinct approaches for quantifying the molecular mobility of amorphous active ingredients in a broad temperature range both above and below the dynamic glass transition temperature T_g. The measurement techniques exercised on the model insecticide imidacloprid (IMI) in this work, include broadband dielectric spectroscopy (BDS), differential scanning calorimetry (DSC) and oscillatory shear rheology.

The structural (α-) relaxation time, which could be seen as a measure for the cooperative molecular motion in amorphous substances, governs many kinetically-bound processes such as diffusion and crystallization. This quantity was investigated above T_g, by means of BDS and oscillatory shear rheology, which record the response of the material after being exposed to periodic perturbations in the form of a characteristic dielectric and viscoelastic structural recovery time, respectively. As evident from Figure 1 presenting the relaxation map of IMI, the electric (●) and mechanical (■) relaxation times of IMI seem to be in reasonably good agreement with each other. To study molecular dynamics below T_g we employed the Adam-Gibbs-Vogel approach (based on the notion of fictive temperature obtained via DSC investigations, **--**), calorimetric aging (see Figure 2, based on the enthalpy recovery of the aged glass at glass transition, **+**), dielectric aging (based on the decrease in dielectric loss upon aging, ×) as well as frequency-temperature superposition (FTS) applied to dielectric (○) and rheological (□) responses of the AI. The apparent discrepancies in the relaxation times below T_g could be explained firstly in light of the ergodic nature of the glass; in other words, the effect of thermal history leading to a decrease in molecular mobility as the glass evolves towards metastable equilibrium. Secondly, the preparation of the glass from the supercooled liquid state, reflected in the applied cooling rate, leads to different energetic states with varying molecular mobilities. Both of these factors were variable in the aforementioned approaches causing the dissimilarities below T_g.

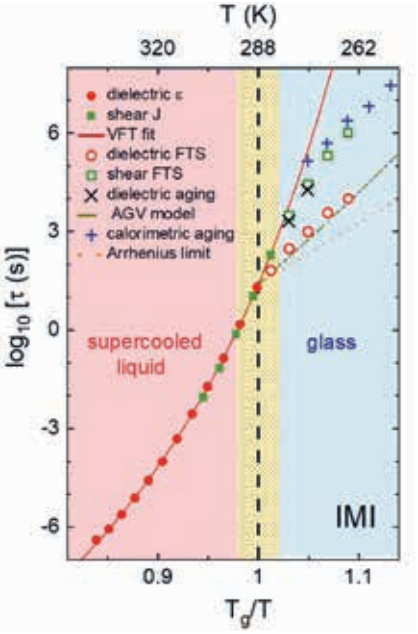

Figure 1: Relaxation map of IMI in the supercooled liquid and glassy states.

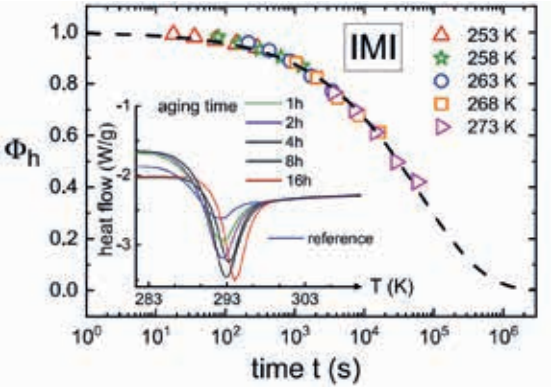

Figure 2: Master plot of the normalized enthalpy relaxation. The inset presents examples of enthalpic undershoots of aged IMI at the glass transition.

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On Hydrodynamic Dissolution Phenomena

Fundamental research on substance-specific dissolution behavior

Amelie Mattusch, Jens Bartsch, Markus Thommes

The solubility of an active pharmaceutical ingredient (API) is an important factor for classification in terms of bioavailability. For an efficient drug product design a detailed, comprehensive understanding of the dissolution process is required. However, frequently used diffusion models are out of date. The investigation of flow-induced effects on the dissolution of APIs can provide evidence about postulated drug-solvent interactions as well as dissolution limitations and make an important contribution to in-vivo-in-vitro *correlations (IVIVC). Therefore, this study focuses on the investigation of hydrodynamic-influenced dissolution of various APIs.*

During dissolution the diffusion layer of a substance can be reduced by increasing the incident flow velocity on a sample and thus the convection. To determine the dissolution rate of pure API, the intrinsic dissolution rate, a new flow channel was designed to in order to ensure defined flow conditions: A sample of pure API is inserted at the bottom of the flow channel and is overflowed by dissolution media.

CFD simulations (Ansys Fluent 2020R1) of the designed flow channel indicated laminar flow conditions and a uniform flow pattern at the sample in the identified valid measuring range. Particle Image Velocimetry (PIV) measurements (DaVis 10 and VE Phantom VEO 410L color) have confirmed this: Exemplary, two flow profiles are shown in Figure 1.

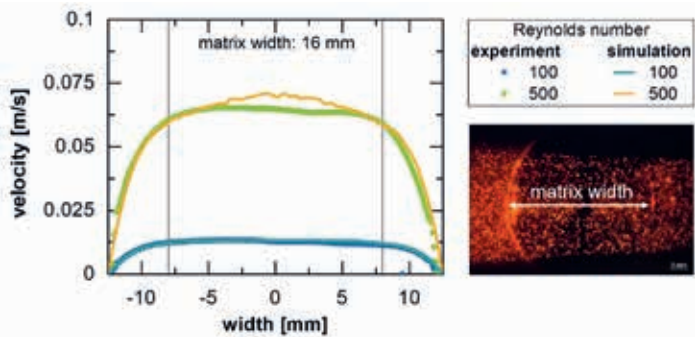

Figure 1: Flow profiles at the sample in the middle plane of the long flow channel measured via PIV measurements (av, n=9) and calculated via CDF simulation for different Reynolds numbers.

The real flow profiles show the same characteristic as the simulatively determined flow profiles over the cross section of the flow channel. The experiment actually shows a more homogeneous distribution of the velocity over the matrix width.

The determined dependencies of intrinsic dissolution rate and flow velocity confirm that with an increasing velocity the dissolution decreases for the investigated substances. Presumably, the diffusion layer becomes smaller at higher velocities and the influence of the surface reaction increases. These statements are in accordance with simulations, where visual differences are immediately noticeable by varying the flow velocity (see Figure 2).

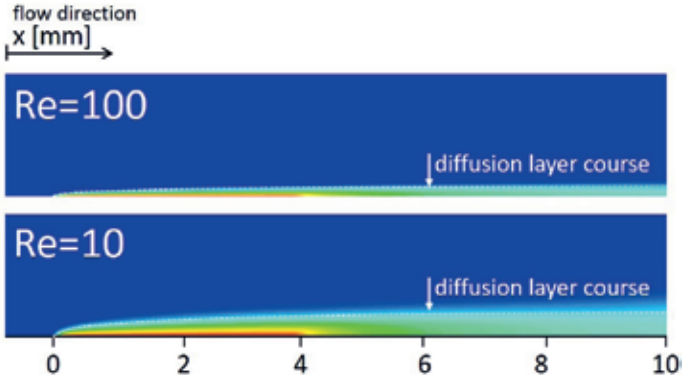

Figure 2: Numerical solution of the dissolution boundary of a sample with 4 mm length in flow direction.

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Fluid Separations (FVT)

Avoiding Co-Product Accumulation in Continuous Processes

A hybrid reaction-separation process combining membranes and homogeneous catalysis

Stefan Schlüter, Christoph Held and Mirko Skiborowski

The transformation of the chemical industry from fossil-based raw materials to renewable resources is a major challenge of the current century. Additionally, reducing the energy demand of chemical processes and greenhouse-gas emissions is important to reach climate goals. Hybrid reaction-separation processes have shown to contribute significantly to save costs and energy. An example of such a hybrid process is the combination of a chemical reaction with membrane separation of the catalyst. In this work, a hybrid process was developed to efficiently convert renewable oleochemicals to valuable aliphatic amines. The amines were synthesized in a continuous biphasic catalytic process including catalyst recycling. Unfortunately, the co-product water accumulated in the process, which dramatically reduced the process efficiency. As a way out, organic solvent nanofiltration was applied to separate the catalyst from the co-product water. Finally, this allowed stable long-term process operation avoiding the accumulation of the co-product with the implemented membrane separation.

Conventionally, amines are produced by multi-step reactions starting from alkenes that are converted to intermediates such as nitriles or alcohols. These intermediates are first isolated and then used in subsequent reactions to produce the amine. Such processes lack sustainability due to intermediate separation steps and often require high temperatures or pressures. Thus, hybrid concepts are a suitable strategy for more sustainable processes.

In the studied process the substrate 1-decene is first converted to undecanal with synthesis gas (CO/H_2) followed by a reaction with diethylamine and hydrogen into a long-chain tertiary amine, while water is formed as the co-product. This reaction takes place in a single continuously stirred tank reactor. A solvent mixture of methanol and *n*-dodecane is used in the reactor, which demixes into two liquid phases in the decanter upon decreasing the temperature from 125 °C to 5 °C. The amine product distributes mainly to the upper non-polar phase, while the catalyst remains in the lower polar phase. However, the co-product water also distributes into the lower polar phase. The co-product separation from the polar phase is essential to avoid that water accumulates in the recycle stream and into the reactor, as this would strongly reduce the reaction performance. Thus, the process was further developed by adding a membrane unit, which partially removes the co-product from the catalyst phase before it is recycled back to the reactor (Figure 1).

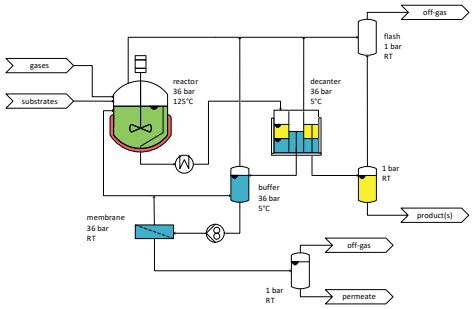

Figure 1: Simplified flowsheet of the continuous production process.

The process concept shown in Figure 1 can only be successful by identifying a suitable membrane that permeates water preferentially while providing high catalyst rejection. The membrane was selected by a structured multi-step screening procedure choosing from a range of different commercially available membranes. Afterwards, the membrane unit was integrated into the continuous process and the process was operated for 75 hours. A constant reaction performance with high selectivity was realized, and more than 99 % of the catalyst was retained by the membrane (Figure 2 a), while water was permeated. Furthermore, the water mass fraction in the recycle stream was maintained as low as 6 wt.% after 75 h of process operation, which is much lower than previously published results without membrane separation (15 wt.%, Figure 2 b). This proves the suitability of the process concept for co-product separation and catalyst recycle.

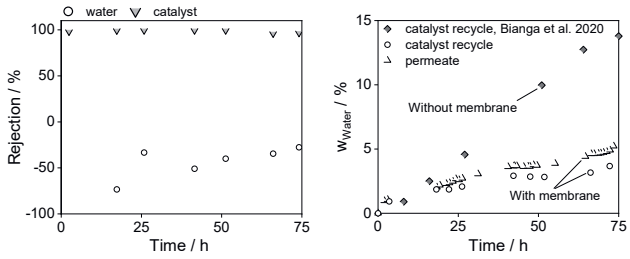

Figure 2: (a) Rejection of water and the catalyst during the continuous process. (b) Mass fraction of water in the permeate and recycle stream during the continuous process compared to previous results without membrane separation.

This work realized a hybrid reaction-separation process for the separation of polar catalyst and water. The resulting integrated process is complex in the design and operation, but it opens the door towards energy savings by synergistic effects of co-product removal and catalyst recycle. The concept is suited for chemical syntheses using renewable feedstock.

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Pervaporation for Homogeneous Catalyst Retention and Water Removal

Jerzy Pela, Mirko Skiborowski, Christoph Held

Recently, homogenous catalysis using ruthenium was identified for clean and efficient epoxidation reactions. The reaction uses hydrogen peroxide H_2O_2 as the oxidant and acetonitrile as the solvent, enabling 99% selectivity and conversion. Therefore, the reaction products are almost exclusively the epoxide product and the co-product water. Having water as the single co-product with almost 100% yield results in a green process, which however requires an effective retention of the catalyst and separation of the products to be economic. While the epoxide can be efficiently separated by means of extraction, separation of the co-product still presents a challenge. For an effective dehydration of the recycle stream, containing the precious ruthenium catalyst and the solvent, a membrane separation by means of pervaporation is proposed and experimentally demonstrated.

Epoxidation reactions are of special importance in the chemical industry e.g., for epoxy glues and structural materials, but also for sterilization of medical instruments. The post-epoxidation reaction mixtures in the respective process contain epoxide, water, the ruthenium catalyst dissolved in solvent (acetonitrile in this work) and the required ligand (dipicolinic acid in this work) of the catalyst complex. In the first step of the downstream processing, the epoxide is extracted by means of an organic solvent. The polar phase contains the remaining polar solvent and ruthenium catalyst, as well as the co-product water, which has to be separated in order to avoid accumulation in the process. Thus, dehydration is required to prevent dilution of the reactive mixture and catalyst deactivation.

This work suggest dehydration of the mixture (acetonitrile, water, dipicolinic acid, and ruthenium catalyst) using a pervaporation membrane with an active layer made of poly(vinyl alcohol). The selected membrane is a commercially available Pervap 4100®. The suitability of the membrane and its performance were quantified by experimental investigations, showing transmembrane flux and separation factors for acetonitrile and water as reported in Figure 1.

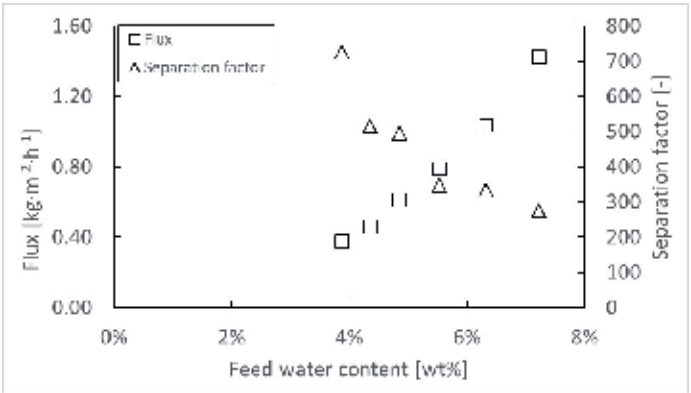

Figure 1: Transmembrane flux (left axis) and separation factor (right axis) between water and acetonitrile at T = 293 K and p = 1 bar.

The process shows very good performance in terms of water removal. Even for low concentrations of water in the feed, a flux above 0.4 kg m^{-2} h^{-1} is achieved. Moreover, the selectivity between acetonitrile and water is high, and separation factors between 200–800 were observed, yielding ca. 96 wt% of water in the permeate throughout the measured range of the feed water contents. Dipicolinic acid and the ruthenium catalyst were retained almost completely in the dehydrated mixture. The content of dipicolinic acid in the permeate was measured at the edge of detectability, i.e. less than 0.005 wt.%. Ruthenium catalyst was detected at 1 ppm in the permeate, compared to 141 ppm in the feed solution. No deterioration of the membrane was observed. Throughout the measurements the investigated PVA membrane showed stable performance in terms of flux and selectivity. The same results were reproduced with a fresh membrane in a repeated measurement.

The results indicate that pervaporation is a suitable technique for downstream processing of epoxidation mixtures. Pervaporation enables complete recycling of the catalyst complex to the reactor without significant solvent loss, while removing the co-produced water at high purity. The developed process combining homogenous catalysis and pervaporation provides an interesting option for an economic green epoxidation reaction path. The further work shall focus on the optimization of the process conditions and a model-based evaluation of a complete reaction-separation process.

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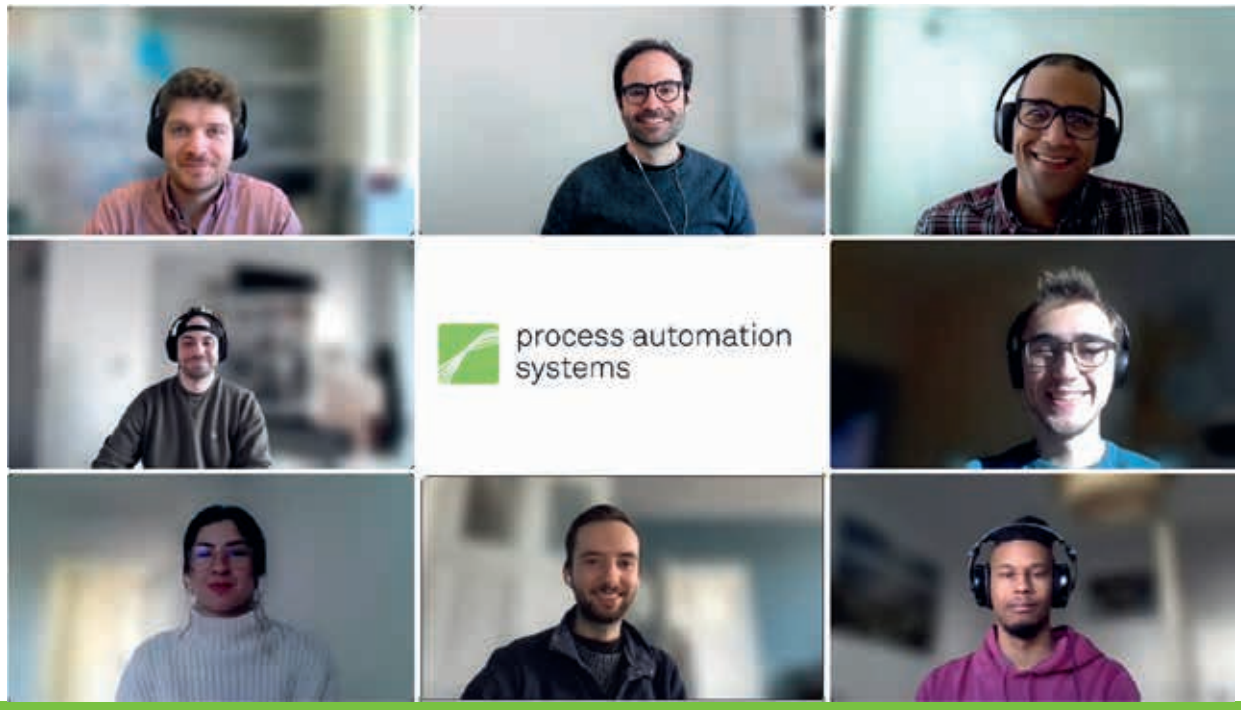

Process Automation Systems (PAS)

Reinforced Approximate Robust Nonlinear Model Predictive Control

Benjamin Karg, Sergio Lucia

Model predictive control (MPC) has become standard in advanced process control because of its ability to directly consider multi-variable processes with constraints by solving an optimization problem online to compute optimal signals. But solving such optimization problems online might be difficult for large problems or when a fast decision is needed. Machine learning, and in particular deep neural networks, can mitigate these limitations with two main methods: imitation learning and reinforcement learning. We show that by combining both strategies, the drawbacks of each method can be alleviated, and high performance levels of the optimization-based controller can be achieved.

MPC is a popular optimal control strategy that enables the operation of complex uncertain systems while considering important process constraints. The main drawback of MPC algorithms is the high computational requirements, which can hinder their real-time applicability. Deep Neural Networks (DNNs), which have recently shown increased capabilities for complex function approximation when compared to traditionally shallow networks, can be used to approximate the solution of the optimal control problems that arise in MPC.

Two main approaches can be employed to obtain a controller in the form of a deep neural network that closely approximates MPC. In imitation learning (IL), data is generated by running closed-loop simulations and generating data from the simulated system state (input to the network) and the corresponding MPC input computed by solving the full optimal control problem (output to the nework). Using this data, the network is trained to mimic the behavior of MPC. The drawback of IL is that the impact of the approximation error on the closed-loop behavior of the resulting controller, which arises from the finite number of samples and the learning algorithm, is not considered in the learning process, potentially leading to undesired behavior. In reinforcement learning RL, the DNN controller interacts with the simulation model and adjusts the parameters of a controller neural network based on the observed performance to optimize the control policy. However, the process of finding (near-) optimal parameters via RL for complex control tasks is difficult in continuous control and action spaces and can lead to a very large number of required data-points. By combining the two learning paradigms as illustrated in Figure 1, the drawbacks of both methods can be mitigated. By first using IL to find a good initialization of the parameters and then applying RL to fine-tune the network with respect to closed-loop behavior, a comparable performance to the one delivered by optimal controllers can be achieved. Figure 2 shows simulation results for MPC and DNN controllers derived with different learning approaches for operating a nonlinear polymerization reactor affected by uncertain parameters. When only RL is used, the DNN controller learns a conservative behavior leading to long batch times and exclusively relying on IL results in sub-optimal behavior towards the end of the control task, as data is scarce in the end phase of the batch process. When both IL and RL are combined, the DNN controller provides optimal control signals over the full batch and even outperforming MPC regarding economic performance with insignificant violations of constraints.

Figure 1: Design approach for high-performant neural network controllers via deep learning.

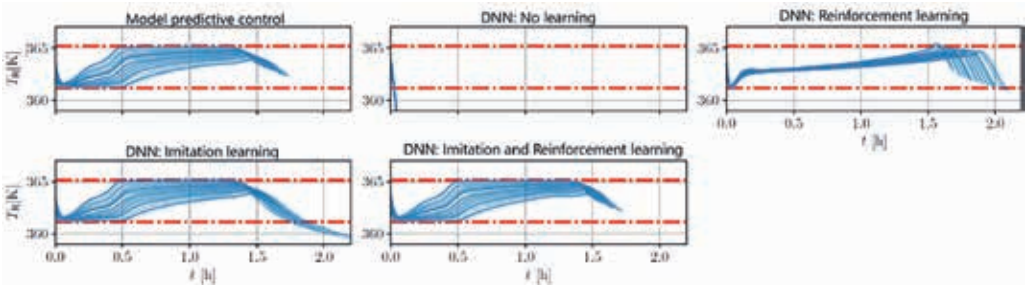

Figure 2: Performance comparison of optimization-based controller and learning-based controller for a batch polymerization reactor with uncertain parameters. Shown is the reactor temperature for 100 simulations (blue) and the temperature constraints (red).

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- Fischer, K.L.; Freund, H.
  Intensification of Load Flexible Fixed Bed Reactors by Optimal Design of Staged Reactor Setups
  Chem. Eng. Process. 159 (2021) 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
  Ind. Eng. Chem. Res. 60(18) (2021) 6753-6766

- Moioli, E.; Schmid, L.; Wasserscheid, P.; Freund, H.
  Kinetic Modelling of Reactions for the Synthesis of 2-Methyl-5-Ethyl-Pyridine
  React. Chem. Eng. 6 (2021) 1254-1264

- 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
  Chem. Eng. Sci. 244 (2021) 116768

- Littwin, G.; von Beyer, M.; Freund, H.
  Detailed Investigation of Liquid Distribution and Holdup in Periodic Open Cellular Structures Using Computed Tomography
  Chem. Eng. Process. 168 (2021) 108579

Further Publications

- Freund, H.; Sauer, J.; Wachsen, O.
  "Circular Economy" – ein neues und zugleich altes Arbeitsgebiet der Reaktionstechnik
  Editorial, Chem.-Ing.-Tech. 93(5) (2021) 735

Conference Contributions: Oral Presentations

- Littwin, G.; Freund, H.
  Heat Transfer Characteristics of Additively Manufactured Periodic Open Cellular Structures as Novel Catalyst Supports
  Jahrestreffen Reaktionstechnik, Web Conference, Germany, May 2021

- Freund, H.
  Optimal Design and Operation of Catalyst-Reactor-Plant Systems: Model Adequacy is Key, MultiMod Workshop
  "Quo Vadis Multiscale Modeling in Reaction Engineering?", Web Conference, September 2021

- Freund, H.
  Additive Manufacturing of Periodic Open Cellular Structures as Tailor-Made Catalyst Supports
  24th International Conference on Chemical Reactors, Web Conference, September 2021

- Littwin, G.; Freund, H.
  Heat Transport Characterization and Geometric Optimization of Periodic Open Cellular Structures
  24th International Conference on Chemical Reactors, Web Conference, September 2021

Conference Contributions: Poster Presentations

- Held, H.; Gstettenbauer, M.; Freund, H.
  Advances in Modelling of a Trickle Bed Reactor for Liquid Phase Hydrogenation Reactions Influenced by Mass Transfer
  Jahrestreffen Reaktionstechnik, Web Conference, Germany, May 2021

- Langer, M.; Kellermann, D.; Freund, H.
  Development of a Semi-Mechanistic Kinetic Model Approach to Describe Dynamically Operated CO_2 Methanation
  Jahrestreffen Reaktionstechnik, Web Conference, Germany, May 2021

- Rudolf, D.; Freund, H.
  An Intelligent Catalyst Carrier Concept with Additively Manufactured Structures to Improve the Wall Heat Transfer in Tubular Reactors
  MultiMod Workshop "Quo Vadis Multiscale Modeling in Reaction Engineering?", Web Conference, September 2021

Invited Talks

- Freund, H.
  Structure: Process Intensification in the Spatial Domain, Webinar Talk
  9th EUROPIC Course "Process Intensification: Fundamentals & Applications", Webinar Series, January 2021

- Freund, H.
  Additive Manufacturing of Periodic Open Cellular Structures as Tailor-Made Catalyst Supports
  DECHEMA Virtual Talks: Smart Reactors, Web Conference, Germany, May 2021

- Freund, H.
  2021 and beyond: REC – Modellbasierter Entwurf optimaler Reaktoren und strukturierter Katalysatoren
  Seminar Talk, Tag des BCI an der Fakultät Bio- und Chemieingenieurwesen, Technische Universität Dortmund, Dortmund, Germany, October 2021

Fluid Mechanics (SM)

Publications 2019 – 2021

2021

- Boettcher, K.; Behr, A.
  Using virtual reality for teaching the derivation of conservation laws in fluid mechanics
  International Journal of Engineering Pedagogy 11, 42-57 (2021)

- Chaudhuri, J.; Boettcher, K.; Ehrhard, P.
  Pressure drop in fibrous filter – Representative domain size and effect of fibre orientation
  Chemical Engineering Science 246, 116865 (2021)

- Chaudhuri, J.; Boettcher, K.; Ehrhard, P.
  Numerical investigation of coalescence filtration: Multiphase flow through fibrous structures
  Separation and Purification Technology 257, 117853 (2021)

- Gödeke, L.; Oswald, W.; Willenbacher, N.; Ehrhard, P.
  Dimensional analysis of droplet size and ligament length during high-speed rotary bell atomization
  Journal of Coatings Technology and Research 18 (1), 75-81 (2021)

- Grünendahl, S.; Danila, K.; Brandner, D. M.; Ehrhard, P.
  Experimental investigations on rising bubbles in stagnant water in vertical capillaries
  Proc. Applied Mathematics and Mechanics 21, e 202100172 (2021)

2020

Peer reviewed Journals

- K. Boettcher, A. Behr
  Usage of a virtual environment to improve the teaching of fluid mechanics
  International Journal of Online and Biomedical Engineering 16, 54-68 (2020)

- K. Boettcher, A. Behr
  Teaching Fluid Mechanics in a Virtual-Realitiy Based Environment
  Proc. IEEE Global Engineering Education Conference, Porto, Portugal 1563–1567 DOI: 10.1109/EDUCON45650.2020.9125348 (2020)

- S. Grünendahl, D. M. Brandner, P. Ehrhard
  Experimental investigations on rising bubbles in vertical capillaries
  Proc. Applied Mathematics and Mechanics 20, e 202000184 (2020)

Books & Book Articles

- P. Ehrhard
  Kapitel Mikroströmungen
  Prandtl-Führer durch die Strömungslehre
  (ed. Oertel jun. H.H.), 15. Auflage, Springer Vieweg, Wiesbaden (2020)

- K. Boettcher, D. Boettcher, A. Behr
  Virtuelle Realität des Unsichtbaren: Verständnisfördernde Visualisierung und Interaktivierung strömungsmechanischer Phänomene
  Sammelband Labore in der Hochschullehre: Labordidaktik, Digitalisierung, Organisation, WBV Verlag (2020)

2019

- Boettcher, K.; Neumann, T.; Ehrhard, P.
  Influence of the wall effect on the flow through a bed of monodisperse spheres
  Chemie Ingenieur Technik 91, 1251-1259 (2019)

- J. Chaudhuri, A. Baukelmann, K. Boettcher, P. Ehrhard
  Pressure drop in fibrous filters
  European Journal of Mechanics B/Fluids 76, 115-121 (2019)

- K. Boettcher, T. Neumann, P. Ehrhard
  Permeability and flow through a packed bed of beads in a rectangular cross-section affected by overlapping wall effects
  Proc. Applied Mahematics and Mechanics 19, e 201900302 (2019)

- A. K. Höffmann, J. Schmidt, P. Ehrhard
  Numerical investigations of the hydrodynamics and the oxygen mass-transfer in aerated tanks
  Proc. Applied Mathematics and Mechanics 19, e 201900279 (2029)

- S. Mohan, J. Chaudhuri, L. Gödeke, P. Ehrhard
  Numerical investigation of aerosol deposition on a single 2D fiber
  Proc. Applied Mathematics and Mechanics 19, e 201900350 (2019)

- W. Oswald, J. Lauk, L. Gödeke, P. Ehrhard, N. Willenbacher
  Analysis of paint flow pulsation during high-speed rotary bell atomization
  Coatings 9, 674 (2019)

- W. Oswald, L. Gödeke, P. Ehrhard, N. Willensbacher
  Influence of the elongational flow resistance and pigmentation of coating fluids on high-speed rotary bell atomization
  Atomization and Sprays 29, 913-935 (2019)

Technical Biochemistry (TB)

Activity of THC, CBD, and CBN on Human ACE2 and SARS-CoV-1/2 Main Protease to Understand Antiviral Defense Mechanism

Thanet Pitakbut, Gia-Nam Nguyen, Oliver Kayser

THC, CBD, and CBN were reported as promising candidates against SARS-CoV-2 infection, but the mechanism of action of these three cannabinoids is not understood. This study aims to determine the mechanism of action of THC, CBD, and CBN by selecting two essential targets that directly affect the coronavirus infections as viral main proteases and human angiotensin-converting enzyme2. Tested THC and CBD presented a dual-action action against both selected targets. Interestingly, only CBD acted as a potent viral main protease inhibitor at the IC_{50} value of 1.86 ± 0.04 µM and exhibited only moderate activity against human angiotensin-converting enzyme2 at the IC_{50} value of 14.65 ± 0.47 µM. THC acted as a moderate inhibitor against both viral main protease and human angiotensin-converting enzymes2 at the IC_{50} value of 16.23 ± 1.71 µM and 11.47 ± 3.60 µM, respectively. Here, we discuss cannabinoid-associated antiviral activity mechanisms based on in silico docking studies and in vitro receptor binding studies.

Plant secondary metabolites have been intensively studied for novel antiviral substances long before the severe acute respiratory syndrome coronavirus2 or SARS-CoV-2 pandemic occurred, but today they gain more attention than before. The principle of antiviral drug discovery from plants is that plants developed defensive metabolites against pathogenic microorganisms such as bacteria, fungi, and viruses to survive. A success story of an approved plant metabolite against the human viral infection is podophyllotoxin, a lignan from Podophyllum peltatum or Podophyllum emodi, approved to treat human papillomavirus infection topically. However, there are much more plant metabolites that are currently under investigation. Since the rise of this pandemic, the interest in the cannabinoids for the SARS-CoV-2 treatment has been rising remarkably, but the direct antiviral activity of cannabinoids is low. Most of the studies were review articles and focusing on the supportive therapy for SARS-CoV-2 infection such as decreasing the inflammation by reducing the cytokine storm, especially interleukin-6 and the agonistic effect of the cannabinoids at PPARγ receptor at lung tissue. Only a few studies have reported the activity of cannabinoids against SARS-CoV-2 infection experimentally. A study by Wang et al showed the downregulation of hACE2 by an extract with a high CBD content. Another study reported the direct and remarkable activity of THC, CBD, and CBN against SARS-CoV-2 infection with the same potency as the standard drugs such as chloroquine, remdesivir, and lopinavir in the cell-based assay. However, the mechanism of action of these three cannabinoids against SARS-CoV-2 infection is not yet known. Therefore, this study aims to reveal the antiviral mechanism of THC, CBD, and CBN. Based on the coronaviruses' pathogenesis (both SARS-CoV1 and SARS-CoV-2), there are two main strategies to stop these coronaviruses' infection. The first strategy is to prevent these viruses from entering the cell. The receptor protein hACE2 which is located on the membrane of immune cells, is considered to be important for cell invasion, and the viral spike protein, a transmembrane protease, serine 2 (or TRPRSS2), is critical for entering the cell. The second strategy is to stop replicating the virus in the host cell by inhibiting the viral proteolysis (stopping the viral main protease activity). Therefore, we selected hACE2 and viral main proteases from both SARS-CoV1 and SARS-CoV-2 as the target proteins to determine the mechanism of action and evaluate the potency of THC, CBD, and CBN against coronavirus infections, as presented in Fig. 1.

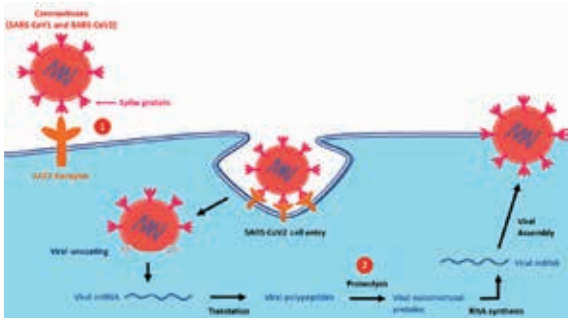

Figure 1: Simplified replication cycle of coronaviruses in the human host cell.

Our finding has confirmed the predicted mechanism and provided more insight information regarding the molecular interactions of how THC and CBD inhibit the SARS-CoV-2 infection in the cell-based assay from previous reports (Figure 2).

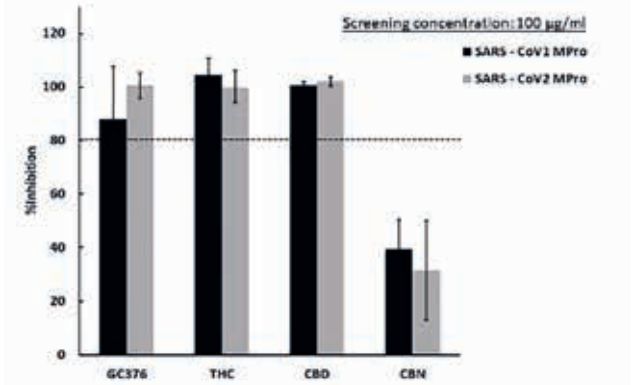

Figure 2: Percent inhibition of GC376 as the positive control, CBD, THC, and CBN against SARS-CoV1 and SARS-CoV-2 main protease (MPro) activities.

Unlike remdesivir (a viral RNA-dependence RNA polymerase inhibitor) and lopinavir (a viral main protease inhibitor), the mechanism of THC, CBD, and CBN against SARS-CoV-2 infection are unknown. Only the predicted mechanism as an inhibitor against viral protease was proposed from the computational experiments. Our experiments showed that only THC and CBD could inhibit SARS-CoV1 and SARS-CoV-2 main proteases but not CBN. Therefore, we partially agree with the previous studies predicted mechanism and propose a new hypothesis that CBN may have a different mechanism of action against SARS-CoV-2 infection. Notably, we evaluated the structure-activity relationship among THC, CBD, and CBN against SARS-CoV-2 main protease for the first time, and the molecular docking experiment supports this discovery. Two major chemical features that are likely to play an essential role in this inhibitory concept are the cyclohexene ring B and the free rotation between ring A and B (Figure 3).

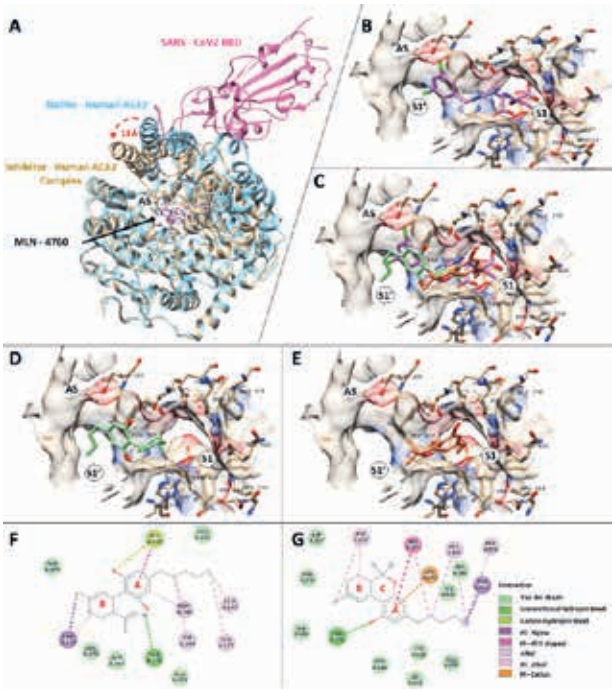

Figure 3: Detailed 3D pose and molecular interaction of THC, CBD, MLN-4760, and hACE2 (PDB ID: 1R4L) including the involved amino acids: (A) The 3D binding pose of the hACE2-MLN-4760 complex (PDB ID: 1R4L, brown color) in comparison to the hACE2-SARS-CoV-2 RBD complex (PDB ID: 6LZG, pink and blue color). The narrow indicates the changing of sub-domain I between native hACE2 and hACE2-inhibitor complex, approximately 13 Å, and AS indicates the active site; (B) The 3D binding pose of MLN-4760 in the binding pocket of hACE2. S1 and S1' indicates the sub-pockets in the active site; (C) Superposition 3D structures of THC, CBD, and MLN-4760 in the binding pocket of hACE2; (D) 3D binding pose of CBD; (E) 3D binding pose of THC; (F) 2D molecular diagram of CBD; (G) 2D molecular diagram of THC and the involved amino acids in the binding pocket of hACE2; A, B, and C indicates the core chemical components on the cannabinoid structure.

Remarkably, THC and CBD are not just only inhibiting the viral proteases like lopinavir (Figure 2), the recommended antiviral main protease inhibitors, but also do the same on hACE2. These data shed light on the discussed mechanism of CB2 receptor interaction to reduce the proinflammatory effect of SARS-CoV-2. THC is known as a partial agonist, as well as CBN being agonist and inverse agonist. Based on recent reports, this must be an obvious contradiction and does not fully explain the proposed immunomodulatory action of cannabis. We suggest a dual-action of THC and CBA against coronavirus infections both from SARS-CoV1 and SARS-CoV-2 by inhibiting viral proteases and hACE2 activities that inhibit viral protease and a distinct effect of CBD as CB2 based immunomodulatory compound. This finding will trigger cannabinoids as an interesting antiviral class of natural products to be explored in the future.

Publications:
Pitakbut, T., Nguyen, G.-N., and Kayser, O. Activity of THC, CBD, and CBN on human ACE2 and SARS-CoV1/2 main protease to understand antiviral defense mechanism. Planta Med 2021, DOI: 10.1055/a-1581-3707.

Contact:
oliver.kayser@tu-dortmund.de

Publications 2019 – 2021

2021

Peer-reviewed Papers

- Riga, R., Happyana, N., Quentmeier, A., Zamarelli, C., Kayser, O. and Hakim E.H.
  Secondary metabolites from Diaporthe lithocarpus islated from Artocarpus heterophyllus.
  Nat Prod Res. 2021, 35:2324-2328

- Pitakbut, T., Nguyen, G.-N., and Kayser, O.
  Activity of THC, CBD, and CBN on human ACE2 and SARS-CoV1/2 main protease to understand antiviral defense mechanism.
  Planta Med 2021, DOI: 10.1055/a-1581-3707

- Hussain, T., Jeena, G., Pitakbut, T., Vasilev, N., and Kayser, O.
  Cannabis sativa research trends, challenges and new-age perspectives.
  ISCIENCE 2021, 24, DOI: https://doi.org/10.1016/j.isci.2021.103391

- Daoud, F., Zühlke, S., Spiteller, M., and Kayser, O.
  Elimination of diethylenetriaminepentaacetic acid from effluents from pharmaceutical production by ozonation.
  Ozone: Science & Engineering, DOI: 10.1080/01919512.2021.1983409

- Hillebrands, L., Lamshoeft, M., Lagojda, A., Stork, A. and Kayser, O.
  In vitro metabolism of tebuconazole, flurtamone, fenhexamid, metalaxyl-M and spirodiclofen in Cannabis sativa L. (hemp) callus cultures.
  Pest Manag Sci 2021, DOI: 10.1002/ps.6575

- Pitakbut, T., Spiteller, M., and Kayser, O.
  In vitro production and exudation of 20-hydroxymaytenin from Gymnosporia heterophylla (Eckl. and Zeyh.)
  Loes. cell culture. Plants 2021, 10, 1493. https://doi.org/10.3390/plants100781493

2020

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- Thomas, F., Schmidt, C., and Kayser, O.
  Bioengineering studies and pathway modeling of the heterologous biosynthesis of tetrahydrocannabinolic acid in yeast.
  Appl Microbiol Biotechnol 2020, DOI: 10.1007/s00253-020-10798-3

- Nguyen, G.-N., and Kayser, O.
  Biosynthesis and chemical modifications of minor cannabinoids.
  In: eLS. John Wiley & Sons, LTD: Chichester. May 2020. DOI: 10.1002/9780470015902.a0028875

- Hensel, A., Bauer, R., Heinrich, M., Spiegler, V., Kayser, O., Hempel, G., Kraft, K.
  Challenges at the time of Covid-19: Opportunities and innovations in antivirals from nature.
  Planta Med 2020, 86: 659-664

- Averesch, N.J.H. and Kayser, O.
  Editorial: Biotechnological Production and Conversion of Aromatic Compounds and Natural Products.
  Front. Bioeng. Biotechnol. doi: 10.3389/fbioe.2020.00646

- Rodziewicz, P. and Kayser, O.
  Cultivation and breeding of *Cannabis sativa* L. for medicinal use.
  In: Handbook of Plant Breeding - Medicinal, aromatic and stiumlant plants.Vol. 12. Eds.: Novak, J., and Blüthner, J.-W. Springer International Publishing, Springer Nature Switzerland AG, ISBN 987-3-030-38791-4, 2020

2019

Peer reviewed Papers and Reviews

- Thomas, F., Kayser, O.
  Minor cannabinoids of *Cannabis sativa* L.
  Journal of Medicinal Sciences 88, 141-149 (2019)

- Vautz, W., Hariharan, C., and Kayser, O.
  Fast Detection of recent *Cannabis sativa* L. consumption in exhaled breath using a mobile ion mobility spectrometer
  Journal of Forensic Research Crime Studies 3, 1-11 (2019)

- Riga, R., Happyana, N., Quentmeier, A., Zammarelli, C., Kayser, O., and Hakim, E.H.
  Secondary metabolites from *Diaporthe lithocarpus* isolated from *Artocarpus heterophyllus*
  Natural Product Research https://doi.org/10.1080/14786419.2019.1672685 (2019)

- Heinrich, M., Appendino, G., Effert, T., Fürst, R., Izzo, A.A., Kayser, O., Pezzuto, J.M., Viljoen, A.
  Best practice in research - overcoming common challenges in phytopharmacological research.
  J. Ethnopharm 2019, https://doi.org/10.1016/j.jep.2019.112230 (2019)

- Rodziewicz, P., Loroch, S., Marczak, L., Sickmann, A. and Kayser, O.
  Cannabinoid synthases and osmoprotective metabolites accumulate in the exudates of *Cannabis sativa* L. glandular trichomes
  Plant Science 284, 108-116 (2019)

- Hussain, T., Espley, R.V., Gertsch, J., Whare, T., Stehle, F. and Kayser, O.
  Demystifying the liverwort *Radula marginata*, a critical review on its taxonomy, genetics, cannabinoid phytochemistry and pharmacology
  Phytochemical Reviews 18, 953-965 (2019)

- Kohnen-Johannsen, K.L., Kayser, O.
  Tropane alkaloids: chemistry, pharmacology, biosynthesis and production
  Molecules 2019, 24: 796

- Aati, H., El-Gamal, A., and Kayser, O.
  Chemical composition and biological activity of the essential oil from the root of *Jatropha pelargoniifolia* Courb. native to Saudi Arabia
  Saudi Pharmaceutical Journal, 27, 88-95 (2019

- Aati, H., El-Gamal, A., Shaheen, H., and Kayser, O.
  Traditional use of ethnomedicinal native plants in the Kingdom of Saudi Arabia
  Journal of Ethnobioloy and Ethnomedicine 2019, 15: 1-9 (2019)

Proceedings & Book Chapters

- Rodziewicz P. Kayser O.
  Cultivation and Breeding of *Cannabis sativa* L. for medicinal use
  Handbook of Plant Breeding – Medicinal, aromatic and stimulant plants (Novak, J. Blüthner J.-W., eds) (2019)

Presentations

- Kayser, O.
  Trends and prospects in biotechnology.
  Trends and Prospects in Medical and Pharma Biotechnologies in Europe 2019, 15.11.2019, Poznan, Poland

- Kayser, O.
  Ethnobotany and medicinal plant biotechnology: From tradition to modern aspects of drug development.
  Trends and Prospects in Medical and Pharma Biotechnologies in Europe 2019, 03.06.–04.06.2019, Bratislava, Slovakia

Technical Biology (TBL)

Biotechnological Production of New Alzheimer's Drugs

Mutasynthesis of physostigmines in *Myxococcus xanthus*

Lea Winand, Sebastian Kruth, Nico-Joel Greven and Markus Nett

In the past decades, the natural product physostigmine has become an important lead structure for the development of new drugs against Alzheimer's dementia. In this study, we produced physostigmine derivatives with improved bioactivity, selectivity and toxicity in a genetically engineered host bacterium. The compounds that were generated include the promising drug candidate phenserine, which was previously accessible only by total synthesis.

Physostigmine is a plant alkaloid, which was originally isolated from the seeds of the Calabar bean. It binds the active site of cholinesterases and reversibly inhibits these enzymes by carbamoylation of the serine residue in the catalytic triade. Since physostigmine improves the transmission of acetylcholine signals, it is medically used for the treatment of glaucoma as well as thorn apple and belladonna poisonings. Physostigmine is also known to enhance memory in patients with Alzheimer's dementia, but a narrow therapeutic window and a short duration of action have precluded its approval. Therefore, the generation of physostigmine analogues with improved properties has attracted considerable attention in both academia and the pharmaceutical industry.

To produce physostigmine analogues, we planned to redirect the biosynthetic pathway and to generate the desired compounds by fermentation. For this, the late stages of physostigmine biosynthesis were reconstituted in the myxobacterial model organism *Myxococcus xanthus* (Figure 1). The necessary biosynthesis genes coding for the enzymes PsmB, PsmC and PsmD were expressed from a myxobacterial vector previously developed in our group. Afterwards, the truncated pathway could be activated in *M. xanthus* by feeding the biosynthetic intermediate 5-*O*-methylcarbamoyl-*N*-acetylserotonin (**1**). Upon its cellular uptake, **1** became converted into physostigmine (**2**). Starting from an initial titer of <1 mg/L, the physostigmine production level was successively increased by reduction of the metabolic burden, implementation of a gene fusion strategy for the expression cassette and selection of an appropriate host strain (Figure 2). In sum, these efforts led to a titer of 72 mg/L physostigmine.

Moreover, we demonstrated that synthetically prepared analogues of **1** can be introduced into physostigmine biosynthesis using the engineered expression strain. In this way, it was possible to produce customized derivatives of physostigmine, including the previously described drug candidate phenserine. All generated compounds were tested for their inhibitory efficiency on acetyl- and butyrylcholinesterase. A new analogue with an *N*-butanoyl moiety at position R^3 showed improved bioactivity and reduced toxicity compared to the parental natural product.

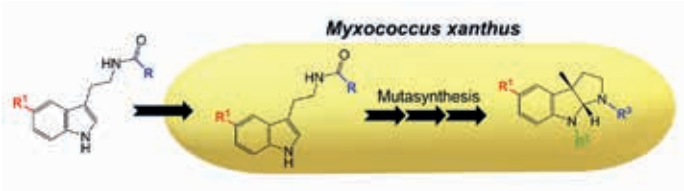

Figure 1: Schematic representation of the mutasynthetic procedure for derivatization of the physostigmine scaffold in *M. xanthus*.

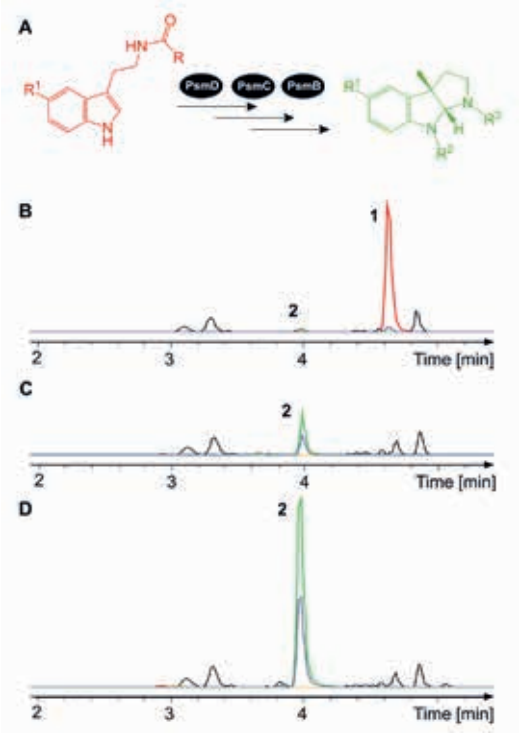

Figure 2: Strain development for increased physostigmine production titers. (A) Biosynthesis of physostigmine (**2**) or physostigmine analogues in the generated *M. xanthus* strains. (B–D) Total ion chromatograms of raw extracts from *M. xanthus* FB:pMEX04 (B), *M. xanthus* FB:pMEX10 (C), and *M. xanthus* NM:pMEX10 (D) after the feeding of **3**.

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Publications:
L. Winand, P. Schneider, S. Kruth, N.-J. Greven, W. Hiller, M. Kaiser, J. Pietruszka, M. Nett, Org Lett, 23, 6563–6567 (2021).

Biocatalytic Production of Heterocyclic Natural Products

MxcM – an unusual, solvent stable amidohydrolase

Lea Winand, Dustin Joshua Vollmann and Markus Nett

Heterocycles, such as imidazolines and imidazoles, are found in many pharmaceutical drugs. Some examples are clonidine, naphazoline, and tetryzoline. Although these compounds are currently made by chemical synthesis, there is an increasing interest in the development of biocatalytic production processes for heterocyclic drugs. In recent years, various enzymes of the amidohydrolase superfamily were reported to catalyze heterocycle-forming condensation reactions. One of these enzymes, MxcM, is biochemically and kinetically characterized in this study.

The amidohydrolases constitute a large enzyme family with more than 36,000 members. They feature a common $(\beta/\alpha)_8$-barrel structural fold and usually possess a metal center, which is required for the activation of a water molecule. While most members of the amidohydrolase family catalyze hydrolytic cleavage reactions, there are noteworthy exceptions. Over the last few years, several amidohydrolases have been reported that are involved in the biosynthesis of pharmacologically active natural products. The corresponding enzymes are engaged in heterocycle-forming condensation reactions, which is consistent with a shifted reaction equilibrium. The amidohydrolase MxcM was shown to catalyze an intramolecular condensation of the β-aminoethyl amide moiety in myxochelin B, thereby generating the characteristic imidazoline moiety of the anti-inflammatory natural product pseudochelin A (Figure 1).

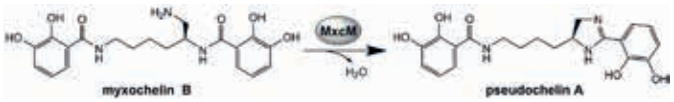

Figure 1: MxcM-catalyzed formation of the imidazoline ring in pseudochelin A biosynthesis.

Characterization of the enzyme MxcM revealed a maximal activity at 50 °C and pH 10 as well as a k_{cat}/K_m value of 22,932 s^{-1} M^{-1} at its temperature optimum. Experimental data suggest that the activity of MxcM does not depend on a catalytic metal ion, which is uncommon among amidohydrolases. Additionally, MxcM was proven to be highly active in different organic solvents. The activity correlates strongly with the log *P* value (Figure 2), which classifies organic solvents into different hydrophobicity groups. Since the intramolecular condensation catalyzed by MxcM produces water as by-product, we assume that the reaction equilibrium is shifted to the product side when the reaction is performed in hydrophobic organic solvents. Because salts generally reduce the water activity of an aqueous solution, the tolerance towards organic solvents is often accompanied by a resistance to high salt concentrations. As expected, enzymatic reactions in presence of 2 M NaCl or urea did not significantly affect the enzymatic activity of MxcM.

The described characteristics and the fact that no (organic) cofactor is required for its action make the amidohydrolase MxcM a promising candidate for biocatalytic imidazoline formation. Heterocycle-forming amidohydrolases are attractive for possible future engineering studies and the integration in chemical process development.

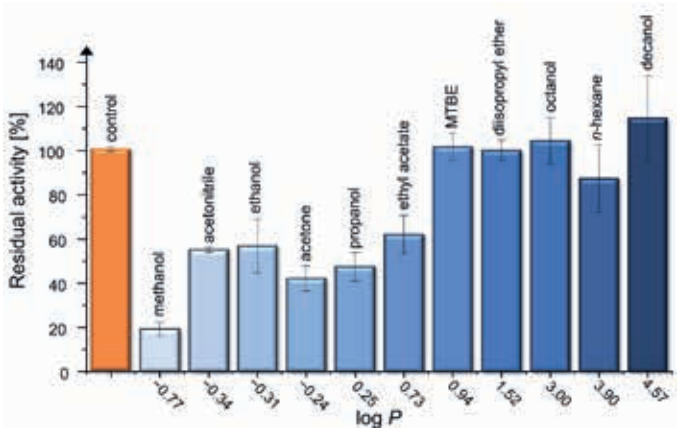

Figure 2: Residual activity of MxcM in diverse organic solvents in comparison to a control reaction in phosphate buffer. The hydrophobicity of each solvent is represented by its log *P* value.

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  Saccharomyces cerevisiae as Host for the Recombinant Production of Polyketides and Nonribosomal Peptides
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  Reconstitution of aurachin biosynthesis in _Myxococcus xanthus_ and _Escherichia coli_
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  Mutasynthesis of physostigmines in _Myxococcus xanthus_
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  Workshop of VAAM special group "Biology of bacteria producing natural products", virtual conference, September 2021

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  Genetic tools for directing natural product biosynthesis in myxobacteria
  Synthetic Biology for Natural Products Conference, Puerto Vallarta, Mexico, June 2019

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- S. Kruth, L. Winand, J. Korp, M. Nett
  Design of a modular vector-based expression system in *Myxococcus xanthus*
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- A. Tippelt, M. Nett
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- A. Sester, K. Stüer-Patowsky, S. Lütz, M. Nett
  Precursor-directed biosynthesis towards aurachin derivatives
  VAAM Workshop Biology of bacteria producing natural products, Jena, September 2019

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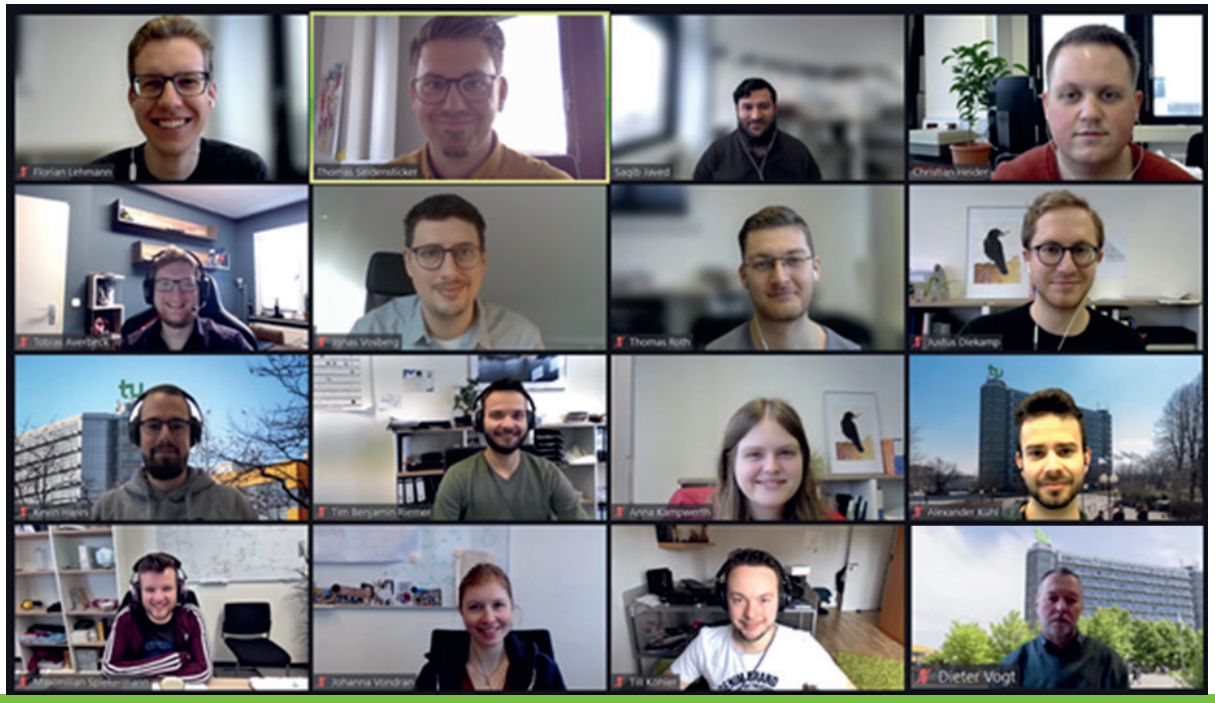

Industrial Chemistry (TC)

Aqueous Biphasic Hydroaminomethylation Enabled by Methylated Cyclodextrins

Sensitivity analysis for transfer into a continuous process

Kai U. Künnemann, Dennis Weber, Chryslain Becquet, Sebastien Tilloy, Eric Monflier, Thomas Seidensticker and Dieter Vogt

Hydroaminomethylation (HAM) represents a highly atom-economic and efficient one-pot process for the synthesis of amines from alkenes using only syngas, and primary or secondary amines. This catalytic autotandem reaction, typically catalyzed by homogeneous Rh- complexes, consists of an initial hydroformylation of an alkene to an aldehyde and subsequent formation of an enamine followed by a hydrogenation. From both economic and environmental points of view, this direct preparation process of amines from low-cost feedstock is superior to traditional procedures, which are mostly multistep and less atom-efficient with a number of byproducts. To make use of those strengths, the development of efficient separation and recycling concepts is required, since recycling of the homogeneous catalysts is indispensable for the economic and ecological sustainability of processes. One promising approach in this respect is the immobilization of the catalyst in multiphase systems. The use of water as a solvent in combination with mass transfer agents (Figure 1) is in these cases particularly beneficial from economic and environmental impact viewpoints since water is fairly accessible, nontoxic, nonflammable, odorless and offers a huge miscibility gap with most of the nonpolar products.

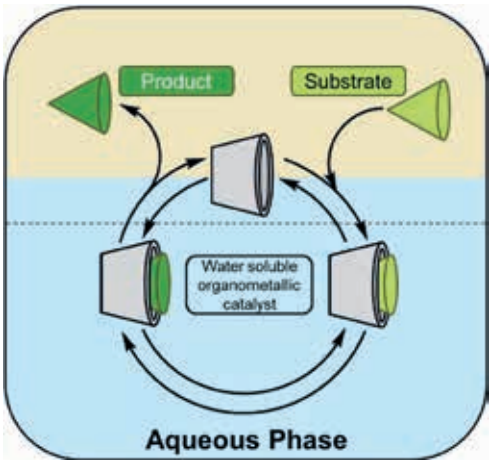

Figure 1: Principle of aqueous biphasic organometallic catalysis mediated by modified cyclodextrins (adapted from Bricout et al. (2009) with permission from MDPI).

This work reports for the first time the scale-up of highly regioselective HAM of 1-decene with diethylamine (Figure 2) in a green and sustainable aqueous biphasic medium. The Rh/SulfoXantphos catalytic system and randomized methylated β-cyclodextrin (RAME-β-CD) were resolved here in the pure aqueous phase. The addition of cyclodextrins as green mass transfer agents significantly increases the reaction rate as well as the selectivity towards linear amines, but may also support the precipitation of solids in this reaction system by upscaling effects. Therefore, parameters such as catalyst concentration, organic volume fraction, cyclodextrin concentration, and recyclability were investigated with respect to the stability and activity of the system. In particular, the organic volume fraction had a decisive influence on the precipitation of the solid content. High regioselectivities and chemoselectivities of 35 and 82 %, respectively, were achieved for the linear product amine with almost complete conversion. The catalytic system was scaled up into a 2100-mL autoclave without loss of activity or selectivity. Finally, a continuous process design was proposed for a comprehensive investigation of the long-term stability of the catalytic system.

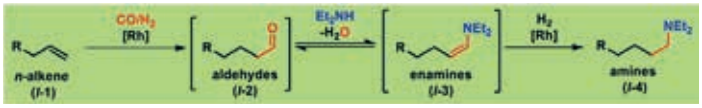

Figure 2: Simplified reaction network of the hydroaminomethylation of 1-decene and diethylamine.

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Publications:
K. U. Künnemann, D. Weber, C. Becquet, S. Tilloy, E. Monflier, T. Seidensticker, D. Vogt, ACS Sustainable Chem. Eng. 2021, 9, 273–283.

Curse and Blessing – the Role of Water in the Epoxidation of Methyl Oleate

Improved homogeneous catalyst recycling through removal of water

Johanna Vondran, Jerzy Pela, Dennis Palczewski, Mirko Skiborowski, Thomas Seidensticker

In times of raising awareness of climate change and raw materials shortage, the aim of sustainability is more important than ever before. Thereby, the chemical conversion of renewable feedstocks such as fats and oils contributes to bio-based products of value, such as epoxy compounds. Epoxy compounds offer versatile applications in plasticizers, lubricants or coatings. As an atom-efficient oxidant for epoxidation, especially hydrogen peroxide stands out as it is easy to handle in aqueous solution and since the only by-product from hydrogen peroxide mediated epoxidation is water. To activate hydrogen peroxide, catalysts are of need. Especially homogeneous catalysts stand out due to high selectivity. However, separation of a homogeneous catalyst to save resources and increase catalyst productivity is a challenge. Here, we develop an approach for recycling of the homogeneous catalyst in the epoxidation of methyl oleate, considering that accumulating water results in reduced catalyst performance so that removal thereof is required.

Methyl oleate was epoxidized using a literature-known, commercially available catalyst system. During a successful catalyst recycling, the product epoxide would be separated, whilst the catalyst remains in the homogeneous, aqueous reaction solution. Assuming a recycling of the homogeneous, aqueous phase, water would accumulate after each run due to three effects: first, water is a by-product from hydrogen peroxide mediated epoxidation. Second, hydrogen peroxide is applied as a 50 wt% aqueous solution. Third, excess hydrogen peroxide is decomposed to water and oxygen. Thus, the effect of water on the epoxidation is studied in first perturbation experiments. At certain concentration of water, the formation of a second phase results in phase transfer limitations. However, dilution of the reactants has no influence in the investigated range. Under homogeneous conditions, forced through the addition of more solvent, the catalyst is inhibited at a certain concentration of water. Consequently, removal of water is required to maintain an active catalyst during recycling.

After optimization of the reaction conditions in terms of hydrogen peroxide concentration and equivalents to initially reduce the amount of water, we have shown general recyclability of the catalyst through extraction of the product epoxide methyl 9,10-epoxystearate into an organic phase. Subsequently, we combined our recycling approach with vacuum distillation for removal of water as a proof of concept. Thereby, we were able to carry out seven recycling runs with excellent selectivity, and 13 recycling runs before complete deactivation of the catalyst occurred respectively. Since water and the solvent form an azeotrope, removal of water comes with the removal of solvent using distillation. However, we assume that acetonitrile stabilizes the catalyst, so that a more catalyst-friendly technique for water removal is of need. Thus, we applied pervaporation to selectively remove water and recycle the solvent. The catalyst was retained efficiently and remained its activity, so that a yield of 93 % of the epoxide was obtained after a reaction time of 3 h using the recycled catalyst solution. In conclusion, pervaporation is a very promising technique for homogeneous catalyst recycling, considering the removal of water.

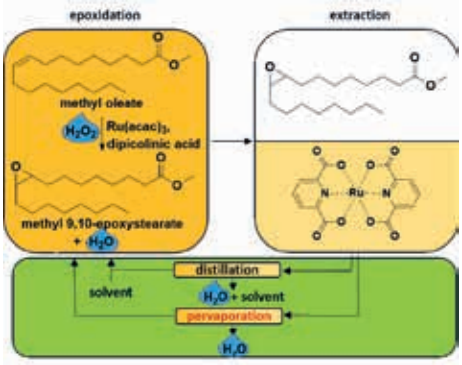

Figure 1: Combined recycling approach of extraction and removal of water in the epoxidation of methyl oleate.

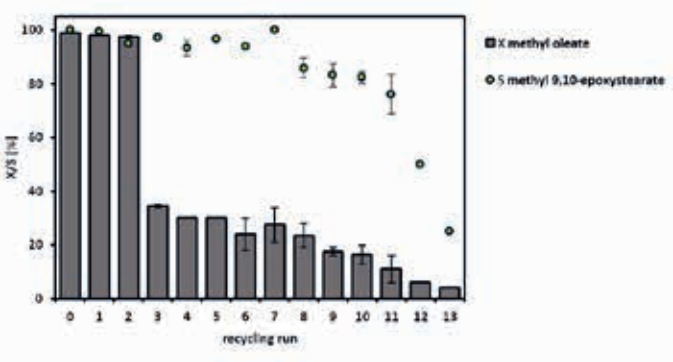

Figure 2: Catalyst recycling in the homogeneously catalyzed epoxidation of methyl oleate using distillation as proof of concept for water removal.

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  "Curse and Blessing–The Role of Water in the Homogeneously Ru-Catalyzed Epoxidation of Technical Grade Methyl Oleate".
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  "Expanding the synthesis tool of carbonylative telomerization – homogeneous palladium catalyzed formation of mixed anhydrides"
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- Heider, C., Evering, L., Vogt, D., Seidensticker, T.
  "Selective synthesis of primary amines from primary, aliphatic alcohols using homogeneous catalysts"
  54th Annual Catalysis Conference (Poster)

- Javed, S., Ropel, D., Vogt, D.
  "Chemical Depolymerization of PET Waste using Sodium Ethoxide as Catalyst: Five-factor Optimization Using Response Surface Methodology"
  DGMK-Chemical Recycling – Beyond Thermal Use of Plastic and other Waste (presentation)

- Kampwerth, A., Terhorst, M., Kampling, N., Seidensticker, T., Vogt, D.
  Sustainable approach for recycling of a homogeneous catalyst: amine syntheses via telomerization of β-myrcene"
  54th Annual Catalysis Conference (Poster)

- Peters, M., Vogt, D.
  "Recycling of Homogeneous Catalysts via Organic Solvent Nanofiltration"
  SusChemSys workshop (presentation)

- Peters, M., Drucks, R., Plischka, W., Spiekermann, M., Vogt, D.
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  "'Solutions' for the Recycling of Homogeneous Catalysts enabling the Separation of Pure Products"
  54th Annual Catalysis Conference (presentation)

- Seidensticker, T.
  "'Solutions' for the Recycling of Homogeneous Catalysts enabling the Separation of Pure Products"
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  l'Université d'Artois, Lens, France (presentation)

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  18th Euro Fed Lipid Congress and Expo (presentation)

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  GdCh Wissenschaftsforum (presentation)

- Seidensticker, T.
  "Homogeneously catalyzed functionalization of renewables: rediscovery"
  DGMK-Vorstandssitzung (presentation)

- Seidensticker, T., Vogt, D.
  "Lösungen für das Recycling homogener Katalysatoren in der Funktionalisierung ungesättigter Oleochemikalien"
  H. P. Kaufmann-Tage der deutschen Gesellschaft für Fettwissenschaften (presentation)

- Vogt, D., Seidensticker, T.
  "Homogeneously Catalyzed Amination Reactions - Towards Sustainable Production of Amines"
  GdCH Ortsverband Gießen (presentation)

- Vogt, D., Seidensticker, T.
  "Phosphorus ligands – the captains of homogeneous catalysis"
  EWPC, European Workshop on Phosphorus Chemistry (presentation)

- Vondran, J., Vogt, D., Seidensticker, T.
  "Curse or Blessing – the role of water in the homogeneously catalyzed epoxidation of methyl oleate"
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Thermodynamics (TH)

Stability of Pharmaceutical Co-Crystals Against Humidity Can Be Predicted

A thermodynamic approach for understanding co-crystal deliquescence and its consequences

Heiner Veith, Maximilian Zaeh, Christian Luebbert, Gabriele Sadowski

For the development of pharmaceutical products, the knowledge about their stability against relative humidity (RH) is crucial. Especially co-crystals (CC), composed from at least two components, present special challenges regarding physical stability at humid conditions. RH can lead to deliquescence and can induce dissociation and transformation to less-soluble solid-state forms of the consisting components. We developed an approach for predicting the CC transformations that may happen upon CC storage at certain RHs. The new approach allows to reliably predict the deliquescence and transformation of CCs even in the presence of common excipients like sugars used in pharmaceutical formulations.

The increasing utilization of CCs as pharmaceutical products intensifies the need for faster development times and predictive in-silico methods for predicting the stability of new products. For predicting the effects of humid conditions on CCs, we used the thermodynamic model PC-SAFT. Particularly, we calculated the deliquescence relative humidity (DRH), above which a crystal (be it a pure component or a CC) is going to be dissolved. As examples, the phase behaviors of the systems succinic acid (SA)/nicotinamide (NA), carbamazepine/nicotinamide, theophylline (TP)/citric acid (CA), and urea/glutaric acid were considered. Figure 1 shows the modeling result and the relevant DRHs for the system SA/NA. The pure CC was predicted to deliquesce above 99% RH (DRH_{CC}). If SA is present besides the CC, the DRH is lowered to 97.8% RH ($DRH_{CC/SA}$). This value further decreases in the presence of NA to 93.6% RH ($DRH_{CC/NA}$).

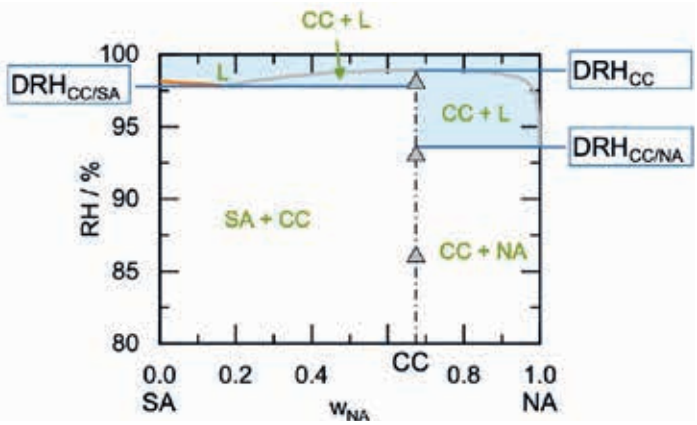

Figure 1: Phase behavior of succinic acid (SA) and nicotinamide (NA) forming a 2:1CC at 25 °C. Light blue areas show regions with deliquescence (L). DRH_{CC}, $DRH_{CC/SA}$, and $DRH_{CC/NA}$ show RHs above which the pure CC, the CC in contact with SA, and the CC in contact with NA dissolves. Triangles show storage conditions for the CC at 86, 93, and 98% RH.

The other systems were modelled accordingly. For the CC of TP and CA, deliquescence was predicted to occur above 99.3% RH. This value was predicted to remarkably decrease in the presence of CA to 79.3% RH which was also experimentally validated.

The modeling also allowed to predict the different behavior of so-called congruent or incongruent CC systems. Whereas deliquescence for congruent systems leads to recrystallization of the CC when decreasing RH below DRH, deliquescence for incongruent CC systems leads to crystallization of other crystal forms. These predictions were also verified experimentally, as shown in Figure 1.

For visualization of the deliquescence phenomenon, we used a RH chamber. Figure 2 shows a polarized-light picture of TP, CA, and their CC at 90% RH and 25 °C. CA with a predicted DRH of 79.4% RH and the CC contaminated with an CA impurity showed deliquescence at that conditions, whereas TP with a predicted DRH of 99.9% RH did not show deliquescence. This was in accordance with the predictions.

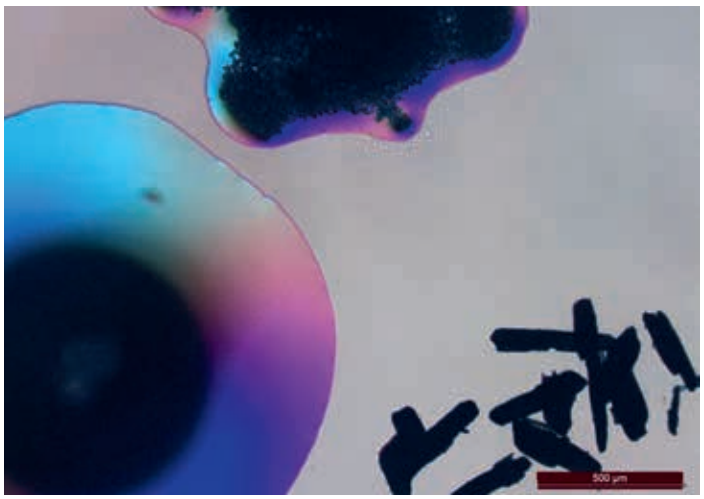

Figure 2: Polarized microscopic image of samples of the TP/CA CC, TP hydrate, and CA hydrate in the RH chamber. Sample positioning: top CC sample, bottom left CA, bottom right TP. Picture shows deliquescence at 90% RH and 25 °C for the CC and CA but not for TP.

Conclusively, we could show that PC-SAFT allows to predict DRHs as well as hydrate transformation RHs, which can also be found in the referenced paper. The new approach thus presents a valuable tool to shorten the development procedure for new pharmaceutical CC products.

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Publication:
H. Veith, M. Zaeh, C. Luebbert, N. Rodríguez-Hornedo, G. Sadowski, Pharmaceutics, 13(3):433 (2021).

Generalized diffusion model for viscoelastic mixtures

Development of a theoretical model capturing both diffusion and polymer relaxation kinetics

Dominik Borrmann, Andreas Danzer, Gabriele Sadowski

Diffusional processes in polymeric mixtures are often governed by the structural relaxation of the macromolecular chains. Due to high molar masses, the polymeric component fails to respond instantaneously to incoming solvent molecules. In fact, the relaxation process is overlaid to translational diffusion of the absorbed species and turns out to be the rate-determining step in many cases. Ignoring this relaxation kinetic leads to concentration- and even time-dependent diffusion coefficients. This work addresses and solves this issue by incorporating the virtue of the relaxation process into the chemical potential of the solvent, enabling quantification the kinetics of both diffusion and relaxation, using established concepts for diffusion modelling.

Polymers absorb solvent molecules from the surrounding atmosphere. During penetration, both polymer and solvent strives to establish configurational equilibrium, requiring relaxation of the polymeric chains. This turns out to be the rate-determining step of the overall diffusion process in many cases. The relaxation kinetics exhibits an instantaneous and a time-delayed contribution, depending on the relaxation time constant as the ratio of elasticity modulus and viscosity of the solvent-loaded polymer. High elasticity moduli lead to minor immediate responses whereas high viscosities cause a strong time-delayed response behavior. By incorporating elasticity moduli as well as viscosity in the expression of the chemical potential of the solvent, all observable diffusion kinetics are accessible (Fig 1).

The interplay between instantaneous and time-delayed response has extensive implications. One fundamental assumption in diffusion modelling is a boundary condition representing local thermodynamic equilibrium. Since instantaneous changes are limited by the elasticity moduli of the polymer, even the reach for local equilibria at the phase boundary exhibits a time dependence, further slowing down the sorption of the solvent into adjoining domains. Thus, the time dependency of solvent sorption at the phase boundary has the capability to set the rate of sorption into the inner domains, determining the kinetics of the complete diffusion process in the polymer. The time evolution of the phase boundary is mainly governed by the elasticity modulus of the polymer, the viscosity of the solvent-loaded polymer and the density dependency of the thermodynamic activity of the solvent.

By considering both diffusion as well as relaxation, this work manages to display and explain all observable anomalous diffusion kinetics with only one coherent framework. Varieties in the temporal progress of the overall sorption kinetics could be traced back to model parameters reflecting physical properties, which are experimentally accessible.

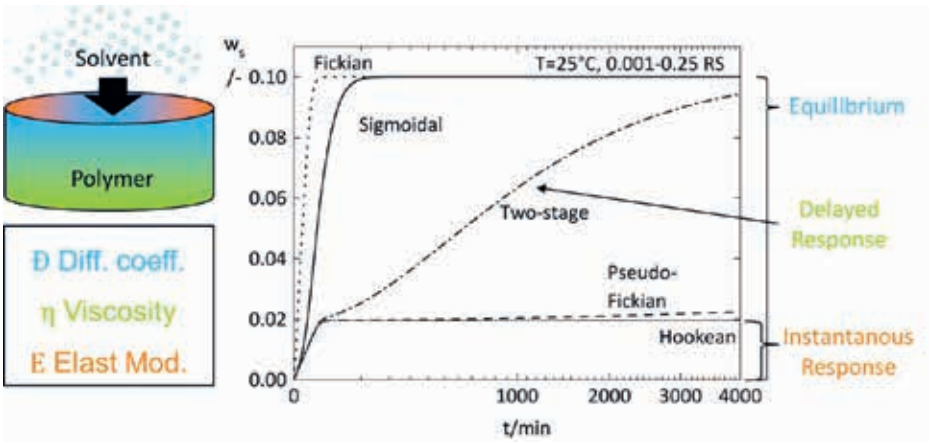

Figure 1: Overall solvent weight fraction in the polymeric sample over time for five different relaxation time constants as the ratio of modulus and viscosity.

Publications:
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ePC-SAFT advanced: A new thermodynamic model for electrolyte solutions

The importance of a concentration-dependent dielectric constant in electrolyte thermodynamic models.

Moreno Ascani, Mark Bülow, Christoph Held.

Non-aqueous electrolyte liquid systems become increasingly important for innovative technical processes. However, modeling such systems is very challenging, and still not all the physical effects are explicitly accounted for in advanced physics-based thermodynamic models. Thus, such models still rely on extensive parameter fitting over large experimental data sets. This does often not allow for extrapolation to other conditions as ion parameters that have been fitted to aqueous electrolyte solutions are not transferable to non-aqueous electrolyte solutions. In this work, a concentration-dependent dielectric constant was accounted for in the electrolyte theories of Born and Debye-Hückel, which were then combined with a classical equation of state, Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). The new model, called ePC-SAFT advanced, allowed successfully predicting thermodynamic properties of alcohol+salt solutions. The highlight is that new model parameters were not required and existing ion parameters fitted to aqueous electrolyte solutions were transferred to the non-aqueous electrolyte solutions.

ePC-SAFT is a broadly applied electrolyte equation of state, which combines the classical PC-SAFT equation of state with the DebyeHückel theory in order to account for the electrostatic interactions among ions. However, ePC-SAFT considers the permittivity of any electrolyte solution as equal to that of the pure solvent, and electrostatic interactions between the ions and solvent are not accounted for explicitly. The drawback of this is that ePC-SAFT cannot be applied to predict physical properties of non-aqueous electrolyte solutions, which requires fitting a huge number of parameters to experimental data. However, the available data of non-aqueous electrolyte systems is rather scarce in the literature. Thus, a robust model is missing in the literature that is accurate for non-aqueous electrolyte solutions.

Within this work, the impact of a concentration-dependent dielectric constant $\varepsilon_r(x)$ was studied on ePC-SAFT modeling results of non-aqueous electrolyte solutions. $\varepsilon_r(x)$ was included in the theories from Debye-Hückel and Born, which was then included as contributions to the Helmholtz energy in ePC-SAFT. The Born energy a^{Born} describes the work required to discharge an ion from the vacuum and recharge it within a solvent of given dielectric constant (Eq. 1).

$$a^{Born} = -\frac{e^2}{4\pi\varepsilon_0 k_B T}\left(1-\frac{1}{\varepsilon_r(x)}\right)\sum_i \frac{x_i z_i^2}{a_i} \qquad (1)$$

In Eq. (1) a_i, z_i and x_i denote the diameter, valence, and molar fraction of ion *i*, respectively. The free energy of solvation of ions changes dramatically between water and low-polar solvents as a^{Born} strongly depends on $\varepsilon_r(x)$. In this work, it was proven that predicting infinite dilution properties, such as the free energy of hydration of monovalent ions, is only possible by including a^{Born} in the modeling; in contrast, the original ePC-SAFT model fails (see Figure 1).

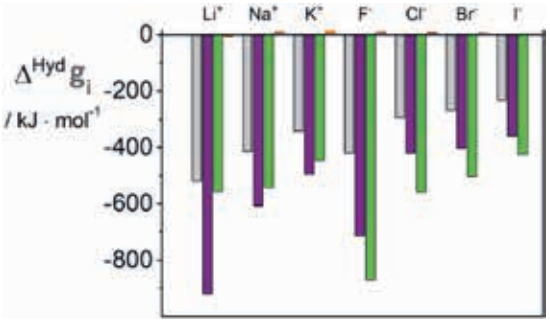

Figure 1: Gibbs energy of hydration at 298 K at infinite dilution. Original ePC-SAFT: orange; ePC-SAFT advanced: green; SAFT-VR: violet (Schreckenberg et al); Literature data: gray (Fawcett et al.). References: see publication.

The new model, called ePC-SAFT advanced, shows excellent accuracy towards predicting free energies of transfer of ions from aqueous to organic solvents (see publication) and towards predicting salt activity coefficients in alcohols, while other models fail (see Figure 2). Most importantly, none of the ion parameters of the original model were re-estimated.

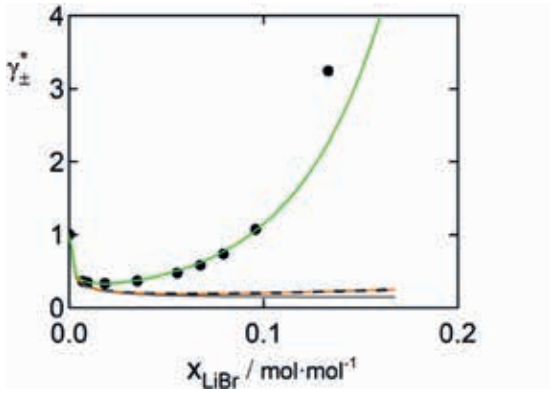

Figure 2: LiBr activity coefficient in ethanol at 298 K. Circles: experimental data (Zafarani-Moattar et al.). Black: original ePC-SAFT, orange: ePC-SAFT + a^{Born}, gray: ePC-SAFT + $\varepsilon_r(x)$ but without a^{Born}, green: ePC-SAFT advanced. References: see publication.

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Publication:
M. Bülow, M. Ascani, C. Held, Fluid Phase Equilibria 535, 1-8 (2021).

Predicting Solvent Effects on Homogeneity and Reaction Kinetics

A Thermodynamic Approach Using PC-SAFT

Fabian Huxoll, Anna Kampwerth, Thomas Seidensticker, Dieter Vogt, Gabriele Sadowski

Solvents provide the reaction environment of all liquid-phase reactions in the chemical industry and may significantly affect reaction rates and the phase behavior of complex reaction media. Especially, if a reaction is performed in solvent mixtures, a high experimental effort is required to quantify these effects. Within this work, we developed a novel thermodynamic-activity-based approach to predict solvent effects on both reaction rates and phase behavior using the PC-SAFT model. This approach allows gaining in-depth process insights and is applicable to a wide variety of liquid-phase reactions.

Solvents can have an enormous impact on the phase behavior and kinetics of chemical reactions. Knowledge and quantification of these effects are of major importance and need to be known to achieve high selectivities and reaction rates.

In this work, the liquid-liquid equilibrium of a multicomponent reaction system was predicted using PCSAFT. At the same time, solvent effects on the reaction kinetics were estimated. For highest reaction rates we searched for reaction mixtures that lead to the highest thermodynamic activities of the reactants. We applied this workflow to the homogeneously catalyzed reductive amination (RA) of undecanal in a solvent mixture of methanol and *n*-dodecane (DDC). During the reaction, water is formed as a by-product, which may lead to an unwanted phase separation during the reaction. An increasing DDC content in the solvent mixture was predicted to limit the working space for the reaction and also to massively reduce the reaction rate. As a result, DDC should be added only after the reaction to form a second liquid phase, thus enabling an efficient catalyst recycling. Validation experiments were in perfect accordance with the modeling results (Fig.1).

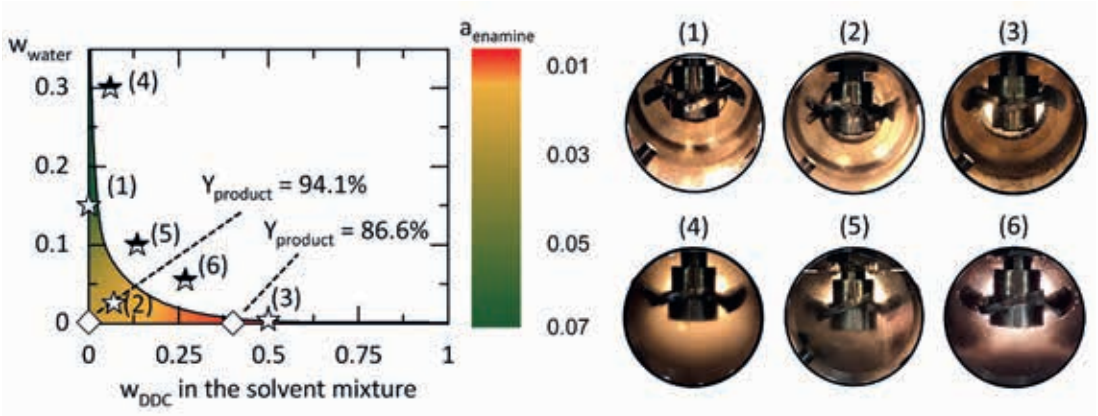

Figure 1: PC-SAFT predictions of enamine thermodynamic activities ($a_{enamine}$) at 373.15 K at 3 MPa as a function of the methanol/DDC solvent composition and the water content in the multicomponent RA reaction mixture (highest $a_{enamine}$ is green; lowest $a_{enamine}$ is red). Homogeneity experiments (1)–(6) and experimental product yield $Y_{product}$ after t = 2 min (diamonds) are compared to the PC-SAFT modeling results. The solid line represents the predicted binodal curve separating the single-phase region (white area) from the two-phase region (colored area). Empty stars denote homogeneous samples; half-filled stars indicate heterogeneous samples.

For samples (1)–(3) indicated as stars in Fig.1, a homogeneous liquid was predicted and also experimentally found at reaction conditions. In contrast, samples (4)–(6) showed strong turbidity caused by the presence of a fine dispersed second liquid phase. The highest product yield $Y_{product}$ = 94.1% was obtained in pure methanol, whereas increasing DDC contents in the solvent mixture resulted in decreasing product yields down to $Y_{product}$ = 86.6 %, confirming the predicted negative effect of DDC on the initial reaction rate.

To conclude, the ability to predict solvent effects on both reaction rates and phase behavior offers the opportunity to identify the most promising solvent compositions for liquid-phase reaction systems while ensuring homogeneous systems during the whole reaction and high reaction rates. As no experimental reaction data is required for the modeling, promising solvent compositions and working spaces are identified fast and reliably, reducing time-consuming experiments to a minimum.

Publication:
F. Huxoll, A. Kampwerth, T. Seidensticker, D. Vogt, G. Sadowski, Ind. Eng. Chem. Res. 61, 2323-2332 (2022).

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Predicting Formulation Windows for Efficient Lipid-Based Drug Delivery Systems

Joscha Brinkmann, Isabel Becker, Peter Kroll, Christian Luebbert, and Gabriele Sadowski

The preclinical development of lipid-based drug delivery systems (LBDDS) requires a very high experimental effort to ensure the efficient formulation and administration of active pharmaceutical ingredients (APIs). Hereby, it is of utmost importance that the API does not crystallize in the LBDDS while storage or after oral administration to the human body. For the first time, we proposed an in-silico tool to predict the degree and location of API crystallization in a LBDDS before and after administration. This allows formulation scientists to design LBDDS with minimum experimental effort.

Since many newly developed active pharmaceutical ingredients (APIs) possess very limited bioavailability, lipid-based drug delivery systems (LBDDS) are used to increase the efficient administration of these APIs into the human body. In these, the API is dissolved in a mixture of a lipid and excipients, which prevents the API from crystallizing during storage and during its pass through the gastrointestinal tract.
The solubility of the API in the water-free LBDDS is the maximum API amount that can be kept amorphous during storage. This solubility of ibuprofen (IBU) in a LBDDS containing the lipid tricaprylin ($TG8_08_08_0$) and the two excipients caprylic acid ($MC8_0$) and ethanol was predicted using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) (dashed lines in Figure 1). For example: given an IBU loading of 40 wt% in the LBDDS, IBU will crystallize during storage for all LBDDS compositions located on the left side of the dashed red line, whereas it will remain dissolved for all LBDDS compositions located right of the red dashed line.

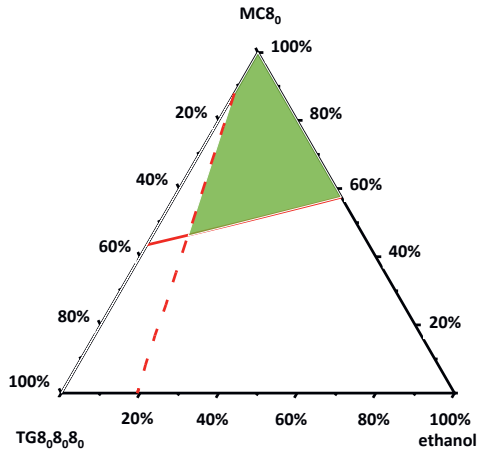

Figure 1: Overlay of the IBU solubility in the water free LBDDS (dashed lines) and in a partitioning test with water (solid lines) to define a formulation window, in which a LBDDS does not show IBU crystallization neither during storage nor during administration. The green area indicates the formulation window for an IBU load of 40 wt% in the LBDDS.

The maximum amount of IBU that can be kept in solution during a partitioning test with water (mixing ratio 1/200 LBDDS/water) was predicted to simulate the mixing conditions after oral administration into the human body (solid lines in Figure 1).

Again: for all LBDDS located below the solid red line, IBU was predicted to crystallize after mixing the LBDDS with water, if the IBU load in the LBDDS is 40 wt%.
The two informations were combined in Figure 1. The dashed and solid lines enclose the formulation window (green area for 40 wt%), in which IBU will not crystallize during storage or after administration. Outside this formulation window, IBU will crystallize either in the formulation or after oral administration.
The predicted results from Figure 1 were experimentally validated (Figure 2). An excipient mixture of 83.5 w% $TG8_08_08_0$ and 16.5 wt% ethanol was used. In this mixture an IBU load of 37 wt% was dissolved. According to the predictions, IBU crystallization was expected not to occur in the water-free LBDDS but was expected after mixing with water. As can be seen clearly in Fig. 2, IBU did crystallize after being in contact with water and it mostly crystallized in the lipid phase (bottom left side) of the LBDDS/water system. This could be explained by the loss of the hydrophilic excipient ethanol from the LBDDS into the aqueous phase, which decreased the IBU solubility in the LBDDS phase and induced IBU crystallization there.
The results of this work now enable formulation developers to in-silico design promising LBDDSs for target APIs without the need of expensive and time-consuming trial-and-error methods.

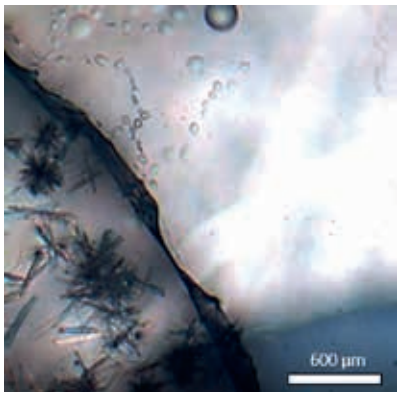

Figure 2: Microscope image of an LBDDS (IBU: 37.4 wt%. $TG8_08_08_0$: 52.3 wt%, ethanol 10.3 wt%) crystallization test with water at 37 °C.

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Boosting the Kinetic Efficiency of Formate Dehydrogenase

Kinetic Efficiency is Increased by 300 % by Combined Effects of High Pressure and Co-solvent Mixtures

Nicolás Gajardo-Parra, Gabriele Sadowski, Christoph Held

The efficiency of homogenous liquid biocatalytic reactions depends on the environment of the catalyst (here: an enzyme) in the solution. This work evaluated the combined effects of temperature, pressure, and co-solvents to increase the kinetic efficiency of NADH synthesis. NADH is a high-value compound (> 10€/g NADH). The synthesis uses formate as substrate, which is oxidized in an aqueous solution with the enzyme formate dehydrogenase. The kinetic efficiency could be increased by 300 % applying a pressure of 2 kbar and a mixture of the co-solvents dextran and trimethylamine N-oxide (TMAO), compared to an aqueous buffer solution at 1 bar. The thermodynamic framework based on the equation of state ePC-SAFT allowed correctly predicting the combined effects of high pressure and co-solvent mixture on the kinetic efficiency without fitting any model parameters to the experimental kinetic data of the co-solvent mixtures.

The application of co-solvents and high pressure is an efficient means to modify the kinetics of enzyme-catalyzed reactions in aqueous solutions without decreasing enzyme stability. This is usually not possible by temperature treatment. FDH (formate dehydrogenase) catalyzes the formate oxidation to CO_2 via a complex mechanism partially limited by an irreversible hydride transfer. From a process perspective, it is most important to tune the macroscopic kinetic parameters at steady state. Thus, the kinetic parameters catalytic constant (k_{cat}), Michaelis constant (K_M), and catalytic efficiency ($K_{eff} = k_{cat}/K_M$) were studied in this work. It was known from literature (cf. publication) that K_{eff} was increased by a factor of three upon raising temperature from 25 °C to 45 °C. We were then keen on studying further the benefit of high pressure and cosolvent addition. TMAO and dextran were used as they improve the thermal stability of FDH. The combined effects of pressure and co-solvent on K_{eff} are shown in Figure 1.

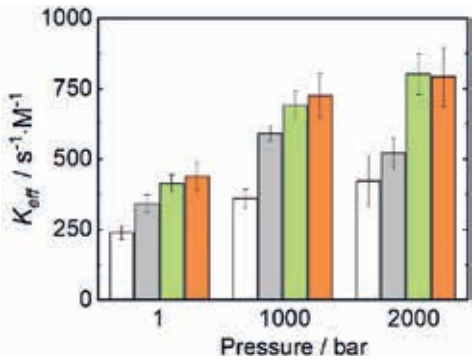

Figure 1: Experimental pressure dependence of kinetic efficiency K_{eff} for the FDH-catalyzed reaction at 25 °C and pH = 7.5 in aqueous buffer solution (white bars) and in aqueous solutions containing co-solvent dextran (gray, 13 mmol/kg), TMAO (green, 1 mol/kg), and a mixture of both co-solvents (orange).

Ultimately, the combined effect of co-solvent addition and high pressure increases K_{eff} by 300 % compared to a buffer solution at 1 bar. This boost is mainly caused by favored interactions of formate and TMAO and by mitigating conformational changes in the active pocket of FDH at high pressures. Conversely, dextran causes favorable FDH-solvent interactions to increase k_{cat}. To conclude, the mixture of the co-solvents positively affects both, kinetics and stability of FDH. However, there is a huge matrix to study the kind and concentration of co-solvent candidates. Thus, a thermodynamic activity-based framework was applied to predict the impact of cosolvent mixtures on the kinetic parameters beforehand. ePCSAFT was applied to predict interactions between formate/solvent and FDH/solvent as a function of pressure and co-solvent mixture. As shown in Figure 2, the ePC-SAFT predicted K_{eff} values are in accurate agreement with the experimental data. This is an excellent result as no ePC-SAFT parameters were fitted to the experimental kinetic data of the co-solvent mixtures. The predictions require only K_{eff} data in buffer as input data.

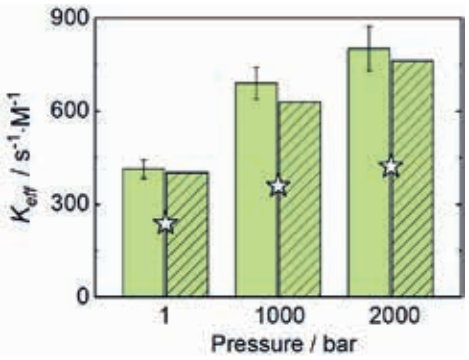

Figure 2: ePC-SAFT modeling of kinetic efficiency. Conditions: 25 °C, pH = 7.5 and 1 mol/kg of TMAO in water. Experimental data (green), ePC-SAFT (green striped), and the TMAO-free values (white stars).

Thus, combining experimental data and thermodynamic predictions allows boosting the kinetic parameters of enzyme-catalyzed reactions. This approach will further contribute to a broader insight into enzyme-catalyzed reactions at crowded cellular conditions, which still remain largely unexplored.

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