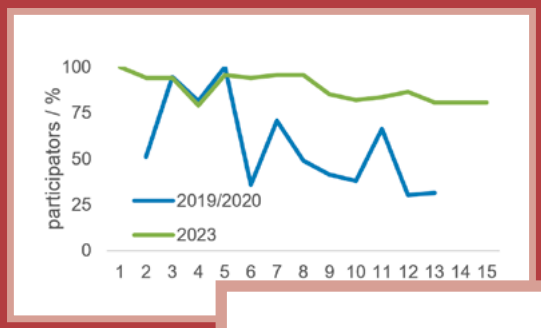
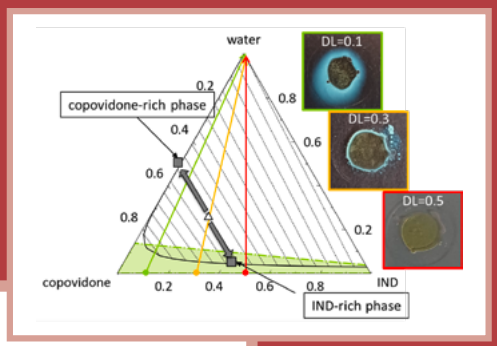
technische universität
dortmund

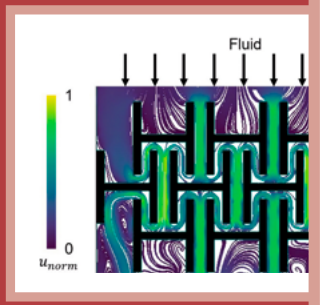
2024

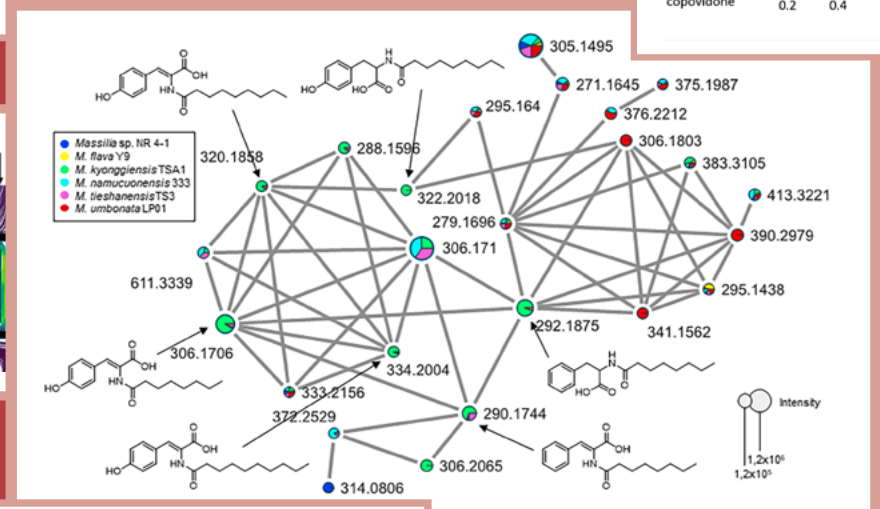
SCIENTIFIC HIGHLIGHTS

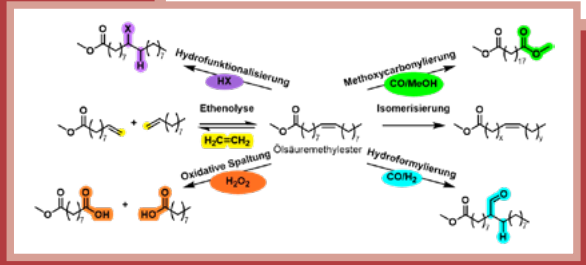
Annual Report

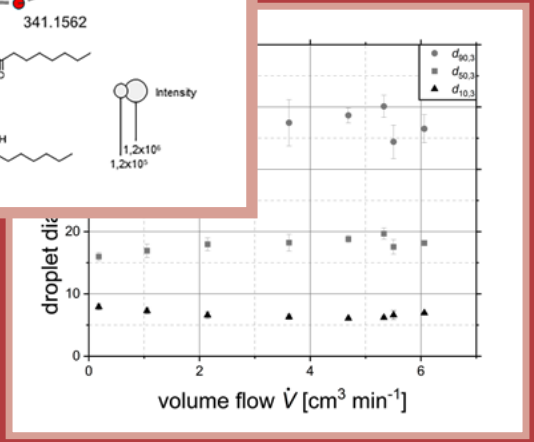






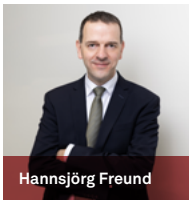




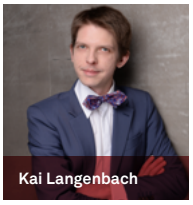


Fakultät Bio- und
Chemieingenieurwesen

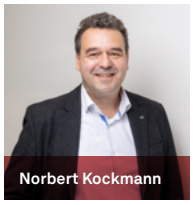
Content


Hannsjörg Freund

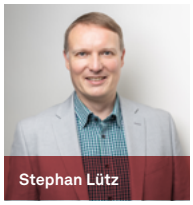

Toni Goßmann


Kai Langenbach


Oliver Kayser

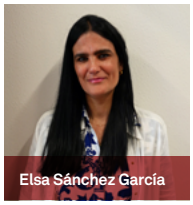

Norbert Kockmann


Sergio Lucia


Stephan Lütz


Markus Nett

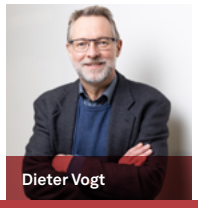

Gabriele Sadowski

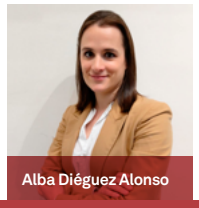

Elsa Sánchez García


Gerhard Schembecker


Markus Thommes


Jörg C. Tiller


Dieter Vogt


Alba Diéguez Alonso

Department of BCI

Preface

Dear Reader,

I am proudly presenting the annual collection of the “Highlights” of the research activities of the faculty of biochemical and chemical engineering (BCI) of the year 2024. Here, we summarize our most remarkable scientific achievements of the last year, which are the result of the multidisciplinary efforts achieved in Bachelor, Master, and PhD thesis of the department. Thereby, the unique combination of natural scientists, pharmacists, computer scientists, and engineers bring exceeding new perspectives to the fields of chemical and biochemical engineering. I hope that reading this collection will encourage our partners from industry and academia to keep existing and open new collaborations. In 2024 BCI was happily welcoming a new member of the faculty. Prof. Kai Langenbach has joined us leading the chair of fluid separations. We wish him a good start and an enjoyable and fruitful time at the department.

Enjoy the reading,

Prof. Joerg C Tiller

Equipment Design (AD)

2-phase capillary flow and biocatalytic reactions

Gas-liquid mixing is beneficial for biocatalytical reactions and related process development

Julia Surkamp, Otto Mierka, Stefan Turek, Norbert Kockmann

Microfluidic devices are an efficient way for the sustainable production valuable products in small scale Gas-liquid reactions present a particularly high challenge for the design of such devices. This research highlight brings the direct numerical simulation to its limit with the sophisticated description of dispersion and mixing in gas-liquid Dean-Taylor capillary flow, particularly examining the effects of a 90 ° bend on these processes. With its application, it explores innovative ethanol production utilizing the bacterium Zymomonas mobilis *combined with in situ extraction within a capillary microreactor. Together, these studies enhance our understanding of fluid dynamics and bioprocessing, paving the way for more efficient and sustainable chemical production methods.*

Gas-liquid capillary flow finds widespread applications in reaction engineering due to efficient mixing. Incorporating compact and regular design with Coiled Flow Inverter (CFI) enhances process efficiency due to improved mixing as well as heat and mass transfer leading to a narrow residence time distribution. The impact of Dean and Taylor flow phenomena on mixing and dispersion is still not yet fully understood. With direct numerical simulation based on finite element method, the full 3D resolution of the flow field and detailed examination of laminar flow profiles provides valuable insights into flow dynamics. Notably, the deflection of flow velocity from the center axis contributes is followed by tracking of particle with defined starting positions, aiding in flow visualization and dispersion characterization, see Fig. 1.

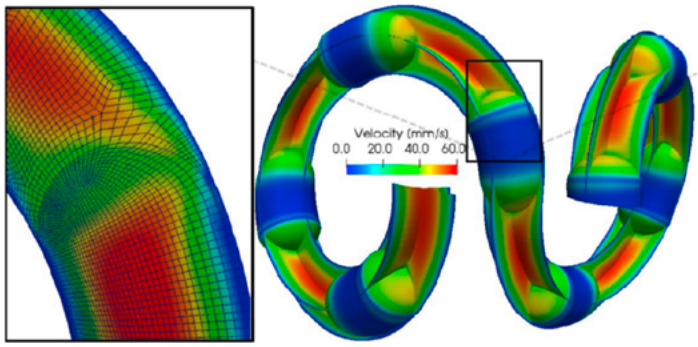


Figure 1. Typical simulation result of the CFI Taylor bubble for the simulation case Geo1/Op1 showing the interface aligned mesh.

In this CFD study, the helical flow with the influence of the centrifugal force and pitch (Dean flow) as well as the capillary two-phase flow (Taylor bubble) is described and characterized by particle dispersion, (see Fig. 2), which were further analyzed in histograms.

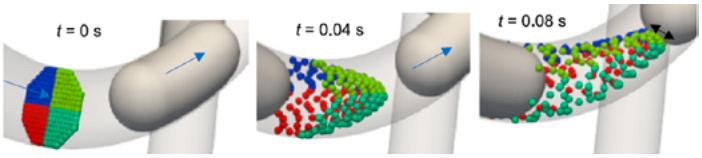


Figure 2. Particle tracing visualization of the superimposed Taylor-Dean flow in the continuous phase.

The bacterium *Zymomonas mobilis* was investigated as model organism for the cultivation and ethanol-as-product separation via in situ extraction in continuous flow capillary CFIs (see Fig. 3). The simplicity of the design makes the CFI particularly suitable for biochemical applications as cells do not get stuck or damaged by internal structures. Despite this simplicity, good mixing is still achieved through flow vortices caused by Taylor and Dean vortices.

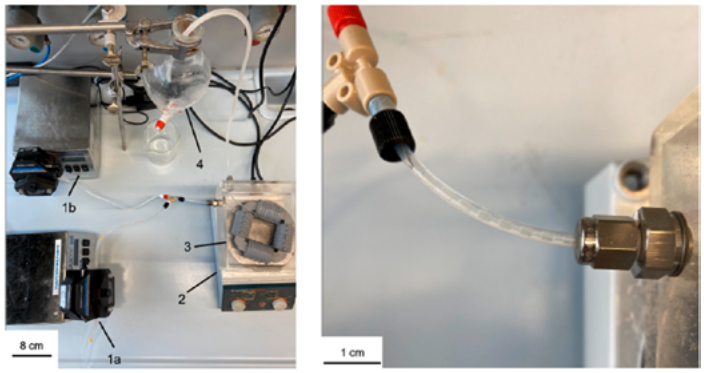


Figure 3. Images of the experimental set-up with pumps (1a and 1b), heating plate (2), CFI in the water bath (3) and separating funnel (4). Observed Taylor flow between the T-junction and the CFI in the water bath.

The reaction system consists of two phases, in which the aqueous phase carries the bacterium and an oleyl alcohol phase is used to extract the ethanol produced. Key parameters for evaluation are bacteria growth and the amount of ethanol produced by the microorganism. The results show the suitability of the CFI for microbial production of valuable compounds. A maximum ethanol concentration of 1.26 g L^{-1} was achieved for the experiment in the CFI. Overall, the cultivation in the CFI led to faster growth of *Z. mobilis,* resulting in 25 % higher ethanol production than in conducted batch experiments.

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Publications:
Mierka, O.; Münster, R.; Surkamp, J.; Turek, S.; Kockmann, N. 2024, Direct numerical simulation of dispersion and mixing in gas-liquid Dean-Taylor flow with influence of a 90 ° bend. Chem. Eng. Sci. 301, 120691.
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AI-Powered Crystal Monitoring: YOLOv8 Segmentation for Precise Sizing

Particle size distribution measurement in flow in continuous crystallization

Laura Marsollek, Julius Lamprecht, Norbert Kockmann

Continuous crystallization is a versatile method to isolate products from complex mixtures. So far, crystallization is difficult to predict and new methods are required to achieve better control over this complex method. The rapid development of AI-methods makes real-time monitoring of crystallization possible by using image recognition. With computer vision methods, crystals are detected in a lab-scale Draft Tube Baffle Crystallizer (DTBC) using a non-invasive analytical bypass. Although detecting crystals smaller than 90 µm remains challenging, improved training and optimized imaging conditions enhanced recognition performance. These findings highlight the potential of AI-methods to improve crystallization monitoring in many applications.

Crystallization is a fundamental process in chemical and pharmaceutical industries, where precise control over crystal size distribution (CSD) is crucial for product quality. Traditional monitoring techniques often rely on offline sampling and manual analysis, which can be time-consuming and prone to inconsistencies. Recent advancements in artificial intelligence (AI) and computer vision have opened new avenues for real-time, automated crystallization monitoring. AI-driven image recognition enables non-invasive and efficient crystal size analysis, reducing human intervention and improving process reliability. This study explores the application of deep learning models to enhance the accuracy and efficiency of online crystallization monitoring in a DTBC (see Fig. 1).

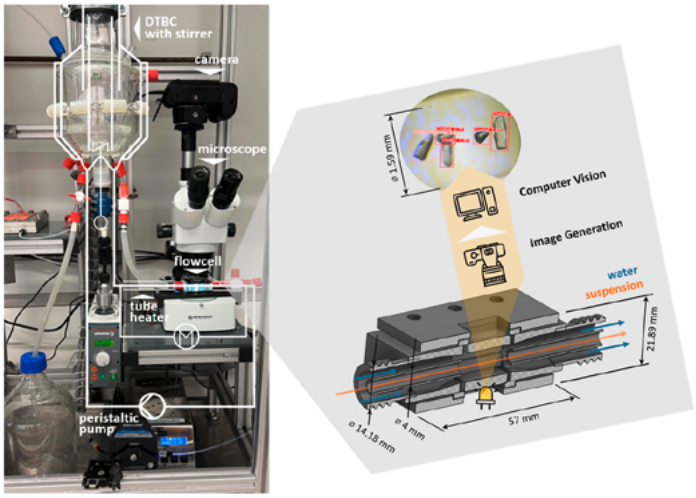

Figure 1. Experimental setup with technical drawing of the developed flow cell and images of crystal suspension.

An intelligent photometric analytics tool was developed to detect individual crystals and generate CSD from photometric images captured via a dedicated flow cell within a specially designed analytical bypass. This setup allows for continuous, non-invasive monitoring of crystallization dynamics without disrupting the process.

To determine the most suitable AI model for crystal analysis, various deep learning algorithms were evaluated, including 8 YOLOv8, YOLOv8 Segmentation (YOLO8seg), and U-Net. Their performance was assessed based on accuracy, processing speed, robustness, and potential distortions, with results benchmarked against manual image analysis and established models such as YOLOv4 and Mask R-CNN.

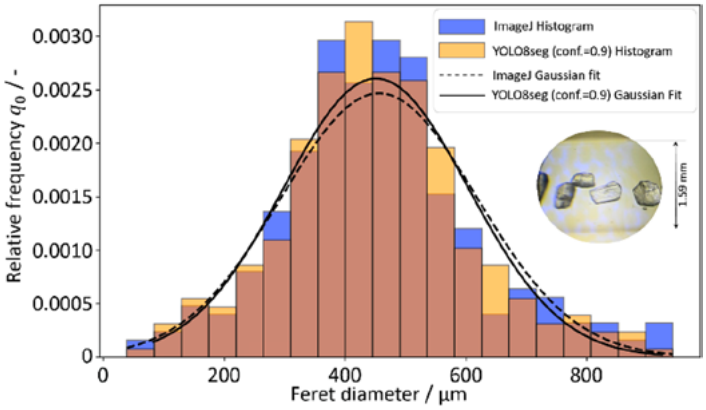

Figure 2. Relative frequency from YOLO8seg model (conf. = 0.9) of crystals assigned to Crystal class (crystal size range: 250-630 µm) compared to ImageJ.

The analysis revealed that U-Net was unsuitable due to computational complexity and accuracy limitations. In contrast, YOLOv8 and YOLO8seg demonstrated higher efficiency and precision, with YOLO8seg achieving the highest mean average precision (mAP) of 82.3 % (see Fig. 2). It outperformed Mask R-CNN and manual methods in detecting larger crystals, though its performance declined for crystals smaller than 90 µm.

The results of this study demonstrate the feasibility of integrating AI-driven image analysis into crystallization process control. Future work will focus on refining AI model training, optimizing imaging conditions, and enhancing detection accuracy for smaller crystals. Further improvements in real-time processing capabilities and model adaptability could pave the way for fully automated crystallization control, ensuring greater efficiency and consistency in industrial applications.

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Publications:
Marsollek, L.; Lamprecht, J.; Kockmann, N.; Investigation of AI Algorithms for Photometric Online Analysis in a Draft Tube Baffle Crystallizer 14, 1045 (2024)
https://doi.org/10.3390/cryst14121045

Ontology Development for Catalytic Process Research Data Management

From ontologies to fluent integration of laboratory data to process simulations

Alexander S. Behr, Hendrik Borgelt, Norbert Kockmann

Modelling and prediction of catalytic processes for optimal reaction conditions in production of chemicals is based on processing vast amounts of data derived from various sources. Achieving this, requires the development of novel data processing tools. Ontology-based knowledge graphs are a key element in research data management research by enabling structured, machine-readable, and FAIR-compliant data. This highlight shortly presents tools and methods, including NLP-driven ontology expansion, to automate and improve semantic modeling, particularly through the Reac4Cat ontology for catalytic reactions. The benefits of this approach are demonstrated through automated process simulations using knowledge graphs for laboratory and simulation data.

Catalysis research is highly interdisciplinary, producing increasingly heterogeneous data, especially with digitalization and the growing number of scientific publications. The FAIR (Findable, Accessible, Interoperable, Reusable) guidelines address the need to improve the data quality and thus the data value chain. To achieve this, data must not only be stored in a structured manner but the foundations for new data standards must also be created. Ontologies, which can be used to model conceptual knowledge in a structured and machine-readable way, provide a basis for this. Ontology-based knowledge graphs are therefore a key technology for storing implicit knowledge in a machine-readable and FAIR manner, thereby significantly improving the data value chain in catalysis research. With a focus on semantic modeling of research data in the field of catalysis and related sciences, various tools for a pipeline for semantic data enrichment and applications of the resulting workflows are composed as depicted in Figure 1.

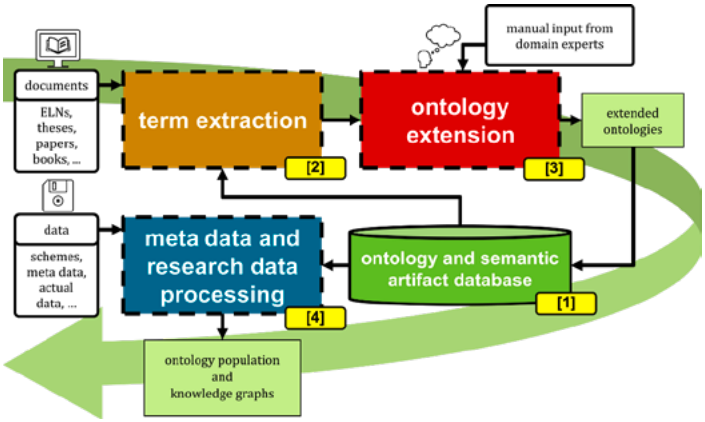

Figure 1. Overview of the ontology-centered applications for the extensions of ontologies and generation of knowledge graphs in a semantic enrichment pipeline. The yellow boxes denote the respective publication on the topic (as listed below).

An overview of existing ontologies related to catalysis science is provided [1]. In contrast to existing ontology portals, metadata on the ontologies is also included here, which, for example, shows the proximity to certain subdomains of catalysis research. This enables a more detailed classification of the ontologies, which also shows that catalysis science has not yet been sufficiently modeled by ontologies. Natural Language Processing (NLP) is therefore used to develop methods that automate and facilitate the creation and expansion of ontologies [2]. Since ontologies can model a high degree of semantic complexity, the modeling of arbitrary catalytic reactions in a new ontology developed, Reac4Cat, is introduced [3]. Finally, to demonstrate the advantages of ontology-based modeling, automated process simulations are carried out using the example of a biocatalytic process [4]. For this purpose, a knowledge graph for laboratory and simulation data is created automatically, based, among other things, on the previously developed Reac4Cat ontology.

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Publications:
[1] Behr, A.S.; Borgelt, H.; Kockmann, N.
Ontologies4Cat: Investigating the Landscape of Ontologies for Catalysis Research Data Management.
J. Cheminformatics, 16(1), 16 (2024).
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[2] Behr, A.S.; Chernenko, D.; Koßmann, D.; Neyyathala, A.; Hanf, S.; Schunk, S.A.; Kockmann, N.
Generating knowledge graphs through AI-assisted text mining of catalysis research related literature.
Catalysis Science & Technology, 14, 5699-5713 (2024).
https://doi.org/10.1039/D4CY00369A
[3] Behr, A.S.; Borgelt, H.; Kockmann, N.
Reac4Cat-Ontology: Harnessing the Power of Ontological Description Logic in Catalysis Research as a Practical Approach to Knowledge Inferences.
Datenbank-Spektrum, 24, 139-150 (2024).
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[4] Behr, A.S.; Surkamp, J.; Abbaspour E.; Häußler, M.; Lütz, S.; Pleiss, J.; Kockmann, N.; Rosenthal, K.
Fluent Integration of Laboratory Data into Biocatalytic Process Simulation Using EnzymeML, DWSIM, and Ontologies.
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Design and Application of Additive Manufactured Microfluidics

Multidimensional Analysis of Droplet and Bubble Formation, Manipulation, and Separation in Microchannels

Bastian Oldach and Norbert Kockmann

Microfluidic applications have revolutionized various scientific fields such as biology, chemistry, and medicine in the last decades. By manipulating fluids on the microscale, eminent control and precision enable innovation in diagnostics, analytics, drug development, and life sciences. Although the conventional manufacturing processes are well established, they come along with some disadvantages that limit the accessibility and hinder the further development of microfluidics. In the frame of additive manufacturing, we present alternative fabrication methods to promote affordability, accessibility, and functionality for multiphase microfluidics.

The rise and quick development of additive manufacturing techniques are currently causing a paradigm shift in the state-of-the-art fabrication of microfluidics. The focus of the contributions is on design, prototyping, fabrication, and postprocessing to create proper working multiphase flow systems that are printed using stereolithography. Various microchannel setups were fabricated and coated to increase the contact angles of the dispersed phases as shown in Figure 1.

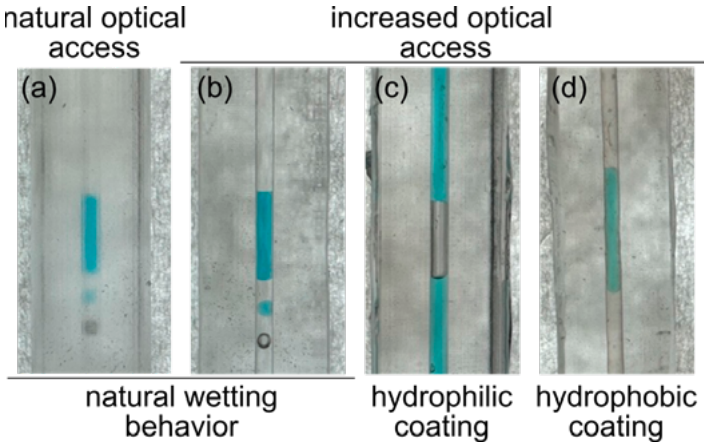

Figure 1. (a) shows a 3D-printed microchannel with its natural optical access and its natural wetting behavior. (b–d) show a channel with increased optical accessibility with (b) natural wetting behavior, (c) wetting after hydrophobic coating, and (d) wetting after hydrophilic coating. The blue liquid is DI water with ink, and the transparent liquid is silicon oil.

A deep understanding of present phenomena is crucial for effective design of microstructured devices, especially when used for multiphase flows. Image analysis is a common choice to understand ongoing physics, but is limited to only two dimensions. X-ray-based Computed Tomography (CT) adds a third dimension to images, which results in more information, but ultimately, in more complex image analysis. A UNet neural network is used to extract certain states during droplet and bubble formation in microchannels as schematically shown in Figure 2 (a). As a result, this highly dynamic processes is transferred into static observation. The subsequent reconstruction of several ascending states enables time-resolved 3D analysis of the present phenomena. 3D-printed microchannels with circular and square cross-sections were investigated. Water or air serve as the dispersed phase with silicon oil as the continuous phase in each case. The U-Net achieves a mean Intersection over Union (IoU) of 0.732 for a training of 50 epochs and it takes 120 ms per image to process 60,000 images to categorize emerging droplets or bubbles. 2D and 3D quantification of emerging droplets or bubbles emphasize the significant geometric influence of microchannels as emphasized in Figure 2 (b).

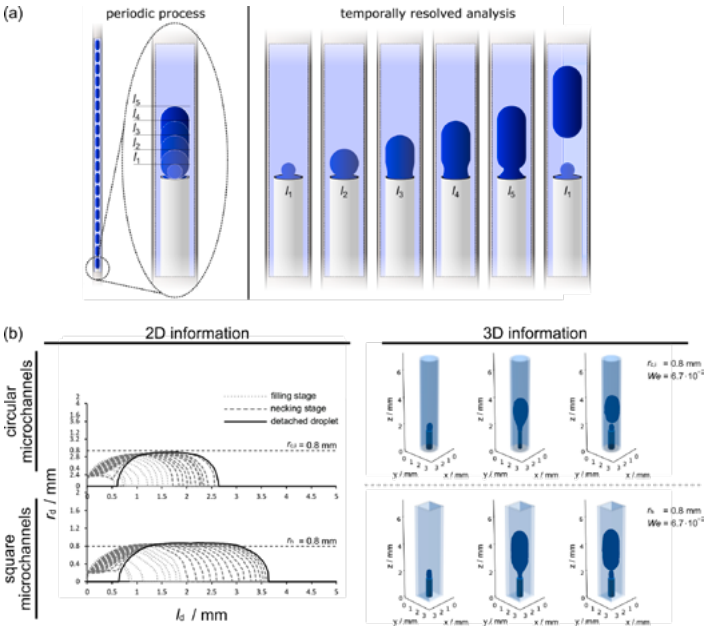

Figure 2. (a) principle sketch of how a periodic process like repeated slug formation can be classified according to the state of droplet formation. (b) emphasizes the 2D and 3D image evaluation of emerging droplets and bubbles in microchannels.

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Publications:
Oldach, B.; Fortmann, R.; Pleie, T.; Timm, P.; Kockmann, N., Design and Rapid Prototyping of 3D-Printed Microfluidic Systems for Multiphase Flow. MDPI-chemistry, 6, 1458–1476 (2024).
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Gamification in Teaching Fluid Mechanics

Investigating effects in effectiveness, efficiency and appeal

Konrad Boettcher, Michael-David Fischer

In engineering many modules are perceived as difficult. This usually concerns compulsory courses in the undergraduate degree programme, in which natural behaviour is described mathematically. On the one hand, this is necessary to enable engineers to optimise technical products and processes. On the other hand, many students are less motivated, be it due to the heavy emphasis on maths, the degree of abstraction or other obstacles such as competition with far more enjoyable and motivating pastimes. This results in less than optimal learning outcomes, which have a detrimental effect on further studies, the postponement or failure of exams and thus an extension of the study period. In this study, some game elements are used to increase motivation and study success.

According to the most common theory of motivation (Ryan and Deci's self-determination theory), motivation develops from three elements: 1. experience of autonomy, 2. experience of competence and 3. social integration. If a normal lecture is measured against these elements, the autonomous choices are rather limited and an experience of competence only arises - if at all - after the exam and therefore too late. If students do not learn in study groups, there is no social integration either - although this point is also the least important factor influencing motivation. It is therefore not surprising that in the meta-meta study on factors influencing learning (so-called Hattie study) the effect size for a lecture with Cohen's d = - 0.41 is even more negative than corporal punishment at home (d = - 0.33).

To strengthen the internal coherence of the course, the separation into lecture and exercise is cancelled. Hence, problem-related tasks result in approaches or needs for new theories, which can also be directly applied to problems. In order to increase participation and not leave anyone behind, the lectures are also streamed, recorded and made permanently available. Additional gamification elements serve to increase motivation, participation, activation of learners and curiosity. Students can collect points in the courses, which give them a bonus on the exam. Points can be collected by correctly answering multiple choice or free text questions. The didactic principle of think-pair-share is emphasised. Points can also be earned by acting as a tutor during tutorials. The students act like the actual tutors from higher semesters, but are accompanied by them in a corrective and supportive manner. These points increase the experience of autonomy, as students can decide whether they want to prepare or follow up with the flipped classroom material, lead tutorials themselves or use various learning materials such as desktop VR labs. The competency experience is strengthened by initially simple and methodical recurring questions, social integration through think-pair-share, learning through teaching, and a leaderboard.

Contrary to expectations, the participation rate of 80 % in the mixed course was higher than in previous exercises (30 %), see Figure 1. The on-site participation rate increased during the course, proofing an increased appeal.

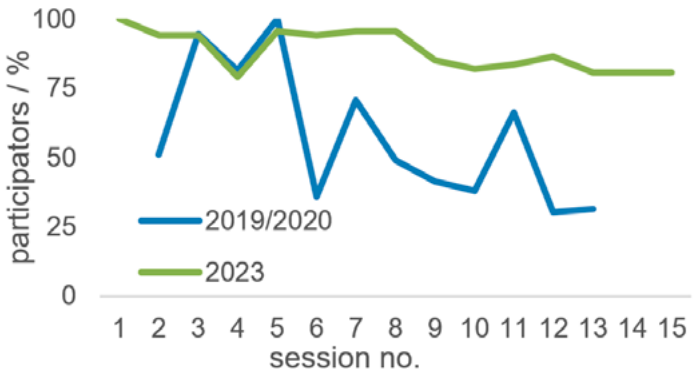

Figure 1. Participators against session number in year 2019/20 in the exercise and 2023 in the gamification run in the combined lecture and exercise.

Figure 2 describes the distribution of marks in the gamification round and the average of previous years (excluding coronavirus). The extra points due to gamification were deducted. It is clearly recognisable that the students achieved a better learning outcome in the exam proofing an increased effectiveness. Fewer failed students partially compensate for the additional workload caused by gamification in terms of efficiency.

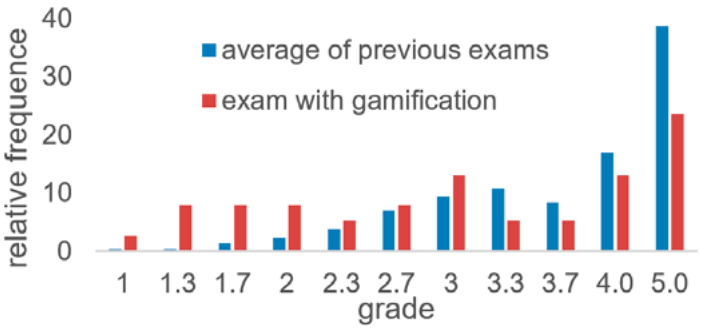

Figure 2. Relative frequency of grades (1: very good, 4: passed, 5: failed) in the average of previous years and the gamification course without considering the gamification points for the exam.

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AI-based integrated smart process sensor for liquid-liquid processes

From laboratory to industrial emulsification processes

Inga Burke, Thajeevan Dhayaparan, Sebastian Derkum, Tom O O Olusanya, Ole F Thiel, and Norbert Kockmann

In emulsification processes, droplet size distribution (DSD) is a key quality attribute that significantly impacts product properties. Image-based evaluation techniques provide a viable approach for DSD assessment; however, their implementation requires direct optical access to the product, presenting challenges in industrial environments. To overcome these limitations, an integrated smart sensor was developed, systematically validated, and tested. The sensor design process followed a design strategy incorporating multiple iterations, prototyping, and testing. The final sensor design provides a reliable and accurate DSD monitoring, enhancing process control and product quality.

Developing an AI-based integrated smart process sensor for emulsification processes requires several design steps and specifications. This development strategy needs to include the identification of critical process conditions, quality attributes, and the integration of an optical access to the final product. The main steps of this iterative procedure involves the design of an optical sensor including an optical measurement flow cell, an automated droplet size analysis as well as the integration into the process plant. The investigated steps, depicted in Figure 1, were tested and validated regarding their capability to characterize emulsification processes.

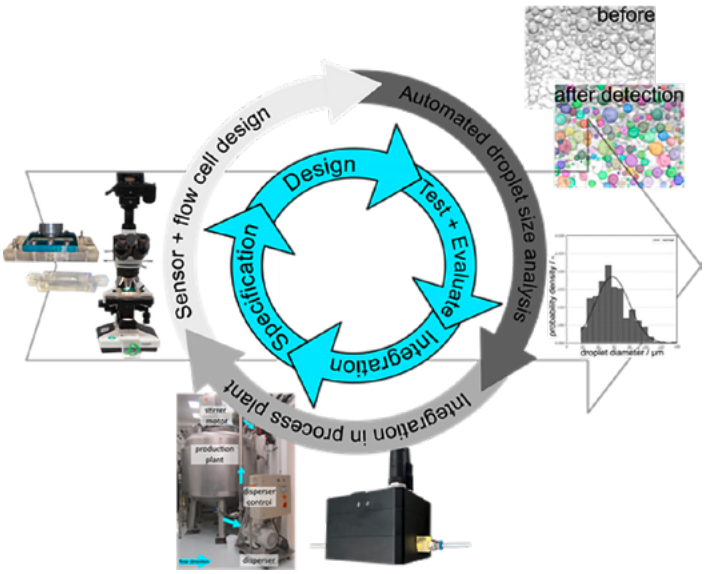

Figure 1. Iterative sensor development strategy including the optimization steps for sensor development and plant integration.

The optical measurement flow cell is 3D printed using the SLA fabrication. Here, a clear resin is used for optical access. The flow cell is assembled in a modular way providing the opportunity of different channel depth at the observation window. Transferring the setup from laboratory to production scale requires further adaptation and iteration steps. The integration into a camera system is required as well as the reduction of complexity for easier handling during production.

The automated droplet size analysis is an AI-based strategy using the YouOnlyLookOnce (YOLO) model for object detection. Several training and optimization steps were performed here as well as the integration of the network on the optical sensor for final process plant integration. The final model was tested on different datasets to validate its accuracy in droplet size determination as well as its trustworthiness and robustness regarding different image qualities and compositions. Figure 2 illustrates an example image and distribution.

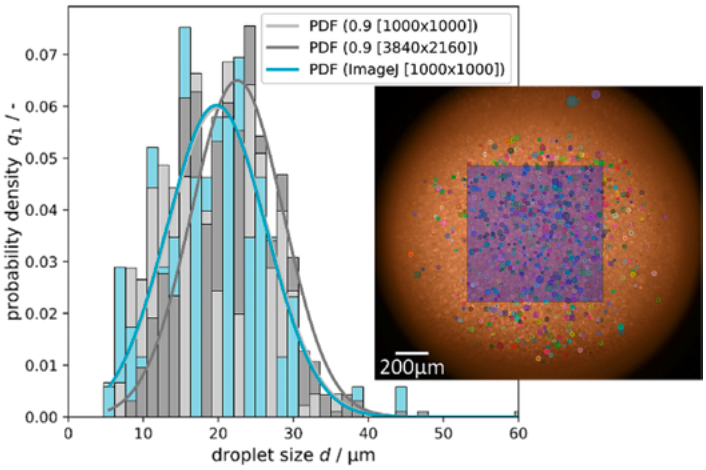

Figure 2. AI-based droplet size evaluation using YOLO and its corresponding droplet size distribution. Detection was performed with a confidence score of 0.9.

The final integration of the sensor into an industrial plant requires the incorporation into a smart camera system. The integration into a 4-ton production plant for emulsification processes was successful and shows a first feasibility using the sensor setup for real-time process characterization. The general measurement concept as well as the combination of the optical measurement cell and the camera system, shows a reliable evaluation of the emulsification process, allows faster process evaluation, and provides a basis for process control.

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Smart Reactor Design for Miniatured Optimal Equipment

Lisa Schulz, Stefan Höving, Biborka Boga, Norbert Kockmann

The development of smart reactors is an innovative approach for enhancing chemical processes. One major challenge of such reactors is their complex individual design. This study demonstrates the use of advanced techniques toward smart reactor on three examples. The model-based scale-up of a Sonogashira coupling reaction is performed in 3D printed continuous-flow reactors from stainless steel. The photocatalytic antibiotic degradation is investigated in coated microchannels using advanced flow modeling for catalytic photodegradation of a drug substance. Robust micromixer design facilitates the continuous particle precipitation in curved flow elements to improve batch production.

The photocatalytic degradation of ciprofloxacin in aqueous solution was assessed over P25-TiO2 coated open microchannels with gravity-driven flow under UV-A irradiation. The deposition of TiO2 in the microchannels was carried out via a facile, own-developed procedure at LIKAT, see Fig. 1. The degradation kinetics of ciprofloxacin was described via the Langmuir-Hinshelwood mechanism. The flow characteristics in the microchannel with influence on the concentration distribution was numerically simulated MATLAB (2D case) and in ANSYS Fluent (2D and 3D cases). The 2D and 3D models predicted efficiently the outlet concentration of ciprofloxacin for different inlet CIP concentrations and liquid phase flow rates.

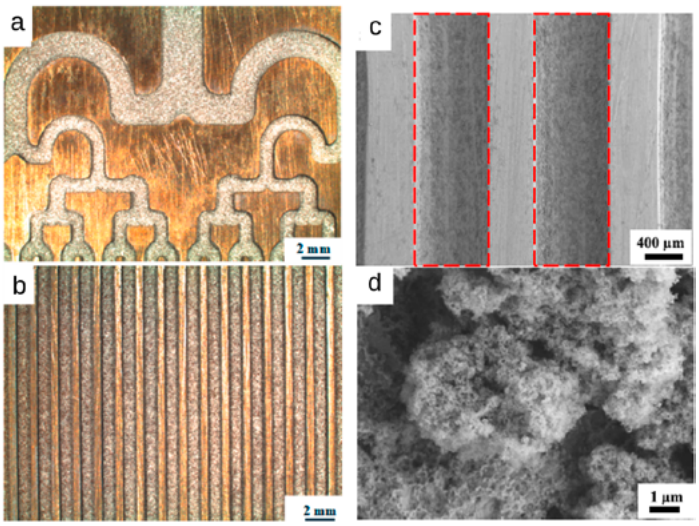

Figure 1. a+b) Falling film reactor plate (Boga et al., 2024a); **c+d)** channel surface and catalytic coating (Boga et al., 2024b), SEM micrographs of the P25 catalyst inside the FFMR channels at (the red mark shows the microchannel, a. 30 x, b. 1000 x, c. 10 000 magnification)

The model-based scale-up of a homogeneously catalyzed Sonogashira coupling reaction is performed in a 3D printed metal continuous-flow reactor, see Fig. 2. The reaction is scaled-up from a continuous-flow microreactor with an internal volume of 2.5 mL and an inner diameter of 1 mm to a 3D printed metal reactor with 4 residence time modules with an overall internal volume of 190 mL (scale-up factor of 76) and an inner diameter of 3 mm. The high heat transfer, narrow residence time distribution, and rapid mixing enables a fast and reliable model-based scale-up. The reaction is monitored with inline Raman spectroscopy with a low calibration effort, applying a multivariate curve resolution approach. Manufacturing conditions result in a space time yield of 412 kg m^{-3} h^{-1}.

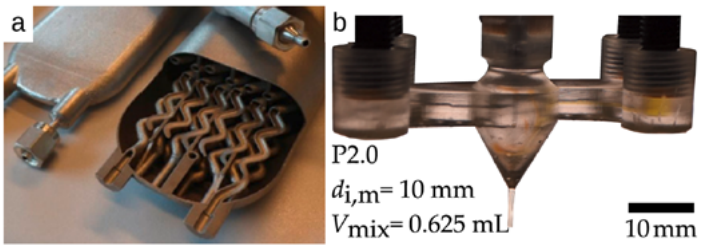

Figure 2. a) 3D printed metal reactors with zigzag channels from InnoSyn B.V. (Schulz et al., 2024) and **b)** solids formation mixer made by photolithography (Höving et al., 2024)

Improved particle generation and characteristic control can benefit from continuous processing and intensive mixing. Höving et al. developed an iterative method for micromixer design to quickly generate a continuous process optimization platform for continuous, plugging-free particle generation with the required characteristics. Assisted by rapid prototyping and additive manufacturing, a vortex mixer was produced that delivers satisfactory long-term results, see Fig. 2b.

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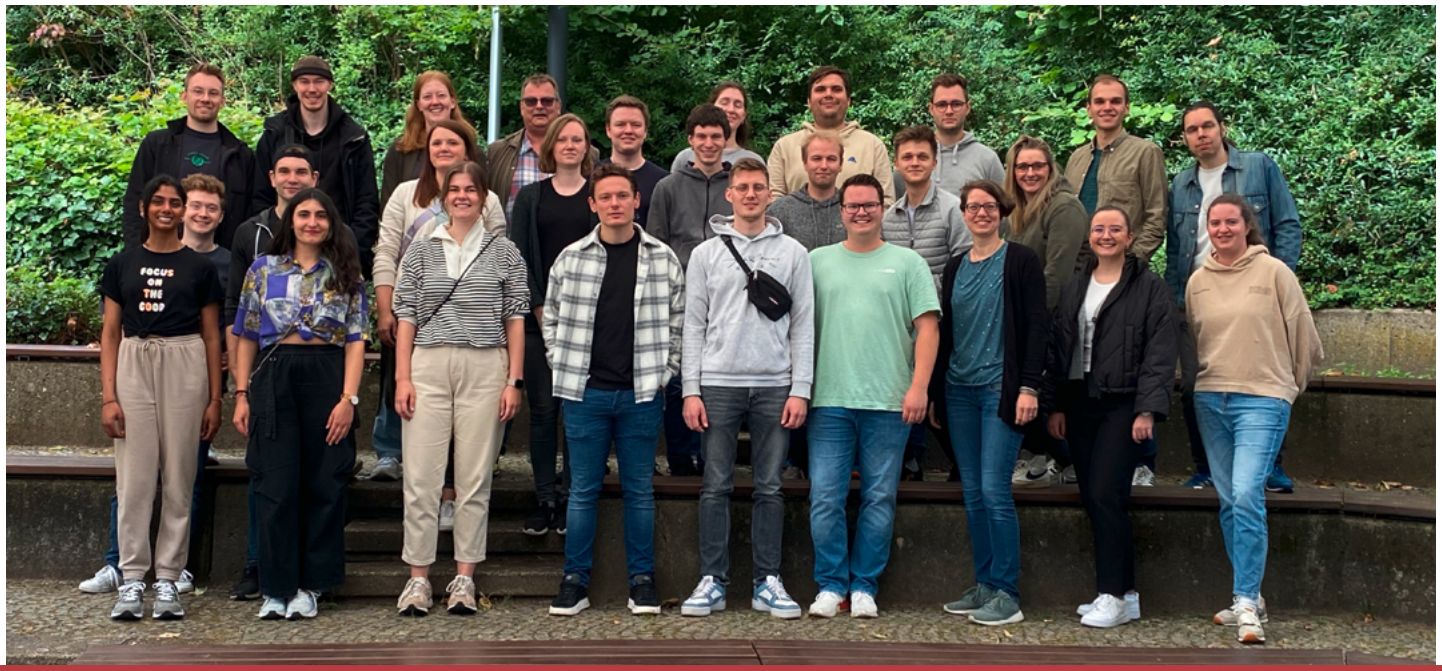

Plant and Process Design (APT)

Optimizing Chromatographic Separation with Redosing in Centrifugal Partition Chromatography

Buthmann F., Volpert S., Hohlmann J., Laby P., Hamza D., Neuwald M., Koop J., Schembecker G.

Centrifugal Partition Chromatography (CPC) is a liquid-liquid separation technique that employs immiscible liquid phases for efficient compound purification. Downside of this method is the loss of separation efficiency due to bleeding of the solid phase. This study explores and optimizes chromatographic separation in CPC by implementing a novel operational mode called redosing of the stationary phase. The findings indicate that this approach effectively mitigates the hydrodynamic issue of bleeding, which results in the loss of stationary phase over time. By maintaining a consistent amount of stationary phase within the rotor, we observed stable separation performance and significant improvements in solvent efficiency and chromatographic resolution.

Centrifugal Partition Chromatography (CPC) is an innovative technique that uses two immiscible liquid phases as mobile and stationary phases for separation tasks. Unlike traditional chromatography with solid stationary phases, CPC immobilizes the liquid phase using centrifugal force generated by spinning rotors with interconnected chambers. This method offers advantages such as reduced costs and improved recovery rates due to the lack of irreversible adsorption. A significant challenge in CPC operations is bleeding, which occurs when droplets of the stationary phase are unintentionally carried out of the system due to incomplete coalescence at chamber outlets. This leads to a gradual decrease in retention values over time, diminishing separation efficiency and impacting productivity.

In our research, we simulated the bleeding effect using computational fluid dynamics (CFD) models to understand its dynamics under various operational scenarios. The simulations revealed how different flow rates influence bleeding rates and identified critical parameters affecting retention stability across multiple chambers. Furthermore, our CFD results showed that varying volumes of redosed stationary phase affect flow regimes within the apparatus while minimizing downstream disturbances. The results confirmed that redosing stabilizes retention values across all rotor chambers. Following these simulations, we conducted experimental validations. The experimental results confirmed our simulation findings; specifically, we observed that implementing redosing allows for stabilization of retention values consistently high at approximately compared to control runs without redosing which showed significant declines. An example is provided in Figure 1.

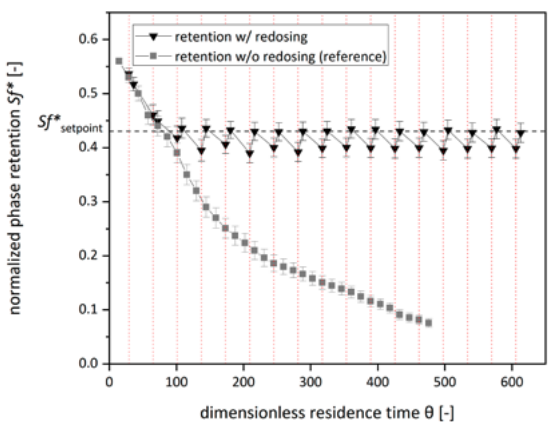

Figure 1. Phase retention against dimensionless residence time with and without closed-loop redosing.

Introducing an automated control mechanism for redosing marks a significant advancement in CPC operation strategies aimed at mitigating bleeding effects while ensuring optimal chromatographic performance over extended periods without sacrificing quality or increasing solvent usage unnecessarily. Figure 2 highlights the improvement due to closed-loop redosing in CPC applications.

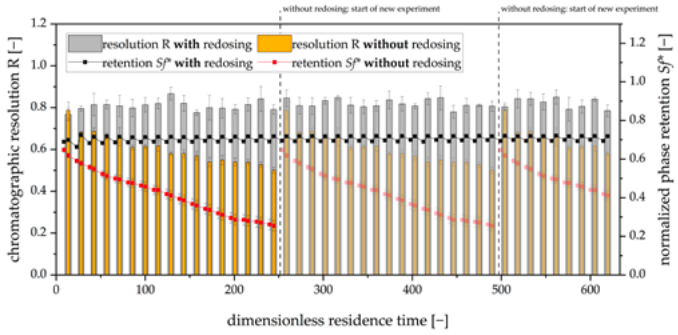

Figure 2. Normalized phase retention and chromatographic resolution against the dimensionless residence time with and without closed loop redosing.

Through this innovative approach we not only improved retention but also enhanced chromatographic resolution significantly. As we move forward with this research direction, it is imperative to explore further applications of closed-loop redosing strategies across various biphasic systems while developing robust sensors capable of real-time monitoring to ensure continuous optimization in industrial settings.

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Advancements in Water-Free Polyethylene Terephthalate Recycling via Glycolysis

Innovative Strategies for Enhancing Efficiency and Sustainability through Glycolysis

Schlüter M., Zimmer J., Held C., Wohlgemuth K.

Recycling PET is a widely investigated current engineering issue. Recent advancements in the recycling processes for polyethylene terephthalate (PET), particularly through glycolysis, have shown significant promise in enhancing efficiency and sustainability. The research emphasizes innovative strategies aimed at enhancing the efficiency and sustainability of PET recycling, addressing critical environmental challenges associated with plastic waste. However, a problem of the recycling process is that it is not yet more sustainable than the production of new PET. By optimizing reaction conditions and implementing closed-loop systems, significant improvements are achieved in resource recovery and process yields. These developments not only contribute to reducing reliance on virgin materials but also promote a circular economy where waste is minimized, and valuable resources are effectively reused.

Our research has illustrated substantial progress in optimizing PET recycling via glycolysis, focusing specifically on methodologies that enhance both efficiency and sustainability within the recycling framework. Glycolysis has emerged as a promising chemical recycling method that converts PET back into its monomeric components through the use of ethylene glycol as a reactant. This process offers notable advantages over traditional mechanical recycling methods by allowing for the recovery of high-quality monomers suitable for repolymerization into new PET products. The crystallization step plays a pivotal role in separating the reaction product, Bis(2-hydroxyethyl) terephthalate (BHET), from the mixture. The efficiency of this step directly impacts both the overall process yield and the purity of the recovered BHET. Optimizing crystallization conditions is crucial to achieving high-quality crystals with minimal impurities while ensuring maximum recovery of the monomer.

The study identified natural cooling without stirring as the most effective method for BHET crystallization in a water-free PET glycolysis process, achieving a crystallization time of 180 minutes and a process yield of 71 %. However, the crystallization was strongly inhibited by BHET dimer formation and dissolved impurities from the PET input material, such as colorants. Further optimization is needed to address these challenges and improve the process efficiency and product purity.

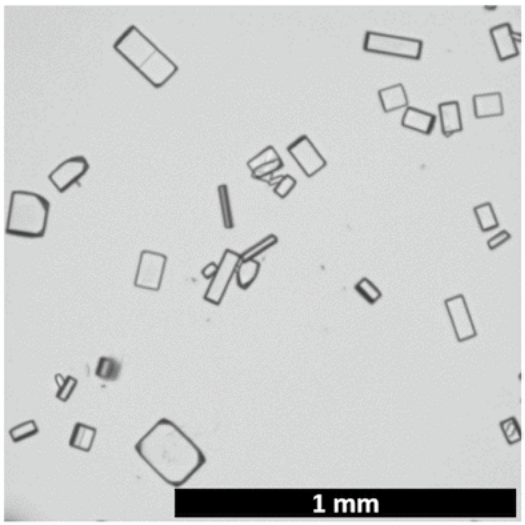

Figure 1. Exemplary image of crystals retrieved directly after the crystallization with natural cooling without stirring.

Another key area of advancement in our research lies in the development of closed-loop systems that effectively recycle essential reactants such as ethylene glycol and zinc acetate catalysts used during the glycolysis process. Our findings demonstrate that through optimized washing procedures, we can save up to 48.6 % of ethylene glycol and 50 % of zinc acetate during multiple reaction cycles. Additionally, these innovations led to an overall process yield of 80.6 % in our recycling runs, showcasing significant improvements compared to conventional methods.

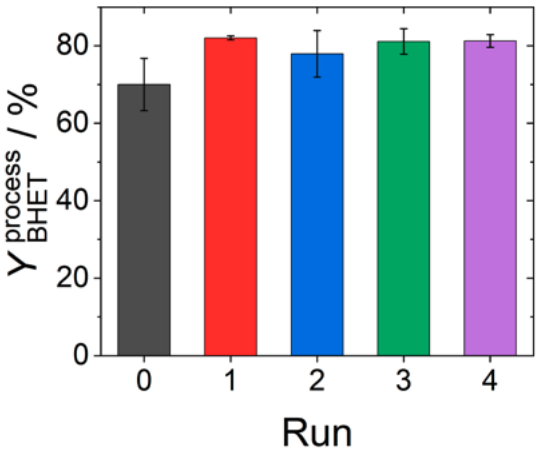

Figure 2. Overall BHET process yield along the runs with mean value and standard deviation from the duplicate series.

Finally, we demonstrated that the recycled BHET product, consisting of 90 % monomer and 10 % dimer, could be successfully repolymerized into PET. This indicates that separating the monomer and dimer is unnecessary for producing high-quality PET, making the process more efficient and scalable.

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Biomaterials and Polymer Science (BMP)

Boosting the Activity of Ciprofloxacin with Vitamin E-POx Conjugates

Conjugation of Ciprofloxacin with Poly(2-oxazoline)s with a Vitamin E End group are active against resistant *E.coli*

Alina Romanovska, Jonas Tophoven, Marina Breisch, Joerg C Tiller

Antibiotics are becoming increasing less active against infections due to the spread of resistant bacteria. This will cause a dramatic problem in medicine in the future, because bacterial infections are still the number one cause of death world-wide. The present study addresses this problem by modification of the antibiotic ciprofloxacin (CIP) with the polymer poly(2-methyl-2-oxazoline), which carries Vitamin E as end group. This fully biocompatible modification leads to a dramatic increase in activity of the antibiotic and even works 100 times better against resistant E. coli *bacteria compared to the unmodified CIP.*

Amphiphilic POx-CIP-conjugates are highly active, but their hydrophobic block limits solubility and induces cytotoxicity. In order to substitute the hydrophobic block with a respective biocompatible hydrophobic function, we choose to use α-Tocopherol (Vitamin E, VitE) as substitute. The vitamin was rendered into an initiator for the cationic ring-opening polymerization of 2-oxazolines by modifying it with 4-(bromomethyl)benzoyl bromide (BMB). This initiator was found to be very efficient and a series of poly(2-methyl-2-oxazoline) (PMOx)-conjugates with VitE at one terminal and CIP at the other could be successfully synthesized (structure depicted in Fig. 1).

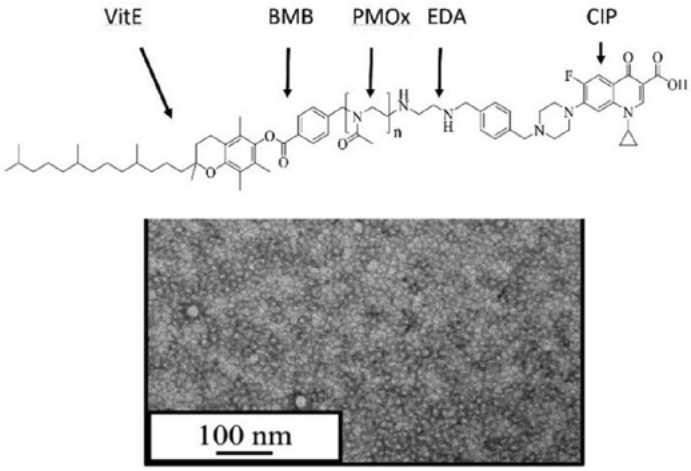

Figure 1. Structure of VitE-PMOx-CIP conjugates and TEM image of micelles of VitE-PMOx$_{31}$-CIP formed in water.

These water-soluble micelle-forming amphiphilic PACs exhibit the 5 times higher molar antibacterial activity against the bacterium *S.aureus*. Thereby, the activity is decreasing with the length of the PMOx chain, when the chains have more than 50 repeating units. This is most likely due to the fact that these PACs due not form micelles but larger aggregates. Additionally, the CIP conjugates show a strong tendency to enter Gram-negative *E.coli* cells via their efflux pumps, which leads to greatly increased activity against *E.coli* with over-expressed efflux pumps (Fig. 2). The VitE-PMOx$_{31}$-EDA-CIP conjugate is more than 100 times more active against such cells compared to the antibiotic CIP, while the latter is more than 100 times more active than the respective conjugate in case of *E.coli* cells with suppressed efflux pumps.

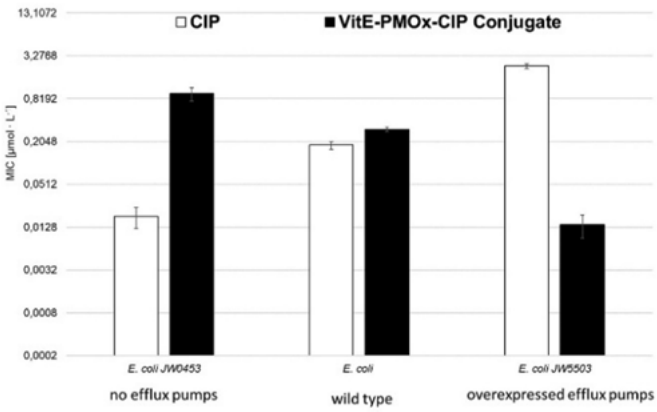

Figure 2. Antimicrobial activity of CIP and VitE-PMOx$_{31}$-EDA-xCIP against *E. coli* ATCC 8739 and its mutants, JW0453 without AcrAB-TolC efflux pumps and JW5503 with overexpressed AcrAB-TolC efflux pumps.

In order to investigate membrane activity of the amphiphilic structure as additional antibacterial mechanism, the PACs were tested regarding their ability to lyse erythrocytes (red blood cells). It was found that even at a concentration of 20000 µg/mL none of these cells are destroyed, which excludes the membrane activity as mechanism. Further, it could be shown in collaboration with the Breisch group at Bergmannsheil Hospital, Bochum, that the PACs are not cytotoxic exemplified on macrophages.

This in combination with the fact that the formation of bacterial resistance against the CIP conjugates is greatly delayed and that they overcome bacterial efflux pumps makes these novel conjugates an interesting candidate for a next generation antibiotic.

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Nonionic POx-Based Tough and Strong Double Network Hydrogels

Controlling the Mechanics of POx/Acrylate DNHs by Variation of Functional Groups

Paola Benitez-Duif, Sebastian Weckes, Joerg C Tiller

Double network hydrogels (DNHs) are the only hydrogels with the strength and the toughness required for applications such as artificial cartilage, pressure resistant separation membranes, or bendable electronics. Although numerous of such materials are known, they all are based on ionic systems, which cause problems with environmental factors such as pH or ionic strength are changing. Here, we present a way to realize strong and tough DNHs composed of on nonionic system based of poly(2-oxazoline)s (POx) as primary and different poly(acrylate)s as secondary network.

A series of DNHs with cross-linked poly(2-methyl-2-oxazoline) (PMOx) and poly(2-ethyl-2-oxazoline) (PEtOx), respectively, as primary network and different poly(acrylates) as secondary network was synthesized. The investigated acrylates, depicted in Figure 1, were chosen regarding their capability to build hydrogen bonds with the carbonyl groups of POx. Poly(N,N-dimethylacrylamide) (PDMA) was used as negative control, because no hydrogen bonding is expected in the respective DNHs.

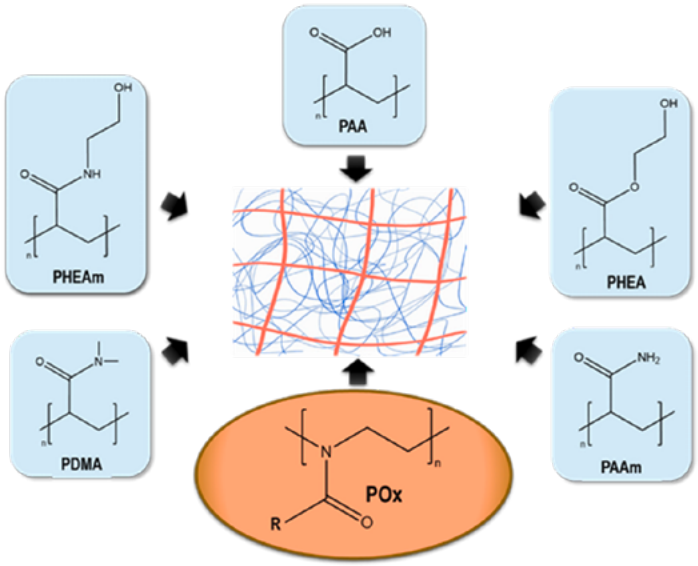

Figure 1. Polymers used to design DNHs with different cross-linked POx as primary and various poly(acrylate)s as secondary network.

The results show that the secondary network for POx-based DNHs evidently needs to be a proton donor to sufficiently dissipate energy for superior mechanical properties. The high compression strength of $PMOx_{50}$/PAA was found to be caused by the strong hydrogen bonds formed within the PAA network and this could not be achieved by any other POx-based DNH. Furthermore, the role of the POx side chain plays an important factor for the mechanical properties of the respective hydrogels. An increase of the side chain from a methyl to an ethyl groups (PMOx to PEtOx) changes the interactions with the secondary poly(acrylate) network in a way that longer proton donating side chains on the acrylate are required to reach the carbonyl group of the POx network. Thus, the binding between the two networks is very sensitive to the smallest changes in the structure of the side groups.

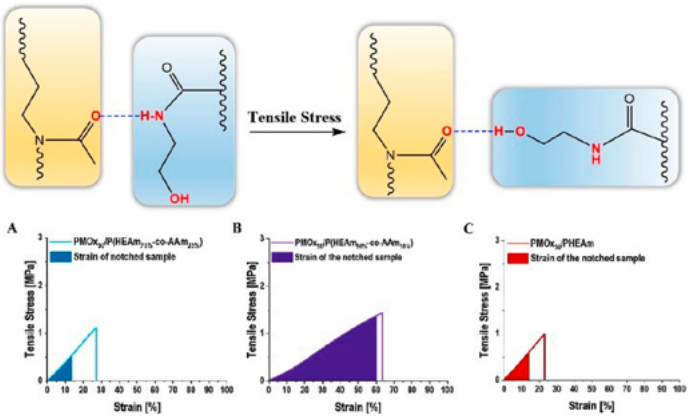

Figure 2. Proposed toughness mechanism (top) and stress strain curves of PMOx/PHEAm DNHs (bottom) with different amounts of the comonomer AAm in the PHEAm network ((A) 25 wt%, (B)10 wt%, and (C) 0 wt% AAm). The filled areas are the stress strain curve of samples notched to approximately 1/3 of their width in the middle of the sample.

When mixing monomers in the secondary poly(acrylate) network, the mechanical properties such as toughness could be dramatically influenced as shown in the case of a PMOx/poly((2-hydroxyethyl) acryl amide)) (PHEAm) DNH (Figure 2). The addition of a small fraction of acryl amide (AAm, 10 wt%) leads to a ten-fold increase in toughness, more than the double the tensile strength, and almost double compressive strength compared to the $PMOx_{50}$/PHEAm DNH In terms of tensile toughness this DNH even exceeds the overall best performing $PMOx_{50}$/PAA. Further increasing the AAm content is resulting in a drop of those properties.

The results show that it is possible to obtain non-ionic DNHs for POx-based systems, but further studies will be needed to fully match the mechanical properties of ionic systems.

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Shaping the Future: Heating Rate-Sensitive Polymer Network for Smarter Material Responses

A route towards smart polymers that can intrinsically predict processes

Robert David Ludwig Jerusalem, Michail Maricanov, Thomas Raidt, Frank Katzenberg, Joerg C. Tiller

Shape memory materials are smart materials that change their shape according to environmental changes, such as temperature or moisture, and are therefore used as adaptive actors in numerous applications. A breakthrough in polymer science introduces materials that can react not only to temperature but also to how quickly they are heated. This study presents cross-linked polyethylene terephthalate (x-PET) as a novel heating rate-sensitive shape memory polymer. By quenching stretched x-PET into a fully amorphous state, it becomes capable of responding specifically to different heating rates. The shape change at a certain temperature is then a measure of the heating rate that was applied to reach it. This way the material can intrinsically react to the variation of temperature and is thus capable of preventing, for example, an overheating.

Polyethylene terephthalate (PET) was crosslinked by end group modification with phthalic anhydride (PA) and simultaneous crosslinking with a tetra-functional epoxide (TGDDM). x-PET is already known as an efficient high temperature shape memory polymer (SMP) due to the high melting temperature of its crystallin phase. In this case, however, x-PET was oriented in the melt and quenched in ice water to inhibit crystallization. This transforms the x-PET into a SMP capable of reacting not only to exceeding its melting temperature (T_m) but also its glass transition temperature (T_g), since the frozen shape is not stabilized by the crystals but the glassy amorphous phase.

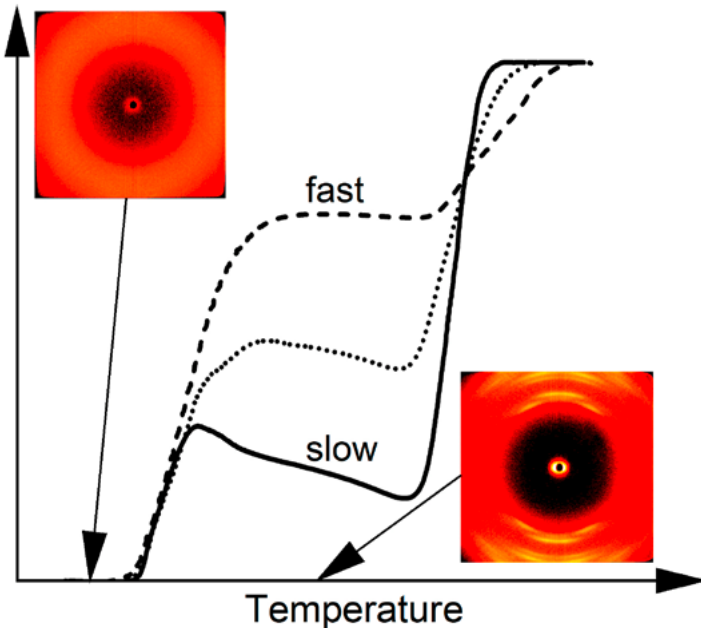

Figure 1. Degree of recovery versus temperature plots for different heating rates including WAXS of the programmed and intermediate shape.

Heating x-PET in a Dynamical Mechanical Analyzer (DMA) while applying a small axial force of 0.01 N allowed the monitoring of the shape recovery during heating and revealed a triple shape. The shape recovery is initiated by surpassing the glass transition temperature allowing the retractive forces to initiate the recovery and completes once the melting temperature of x-PET is reached. In between these boundaries lies the intermediate shape of the triple shape memory polymer. This intermediate shape is stabilized by the onset of crystallization. Heating the samples with different heating rates revealed, that the height of the intermediate shape is strongly dependent on the applied heating rate (Figure 2).

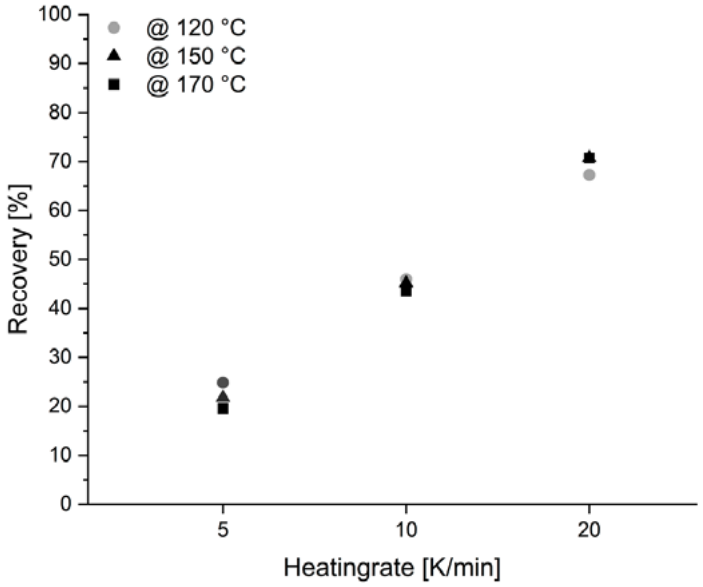

Figure 2. Degree of recovery at different temperatures as a function of the applied heating rate.

It is shown that the interplay of two counteracting processes – the retraction (recovering the original shape) and crystallization (stabilizing the current shape) – is responsible for the stabilization of different intermediate shapes (Figure 1). This makes x-PET only the second prophetic material (after our previously published x-sPP) that reacts specifically to the heating rate and allows conclusion to be drawn about the heating rate previously used and react to it.

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Unlocking a New Trigger for Shape Memory Polymers

Harnessing α-Relaxation for Smart Material Transitions

Michail Maricanov, Roman Becker, Robert D. L. Jerusalem, Joerg C. Tiller, Frank Katzenberg

Shape memory polymers (SMPs) represent an important class of smart materials. The polymers can switch between shape at either their glass transition or their melting temperature. Since these temperatures are material-bound, the range of applications is limited for one polymer. Interestingly, many polymers have more than one glass transition temperature. In order to broaden potential applications for shape memory polymers, we explored if it is possible to use the α-relaxation — a process linked to molecular chain migration through crystalline structures — as a trigger for shape recovery. This was successfully tested for cross-linked low-density polyethylene (x-LDPE) as a model. The breakthrough opens the door to render each crosslinked semi-crystalline homopolymer to a quadruple SMP upon using glass transition, α-relaxation and melting temperature as trigger.

The study investigates whether α-relaxation can serve as a novel trigger for SMPs. LDPE was chosen due to its ease of cross-linking with DCP and its well-defined T_α in a practical temperature range for various shape-memory applications. Figure 1 shows the DMA- and DSC-plots of a x-LDPE sample.

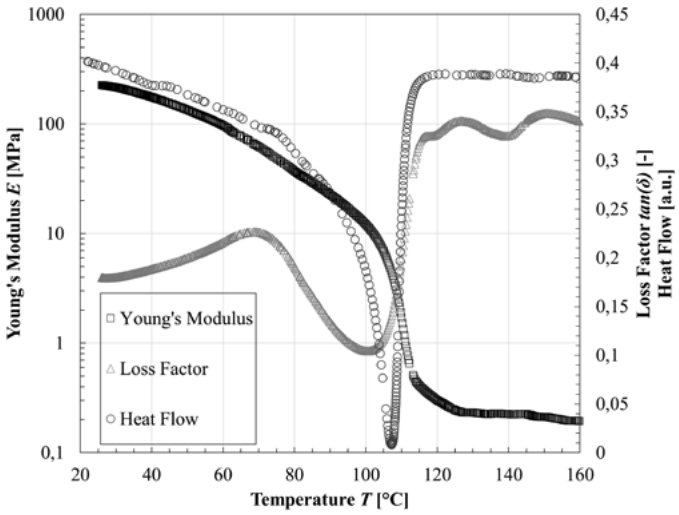

Figure 1. DMA and DSC-plots of x-LDPE.

The stability of the Young's modulus beyond T_m indicates a well-crosslinked x-LDPE network. The loss factor *tan(δ)* marks the α-relaxation peaking at 70 °C. The samples were programmed to an intermediate shape upon stretching at 130 °C (above melting temperature) to a stretching ratio λ_1 and cooling under constraint to room temperature. Programming it to its temporary shape was performed upon further stretching at 80 °C (between α-relaxation and melting temperature) to a stretching ratio λ_2 and cooling under constraint to room temperature. The shape memory performance for switching x-LDPE from the temporary shape λ_2 back to the intermediate shape λ_1' was tested upon heating again to 80 °C. The programming and recovery steps are shown in Figure 2. Shape memory parameters were determined using a strain controlled custom-made stretching apparatus.

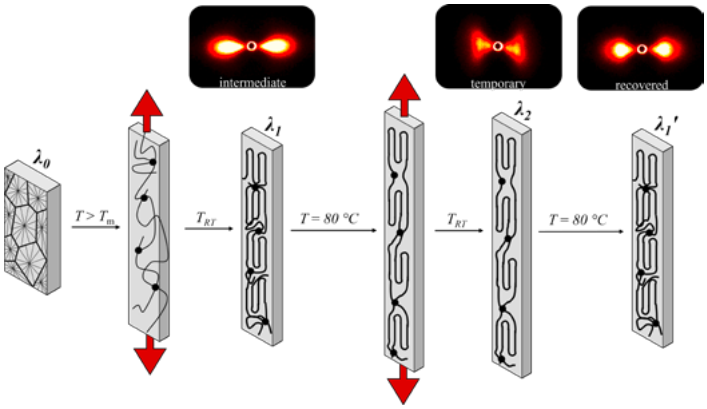

Figure 2. Illustration of the programming and recovery process of x-LDPE.

It was found that the intermediate shape of x-LDPE can be fully restored for certain λ_1/λ_2-combinations. Furthermore, SAXS and TEM show reversible morphological changes (see Figure 3) and indicate that chain migration through lamellar crystals play a key role for shape recovery. This confirms that the α-relaxation is suited to effectively trigger shape recovery, providing a novel trigger beyond the traditional glass transition and melting temperature-based triggers.

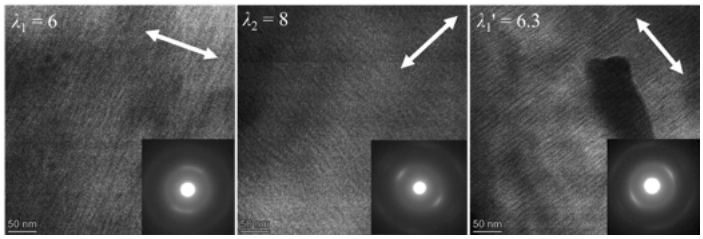

Figure 3. TEM-Images of x-LDPE after constrained crystallization in the intermediate shape (λ_1), after stretching to the temporary shape (λ_2) and recovering the intermediate shape (λ_1'). White arrows indicate stretching direction.

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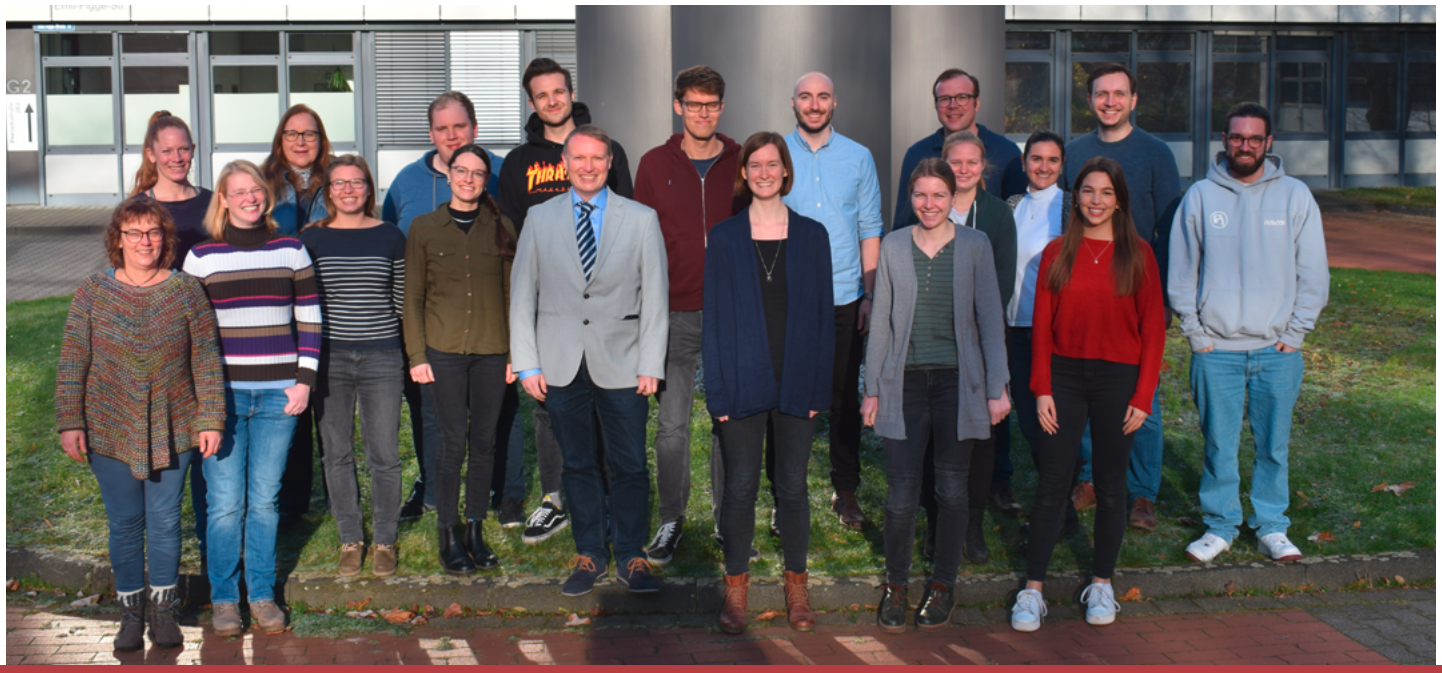

Bioprocess Engineering (BPT)

Development of a multi-enzyme cascade for 2′3′-cGAMP synthesis from nucleosides

Martin Becker, Isabel Nowak, Katharina Hildebrand, Stephan Lütz, Katrin Rosenthal

Enzyme cascades allow multi-step synthesis in one-pot reactions without the need for purification of intermediates. First, the substrate scope of nucleoside kinases and polyphosphate kinases was investigated. Based on the results, an enzyme cascade for the synthesis of 2′3′-cGAMP from guanosine was developed. Subsequently, the cascade was extended to enable the first 2′3′-cGAMP synthesis from the nucleosides adenosine and guanosine in four reaction steps. In total, 57 % of the guanosine was converted to 2′3′-cGAMP. This shows that it is possible to develop shorter drug synthesis routes by combining several biocatalytic reactions, supporting the chemical and pharmaceutical industry's goal of moving towards more sustainable processes.

In the present study, a screening process was employed to identify enzymes that were subsequently used in the design of an enzyme cascade for the biosynthesis of 2′3′-cGAMP from nucleosides. The identification of a suitable nucleoside kinase (NK) and polyphosphate kinase (PPK2) was essential for the establishment of a one-pot reaction. Two specific nucleoside kinases were investigated: ScADK from *Saccharomyces cerevisiae* and MjNK from *Methanocaldococcus jannaschii*. The capacity of these enzymes to phosphorylate adenosine and guanosine was assessed, with ATP or GTP acting as phosphate donors (see Figure 1).

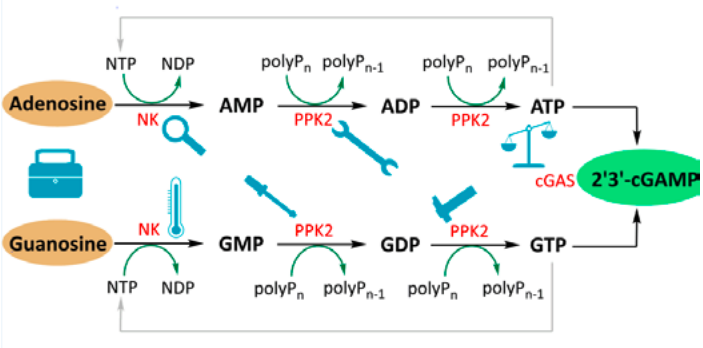

Figure 1. The following simplified scheme illustrates the enzyme cascade 2′3′-cGAMP synthesis from nucleosides using NKs, PPK2s and thscGAS. NK: nucleoside kinase; PPK2: polyphosphate kinase 2; polyPn: polyphosphate; polyPn−1: polyP truncated by one phosphate monomer.; GMP: guanosine monophosphate; GDP: guanosine diphosphate; GTP: guanosine triphosphate; AMP: adenosine monophosphate; ADP: adenosine diphosphate; ATP: adenosine triphosphate; NDP: nucleoside diphosphate; NTP: nucleoside triphosphate; 2′3′-cGAMP: 2′3′-cyclic GMP-AMP; HT-DNA: herring testis DNA; PPi: pyrophosphate.

Next, we focused on PPK2s such as *Aj*PPK2 and *Sm*PPK2, along with class III PPK2s such as *Mr*PPK2, *Eb*PPK2 and *Ch*PPK2. These enzymes were tested for their ability to convert ADP/GDP and AMP/GMP to ATP/GTP using polyP as a phosphate donor. Among them, *Ch*PPK2 showed high conversion rates.

We then designed a four-step enzyme cascade to synthesize 2′3′-cGAMP from guanosine and ATP. The process started with MjNK converting guanosine to GMP at an elevated temperature. After this step, the temperature was lowered and we added *Ch*PPK2, *Eb*PPK2, thscGAS (for cyclization), polyP and HT-DNA. This approach yielded 1.21 mM 2′3′-cGAMP after just 24 hours - a threefold increase over existing methods.

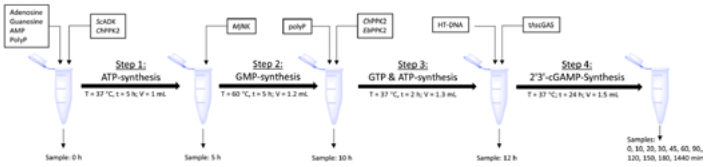

Figure 2. Schematic workflow of the sequential one-pot approach for 2′3′-cGAMP formation starting from adenosine and guanosine.

Our next goal was to create an enzyme cascade that phosphorylates both adenosine and guanosine to ATP and GTP, before cyclizing them to 2′3′-cGAMP. We carefully controlled the temperatures over four steps: first forming ATP from adenosine with *Sc*ADK and *Ch*PPK2; then converting guanosine to GMP with *Mj*NK; followed by phosphorylating AMP and GMP to ATP and GTP with *Eb*PPK2 and *Ch*PPK2; finally cyclizing these products to 2′3′-cGAMP. The results were promising - our cascade achieved up to 57 % yield while continuously producing significant amounts of ATP and GTP without inhibition during cyclization. The use of polyphosphate instead of acetyl phosphate as the phosphate donor also provided cost benefits.

In conclusion, our research shows that the development of complex enzyme cascades is valuable for efficient biosynthesis in sustainable biotechnological processes. We see opportunities for further optimization by adjusting enzyme ratios or exploring alternative enzymes under similar conditions. This work sets the stage for future advances in environmentally friendly biocatalytic processes.

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Metabolic bottlenecks of *Pseudomonas taiwanensis* VLB120 during growth on D-xylose via the Weimberg pathway

Philipp Nerke, Jonas Korb, Frederick Haala, Georg Hubmann, Stephan Lütz

The microbial production of value-added chemicals from renewable feedstocks is crucial for establishing a sustainable, bio-based economy. Efficient utilization of lignocellulosic biomass, particularly D-xylose, is essential in this process. Pseudomonas taiwanensis VLB120 uses the Weimberg pathway to assimilate D-xylose; however, understanding its metabolic constraints and regulation remains limited. This study investigates the Weimberg pathway's activity in P. taiwanensis VLB120 by analyzing biomass growth and the pathway's intermediate dynamics during batch cultivations. Results revealed significant accumulation of intermediates D-xylonolactone and D-xylonate, indicating bottlenecks in their synthesis and uptake, which were influenced by D-xylose concentration and extracellular pH.

The microbial production of value-added chemicals from renewable feedstocks is crucial for transitioning from a petrochemical industry to a sustainable bioeconomy. First-generation feedstocks, primarily D-glucose from sugarcane or corn, compete with food sources. In contrast, second-generation feedstocks come from non-edible lignocellulosic biomass, reducing this competition. After D-glucose, the most abundant sugar in lignocellulose is the pentose D-xylose. In this study, we focused on identifying and addressing the metabolic bottlenecks encountered by *Pseudomonas taiwanensis* VLB120 when utilizing D-xylose through the Weimberg pathway to understand how to efficiently convert lignocellulosic biomass, especially D-xylose (Figure 1). Our research findings revealed that while *P. taiwanensis* VLB120 demonstrated effective D-xylose assimilation capabilities, substantial intermediates, such as D-xylonolactone and D-xylonate, were observed to accumulate during batch cultivations (Figure 2). This accumulation signifies the presence of potential bottlenecks in the hydrolysis of D-xylonolactone and the uptake of D-xylonate, which are influenced by factors including substrate concentration and extracellular pH.

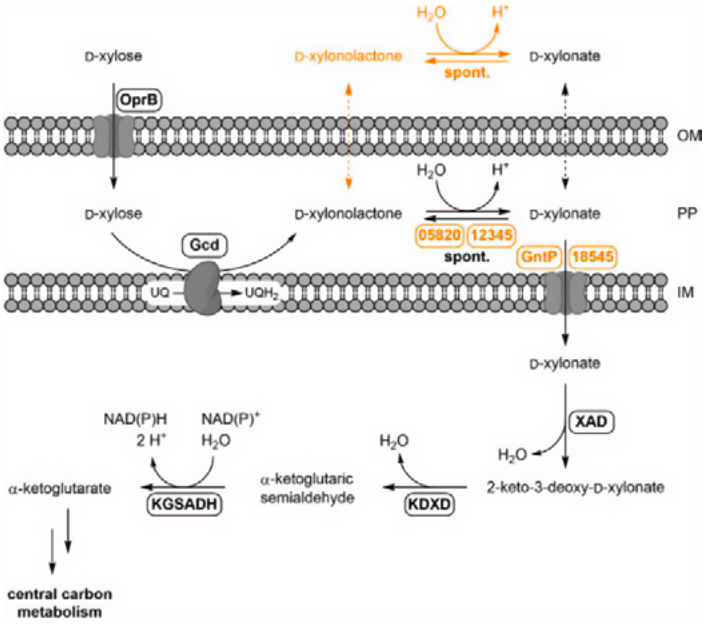

Figure 1. Schematic representation of the Weimberg pathway from *P. taiwanensis* VLB120. New insights from this publication are highlighted in orange. D-xylonolactone is hydrolyzed spontaneously or by a xylonolactonase (XLA, PVLB_05820/PVLB_12345) to D-xylonate. D-Xylonate is taken up into the cell by the two transporters GntP (PVLB_13665) and PVLB_18545.

To overcome these challenges, we employed rational metabolic engineering strategies, including the overexpression of two genes encoding putative xylonolactonases (PVLB_05820 and PVLB_12345). This resulted in notable improvements in growth rates and biomass yields. Furthermore, we identified and overexpressed two transporter genes (PVLB_18545 and gntP) to enhance D-xylonate uptake.

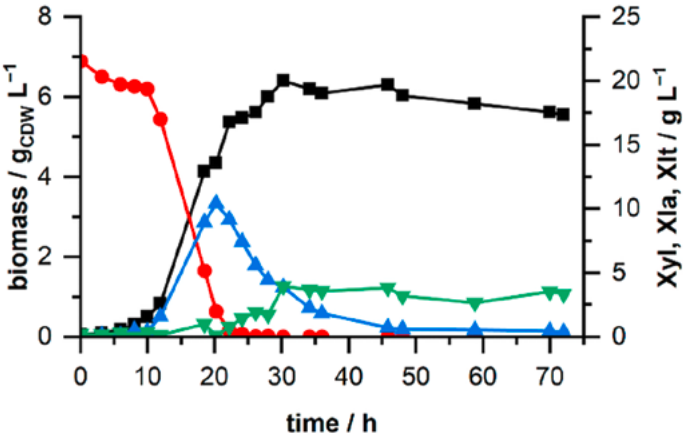

Figure 2. Bioreactor cultivations of multiple engineered *P. taiwanensis* VLB120ΔC were cultivated in 200 mL M9. Cultivations were performed in the DASbox over 75 h at 30 °C at 1000 rpm and an aeration of 3 L h^{-1}.

Our findings underscore the importance of targeted genetic modifications to optimize metabolic flux through the Weimberg pathway. By alleviating these bottlenecks, we contribute valuable insights into enhancing *P. taiwanensis* VLB120 as an effective cell factory for converting renewable feedstocks into valuable chemicals. However, further research is necessary to explore transporter mechanisms and optimize this pathway for industrial bioprocesses.

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Avoiding Replicates in Biocatalysis Experiments: Machine Learning for Enzyme Cascade Optimization

Regine Siedentop, Maximilian Siska, Johanna Hermes, Stephan Lütz, Eric von Lieres, Katrin Rosenthal

Optimizing enzyme cascades is complex and resource-intensive due to numerous parameters and synergistic effects. Machine learning can support this by identifying optimal conditions, e.g. via Bayesian optimization (BO), suggesting new experiments based on Gaussian process regression (GPR) and expected improvement (EI). In this research, BO is used to optimize enzyme cascade components. The productivity-cost ratio is the optimization objective to maximize productivity while normalizing enzyme concentrations. Replicates were not used to reduce experimental effort; instead, the algorithm and quantification of uncertainty were relied upon. This approach balances exploration and exploitation of the parameter space, which is critical for efficient and effective identification of optimal reaction conditions. The productivity-cost ratio is doubled to 38.6 mmol L^{-1} h^{-1} $€^{-1}$ for the optimized reaction conditions.

In biocatalysis, enzyme cascades use several enzymes in a single reaction to form complex molecules. One challenge with enzyme cascades is making sure there are enough co-factors like ATP for the reactions. Several systems were developed to regenerate ATP, including one that uses acetate kinase (ACK) and pyruvate oxidase (POX) (Figure 1). ACK uses acetyl phosphate as a phosphate donor, which is generated from pyruvate and phosphate by POX. Several factors affect the performance of enzyme cascades, such as the reactants' composition and concentration, pH levels, temperature and ecological considerations. Finding the optimal conditions for these reactions is often complex, but computational methods such as BO can streamline this process. BO is a machine learning technique that helps optimizing multi-dimensional problems without requiring detailed understanding of the underlying mechanisms (Figure 2).

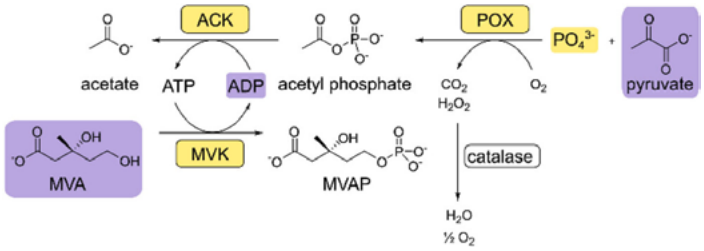

Figure 1. ATP regeneration and mevalonate kinase were the foci of the optimized enzyme cascade, with varying labelled compound concentrations. The yellow-labelled compounds' productivity and cost ratio was prioritized. ACK: acetate kinase; MVA: mevalonate; MVAP: mevalonate phosphate; MVK: mevalonate kinase; POX: pyruvate oxidase.

In the study, an ATP regeneration system involving ACK and POX was used to facilitate the phosphorylation of mevalonate (MVA) to mevalonate phosphate (MVAP), a critical intermediate in terpene production. Our aim was to optimize productivity and cost efficiency in the enzyme system. The optimization strategy involved varying the concentrations of key components. We focused on maximizing productivity while keeping costs manageable by calculating a productivity-cost ratio. Rather than replicate individual measurements, we opted for unique measurements across our experiments to provide more comprehensive data. This allowed us to gain valuable insights into optimal conditions without being constrained by technical errors. We did our screening in a one-factor-at-a-time approach, and then used Bayesian optimization to refine the parameters based on what we got out of the first 26 experiments. As we adapted the BO objective, focusing on productivity and cost, we saw narrower ranges for proposed experiments, showing convergence towards optimal conditions. We found that regions in the parameter space can be more accurately assessed by using an anisotropic GPR model alongside the isotropic model in later stages of analysis. Even low concentrations could therefore be viable, despite earlier assumptions.

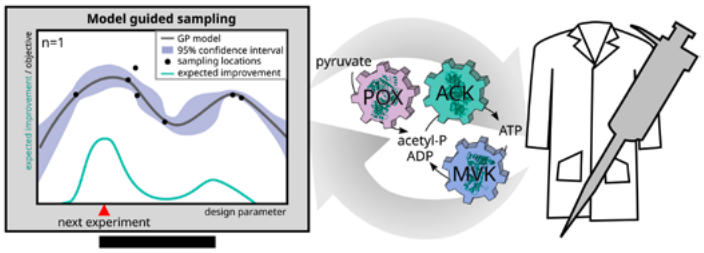

Figure 2. An enzyme cascade was optimized using Bayesian Optimization (BO) to improve productivity and cost-effectiveness, suggesting four-round experiments.

We have shown that BO is an effective tool for optimizing biocatalytic processes. This flexibility allows rapid adaptation to different objectives while maintaining efficiency throughout the experimental workflow. Future work will explore multi-objective optimization, exploiting BO's capabilities in diverse biological systems.

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Computational Bioengineering (CBE)

On-surface alcohol formation from a carbene precursor

Complex on-surface reactions involving water clusters and highly reactive species

Joel Mieres-Perez, Elsa Sánchez García

Catalysis on metal surfaces is an efficient way to enhance reaction rates and selectivity of chemical conversions. Fluorenylidene is a highly reactive carbene, which can be controlled regarding its selectivity by binding to silver surfaces. Understanding the reactions of the carbene on such surfaces with other reactants is key optimize selectivity and reactivity. Fluorenylidene forms a strong bond with Ag(111) surface at cryogenic temperatures. If water is added after the carbene is formed, the carbene-metal complex precludes the carbene reaction with water. However, we showed that if water is already present in large amounts on the surface before the carbene is produced, the reaction occurs at a temperature as low as 80 K, and the alcohol corresponding to the formal O-H insertion product is formed. The reaction can also proceed photochemically if the carbene precursor is in contact with water islands at the metal surface. Our study shows that complex reactions involving several water molecules and highly reactive species can occur on a metal surface by using an excess of water at cryogenic temperatures.

Although the interaction of N-heterocyclic carbenes (NHCs) with metal surfaces is well studied, the chemistry of highly reactive carbenes on metal surfaces is much less known. Highly reactive carbenes such as fluorenylindene (FY) strongly chemisorb on metal surfaces, and the surface donates electrons to the carbene in a charge transfer process. On-surface reactions of highly reactive carbenes involving more than two reactants are difficult due to diffusion constraints imposed by the strong binding of the carbenes to the surface. Our research expands the understanding of chemical reactions on surfaces by addressing those issues. It also highlights ways to utilize on-surface reactions for selective chemical syntheses.

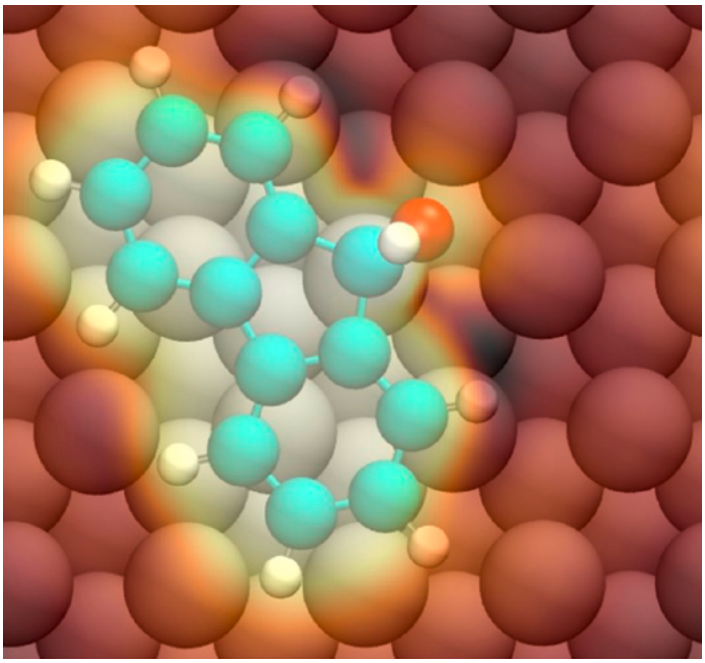

Figure 1. Superposition of the calculated geometry and the simulated STM image of the final product (fluorenol) of the reaction of FY with excess of water on a silver surface.

In collaboration with experimental partners of the Ruhr University Bochum, we addressed this challenge by studying the reactivity of FY with water, using an excess of water already present on the surface before carbene generation. Employing a suitable diazo precursor for the synthesis of FY we were able to obtain high yields of FY on Ag(111). The carbene subsequently reacted with the excess of water to form fluorenol as the final product (Figure 1). The reaction can occur at temperatures as low as 80 K if the precursor is in contact with large amounts of water molecules on the surface.

By means of scanning tunneling microscopy (STM) and quantum chemical calculations, the product of the on-surface reaction between FY and water was identified and characterized. The combination of experiments and simulations allowed us to assign the final product as fluorenol and exclude other possible species, such as the fluorenol anion, the fluorenol radical, or the fluorenylidine cation FY^+.

The simulated images of fluorenol nicely matched the experimentally observed asymmetric protrusions in the STM images. The simulations also predict that the conformation observed on the surface is the one where the OH group of fluorenol is pointing towards the surface, a result that could not be obtained from the experiments alone. The same product is formed if the reaction is induced photochemically by using UV light irradiation of the precursor in close contact to water islands on the surface.

This study highlights the complexity of on-surface reactions with more than two reactants. By combining experiments and calculations, the regulation of chemical reactivity on surfaces can be revealed and utilized for the rational development of new synthetic pathways.

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Rational correction of pathogenic conformational defects in a serine protease

Restoring enzymatic activity and trimer stability to the serine protease HTRA1, an important target in drug development

Joel Mieres-Perez and Elsa Sánchez García

Mutations and deregulation of enzymes may lead to their inactivation, which can be the cause of diseases, such as Alzheimer's, as in the case of the serine protease trimeric HTRA1. Therefore, finding ways to correct the functional loss of HTRA1 is of key importance to cure or prevent such diseases. By using a combination of experimental and theoretical techniques, key mutations affecting the enzymatic activity and trimer stability of HTRA1 were targeted. The study delivered novel strategies for HTRA1 protein repair based on: i) the identification of an HTRA1 variant that promotes trimer formation and therefore restores enzymatic activity, and ii) shifting the inactive monomer-active trimer equilibrium towards active trimers via supramolecular ligands. In addition, a peptide was identified that activates the inactive HTRA1 monomers.

High requirement temperature A1 (HTRA1) is a serine protease involved in many biological processes. The deregulation of HTRA1 is related to several diseases, including Alzheimer's. Mutations in the protein can affect the formation of the active homo-trimer, which results in detriment of enzyme function. In collaboration with experimental partners, our study delivered protein (and function) repair strategies (Figure 1).

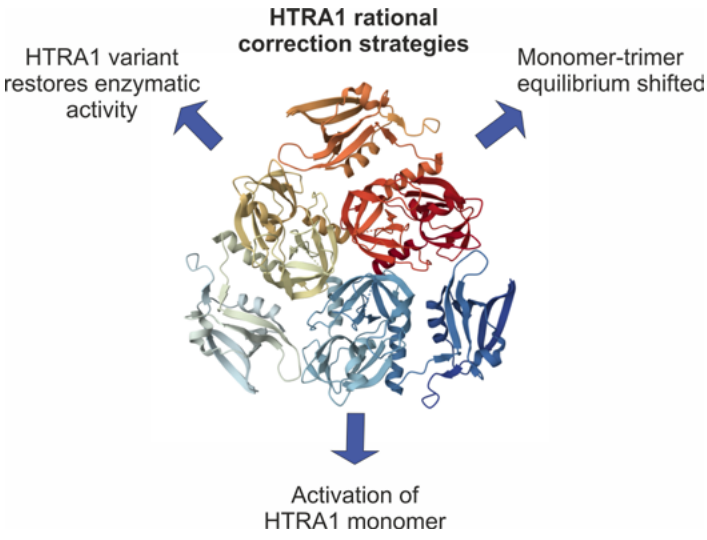

Figure 1. Rational strategies devised in this work, tackling the correction of pathological defects from different perspectives.

First, an HTRA1 variant was identified that is able to effectively promote the formation of the HTRA1 trimer, restoring enzymatic activity. This strategy focused on reversing the effect of the R274Q mutation of HTRA1. The R274Q mutation occurs at the interface between the protomers of the HTRA1 trimer and is related to the CARASIL disease, a genetic disorder that affects brain vessels. By using a compensatory mutant HTRA1-D174R-S328A, the effect of the Q274R mutation was counteracted. The functional correction, which involved the increase of the surface area between protomers in the trimer, was validated in experiments with mice. Supramolecular ligands also restored the trimeric form of the enzyme by shifting the trimer-monomer equilibrium towards the formation of the active trimeric form. In this approach, the trimers of HTRA1 are stabilized by using positively charged ligands that bind adjacent protomers at anionic sites. Our molecular dynamics simulations and free energy calculations showed that, in the absence of these ligands, the R274Q, R166H, and A173T mutations destabilize the trimers.

In addition, another strategy was devised in which the monomers of HTRA1 were activated using a peptide ligand. To achieve this, peptides covering the C-termini of the Voltage Dependent Anion-selective Channel (VDAC) isoforms 2 (VDAC2) and 3 (VDAC3) were used to activate wt-HTRA1 as well as the R274Q, R166H, and A173T mutants in biochemical essays. The essays demonstrated that the mechanism of action is via the binding of the peptide to the protease domain of HTRA1. Our computational modelling was key to understand the binding of the peptide to the protein and its mechanism of action. This work paves the way for the development of therapeutic approaches against HTRA1-related disorders.

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Computational Systems Biology (CSB)

Diverse Evolutionary Trajectories of Mitochondrial DNA in Mammalian and Avian Nuclear Genomes

Insights into the Functionality and Evolutionary Dynamics of NUMTs Across Species

Yu-Chi Chen, David L. J. Vendrami, Maximilian L. Huber, Luisa E. Y. Handel, Christopher R. Cooney, Joseph I. Hoffman, Toni I. Gossmann

Mitochondria, the cell's energy producers, occasionally transfer their own DNA into the cell nucleus, forming fragments called NUMTs. Long seen as inactive genetic remnants, this extensive study of over 1,000 mammals and birds reveals some NUMTs may actively influence genetic functions and offer evolutionary benefits. Recognizing NUMTs' potential opens new opportunities in biotechnology, such as developing precise genetic markers for tracking species evolution and hybridization. Additionally, insights into NUMTs may enhance genome-editing technologies, improve gene therapies, and inspire innovative approaches in agriculture, medicine, and bioengineering.

Nuclear mitochondrial DNA sequences (NUMTs) are fragments of mitochondrial DNA that have become integrated into the nuclear genome. For decades, these sequences were predominantly viewed as non-functional genetic relics, simply remnants of ancient genetic integration events. However, accumulating evidence suggests that some NUMTs may retain functional elements and could be subject to evolutionary pressures.

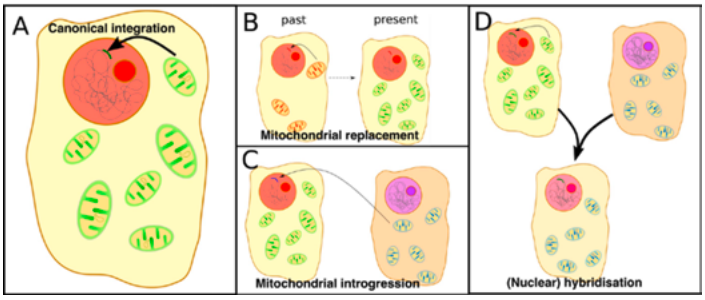

Figure 1. (A)-(D) Potential sources of NUMTs.

In this extensive genomic analysis, we examined the prevalence and evolutionary fate of NUMTs across more than 1,000 mammalian and avian species. We specifically targeted NUMTs containing intact mitochondrial coding sequences, known as coding NUMTs (cNUMTs), to determine their potential biological roles and evolutionary significance.

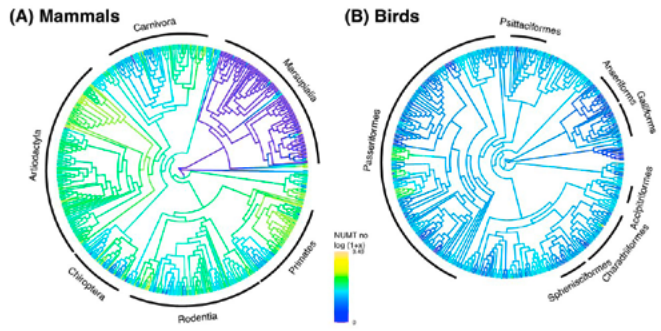

Figure 2. Phylogenetic distribution of NUMT occurences in mammals and birds.

Our comprehensive survey identified over 110,000 NUMTs distributed among mammals and birds, revealing a notable difference in frequency between the two groups. Mammalian genomes, on average, contain nearly twice as many NUMTs (approximately 125 per species) compared to avian genomes (around 63 per species). Within these numerous NUMTs, we found many cases of divergent cNUMTs (dcNUMTs), which exhibited substantial genetic divergence while preserving their coding potential. Such findings strongly suggest ancient or unconventional integration pathways, including possibilities such as introgression events between different species or hybridization.

Further evolutionary analysis revealed compelling evidence that several of these divergent NUMTs are actively maintained by selective forces, suggesting their potential functionality or adaptive value. Notably, one particularly striking example involves a positively selected NUMT found in the human genome, a genetic element shared with seven other ape species, pointing towards an intriguing evolutionary role and possible adaptive benefit in primate evolution.

This research significantly challenges the traditional view of NUMTs as merely passive genetic fossils. Instead, it indicates that NUMTs could represent important and previously overlooked elements of genomic evolution and adaptation. Future research, particularly employing advanced genomic technologies and detailed sequencing techniques, promises to reveal further insights into the genomic contexts, integration mechanisms, and functional roles of NUMTs, reshaping our understanding of genome evolution.

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Solids Process Engineering (FSV)

Prediction of Moisture Uptake in Blister-Packed Solid Pharmaceutical Dosage Forms – Insights from a Case Study

Jan Pech, Christoph Kaminski, Matthias Markus, Werner Hoheisel, Roman Heumann, Judith Winck, Markus Thommes

Blister packs represent one of the most prevalent forms of packaging utilized for solid pharmaceutical dosage forms. A principal objective of blister packaging is to preserve the product and thus ensure the quality and safety of the medicine. For a considerable number of pharmaceutical products, water represents a factor that impairs stability and is consequently regarded as a critical attribute in this context. In this study, a modeling framework was developed with the objective of predicting the moisture uptake of pharmaceutical tablets.

A numerical approach to the interconnection of the diffusion processes of water was utilized for the prediction of moisture sorption in a blistered solid dosage form, as well as the subsequent course of relative humidity within the blister cavity. In the model, the water barrier properties and geometric information of the packaging material, as represented by the rate constant k_{perm}, were combined with the sorption properties of the tablet (Figure 1).

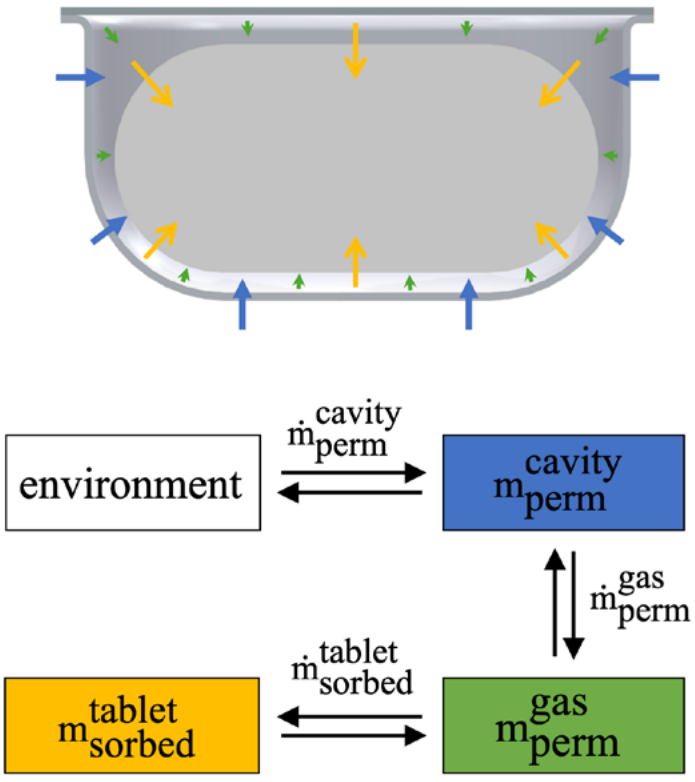

Figure 1. Overview of mass flows of water in blister packs.

In order to ascertain the sorption kinetic, expressed by the sorption rate constant k_{sorp}, and sorption isotherm of the tablet, a dynamic vapor sorption (DVS) analysis was conducted, whereby the masses of unpackaged tablets were measured over time within various relative humidities. Simultaneously, the conducted simulation was validated by monitoring the mass increase of blistered tablets within the DVS analysis.

The moisture uptake of the packaged tablets and the relative humidity in the blister cavity over time were simulated based on the barrier properties of the blister and the sorption properties of the tablets (Figure 2, solid red line). The higher relative humidity of the environment results in the ingress of moisture into the blister, which is subsequently sorbed to the tablet.

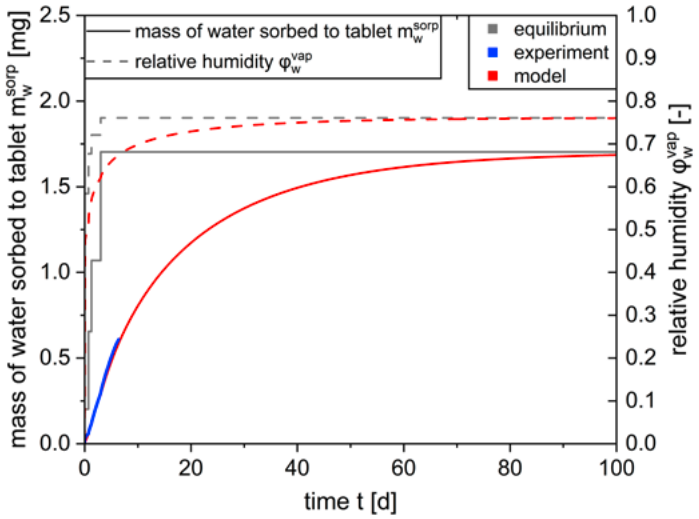

Figure 2. Time-dependent moisture uptake of tablet with a dry weight of 88.6 mg in PVC blister at 40 °C. Solid lines are indicating mass of water sorbed to tablet. Dashed lines are representing relative humidity in environment (grey) and in blister cavity (red).

The width of the time step was determined dynamically on the basis of the underlying rate constants. The simulation was confirmed by the observed increase in tablet mass within the available time frame for the current experiment (Figure 2, blue solid line).

This case study demonstrates the feasibility of forecasting the moisture uptake of blister-packed tablets through the presented numerical approach. As the modeling framework is founded upon parameters that can be determined comparatively fast, a reduction in time can be achieved in contrast to a purely experimental assessment. This allows for greater efficiency in addressing key questions associated with the selection and design of blister packs.

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Publications:
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ISBN: 978-8-40962-597-0

Continuous melt granulation with planetary roller systems

Utilizing the module configuration to design the performance

Tom Lang, Jens Bartsch

Planetary roller melt granulation (PRMG) is a new and innovative method for the continuous particle design typically aiming for a tailoring of the bulk material flowability. In comparison to standard equipment, the unique process concept of free flowing planetary spindles driven by a heated, rotating central spindle in a stagnant, heated roller cylinder (Figure 1) leads to an enhanced ratio of processed volume to heated surface. This is beneficial in terms of process control, especially since melt granulation is executed at elevated temperatures above the glass transition or melt temperature of a binder. Consequently, the number of planetary spindles applied in a module is a crucial aspect of the process design as this parameter defines the free processing volume.

In this study, a machine set-up with a single module was applied consisting of a roller cylinder, a central and multiple planetary spindles. For the later one, the number was varied from three as minimum with respect to mechanical stability over five as mean reference to seven as maximum with respect to the available space of the utilized lab-scale machine (Fig. 1).

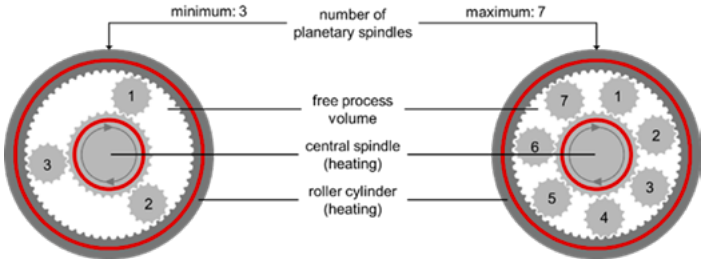

Figure 1. Schematic cross-sectional area of the planetary roller granulator for a minimum (left) and maximum (right) number of planetary spindles within a module for the lab-scale machine size [1].

During the experimental investigations, a pre-blend consisting of 90 wt.% lactose monohydrate (Lactose 310, Foremost Farms USA, Baraboo, Wisconsin, USA) as model substance and 10 wt. % hydroxyl-propyl-cellulose (Klucel EXF Pharm, Ashland Inc., Covington, USA) as meltable binder was fed gravimetrically (DDW-M-DS(R) 28, Brabender GmbH & Co. KG, Duisburg, Germany). The total feed rate (m.) and the rotation speed of the central spindle (n_{cs}) were varied on four distinctive levels each ranging from 0.3 to 1.2 kg h^{-1} respectively 60 to 240 min^{-1}. Thereby, the set temperature for the central spindle and roller cylinder heating were kept constant at a 150 °C, which is above the glass transition temperature of the melt binder and below the degradation temperature of the model substance.

The granule size as central quality objective of the product was determined via image analysis. Based on the volumetric density distribution of the product ($q_{3,product}$) in comparison to the model substance ($q_{3,lactose}$), the net fraction of input material granulated during processing ($w_{net,g\ ran.}$) was calculated as indicator for the granulation performance. Here, the shift function ($\Delta q_{3,shift}$) symbolizes the modification in the individual particle size classes represented by the mean class diameter ($\bar{d}_p$) and the corresponding class width (Δd_p).

$$w_{net,gran.} = -\sum \Delta q_{3,shift}(\bar{d}_p)\,\Delta d_p \quad for\ \Delta q_{3,shift} < 0$$

$$\Delta q_{3,shift}(\bar{d}_p) = q_{3,product}(\bar{d}_p) - q_{3,lactose}(\bar{d}_p)$$

The net fraction of material granulated during the PRMG process is reduced for higher rotation speed at constant feed rate or lower feed rates at a constant rotation speed (Fig. 2). This refers to the material hold-up inside the processing section and the energy input. At the same time, a lower number of planetary spindles results in a reduced number of shear events and shear stress and in consequence the granules grow larger. Thereby, the impact of the feed rate is enhanced for the highest rotation speed and maximum module configuration and almost nullifies in turn for the lowest rotation speed. This shift of the correlation between process settings and granulation performance indicates an alteration of the granulation regime.

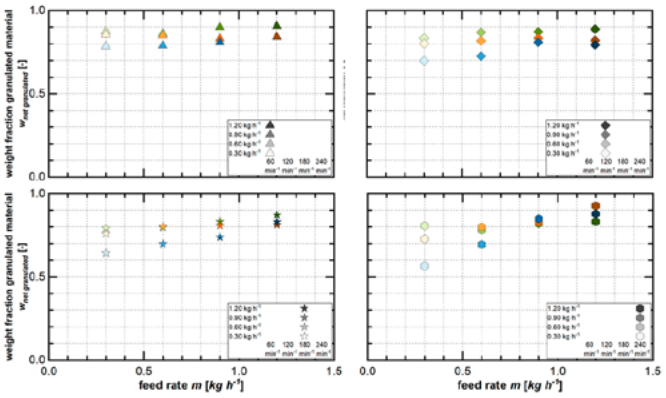

Figure 2. Net weight fraction of granulated material during PRMG for different configurations and process settings. Colors encode for three (green), five (orange) and seven (blue) planetary spindles within the module, color saturation for the feed rate and symbol type for the rotation speed within the experimental design space [2].

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Droplet Formation Mechanism by Vibrating Mesh Atomizers

Experimental investigations

Enrico Ercolin, Joshua Fricke, Daniel Lehmann, Gerhard Schaldach, Tamara Nestorović, Markus Thommes

Metal Mesh Atomizers (MMA) are commonly used for particle generation in spray dryers or in inhalation devices. The corresponding process is characterized by the resonance frequency, volume flow rate, droplet size distribution, and atomization efficiency. However, the fundamental droplet formation mechanism is unresolved up to date. Therefore, this kind of atomizers was investigated with the aim to gain a deeper understanding of its functionality.

The MMA under investigation in this study is assembled with a two-centimeter, perforated metal sheet positioned between two rings of piezoelectric ceramics. The orifices in the perforated metal sheet have a conical shape and the side of the MMA with the larger diameter orifice (≈ 25 µm) is facing the liquid. The piezoelectric ceramic is set in motion respectively vibration by applying an electric voltage, which causes an oscillation of the perforated metal plate (see Fig. 1). The result is a volume flow rate depending on the liquid properties, the applied voltage and frequency. The volume flows applied in this study ranged from 0.26 to 5.95 ml min^{-1} at a constant frequency of 95 kHz and a voltage amplitude of 20 to 90 V_{pp}. The determination of the volume flow was conducted gravimetrically, whilst the droplet size distribution was measured via laser diffraction.

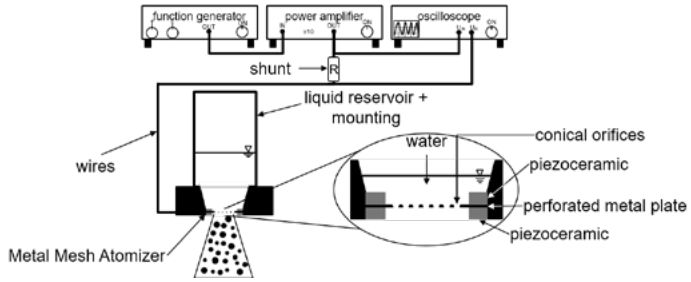

Figure 1. Operating setup of the atomization with an MMA (not in scale).

In Fig. 2, the results for the volumetric droplet size distribution are expressed by the characteristic values $d_{10,3}$, $d_{50,3}$ and $d_{90,3}$ for water. By increasing the volume flow rate, the median droplet size remains in a range between 16 µm and 20 µm.

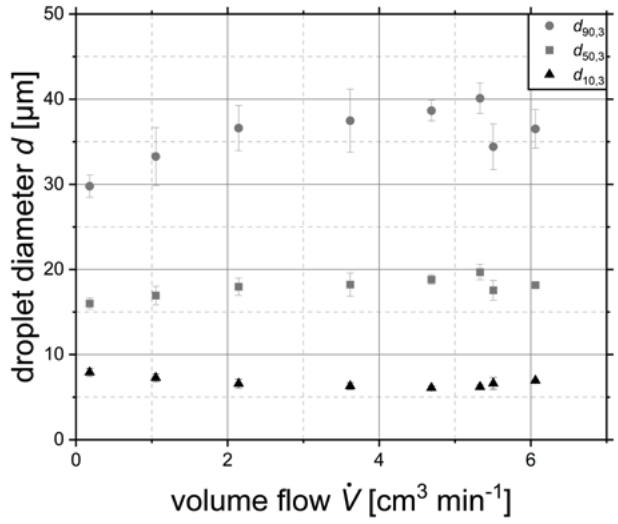

Figure 2. Characteristic droplet diameters ($d_{10,3}$, $d_{50,3}$, $d_{90,3}$) of demineralized water for various volume flow rates (left, n = 3, $\bar{x} \pm s$).

To identify the underlying droplet formation mechanism, the Reynolds-Numbers (Eq. 1) as well as the Ohnesorge Numbers (Eq. 2) were considered. Here, η, ρ, σ, v and L denote respectively the dynamic viscosity, the density, the surface tension of the liquid, the average velocity of the fluid and the diameter of the smaller orifice of the MMA (≈ 7 µm).

$$Re = \frac{\rho\, v\, L}{\eta} \quad (1) \qquad Oh = \frac{\eta}{\sqrt{L\,\rho\,\sigma}} \quad (2)$$

Further investigations have indicated that the number of active orifices contributing to the volume flow may be considerably lower than the total count, potentially less than 10 %. This is attributable to varying excitation levels among orifices based on the mesh position and different vibration modes, resulting in a higher average jet velocity. Consequently, data points in the Ohnesorge-Reynolds diagram are found in the jet break-up regime. The droplet formation process was revealed to be a Rayleigh jet break-up, with the MMA forming a liquid jet, which subsequently disintegrates into droplets (see Fig. 3).

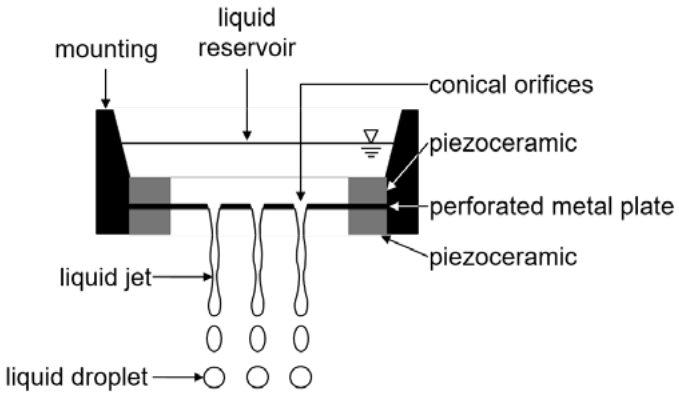

Figure 3. Schematic Rayleigh jet break-up on MMA surface.

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Process Automation Systems (PAS)

Robust nonlinear model predictive control of continuous crystallization

Using Bayesian last layer neural networks as surrogate models with uncertainty quantification

Collin R. Johnson, Felix Fiedler, Sergio Lucia

Continuous crystallization is an important separation technology for the chemical industry, but difficult to control, because of its high complexity. Developing system models is essential for advanced model-based control but it is challenging due to the complexity and computational cost of detailed process models. Data-driven models trained on real or simulated data offer an alternative but are only reliable within their operation region used for training. To address this challenge, we propose using last layer Bayesian neural networks as data-based surrogate models, providing both accurate predictions and uncertainty estimates of such predictions. This enables the design of model-based controllers that are computationally tractable and can lead to robust advanced control of complex systems.

Surrogate models enable model-based control algorithms, such as model predictive control, for systems that are otherwise difficult to model or where the models are very complex. This is often the case for distributed systems. Continuous reactors or crystallizers, for example, can feature process parameters distributed in several dimensions, leading to numerically complex and non-optimizable models. Large amounts of training data can be generated offline by evaluating the model, which can be used to train the data-based model. The data-based model, which is easy to optimize, then approximates the complex first-principles model. However, these models are only valid within their training data range, and direct optimization can produce undesirable extrapolated solutions. To avoid this, we use Bayesian last layer neural networks as surrogate models leading to predictions that are Gaussian distributed. The width of the Gaussian distribution, i.e. the standard deviation, is the measure of uncertainty. Broad distributions indicate high uncertainty while narrow ones show confidence.

We propose incorporating the uncertainty quantification in a multi-stage model predictive control scheme. In model predictive control, the inputs are determined by optimizing a cost function that formulates the desired system dynamics given the model. Figure 1 shows the construction of the method.

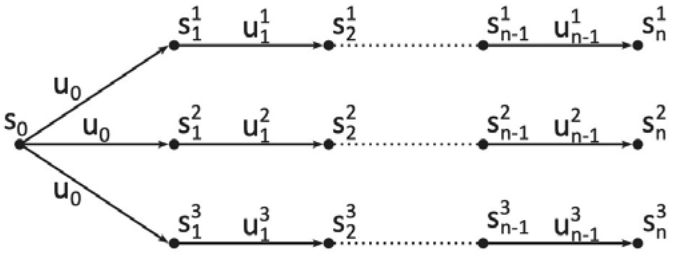

Figure 1. Sketch of the multi stage model predictive control scheme. The branching is performed using the predicted uncertainty of the surrogate model.

The variables s_i and u_i are the states and inputs at different points in time. The branching is performed at the first timestep based on the predicted uncertainty. The middle scenario in Figure 1 is the mean prediction of the neural network while the upper and lower scenarios are computed based on the mean prediction modified by $\pm 3\sigma$, where σ is the standard deviation given by the Bayesian last layer model.

Thus, the predicted uncertainty is directly taken into account and constraint satisfaction is also enforced for the uncertain scenarios.

Figure 2 shows the results for the proposed algorithm (bottom) for application to a continuous crystallizer. The method is compared to the direct use of a standard neural network in the model predictive controller (top). The objective was to maximize the mean diameter of the crystals L_{10} while enforcing a constraint on the temperature.

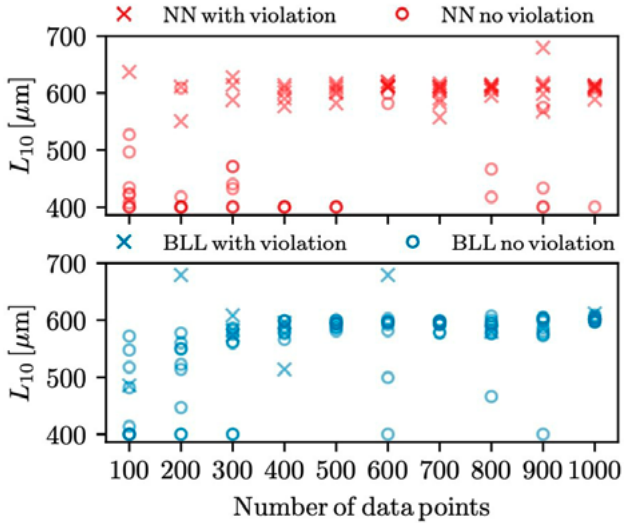

Figure 2. Results of comparing the proposed method with using a standard neural network directly in the controller. The size of the used training data set size has been varied (x-axis). The objective of control was to maximize the mean diameter L_{10}. An 'x' indicates a simulation run where the temperature constraint was violated.

The size of training data sets has been varied to test for different degrees of extrapolation. The proposed algorithm leads to more consistent results and much less violations of the temperature constraints. For small data sets, the proposed method leads to better results on average (larger L_{10}). For large data sets, the mean diameter L_{10} is also consistently maximized with significantly less constraint violations.

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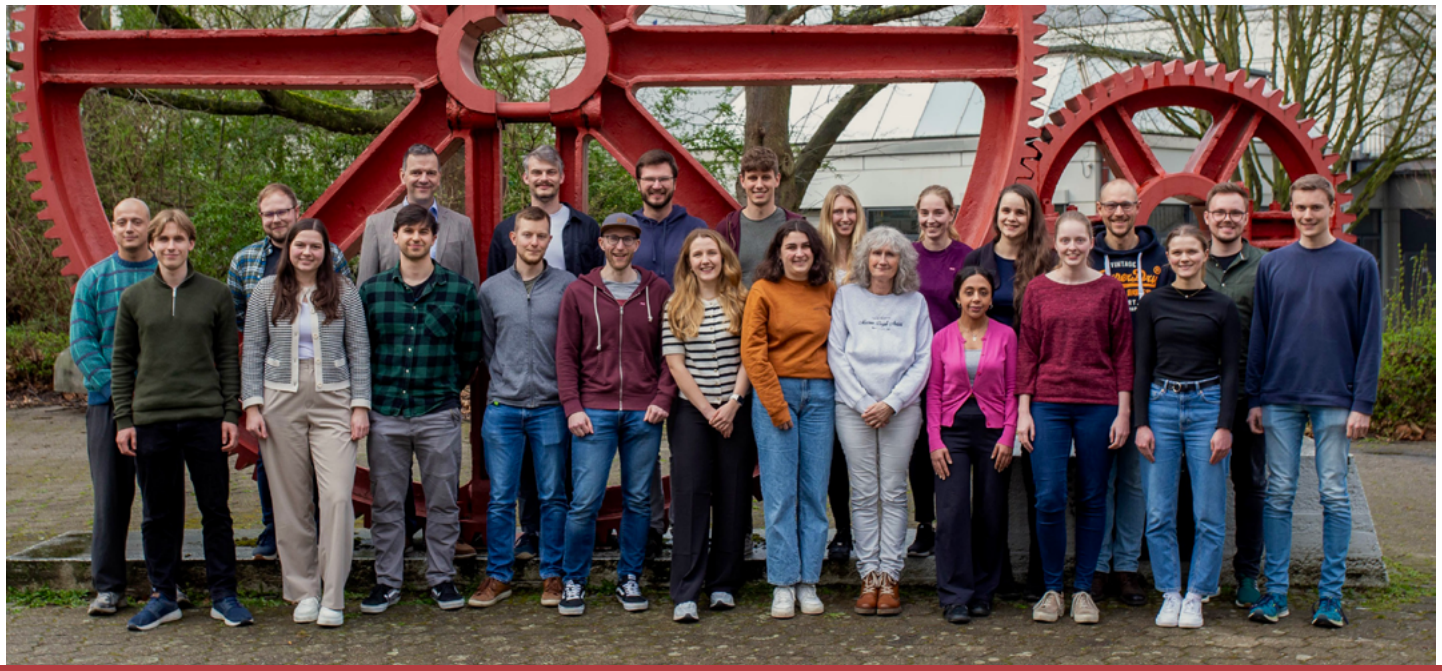

Reaction Engineering and Catalysis (REC)

Periodic open cellular structures in gas-liquid applications

Enhancing the gas-liquid mass transfer in trickle bed reactors by sheet-based periodic open cellular structures

Hendrik Held, Lisa Eckendörfer, Dominik Rudolf, Andreas Brix, Lena Bierhaus, Marion Börnhorst, Hannsjörg Freund

Heterogeneous catalysts are essential in over 80 % of industrial chemical processes. Their performance is significantly influenced by the geometry of the support structures, highlighting the importance of their improvement. Conventional catalyst support structures, typically catalyst particles that form a randomly packed bed in tubular reactors, exhibit inherent limitations. To address this issue, an innovative class of catalyst support structures has been developed that combines low pressure drop with enhanced radial mass and heat transport. These lattice like structures, known as periodic open cellular structures (POCS), are manufactured using additive manufacturing techniques. The adjustable design of POCS is based on representative unit cells, which are periodically repeated in all three spatial directions.

In recent studies, POCS were used as catalyst support structures in trickle bed reactors with the objective of mitigating gas-liquid mass transfer limitations. Therefore, the two-phase pressure drop as well as the desorption of oxygen dissolved in water were investigated in strut-based POCS with Kelvin and Diamond unit cells and compared to randomly packed beds of spherical particles.

For all investigated structures, the pressure drop increases with increasing liquid and gas flow rates. Strut-based POCS with Kelvin and diamond unit cells show a significantly lower pressure drop than packed beds. However, the strut-based POCS offer lower gas-liquid mass transfer coefficients than the packed beds and, consequently, do not effectively overcome the gas-liquid mass transfer limitation in trickle bed reactors. This phenomenon can be attributed to the lower interfacial area, which is affected by the flow pattern. In a gas phase system, the phenomenon of fluid channeling is observed (see Fig. 1), which is minimally affected by the struts of the POCS. Since the gas phase takes up the largest volume in the trickle bed reactor, this behavior is transferable to the two-phase system.

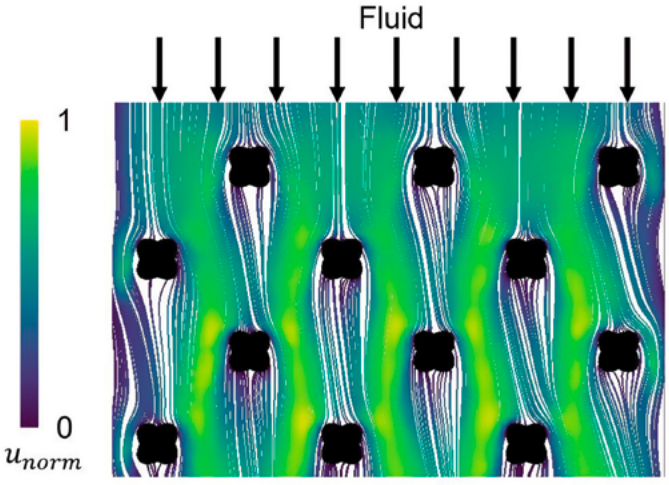

Figure 1. Two-dimensional visualization of the fluid flow within strut-based POCS with diamond unit cells.

To address the challenge of mass transfer in gas-liquid systems, sheet-based POCS with an H unit cell were developed. In these structures, the fluid follows a meandering flow pattern, which increases friction and cross mixing, thereby enhancing gas-liquid mass transfer. This can be inferred from the flow field in the gas phase system (see Fig. 2), which demonstrates a greater influence of the sheets on fluid flow compared to the strut-based POCS (see Fig.1). This improve-ment in gas-liquid mass transfer comes with a moderate increase in pressure drop. Overall, the proposed structure for sheet-based POCS shows an increase in pressure drop by a factor of 1.5 to 2 and an increase in gas-liquid mass transfer by a factor of 5 compared to packed beds.

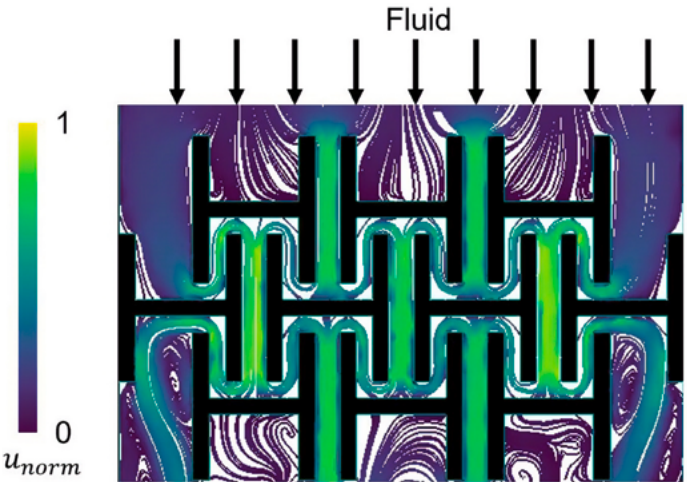

Figure 2. Two-dimensional visualization of the meandering fluid flow within sheet-based POCS with H unit cells.

The adaptability of POCS with respect to hydrodynamics, pressure drop and mass transfer characteristics shows their high potential for process intensification. Strut-based POCS are particularly suitable for processes with a focus on low pressure drop while sheet-based POCS can be used as an alternative to improve gas-liquid mass transfer.

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Publications:
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Novel catalyst support structures for reversible wall contact in chemical reactors

Thermo-Mechanical Study on Auxetic Shape Memory Periodic Open Cellular Structures

Dominik Rudolf, Hannsjörg Freund

In the interests of sustainable development and efficient processes in the chemical industry, process intensification is a high priority in research and industry. As centerpiece of a chemical plant, the reactor plays a key role. To improve heat management of catalytic reactors, we utilize additive manufacturing to realize tailored and optimized reactor designs. Metal periodic open cellular structures (POCS) offer excellent heat transport characteristics due to heat conduction in the continuous solid matrix. However, when inserted into tubular reactors, a loose fit between structure and tube wall results. In case of exothermic reactions, tubular reactors are typically cooled by cooling jackets. The remaining gap between POCS and tube wall considerably hinders the heat transfer across the wall towards the cooling medium in the jacket. In order to intensify the wall heat transfer, a solid contact between the POCS and the reactor tube wall is therefore an essential factor. Yet, this contact must be reversible to take into account the deactivation of heterogeneous catalysts and thus the necessity of an exchange of the POCS.

The novel POCS concept presented here exploits the combination of two effects: the mechanical auxetic and the shape memory effect. Auxetic structures contract perpendicular to a mechanical compression load. If the POCS is made of a shape memory alloy, such as “Nitinol” (NiTi alloy), it can recover its original shape, with a reversible strain of up to 8 %. The principle involves designing an auxetic POCS with radial oversize, catalytic coating, compression and insertion of the POCS into the tubular reactor. Increasing the temperature, the shape memory effect is induced and an interference fit with the tube is established. Based on a reentrant design of auxetic structures, see Figure 1, design equations for a proper description of porosity and volume-specific surface area were developed as fundamental work. These represent important morphological parameters for the design of catalytic reactors. Important geometric parameters are the strut diameter, cell size and the amplitude of the curved struts, responsible for the auxetic effect.

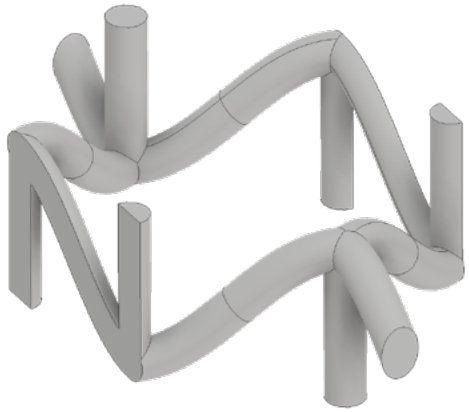

Figure 1. Unit cell of an auxetic hexagonal cell POCS, representing a reentrant design. The curved struts with a high amplitude are responsible for the auxetic effect.

Numerical investigations on both mechanical behavior under compression and heat conduction were carried out, systematically analyzing their dependency on geometric parameters. Regarding the auxetic behavior the results show an increasingly pronounced auxetic effect for higher amplitudes and lower strut diameters (at a constant cell size). This was validated with experimental compression tests using POCS made of Ti-6Al-4V via electron beam powder bed fusion. The main mechanism for material failure during compression is found to be buckling of the vertical struts.

Simulations of heat conduction in the solid reveal a general influence of the solid content on the effective thermal conductivity $\hat{k}_{eff}$. Yet, with higher amplitudes of the curved struts $\hat{k}_{eff}$ decreases. Using the derived equation of porosity, design correlations for $\hat{k}_{eff}$ were set up. Concerning the tubular application of POCS, spatially resolved investigations on the effective radial heat conductivity $\hat{k}_{eff,r}$ were performed. A hyperbolic dependency of $\hat{k}_{eff,r}$ on the number of cells per tube diameter was determined, revealing a threshold value of $\hat{k}_{eff,r}$ approximately 20 % higher than expected from simulations on the unit cell. This phenomenon was identified for the first time in this work and is expected to be valid for structured, cellular materials in general (other POCS, solid foams, monolithic honeycombs).

Finally, thermo-mechanical cycles were experimentally investigated on an auxetic NiTi POCS and compared to simulations. There is a good agreement, and it was concluded that geometric parameters have the greatest influence rather than the non-linear material response of NiTi. Eventually, a strategy for the design of auxetic shape memory POCS was developed in order to realize a reversible wall contact in tube applications. A priori mechanical simulations predict the successful implementation of the concept as described above. First experimental investigations confirm the proof of concept.

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Publications:
Rudolf, D.; Fink, A.; Körner, C.; Freund, H., Thermo-Mechanical Study on Auxetic Shape Memory Periodic Open Cellular Structures—Part I: Characterization of Reentrant Geometry and Effective Heat Conductivity. Advanced Engineering Materials 2024 (published online).
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Power-to-X Technologies: CO_x Methanation for Chemical Energy Storage and Distribution

Reaction Kinetic Modeling of the CO_x Methanation on a Ni/Al_2O_3 Catalyst

David Kellermann, Moritz Langer, Hannsjörg Freund

Power-to-X (PtX) technologies and chemical energy storage such as the methanation reaction of CO_2 with renewable hydrogen play a crucial role in the transition of the energy sector from fossil fuels to renewable energies. The methane produced can be easily stored, distributed, and used as a natural gas substitute by utilizing existing natural gas infrastructure. To model and optimize reactors for this process, sound knowledge about the reaction mechanisms and reaction rates is crucial. Our group investigated a commercial Ni/Al_2O_3 catalyst over a broad range of reaction conditions. This ensures that the reaction rate in the methanation reactor can be described reliably for various operation loads, being of special interest for the Power-to-Gas concept with its fluctuating inlet conditions.

For the investigation of the methanation reaction under conditions close to the use case, a commercial Ni/Al_2O_3 catalyst supplied by an industry partner was investigated in a dedicated laboratory plant. The experimental setup allowed dosing of all reactants as well as products to investigate their influence on the reaction rates. The Berty-type reactor (Fig. 1) was characterized and conditions were determined to achieve ideal mixing in the reactor. To ensure catalyst stability, a conditioning routine was established. Kinetic experiments were conducted in an absolute pressure range of 3 to 10 bar and from 250 to 450 °C. The volume flow rate was varied and methanation of carbon dioxide, carbon monoxide and co-methanation of both reactants was investigated. Furthermore, experiments with dosing of H_2O and CH_4 into the feed were conducted. After data reconciliation and excluding data points which do not fulfill the carbon balance within 3 %, a total set of 403 data points was obtained, which was then used for parameter fitting.

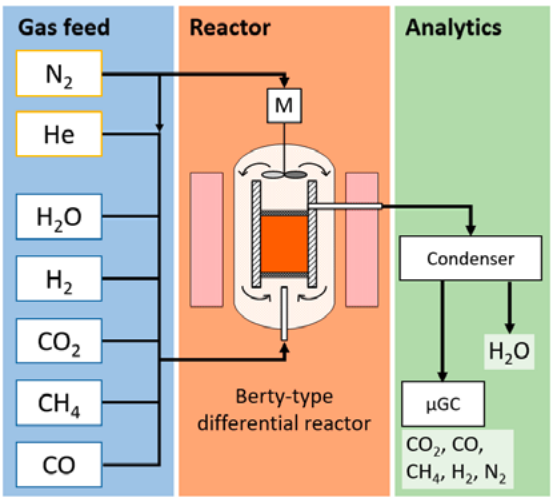

Figure 1. Schematic depiction of the experimental setup with gas dosing unit, the Berty-type differential reactor and the product gas analysis with water condensation.

As key reactions, the reverse water gas shift reaction (RWGS) and the methanation of carbon monoxide were chosen. A total set of 60 kinetic expressions following the Langmuir-Hinshelwood-Hougen-Watson approach were derived for the assumption of different rate determining steps (RDS) and most abundant surface intermediates. The influence of adsorbed carbon monoxide on the activation energy of the surface reactions was considered by a correction factor in some of the models to further improve model accuracy.

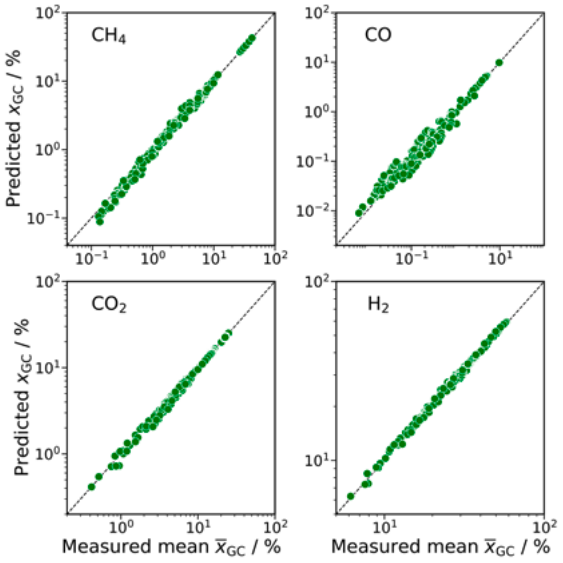

Figure 2. Logarithmic parity plots of the best fitting kinetic model. The prediction shows good agreement with the gas phase composition measured by the gas chromatograph.

The best fitting kinetic model (Fig. 2) describes the experimental data very well over a wide temperature, pressure and gas composition range. This makes it possible to use this kinetic model for the simulation and design of plants that operate under varying conditions, e.g. in dynamically operated plant. A highly relevant example for such plants are Power-to-X plants with fluctuating inlet flows, resulting from unsteady hydrogen generation from upstream water electrolysis.

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Technical Biology (TBL)

Discovery of Tyrosinase Inhibitors in Soil Bacteria

Unraveling the Metabolomic 'Dark Matter' of the Microbial World by Molecular Networking

Till Steinmetz, Anton Lindig, Stephan Lütz, Markus Nett

Many unknown bioactive natural products are hidden in the genome of microorganisms. In recent years, bacteria of the genus Massilia *have been identified as promising sources of such products. In this study, we combined spectroscopic and computational tools for the first comprehensive analysis of the secondary metabolomes of these microorganisms. Our approach led to the discovery of previously overlooked compounds, which we termed kyonggic acids. The kyonggic acid turned out to be potent inhibitors of the enzyme tyrosinase, which is involved in melanin biosynthesis influencing skin and hair pigmentation.*

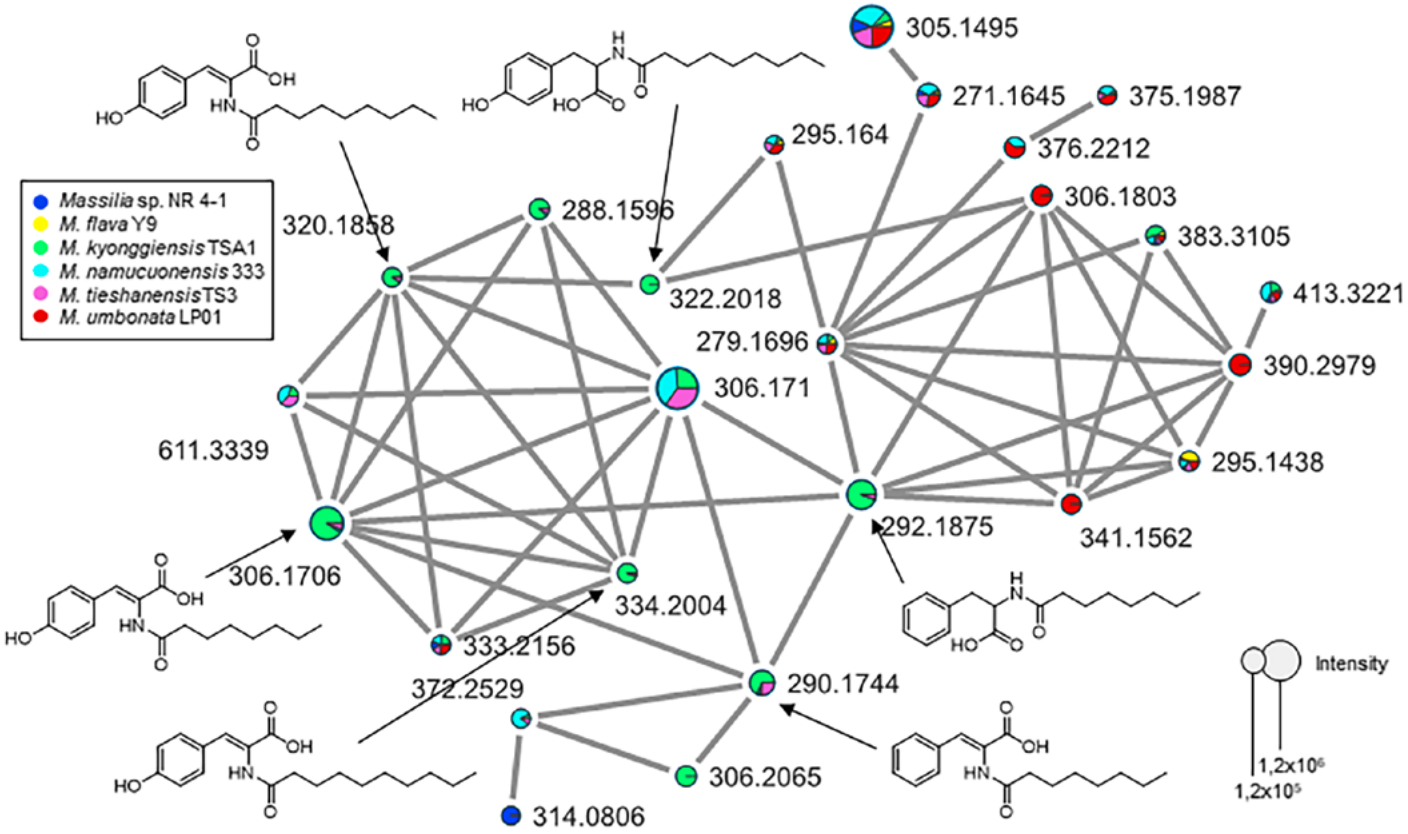

Figure 1. Feature-based molecular networking of *Massilia* culture extracts with the putative NAAA cluster. Every circle represents a distinct mass feature. The circle size corresponds to the highest observed abundance of the respective mass feature in MS/MS analysis. The depicted chemical structures were predicted based upon their *m/z* values and fragmentation patterns.

To analyze the production of secondary metabolites by *Massilia* spp., we collected mass spectrometry (MS)-based metabolomics data from six selected strains and processed this data with the Global Natural Products Social Molecular Networking (GNPS) platform. GNPS compares and clusters the fragmentation patterns of every MS/MS spectra in the dataset using a vector-based computational algorithm. This approach allows the visualization of intricate connections between different metabolites, thereby aiding in the identification of molecules with shared structural features. Most importantly, the clustering of related compounds eliminates the need for time-intensive raw MS data analysis. We aligned the constructed molecular network with reference spectra databases. In this way, we identified a cluster of putative *N*-acyl amino acids (NAAA), which were not known to be produced by these bacteria (Figure 1).

Subsequent fermentation studies confirmed that *Massilia* spp. are indeed capable of NAAA biosynthesis with *Massilia kyonggiensis* TSA1 being a particularly productive strain. A total of four compounds were isolated from this bacterium by reversed-phase HPLC. The postulated structures of these molecules, which were termed kyonggic acids, were verified by NMR analyses. Bioactivity testing revealed the kyonggic acids as potent tyrosinase inhibitors with IC_{50} values comparable to arbutin, a natural product frequently used in skin-whitening products.

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Industrial Chemistry (TC)

Biodiesel as a Sustainable Platform Chemical Enabled by Selective Partial Hydrogenation: Compounds Outplace Combustion?!

Thomas F. H. Roth, Alexander Kühl, Maximilian L. Spiekermann, Hannes W. Wegener, Thomas Seidensticker

The substitution of mineral oil with renewable resources is a necessity for a sustainable defossilization of the chemical industry. A natural plant oil derivative that is already widely used is biodiesel - however, instead of being used as a molecular building block, it is being combusted. One obstacle to the material use of biodiesel is its high content of polyunsaturated components, which presents significant challenges in chemical utilization through homogeneously catalyzed reactions. These, however, succeed very efficiently with monounsaturated components. This work examines this challenging area through a comprehensive analysis of the literature and experimental research. As a solution strategy, the selective partial hydrogenation of polyunsaturated to monounsaturated components is presented as a key technology for the material use of renewable resources, such as biodiesel.

There is a vast discrepancy between the goal of using renewable raw materials as molecular building blocks and the reality that they are currently being burned as biodiesel, for example. Most research on utilising renewables as molecular building blocks in the context of homogeneously catalyzed reactions focuses on highly pure substrates with exactly one unsaturated double bond in a defined position, usually methyl oleate (Figure 1). In contrast, when using "real world substrates", e.g. biodiesel, with more complex compositions and higher proportions of polyunsaturated components (PUFA), losses of selectivity and activity are often observed. The selective partial hydrogenation of PUFAs in vegetable oil (derivatives) is established for use in many areas, such as biofuels and food chemistry. However, no attempts have been made to adapt this technology to the requirements of further chemical use of fatty acid methyl esters. This work highlights the relevance of selective partial hydrogenation in this context by demonstrating the potential for increasing activity in subsequent reactions in three case studies.

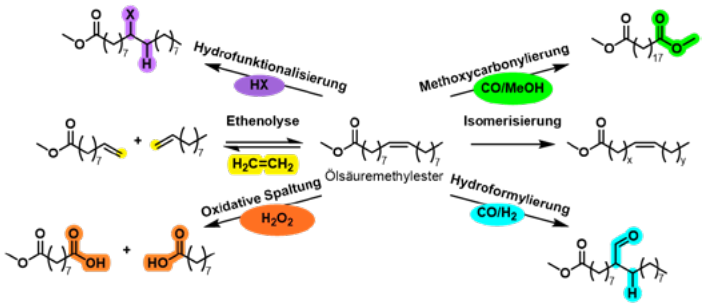

Figure 1. Selection of homogeneous catalytic conversions of C=C double bonds in oleochemicals, using the example of methyl oleate.

It was demonstrated that an already known solventstabilized palladium colloid catalyst could reduce high PUFA contents in canola and soybean-based biodiesels to <1 w% without showing significant overhydrogenation. The following model reactions showed that a significant increase in selectivity and activity can be achieved using preliminary selective partial hydrogenation, which led to a significant increase in final yields (Figure 2). In ethenolysis, turnover numbers increased by 80 %, and activity gains were observed for both soybean- and canola-based biodiesels compared to untreated samples. In isomerizing methoxycarbonylation, these increases amounted to a fivefold increase in activity, while a selectivity increase of 20 % was observed, due to reduced side-product formation.

Hydroformylation showed a twentyfold increase in activity with partially hydrogenated substrates while achieving up to 94 % selectivity.

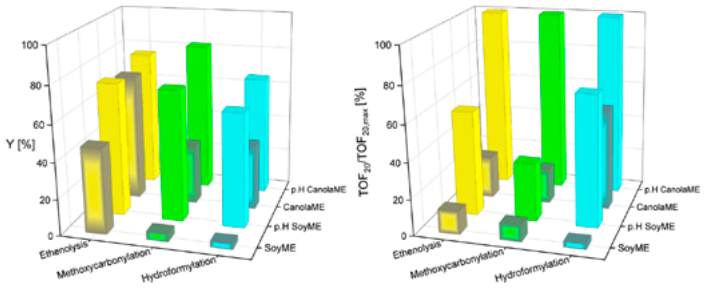

Figure 2. Summarized overview of the yields determined by GC-FID in the investigated reaction with different biodiesels.

This work underscores the importance of selective partial hydrogenation as a critical step in converting oleochemicals into sustainable biobased products and improving reaction activity and selectivity while minimising catalyst deactivation issues associated with PU-FAMEs. This approach offers an economically viable pathway for advancing renewable resources beyond their current use as biofuels. It also provides new opportunities for integrating renewable feedstocks into existing industrial value chains while addressing sustainability goals like decarbonisation and reduced reliance on fossil fuels. The findings support the broader goal of promoting material utilisation of biomass over combustion to achieve sustainability targets in industrial chemistry while fostering innovation in renewable resource applications.

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Primary amines from alkenes and carbonyl compounds: Highly selective hydrogenation of oximes using a homogeneous Ru-catalyst

Kevin Hares, Hannes W. Wegener, Thomas F. H. Roth, René Reichert, Dieter Vogt, and Thomas Seidensticker

The efficient production of aliphatic primary amines is still a major challenge despite their production on a large scale. Particularly when considering the overall production route starting from alkenes, current strategies suffer in at least one reaction step from poor regio- or chemoselectivity. This work presents an efficient and selective synthesis protocol for primary aliphatic amines via *their corresponding aldoximes. These are readily produced from the condensation of hydroxylamine and the respective aldehydes. This straightforward condensation can be carried out either with isolated aldehydes or with crude reaction solutions from the hydroformylation of alkenes. It allows a straightforward separation of the aldoximes* via *their precipitation, which then serve as intermediates for the final reduction. In a newly developed protocol for aldoxime reduction, yields of up to 90 % of the desired primary amines from several different aldoximes are achieved.*

This study addresses the challenges in producing primary amines with high selectivity and efficiency from alkenes, overcoming limitations such as poor regioselectivity and atom economy in existing methods (Figure 1). By employing a ruthenium/triphos catalyst system for aldoxime hydrogenation, yields of up to 90 % for various amines with exceptional turnover frequencies exceeding 7500 h^{-1} were achieved.

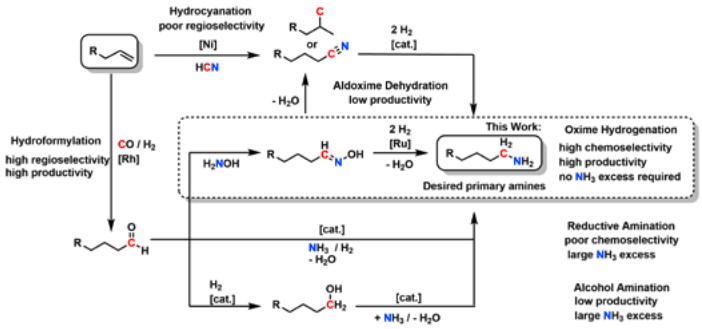

Figure 1. Reaction pathways toward primary amines starting from alkenes.

The process begins with the condensation of hydroxylamine with aldehydes to form aldoximes. This reaction can be carried out either using isolated aldehydes or directly from crude solutions obtained during hydroformylation of alkenes. The aldoximes are easily separated through crystallization before undergoing selective hydrogenation to yield primary amines. The newly developed protocol demonstrated remarkable chemoselectivity toward primary amines while suppressing side reactions that typically lead to secondary or tertiary amine formation.

Experimental optimization revealed that tridentate ligands, particularly triphosphine (triphos), significantly enhanced activity and selectivity for the desired products. Nitrogen-based bases such as DBU further improved reaction outcomes by favoring direct reduction pathways over intermediate nitrile formation. Temperature played a critical role in balancing reaction speed and selectivity; optimal results were obtained at 200 °C, where high productivity (TOF_{20} = 847 h^{-1}) was combined with excellent selectivity (up to 90 %) for primary amines.

The scope of the reaction was tested on various substrates, including linear and branched aldoximes as well as those containing functional groups like double bonds or aromatic rings. Most substrates were converted with high yields while maintaining functional group tolerance, showcasing the versatility of this method for industrial applications.

To demonstrate its practical applicability, the study integrated this protocol into a three-step sequence starting from alkenes: hydroformylation to produce aldehydes, aldoxime formation through condensation with hydroxylamine, and final hydrogenation to yield primary amines. Using methyl 10-undecenoate as a renewable feedstock derived from castor oil, the researchers synthesized methyl 12-aminododecanoate - a precursor for polyamide-12 - with an overall yield of up to 68 %. This highlights the feasibility of scaling up this approach while maintaining efficiency.

This work offers a sustainable alternative to conventional methods by combining high chemoselectivity with fast reaction rates without requiring large excesses of ammonia or other nitrogen sources. It provides an efficient pathway for converting renewable raw materials like alkenes into valuable intermediates such as polymer precursors or specialty chemicals while minimizing waste generation. The findings pave the way for broader adoption of catalytic oxime hydrogenation in industrial processes aimed at producing bio-based products efficiently and sustainably.

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Hydroaminomethylation of methyl 10-undecenoate with integrated catalyst recycling *via* a thermomorphic multiphase system for the continuous production of renewable amines

Anna Kampwerth, Tim B. Riemer, Jonathan Pöttker-Menke, Nadine Oppenberg, Arno M. Windisch, Dieter Vogt, Thomas Seidensticker

The industrial production of amines is mainly carried out using heterogeneous catalysts under harsh conditions and high energy input. Homogeneous catalysts, on the other hand, are more efficient and selective, helping to lower energy use and reduce waste. In this study, we explored a more sustainable method for producing special types of amines – called α,ω-bifunctional amines – which are important building blocks for making polymers, as they have functional groups at both ends of their carbon chain, which is ideal for linking them. To produce these, we incorporated the renewable methyl 10-undecenoate. Our results show that a range of these amines can be produced efficiently using a step-by-step hydroaminomethylation process. We also demonstrated that the catalyst can be reused, both in repeated batch runs and in a continuously operating miniplant, showcasing the potential of this approach for practical and eco-friendly chemical production.

An innovative approach to producing renewable bifunctional amines using hydroaminomethylation (HAM) in a thermomorphic multiphase system (TMS) was investigated. The focus is on methyl 10-undecenoate, a renewable feedstock derived from castor oil, to produce α,ω-bifunctional compounds suitable as polymer intermediates (Figure 1). By integrating homogeneous catalysis with efficient catalyst recycling in a continuous process setup, high yields and selectivity while minimizing waste and resource consumption were achieved.

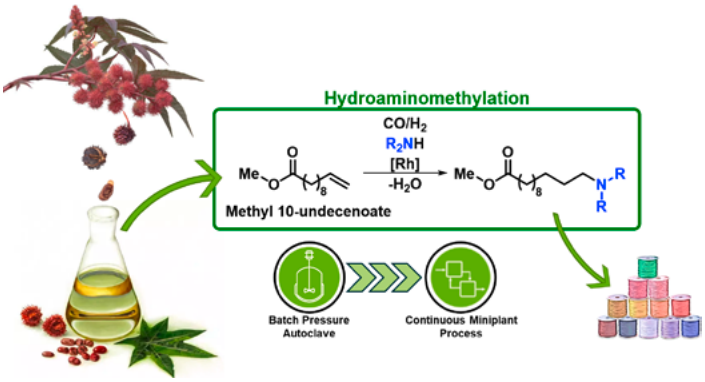

Figure 1. Concept of the Hydroaminomethylation process.

The TMS used methanol and n-dodecane as solvents, which exhibit a temperature dependent miscibility gap. At reaction temperature (125 °C), the mixture formed a homogeneous phase to optimize catalytic activity. Upon cooling (5 – 10 °C), the mixture separated into two phases: the polar phase, containing the rhodium/SulfoXantphos catalyst complex, and the non-polar phase, enriched with amine products. This configuration allowed efficient product extraction while retaining and recycling the catalyst for multiple cycles.

In batch experiments with various primary and secondary amines as substrates, yields reached up to 96 % for linear amine products with selectivities over 90 %. Cyclic amines like piperidine, also performed well. Longer carbon chains or less polar substituents favored product partitioning into the non-polar n-dodecane phase. Catalyst leaching was minimal across all experiments, with rhodium losses below 1 %.

To validate scalability, a continuous experiment was performed in a miniplant, integrating organic solvent nanofiltration (OSN) to remove water - a byproduct of HAM - from the recycled polar phase. Continuous operation over 90 hours with stable performance resulted in an average yield of 70 % linear amine product with selectivities of approximately 80 %. The OSN membrane effectively maintained water concentrations below 4 %, preventing side reactions such as aldol condensation and segregation in the reactor while ensuring minimal loss of catalyst (rhodium loss: 2.5 %; SulfoXantphos loss: 0.4 %).

This study highlights TMS as a versatile platform integrating homogeneous catalysis with sustainable processes aimed at converting renewable resources into valuable chemical intermediates. Combining high activity and selectivity with low environmental impact through efficient recycling strategies aligns this method with global sustainability goals such as reducing fossil fuel reliance while promoting circular economy principles in industrial chemistry.

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Neural Network-Based Tensor Completion: Advancing Predictions of Activity Coefficients and Beyond

Tobias Averbeck, Gabriele Sadowski, Christoph Held, Thomas Seidensticker

The prediction of activity coefficients is a pivotal aspect of chemical reaction modeling. Machine learning via neural networks has emerged as a promising approach to address this challenge. While existing tensor completion methods have demonstrated progress in predicting two- and three-dimensional data, they continue to face challenges in effectively capturing nonlinearities and temporal dependencies in relational data. In addressing this research gap, we propose a novel 3D-DMF-H method for tensor completion, representing a significant advancement in the field. This method is developed as a neural network-based matrix completion approach, extending the Deep Matrix Factorization (DMF) method. It effectively handles nonlinear data structures and seamlessly incorporates additional data points. The efficacy of our method is evident in its wide applicability to diverse three-dimensional tensor completion problems, with notable success in predicting activity coefficients for modeling phase equilibria. The findings underscore the considerable potential of machine learning in propelling advancements in the chemical industry and underscore the imperative for further refinement and exploration of algorithms.

This study introduces a novel machine learning method, the 3D-DMF-H approach (Figure 1), for tensor completion to predict activity coefficients (γ values) with high accuracy. This method addresses limitations in traditional models like UNIFAC and COSMO-RS by leveraging neural networks to capture nonlinear relationships in sparse data sets and offering significant improvements in predictive performance.

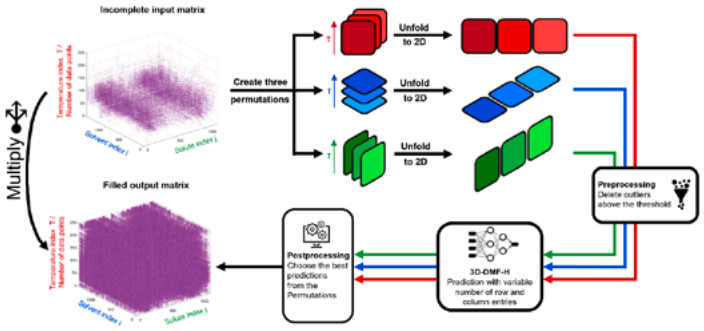

Figure 1. Simplified overview of the proposed method.

The study highlights the importance of accurate γ value predictions for modeling phase equilibria and designing separation processes. Traditional methods such as group contribution models or quantum chemistry approaches often face challenges like limited accuracy or high computational costs. The 3D-DMF-H method builds on Deep Matrix Factorization (DMF) techniques but extends them to three-dimensional tensors using hierarchical adjustments across multiple matrix permutations. This allows the algorithm to extract richer information from input data while addressing nonlinearities inherent in chemical systems.

Empirical validation was conducted on a subset of the Dortmund Database containing over 42,000 experimental γ^{∞} values at infinite dilution for various solvents and solutes across 239 temperatures. The 3D-DMF-H method predicted more than three million γ^{∞} values based on this input data set, achieving a mean absolute error (MAE) of 0.109 compared to 0.647 for standard UNIFAC calculations. Approximately 73 % of predictions had an absolute error below 0.1, aligning well with experimental uncertainties (0.1–0.2). These results demonstrate that the method provides superior accuracy while maintaining robustness across diverse chemical systems.

To further test its applicability, the study integrated 3D-DMF-H-predicted γ^{∞} values into hybrid modeling frameworks using PC-SAFT equations of state for vapor-liquid equilibrium (VLE) predictions. Adjusting binary interaction parameters (k_{ij}) based on predicted γ^{∞} significantly improved VLE modeling outcomes compared to default settings (k_{ij} = 0). For example, azeotropic behaviors in mixtures like cyclohexane/ethyl acetate were accurately captured with adjusted k_{ij} values derived from the ML-based predictions.

This work underscores the potential of machine learning to revolutionize thermodynamic modeling by improving efficiency and accuracy while reducing reliance on extensive experimental campaigns or computationally expensive approaches like quantum chemistry simulations. While current limitations include its focus on infinite dilution conditions and dependency on known substances within training data sets, future research aims to expand its scope toward broader applications such as solubility prediction or concentration-dependent activity coefficients.

By bridging gaps between theoretical models and practical applications, this study establishes the 3D-DMF-H method as a transformative tool for advancing predictive capabilities in chemical engineering and beyond.

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Advancing the aqueous biphasic hydroformylation of oleochemicals in the loop: Continuous reaction and separation using a jet-loop reactor concept

Thomas F.H. Roth, M. Häusler, Dieter Vogt, Thomas Seidensticker

In modern chemical manufacturing, producing materials efficiently and sustainably is a major challenge, which can be solved by applying highly productive homogenous catalysts. These reactions are essential for creating valuable chemicals from renewable sources, but they are not economically viable if the precious catalyst is not recycled afterwards. To solve this challenge, biphasic systems were developed. In these, two liquids must interact, which is challenging when renewable resources such as plant oils and water are to be mixed. To bring these highly sustainable yet challenging reaction systems into effective application, this publication focuses on the continuously operation of a jet-loop-reactor.

This study explores the continuous hydroformylation of renewable oleochemicals using a jet-loop reactor (JLR) to achieve efficient catalyst recycling in liquid-liquid multiphase systems (Figure 1). The study focuses on two case studies converting methyl oleate (MO) and methyl 10-undecenoate ($M_{10}U$), demonstrating the potential for long-term stable operation while addressing challenges such as catalyst retention and emulsion formation.

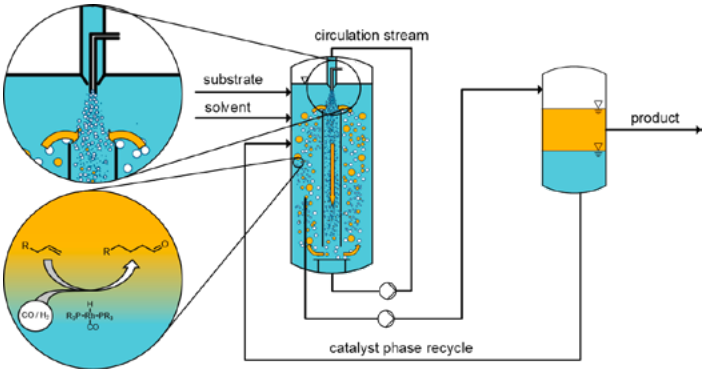

Figure 1. Concept of a continuously operated jet loop reactor with venturi ejector and general scheme of biphasic rhodium-catalyzed hydroformylation of a terminal alkene using water-soluble phosphine ligands.

Hydroformylation is a key reaction that converts olefins into aldehydes, which serve as intermediates for various applications like polymer precursors or lubricants. However, achieving high activity and selectivity while minimizing catalyst loss remains a challenge when processing renewable feedstock with different physical properties compared to petrochemical raw materials. Therefore this study employs an aqueous biphasic system with water-soluble rhodium catalysts due to a sulfonated ligand to enable efficient phase separation enabling the catalyst recycling.

In the first case study, MO was hydroformylated in an isopropanol/water solvent system using trisodium triphenylphosphine-3,3',3''-trisulfonate (TPPTS) as a ligand. Continuous operation over 55 hours achieved steady-state yields of up to 35 % with high selectivity (>90 %) for aldehyde products. Catalyst loss was limited to just 0.1 % per hour without requiring makeup flows, demonstrating effective retention in the polar phase despite cross-solubility of solvents.

The second case study applied $M_{10}U$ hydroformylation in a butanol/water system using sulfoxantphos as the ligand to enhance linear aldehyde formation. In this system, an additional challenge appeared in the emulsion formation during phase separation due to polarity differences between the components. By optimizing butanol concentration and separation temperature, this was overcome and stable yields exceeding 80 % were achieved over continuous operation while reducing rhodium loss to 16.7 mg per kilogram of product—a significant improvement compared to earlier batch processes.

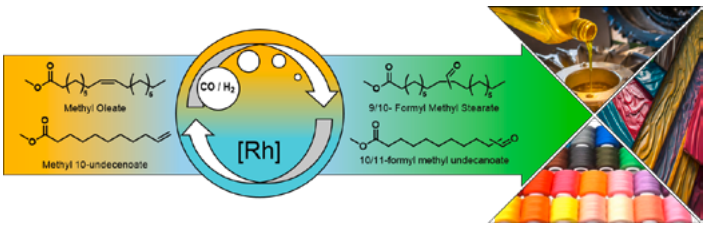

Figure 2. Conceptual visualisation of the biphasic rhodium-catalyzed hydroformylation of MO and $M_{10}U$ and potential applications of the corresponding products as polymer precursors or lubricants.

Both case studies highlight the advantages of JLRs for intensifying mixing and enhancing mass transfer in multiphase reactions compared to conventional stirred tank reactors (Figure 2). The innovative reactor design enabled higher substrate loadings and reduced solvent requirements without compromising reaction performance or catalyst stability.

This work demonstrates that combining advanced reactor concepts like JLRs with well-designed biphasic systems can overcome limitations associated with renewable feedstock hydroformylation even at miniplant scale. It provides a robust framework for integrating homogeneous catalysis into sustainable chemical production by achieving long-term operational stability, efficient resource use, and effective catalyst recycling strategies.

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Robust and flexible continuous operation of homogeneous catalysis in thermomorphic multiphase systems - On-stream switching of substrates and reactions in amine production

Tim B. Riemer, Arno M. Windisch, Dieter Vogt, Thomas Seidensticker

Catalysts are essential in chemical processes because they save energy and raw materials, making production more efficient and sustainable. Among the different types, homogeneous catalysts have advantages like high selectivity and mild operating conditions. However, they are difficult to separate and reuse, which is a major drawback—especially since leftover metal in the final product must be avoided for purity and safety reasons. One promising solution is the use of thermomorphic multiphase systems (TMS). In these systems, the catalyst and product form two separate liquid phases, similar to oil and water. When heated, they mix completely, allowing the reaction to proceed efficiently. After cooling, the phases separate again, making it easier to recover and reuse the catalyst. However, this system is sensitive to impurities and process conditions. Small changes can cause the liquids to stay mixed, preventing separation and stopping the process. In this study, we tested for the first time how well TMS can handle different starting materials and products without needing system changes. This opens up new opportunities for flexible production, where different products can be made one after another without cleaning or adding fresh catalyst, saving both time and resources.

This study explores the continuous operation of homogeneous catalysis within thermomorphic multiphase systems (TMS) for amine production. The authors present an innovative miniplant setup that integrates catalyst recycling and allows for on-stream switching of substrates and reactions (Figure 1). Over three consecutive experiments, with a total operating time of over 275 hours, five different tertiary product amines were synthesized through hydroaminomethylation and reductive amination processes. The findings highlight the robust performance of the methanol/*n*-dodecane TMS, achieving yields of up to 71 % for tertiary amines while maintaining high reaction efficiency.

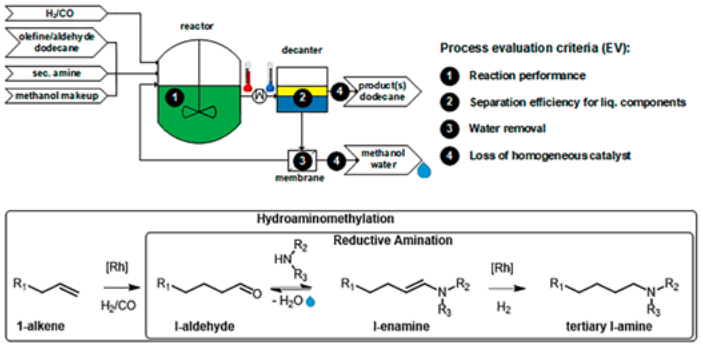

Figure 1. Principle of continuous catalyst recycling *via* TMS in reductive amination/ hydroaminomethylation and criteria for evaluating the process robustness.

The methodology involved carefully controlling system variations while analyzing over 700 samples through gas chromatography (GC) and inductively coupled plasma (ICP) techniques. Results demonstrated consistent phase separation throughout the process, effectively removing coproduct water *via* organic solvent nanofiltration (OSN). This approach facilitated stable long-term operations by ensuring that water was removed at a rate equal to its formation, thus preventing detrimental effects on reaction performance.

Additionally, the study underscores the importance of selecting appropriate catalysts and solvents to enhance overall process efficiency. The use of rhodium-based catalysts with diphosphine ligands proved effective in maintaining high selectivities during both hydroaminomethylation and reductive amination reactions. By employing TMS technology, transition metal catalyst losses were minimized to less than 1.7 mg Rh per kg of product across all experiments.

The results indicate that this TMS offers flexible adaptation to changing market demands, enabling substrate switching without significant downtime or productivity loss. Furthermore, continuously maintaining syngas pressure during substrate switching preserves catalytic activity and prevents deactivation due to agglomeration.

In conclusion, this work presents a significant advancement in sustainable chemical processes by demonstrating that thermomorphic multiphase systems can facilitate efficient catalyst recycling while enabling flexible production capabilities in continuous operations. These findings not only pave the way for future industrial applications but also emphasize how integrating advanced technologies can lead to more sustainable practices in chemical manufacturing.

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Thermodynamics (TH)

Highly efficient lithium extraction from magnesium-rich brines with ionic liquid-based collaborative extractants

Thermodynamics and molecular insights

Gangqiang Yu, Tobias Hubach, Christoph Held

The recycling of lithium ion batteries, particularly the isolation of lithium, is an important economically and ecologically relevant topic. The isolation of lithium ions is a challenge, because existing extractants have a low selectivity for these ions. Selective extraction of Li^+ from high Mg^{2+}/Li^+ ratio brines with ionic liquid (IL) based collaborative extractants was investigated by experiments, thermodynamic analyses, and quantum chemical (QC) calculations. The results demonstrated that the system 1-(2-hydroxyethyl)-3-methylimidazolium bis(trifluoromethylsulfonyl)imide + trioctyl phosphate ([HOEMIM][Tf2N] + TOP) was considered as the best extractant, with the very high extraction efficiency of Li^+ (E_{Li+}≈83 %) and separation selectivity of Li^+/Mg^{2+} (≈742), which is higher than any known report from the open literature. The thermodynamic model ePC-SAFT was extended to quantitatively predict the phase equilibria of the so-called "organic-inorganic complex strong electrolyte system" presented in this work as well as the related extraction indicator E_{Li+}. The molecular-level extraction mechanism was explored by QC calculation, indicating that the strong multi-site intermolecular interactions between Li^+ and [HOEMIM][Tf2N] + TOP break the Li^+ hydration.

The molecular-level Li^+ extraction mechanism from aqueous to organic IL+TOP phase was explored by QC using independent Gradient Model (IGM) analysis. Li^+ and Mg^{2+} are hydrated by strong interaction of "Metal-O-H", and Li^+ hydration is weaker than Mg^{2+} hydration. Thus, Li^+ can be extracted from the aqueous to organic phases by Li^+ hydration break, producing the complex Li^+-TOP-$[Tf_2N]^-$ dominated by the multi-site interaction consisting of $Li^+ \rightarrow$ O=P, S-N···Li^+, S=O···Li^+ C-H···O, and vdW dispersion interactions. In this case, TOP acts as extractant by coordinative interactions ($Li^+ \rightarrow$ O=P,) and the IL acts a co-extractant stabilizing the Li^+-TOP-$[Tf_2N]^-$ complex in an electrically neutral form (see Fig.1).

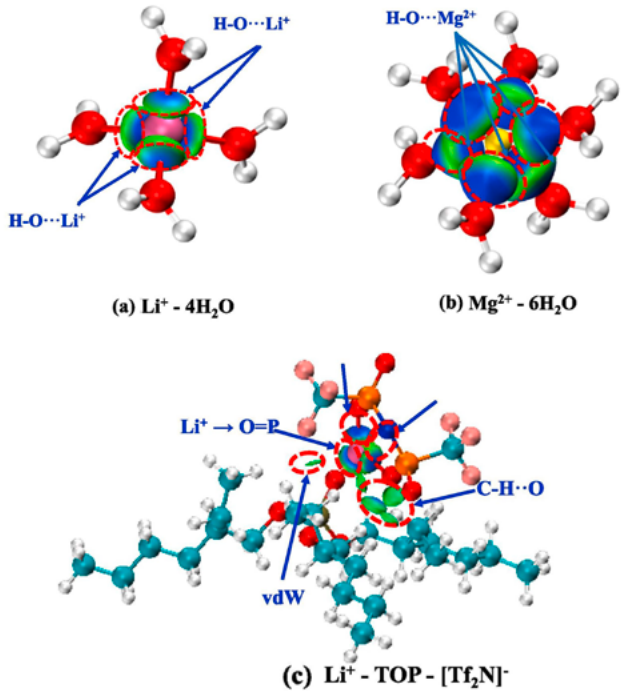

Figure 1. IGM visualization of ion hydration: Li^+-H_2O (a), Mg^{2+}-H_2O (b) and IGM visualization of the complex Li^+-TOP-$[Tf_2N]^-$ (c).

The extraction indicators for Li^+ extraction were predicted by ePC-SAFT. All the underlying phase equilibria of the subsystems were modeled as well based on the isofugacity criterion. One of the key results was that ePC-SAFT allowed predicting that Li^+ is transferred to the organic phase while Mg^{2+} stays in the aqueous phase, thereby allowing Li^+/Mg^{2+} separation. The key method for this was an induced association treatment between Li^+ and TOP in order to mimic the complex formation shown in Fig. 1c, which required only one binary parameter between Li^+ and TOP. Remarkably, E_{Mg2+} was obtained without any Mg^{2+}-extractant binary parameters. Further, the influence of organic:aqueous phase ratio (O:A) on E_{Li+} could be predicted well with ePC-SAFT, and E_{Li+} finally reaches a limiting value of ≈85 % (see Fig. 2).

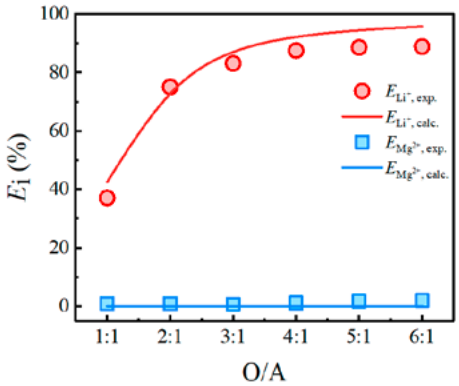

Figure 2. Comparison of the calculated (lines) and experimental (points) on the effects of the volume ratio for the organic to aqueous phase (O/A) on Li^+ and Mg^{2+} extraction efficiency with [HOEMIM][Tf_2N] + TOP as extraction system (Mg^{2+}/Li^+ = 40:1; and pH = 7 and C_{IL} = 0.09 mol/L), and the parameters were fitted to E_{Li+} at O/A = 2:1 and 298.15 K, i.e., all other modeling lines are predictions.

To conclude, we could demonstrate the powerful prediction capacity of ePC-SAFT and its first successfully extended application to so-called "organic-inorganic complex strong electrolyte system" in Li^+/Mg^{2+} extraction separation with ILs.

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Predicting Kinetics of the PET Glycolysis Reaction using an electrolyte thermodynamics-based framework

Accounting for the thermodynamic activity of the Zn^{2+}-catalyst on reaction kinetics of PET depolymerisation

Maria Schlüter, Christoph Held

Recycling of plastics is an important current environmental issue. Plastics can either be recycled by purification and reprocessing or by depolymerization into the monomers and renewed polymerization. One of the most important depolymerization reactions is the polyethyleneterephthalate (PET) glycolysis reaction. The optimization of the reaction conditions of this chemical reaction usually requires extensive experimental efforts to maximize kinetics. Currently, only empirical methods are available for modeling PET glycolysis kinetics. Such models do not have any predictive power and thus, these rely heavily on experimental data and are limited to defined operation conditions. In this work, a predictive model was developed aiming at predicting the impact of reactant ratio, catalyst concentration, and co-solvent effects on the equilibrium + kinetics of the PET glycolysis. To this end, the electrolyte equation of state ePC-SAFT was used in an activity-based kinetic framework. The thermodynamic activity of the catalyst zinc acetate was included, enabling the incorporation of catalyst interactions with the liquid environment in the reaction phase. The results showed very promising results, meaning that thermodynamics is highly useful to screen the most promising reaction conditions that allow fast reaction kinetics and maintain the high equilibrium yield of PET glycolysis.

In the present study, we developed an activity-based model to predict the kinetics of the PET glycolysis reaction, given by the following expression for the rate *r:*

$$r \cdot \bar{a}_{ZnAc_2} = k^{int} \cdot x_{PETru} \cdot \gamma_{PETru} \cdot x_{EG} \cdot \gamma_{EG} - \frac{k^{int}}{K_{th}} \cdot x_{BHET} \cdot \gamma_{BHET} \qquad (1)$$

Here, x and γ denote the mole fraction and the activity coefficient of the reaction partners PETru (ru=repeating unit), EG (ethylene glycol) and BHET. k^{int} and K_{th} are the intrinsic kinetic constant and the thermodynamic equilibrium constant. An electrolyte theory was necessary to model the activity of the catalyst ($ZnAc_2$) as well as γ of the reaction partners PETru, EG and BHET. In this work, ePC-SAFT was used to model the interactions of Zn^{2+} with the solvent and with the reactants as well as among the reaction partners. The pure-component parameters and binary interaction parameters were obtained from reaction-independent data (e.g., solubility data). We used the hetero-segmented approach to retrieve PCSAFT parameters for the PET repeating unit to reduce the number of parameters (strength of PC-SAFT for polymer systems).

In a first step, new experimental data were provided in this work tackling the influence of different reactant ratios and of the catalyst concentration on the kinetics of the PET glycolysis reaction. One experimental kinetic curve was used to determine the experimental kinetic constant, which was then used as input data to enable the development and validation of the predictive ePCSAFT-based kinetic model in Eq. (1) including k^{int}, which is not a function of catalyst or concentration. The latter is included in the catalyst activity coefficient and thus, in a_{ZnAc2} in Eq. (1). This approach allows predicting reaction kinetics as a function of reactant ratio and of catalyst concentration (cf. Fig. 1 (upper)) as well as of the green co-solvent γ–valerolactone (GVL), cf. Fig 1 (lower), which is an outstanding result. This big advancement not only contributes to the theoretical understanding of PET glycolysis but also reduces the need for extensive experimental work in the future.

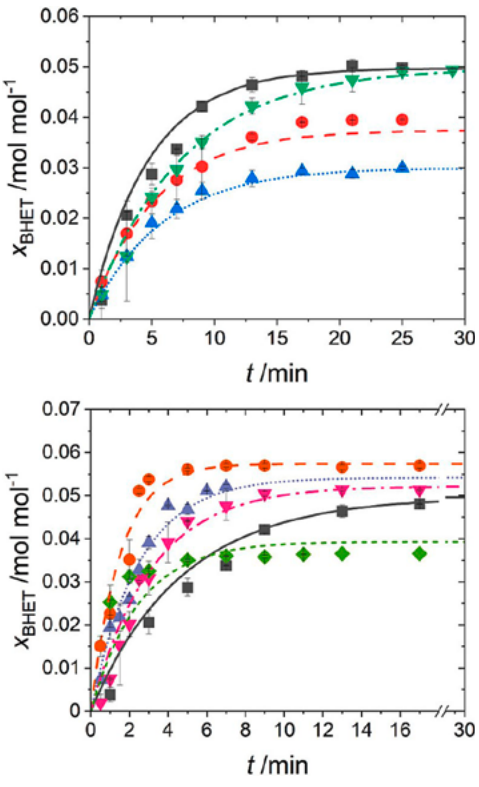

Figure 1. BHET mole fraction x_{BHET} over reaction time t for different GVL ratios and catalyst concentrations at 190 °C and 1 bar. Experimental data (symbols) vs. ePC-SAFT modeling (lines).

Black: co-solvent free reaction with PETru:catalyst ratio of 50.

Upper: Red, blue: Same as black but with higher EG excess over PETru (30 %, 60 %). Green: Same as black but halved catalyst concentration.

Lower: Pink, violet, orange: Same conditions as black but with GVL addition (12 %, 24 %, 48 %). Green: Same conditions as black but with GVL addition (48 %) and halved catalyst concentration.

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Counteracting the loss of release for indomethacin-copovidone ASDs

Dominik Borrmann, Pascal Friedrich, Justin Smuda, Gabriele Sadowski

The bioavailability of an active pharmaceutical ingredient (API) with low water solubility can be enhanced by dissolving the API in a polymer matrix generating an amorphous solid dispersion (ASD), which used as tablets. Upon ASD dissolution, the polymer and the API are supposed to simultaneously release from the ASD. However, ASDs often show simultaneous and fast release at low API to polymer ratios (low drug loads (DL)), while ASDs with high DL show a loss of API release. This study explained this phenomenon via investigating the release kinetics and phase behavior of an ASD consisting of the API indomethacin (IND) and the polymer copovidone both experimentally and theoretically. Modeling the experimental release kinetics, we were able to predict the formation of an ASD layer at the ASD-water interface, which almost exclusively contains amorphous indomethacin (IND). Our phase-diagram predictions and experimental data verify that water-induced phase separation during ASD dissolution. Whereas the evolving copovidone-rich phase dissolves, the IND-rich phase remains undissolved and forms a super-hydrophobic layer that covers the remaining inner core of the ASD, thus finally completely preventing its dissolution.

Figure 1 shows the measured and modeled release kinetics of IND-copovidone ASDs with DLs of 0.1, 0.3, and 0.5 in water. The release of IND was found to be highest for the ASD with the lowest DL 0.1. After 70 minutes, both IND and copovidone fully released from the ASD (Figure 1a).

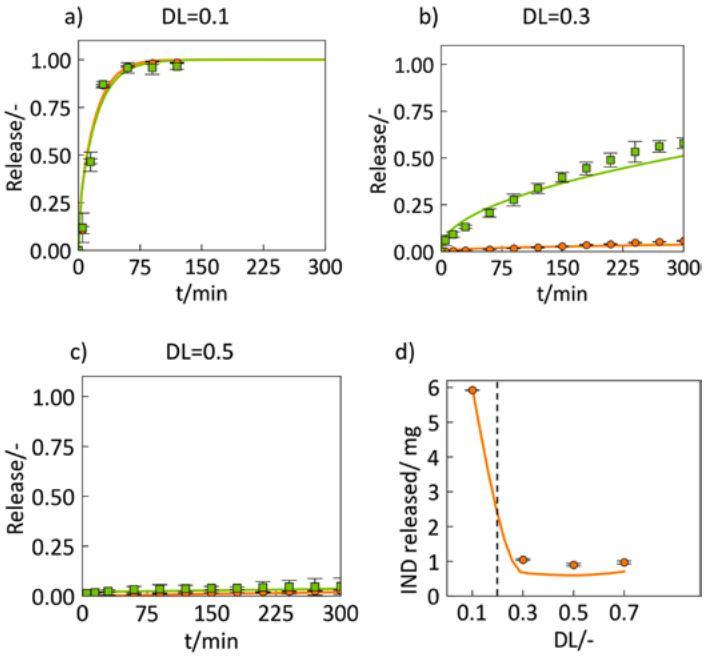

Figure 1. Releases of IND and copovidone from IND-copovidone ASDs and with DLs of 0.1 (a), 0.3 (b), and 0.5 (c) at 25 °C. Experimental data points are displayed as green squares for copovidone and as orange circles for IND. Model results are displayed as solid lines. (d) released mass of IND after 300 min as a function of the ASD DL.

For the ASD with a DL 0.3 (Figure 1b), the IND release was only 5 % after 300 min while the copovidone release was still 58 %. Counterintuitively, the higher the drug load of the ASD, the lower the absolute mass of IND released (Figure 1d). Thus, increasing the DL beyond 0.2 does not increase the mass of released IND, but only increases the mass of IND remaining undissolved in the ASD.

The phase diagram of the IND-copovidone-water ternary system predicted by PC-SAFT shows a large miscibility gap between IND and water (Figure 2).

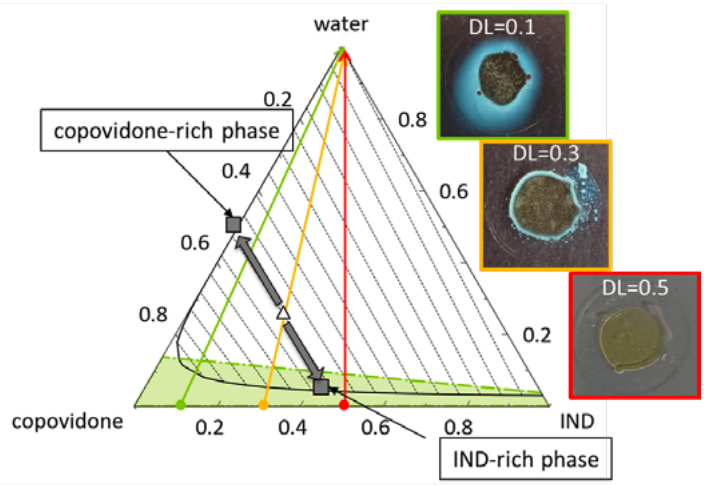

Figure 2. Phase diagram of the IND-copovidone-water system at 25 °C. The solid black line frames the miscibility gap. Green, yellow, and red arrows show the pathways for ASDs of different DLs (0.1, 0.3, and 0.5) during the release experiment. The white triangle exemplifies the demixing of a wet ASD along a tie line (dashed black lines).

During the release of an ASD, the ASD-water system moves along a line that connects the lower side of the triangle with its upper edge indicating pure water. The ASD with DL 0.3 demixes upon water sorption into a continuous IND-rich phase and copovidone-rich droplets. IND accumulates near the ASD-water interface and covers the inner of the ASD with a poorly-water-soluble IND layer which becomes thicker the higher DL is (about 80 μm). Since the solubility of IND is poor, at DL 0.5 even the polymer release (Figure 1c) breaks down. Thus, increasing the DL of the ASD beyond 0.2 will not lead to a further increase the amount of IND released. If higher DLs are required, full release of IND from the ASDs is only guaranteed if the size of the ASD is reduced below the size of the layer. Otherwise, significant amounts of polymer and IND remain in the ASD and thus will not be released at all.

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Publications:
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Thermodynamic modeling of aqueous surfactant solutions

Development and validation of a new modeling framework

Marius Rother, Gabriele Sadowski

The low solubility of active pharmaceutical ingredients (APIs) in aqueous solutions is a persisting challenge in drug development and design. Surfactants can be used to encounter this challenge. Once the surfactant concentration exceeds the Critical Micelle Concentration (CMC), the formed aggregates serve as vehicles for the hydrophobic APIs increasing their overall solubility. As a first step towards modeling and understanding aqueous surfactant systems, we present a newly-developed and generic thermodynamic framework. Such a thermodynamic framework provides a valuable tool for tailoring surfactants for solubilizing for target APIs.

The new framework assumes that surfactant molecules exist in two different conformations: either singly-dispersed in solution (free surfactants) or confined in an aggregate (confined surfactants). These two conformations were treated as different species, each with a distinct chemical potential.

The fractions of the two species are related to the overall surfactant concentration by imposing chemical equilibrium between the two conformations and applying the mass-action law (Figure 1).

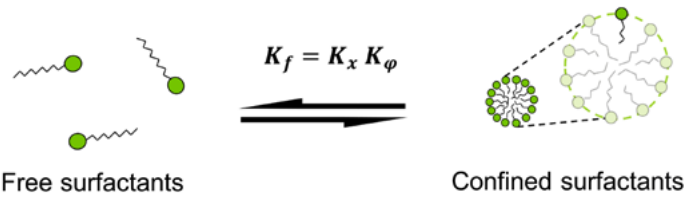

Figure 1. Equilibrium between the surfactant conformations. K_f is the equilibrium constant. K_φ accounts for the influence of interactions.

Application of the chemical-equilibrium condition requires a thermodynamic model to calculate K_φ. For this purpose, we used the hetero-segmented Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). By means of this group-contribution model, we generated a minimal set of universal parameters to describe a variety of homologous series including three different non-ionic surfactant classes. The model was validated against vapor-liquid equilibria, solid-liquid equilibria, infinite-dilution properties, as well as octanol/water partition coefficients (Figure 2).

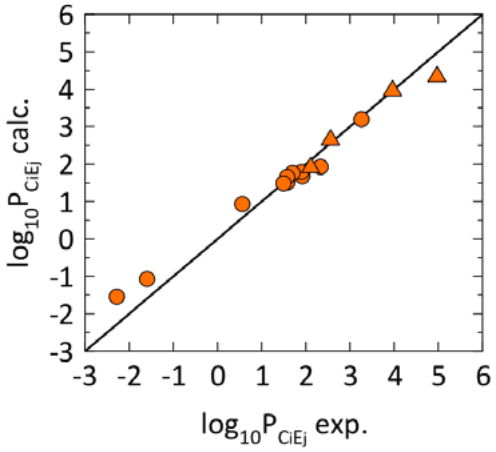

Figure 2. Parity plot of experimental versus correlated partition coefficients between n-alkane/water (circles) and n-octanol/water (triangles) for different poly(ethylene oxide) n-alkyl ether (C_iE_j) surfactants.

As part of the new framework, we developed a new relationship to calculate CMC. This new relation was applied for members of the n-alkyl-β-D-glucopyranosides (C_iG_1), C_iE_j, and N-alkanoyl-N-methyl-D-glucamides (MEGA-i) classes. Figure 3 shows the results of the CMC modeling for the surfactants C_iG_1 and MEGA-i.

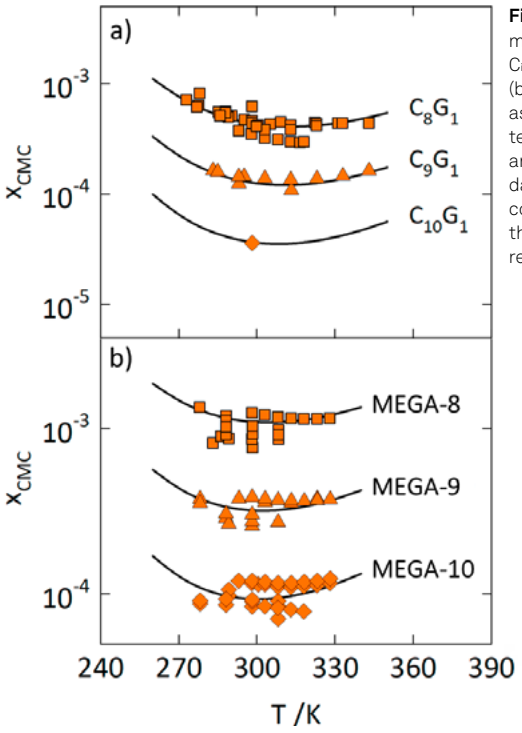

Figure 3. CMCs in mole fraction of the C_iG_1 (a) and MEGA-i (b) surfactants as function of temperature. Symbols are experimental data. Solid lines are correlations using the newly-developed relation.

Accordingly, the CMCs were quantitatively described over a broad temperature range. The temperature behavior can be fully attributed to the electrostatic characteristics of the surfactant heads and is correctly predicted by our modeling approach.

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Transport Processes (TP)

Investigation on the intra-particle anisotropic transport properties of a beech wood particle during pyrolysis

Andrea Dernbecher, Supriya Bhaskaran, Nicole Vorhauer-Huget, Jakob Seidenbecher, Suresh Gopalkrishna, Lucas Briest, Alba Dieguez-Alonso

Biomass and plastics are important sources of renewable and waste carbon that may play a key role in the development of a sustainable and circular economy. Thermochemical and thermocatalytic conversion processes like pyrolysis, gasification, combustion, or hydroliquefaction enable the conversion of these carbon sources into useful products such as chemicals, materials, fuels, and heat, contributing thereby to the defossilization of the chemical industry and the energy sector. However, their high chemical, physical, and morphological complexity constitute an important challenge in the development of flexible and highly selective conversion processes. Such processes occur often in particle bulks passed by a gas (or liquid) flow, where the physical and chemical phenomena occurring both inside the particles or in the flow may be decisive for process selectivity and product quality. This poses a multi-scale and multi-phase problem that needs to be effectively addressed to enable the development of flexible, selective, and efficient thermochemical and thermocatalytic conversion processes.

The development of high-resolution models is essential for understanding the interaction between chemistry and transport in multiphase reactive systems. When porous particles are involved, their morphology and pore microstructure may significantly influence transport phenomena and eventually chemistry, especially if the particles have a hierarchical and anisotropic pore structure that evolves during conversion, as seen with biomass. This study represents an initial effort to integrate particle morphology, transport, and chemistry within highly-resolved particle models.

We captured the evolution of particle morphology and pore microstructure of a beech wood sphere during pyrolysis (at 100, 200, 300, 400, and 500 °C) using ex-situ X-ray micro-computed tomography (X-ray µ-CT) (Fig.1).

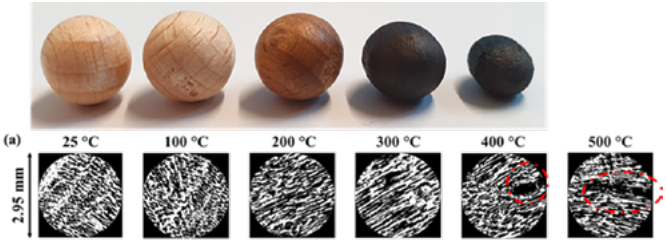

Figure 1. External shrinkage (top) and internal shrinkage (bottom) of a beech wood particle during the pyrolysis process. Solid in white.

The resulting realistic structural geometries (Figure 2) were used in pore-resolved (pores larger than 15 µm) computational fluid dynamic (CFD) simulations (Figure 3) to examine how the dynamic and anisotropic pore microstructure influenced intra-particle flow permeability and tortuosity.

The results revealed a non-monotonic increase of intra-particle permeability and decrease of tortuosity with pyrolysis temperature. Furthermore, an order of magnitude difference between the permeability parallel and perpendicular to the main pore direction was observed, underscoring the necessity to use conversion and direction-dependent effective transport parameters in particle models. Future work will focus on the investigation of thermal transport properties and the interaction of intra-particle transport and chemistry. This step is fundamental to identify the governing phenomena at particle level that need to be then transferred to multi-scale reactor models.

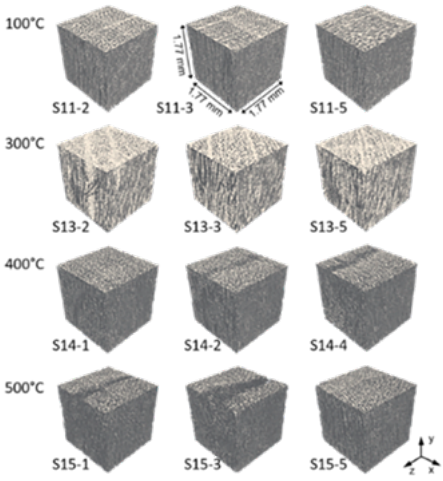

Figure 2. Structural geometries of three intra-particle subdomains for each temperature level (100, 300, 400, and 500 °C) obtained with X-ray µ-CT. Domain size 300 x 300 x 300 voxels, with resolution of 5.9 µm per voxel (solid in grey) used for CFD simulations.

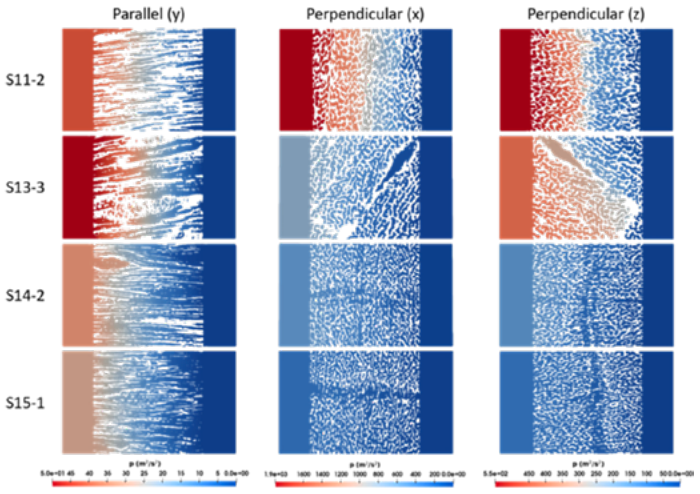

Figure 3. Simulated pressure loss in the parallel and perpendicular directions to the main pore direction for a subdomain with intermediate porosity for the four considered temperature levels (Figure 2).

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