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2017

SCIENTIFIC HIGHLIGHTS
Annual Report

bci Fakultät Bio- und
Chemieingenieurwesen
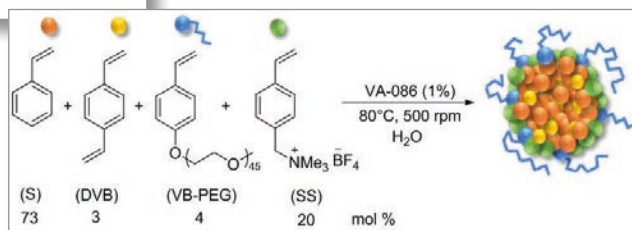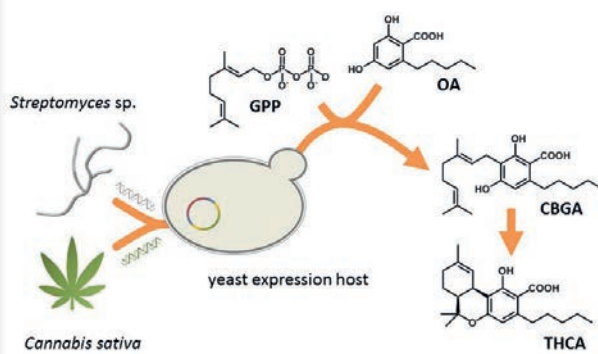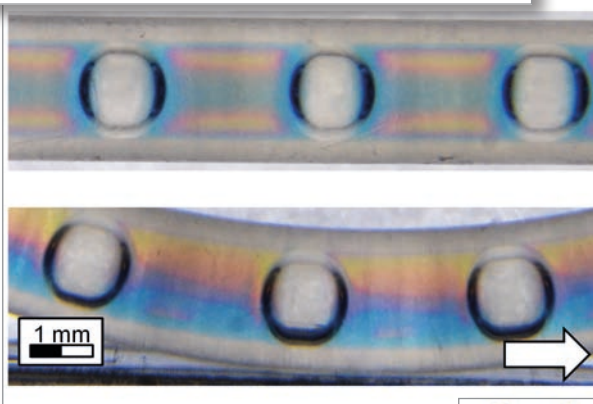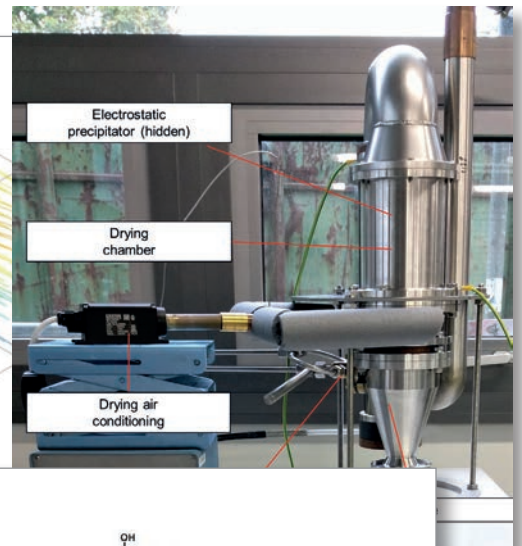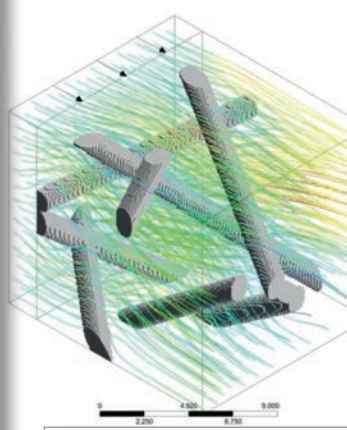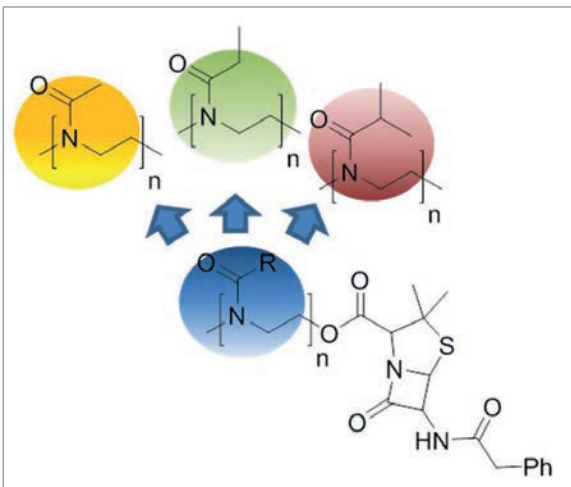
Content

Content

Department of BCI

Preface

Dear Reader,

You will find the best off of the scientific work of the Department of Biochemical and Chemical Engineering (BCI) from the year 2017 on the following pages. The modern scientific methods, the broad faculty with mixed natural scientists and engineers, and the excellent equipment enable us to perform cutting edge research, which is one of the great benefits to our well educated Master and Bachelor absolvents, PhD students, and Postdocs. It is also a platform for collaborations with academic and industry partners, which are always welcome for joined research projects. Maybe you find some common interest in the following pages and join us in one way or another.

Enjoy the reading,

Joerg C. Tiller
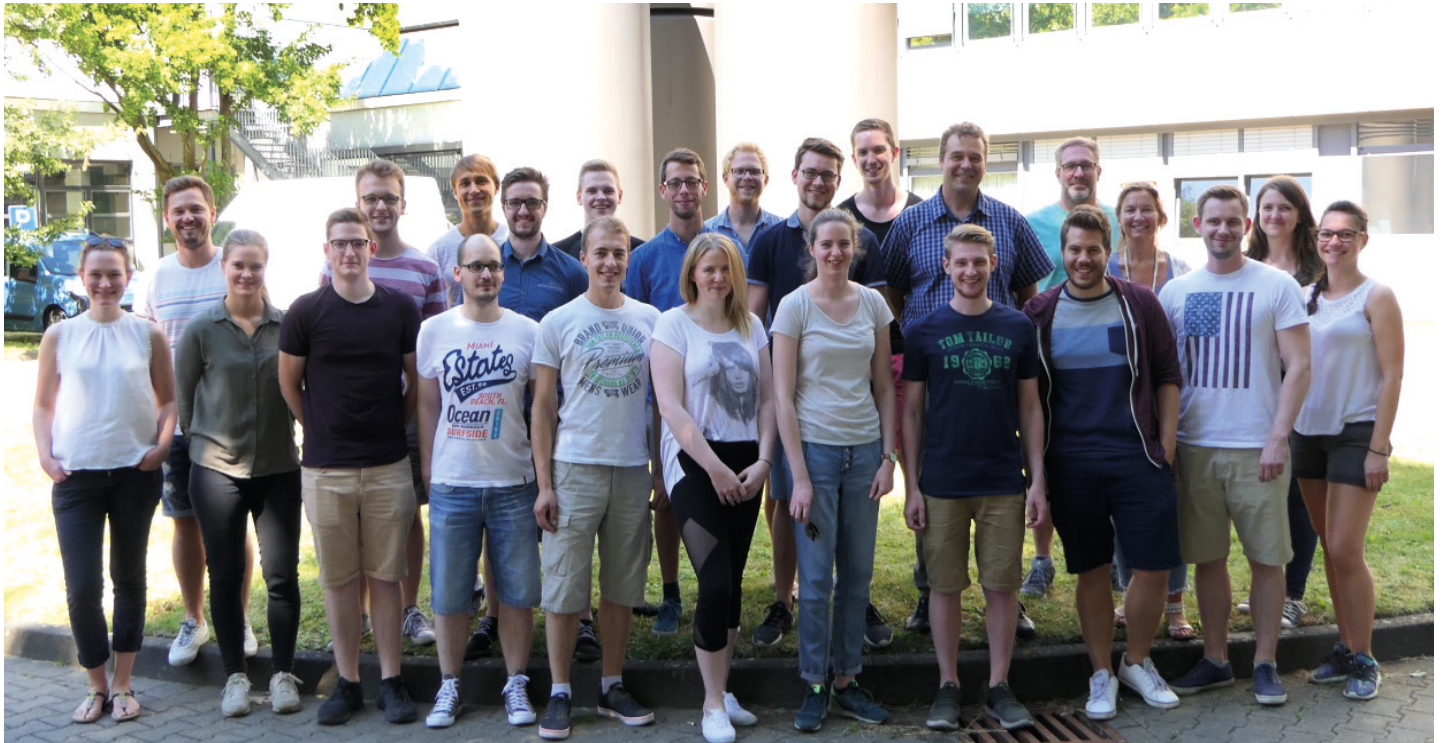
Equipment Design (AD)

Process Intensification of Catalytic Processes and Multiphase Flow Devices

Catalytic processes as well as multiphase flow devices benefit from miniaturized equipment

Norbert Kockmann

Fluid dynamics, mixing, and heat transfer are very important for performing exothermic chemical reactions in microchannels under stable and robust conditions. However, the complex interplay of single and multiphase flow, residence time, mixing, and heat transfer with chemical kinetics has to be considered in chemical engineering tasks. Well-characterized, modular equipment can be described by short cut methods following the toolbox concept enabling consistent process development and scale up.

Research on transport phenomena in microstructured devices is increasing over the last 15 years. Profound understanding of fluid flow, residence time, mixing, and heat transfer is important for performing chemical reactions in small channels [1]. Well-characterized channel elements and coiled tubular devices are the basis for the toolbox and platform concept of a modular plant design on lab scale with consistent scale-up to higher flow rates with similar process performance. Experimental reference investigations guide the definition of dimensionless numbers, characteristic time scales, or temperature ratios for successful reactor design [2]. Similar approach is followed for separation units, e.g. a tubular device for cooling crystallization with 4 mm or a miniaturized extraction column with 15 mm inner diameter for intensified mass transfer and separation performance. Current work is focused on deeper understanding of the described phenomena regarding separation processes in miniaturized equipment [3]. The extraction column was scaled-up to a DN50 column, while the tubular device was tested with 4 mm inner diameter, then scaled up to 10 mm, and recently down to 1.6 mm.

Process Intensification (PI) aims at dramatic improvements, but also continuous improvement, in chemical processes leading to higher efficiency, lower production cost and safer, environmentally benign processes. Besides improved catalytic materials and processes, augmented transport processes, alternative energy sources, and integration/combination of various process steps are key tools of PI. Holistic design methods are required, including 'Conceive and Identify' the task, 'Design' various alternatives, 'Optimise' promising routes, 'Validate and Implement' the solution, and 'Operate' the improved plants [4]. Knowledge-based design, with help of a database and methods from process system engineering such as multiscale simulation or improved measurement and systems automation, assist the implementation into modern process design and production.
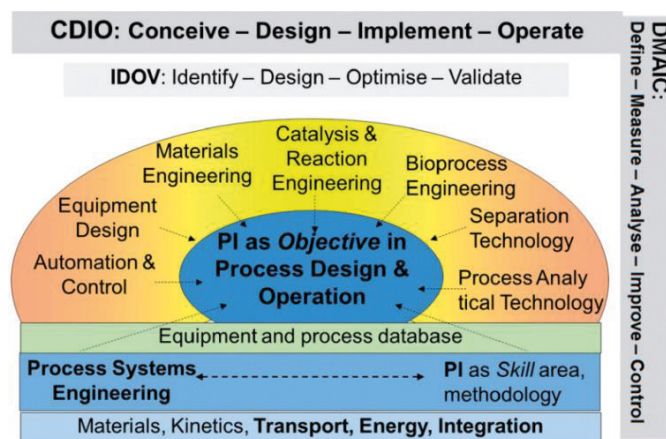
Figure 1: Process intensification as objective and methodical area integrating tools and methods. Design is facilitated with a database on equipment and processes in the framework of engineering design.

The future will bring more realised examples and success stories for process and equipment design and operation. It will be important to find the way from innovation to implementation by bridging the gap over the valley of death to innovation. As F. Keil already stated "In PI, the journey is the reward"; and so, let's proceed …

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Optimal Micronozzle Design for Energy Effective Bubble Breakup

Design-of-Experiment assisted evaluation of turbulent bubble flow redispersion in microchannels

Felix Reichmann, Fabian Varel, Norbert Kockmann

In recent years, gas–liquid flow in microchannels has drawn much attention in the research fields of analytics and applications, such as in oxidations or hydrogenations. Since surface forces are increasingly important on small scale, bubble coalescence is detrimental and leads to Taylor bubble flow in microchannels with relatively low surface-to-volume ratio. To overcome this limitation, the micronozzle induced bubble breakup was investigated. An optimal nozzle design for pressure drop-effective bubble breakup was found via Design-of-Experiment (DoE).

Gaseous reagents are often used in large stoichiometric excess due to insufficient interfacial mixing. Thus, extended reaction times and, consequently, prohibitively slow processes result. In microchannels, mainly Taylor bubble flow is achieved due to dominating surface forces. Here, refinement of gas–liquid dispersion using converging–diverging micronozzles has been found to be highly effective by breaking up larger bubbles into considerably smaller ones. Particularly, the turbulent bubble breakup regime, with characteristic high volumetric flow rates and Reynolds numbers in the continuous liquid phase, results into small daughter bubbles featuring a narrow size distribution (Figure 1). Bubbly flow regime presents highest interfacial area per unit volume compared to the other flow regimes existing in gas-liquid flow.
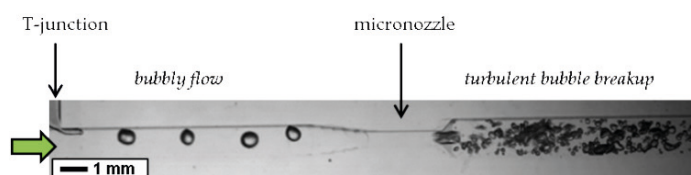
Figure 1: Turbulent mother bubble breakup into numerous daughter bubbles with narrow size distribution in a converging-diverging micronozzle, Re_{nozzle} = 3732.

Although high flow rates lead to small daughter bubbles, they also result in high pressure losses. In particular, the nozzle geometry takes influence on flow detachment and eddy generation in the diverging part. Thus, a compromise between pressure drop and bubble size has to be found and had been attended to in a DoE. Here, the hydraulic diameter of smallest cross section, the length of the smallest cross section, outlet angle, hydraulic diameter of the downstream channel, and the volumetric flow rate were implemented to find optimal parameter settings for an energy effective turbulent bubble breakup. The influence of single parameters and their interactions on pressure drop and daughter bubble size were investigated regarding their significance in a Pareto diagram of effects. Highest impact on pressure drop and bubble size was found for the hydraulic diameter of the smallest cross section.
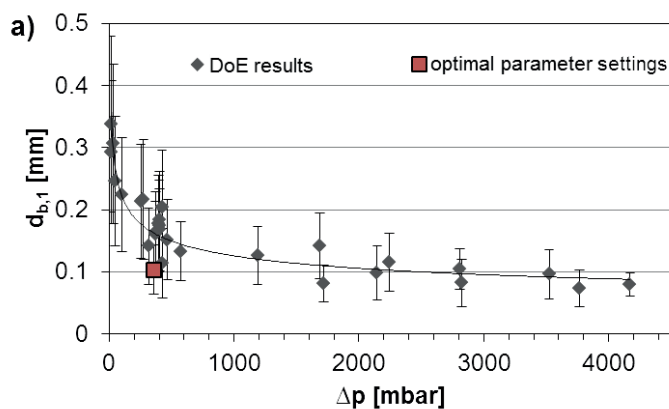
Figure 2: Daughter bubble size in dependence of the pressure drop from the Design of Experiment (grey diamond symbols). Experiment with optimal parameter setting is marked red.

After factor optimization regarding both output variables, an optimal nozzle design was obtained, manufactured, and tested. Figure 2 shows the results of all performed experiment within the DoE and the results from the experiment employing the optimal parameter setting. Obviously, small daughter bubble diameters are achieved at high pressure loss due to the asymptotic behavior of the trend line. The result of the optimal parameter setting experiment is right at the steep decline of the trend line. With a low pressure drop of 250 mbar, a daughter bubble diameter of 100 µm is obtained.

The optimal nozzle design can now be used for chemical gas-liquid reaction in order to attain high interfacial areas for intensified mass transfer and increased conversions.

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Local Gas-Liquid Mass Transfer in Straight and Coiled Capillaries

Superposition of Taylor and Dean Flow and the Effect on Mass Transfer with Chemical Reaction

Waldemar Krieger, Norbert Kockmann

Microreactors are used to enhance heat and mass transfer overcoming mass transfer limitations in gas-liquid reactions. This influence can be further increased by employing coiled capillaries, which induce Dean vortices and improve radial mixing. In this work, a colorimetric technique is proposed in order to visualize local mass transfer phenomena and concentration distributions with high spatial and temporal resolution. Further, this method enables the local investigation of selectivity for gas-liquid reactions, which is a major topic in current research.

Mass transfer studies have been performed utilizing the consecutive oxidation of leuco-indigo carmine as colorimetric reaction with two distinct color changes (yellow-red-blue). This allows for comprehensive studies of local gas-liquid mass transfer and local chemical selectivity by using the information in the different color channels. Further, this technique was applied in straight and coiled capillary setups in order to study the differences in fluid dynamics, mass transfer and chemical selectivity. Slug flow was generated by means of a hypodermic needle, which was positioned at the center of an FEP tube through a T-junction ensuring stable bubble generation with low mass transfer contribution.

Higher conversions are achieved in coiled capillary due to enhanced radial mixing, which agrees with experimental investigations in coiled tubes from literature. On the other hand, selectivity related to the intermediate is higher in straight capillary, due to a lower degree of mixing compared to coiled capillaries (Figure 1).
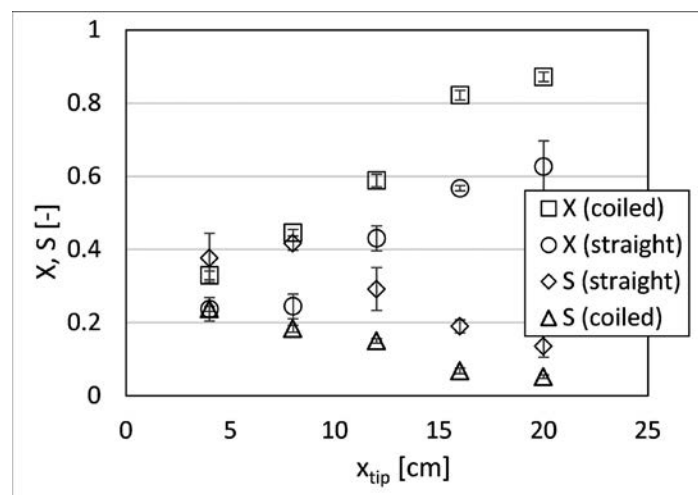
Figure 1: Comparison of conversion and selectivity of leuco-indigo carmine oxidation in straight and coiled capillary.

Very short reaction times in the order of a few milliseconds lead to fast oxidation of the intermediate in areas with increased oxygen concentration. Hence, elevated intermediate concentrations are only observed in areas of limited oxygen access (Figure 2). These areas occupy a larger volume fraction in the straight capillary, which results in a higher intermediate selectivity.
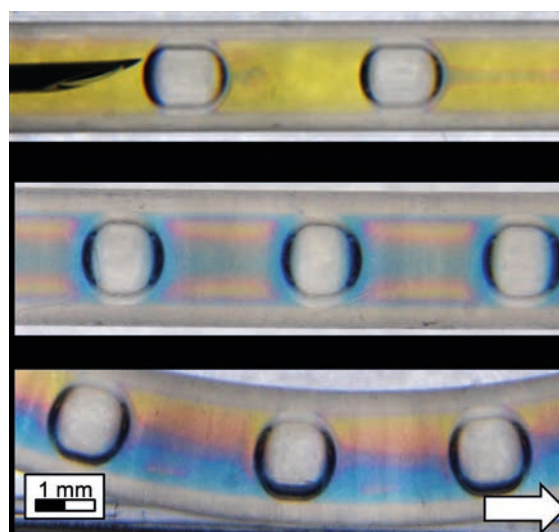
Figure 2: Oxidation of leuco-indigo carmine in straight and coiled capillary.

This work provides a non-invasive tool that can be used to characterize gas-liquid contactors in terms of mass transfer and chemical selectivity. Such information is valuable for the still challenging scale-up of gas-liquid processes and the development of theoretical models and numeric simulations. In future work, local quantitative mass transfer and selectivity studies will be carried out for varying process parameters in order to obtain a deeper understanding of flow structure and mass transfer in coiled capillaries and tubes.

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Gas-liquid-solid flow in Coiled Flow Inverters CFI

The helical structure enables multiphase flow processes under controlled conditions

Safa Kutup Kurt, Krishna D.P. Nigam, Norbert Kockmann

In various studies, a helically coiled tubular device with many 90° bends, called Coiled Flow Inverter CFI, was developed with robust and simple fabrication performing in multiphase reaction systems. The modular CFI is investigated in the production of uniform microscale particles with large throughput in continuous mode operation. A design method is proposed for narrow residence time distribution particularly for laminar flow conditions.

Curved microchannels and capillaries provide enhanced heat and mass transport due to their controllable flow patterns and high surface to volume ratio. Gas−liquid slug flow observations revealed that the Taylor vortices are influenced by secondary flow due to the centrifugal force acting perpendicular to the flow direction. Hence, mixing inside the liquid slug is enhanced by the combination of Dean and Taylor vortices in hellically coiled tubular device (HCTD). The modular design of a specific type of HCTD, that is, the coiled flow inverter (CFI) is elucidated by the representation of a new design space diagram. Continuous precipitation of calcium carbonate ($CaCO_3$) was investigated for modular CFI made of polyvinyl chloride (PVC) tubes (d_i = 3.2 mm) with slug flow patterns. $CaCO_3$ was continuously precipitated along CFI with a conversion of ca. 90%. CFI provided a narrower particle size distribution with mean particle diameters around 28 μm and more uniform morphology in comparison to a batch reactor.
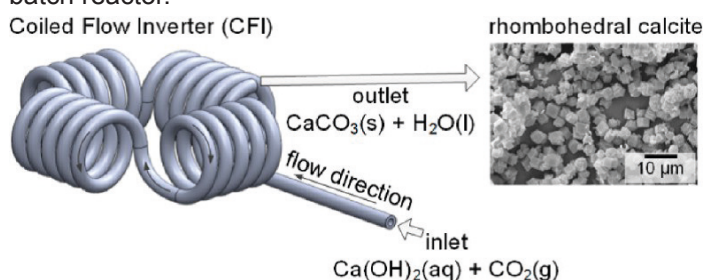
Figure 1: CFI setup with calcium carbonate formation.

A model for the simulation of mass transfer in a liquid/liquid plug flow in a microcapillary reactor is very useful for mass performance prediction. Starting from the interface tracking method, the modeling is carried out in separate form-adapted coupled computing areas on the basis of an imported interface topology. Experimental investigations are carried out with a standard reaction and extraction system.

Summarizing, the CFI device can provide enhanced radial mixing due to the secondary flow profiles and their inversion with 90° bends in the case of G−L slug flow patterns. The three main topics were studied for the first time in this work, that is, the particle tracking in a G−L slug flow within a HCTD, the design and implementation of a modular CFI reactor, and the continuous precipitation of the calcium carbonate.

A comprehensive way to design a modular CFI was developed providing a wide range of residence times displayed in a design space diagram (DSD) for the different volumetric flow rates. The DSD simplifies the selection of the geometrical design parameters of a CFI ensuring enhanced radial mixing by considering the process conditions and physical properties of the fluids.
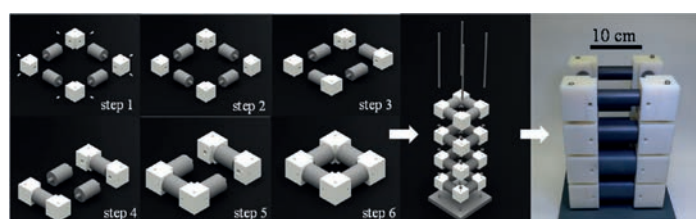
Figure 2: Modular CFI design for stack-wise setup.

Finally, a modular, continuously operated tubular reactor concept, that is, CFI with a robust and an easy fabrication was proposed in the content of this work for the multiphase reaction systems. Standard coil diameter enables rapid design on this flexible, multipurpose equipment for various process tasks.

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Hydrodynamics and Mass Transfer in DN32 Stirred-Pulsed Extraction Column

Process intensification of counter-current extraction in columns through application of two energy inputs

Sebastian Soboll, Isabel Hagemann, Norbert Kockmann

In order to intensify extraction processes in extraction columns, a novel column type was designed, which combines two different energy inputs, stirring and pulsation. After successfully characterizing a stirred-pulsed column with 15 mm inner diameter, a 32 mm inner diameter (DN32) column was designed and investigated. Compared to conventional extraction columns, the DN32 stirred-pulsed column provides a much higher separation performance.

The DN32 column was investigated regarding hydrodynamic behavior and mass transfer performance. The flooding point is an important hydrodynamic parameter, because it limits the maximum throughput of the apparatus. In general, the term flooding denotes the breakdown of the counter-current flow, which occurs at too high flow rates. In the DN32 column, flooding is visually detected (Fig. 1).
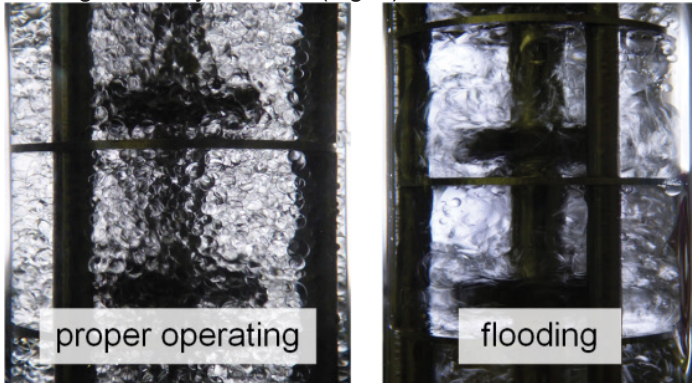
Figure 1: Pictures of the two-phase system inside the column during proper operating and during flooding.

During proper operation, the stirred cells in the column are filled with many small droplets, which are surrounded by the continuous phase. However, when the flooding point is reached, intense coalescence of the droplets at the column wall and column internals happens, leading to plugging of the column.

Determination of the flooding point is done by increasing the throughput stepwise at fixed stirrer speed and pulsation frequency until flooding behavior is visually detected. The throughput is given as loading B, which is the total ingoing volume flow rate divided by the cross sectional area of the column (Eq. 1).

$$B = \frac{\dot{V}_{in,total}}{A_{cross-section}} \qquad 1$$

Flooding points B_{flood} were measured for different stirrer speeds and pulsation frequencies. As illustrated in Fig. 2, flooding occurs earlier at higher stirrer speeds, since the decreased droplet size leads to lower rising velocities of the droplets. In contrast, raising the pulsation frequency results

in higher flooding points, because pulsation helps to transport the droplets through the trays, which are mounted in the column.
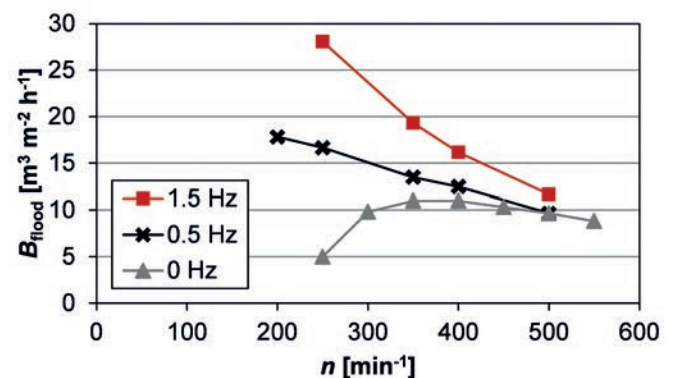
Figure 2: Flooding loading for different stirrer speeds and pulsation frequencies.

As a measure for the mass transfer performance, the number of theoretical stages per meter of column height is applied. The number of stages is determined via mass transfer experiments and a McCabe Thiele stage construction. Highest extraction performance is achieved with low or medium stirrer speeds at high pulsation frequencies (Fig. 3). In comparison with a conventional stirred extraction column of type Kühni, the stirred-pulsed column provides a much higher separation performance.
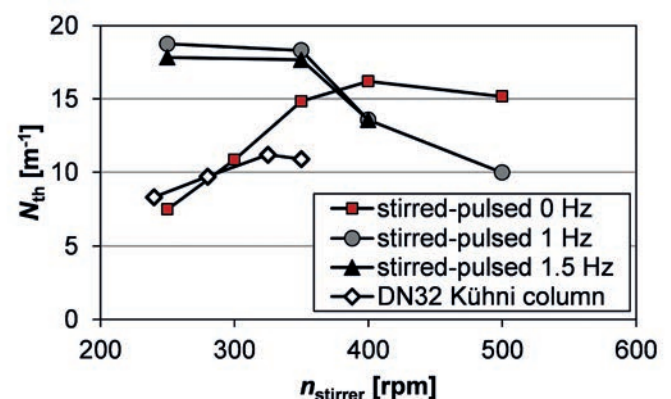
Figure 3: Extraction performance of stirred-pulsed column compared with performance of a comparable Kühni column (Kühni column data from P. Kolb, PhD Thesis, TU Kaiserslautern, 2004).

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Modular Equipment and Module-Based Process Design

Module-based plant design enables shorter time-to-market by reuse of engineering effort

Norbert Kockmann, Lukas Hohmann, Christoph Fleischer-Trebes, Gerhard Schembecker, Christian Bramsiepe

The database with modules and module-based methods are essential for rapid process development and market supply. Modular plant components with defined interfaces and performance are key components of multipurpose, small-scale, continuously operated processes. A toolbox of chemical equipment enables rapid process development and small-scale production. Examples demonstrated shorter development time up to 50% and 10% for energy or material consumption.

Modularly built production plants are considered for planning new chemical plants, in case they shall be designed quickly and transformable, flexible plants are required. This contribution summarizes the module based planning approach, which allows for structured planning of new modular plants in a time-efficient way. All required documents for building modules are stored in the Process Equipment Design PED documentation, which is available for re-use in future projects (Fig. 1).
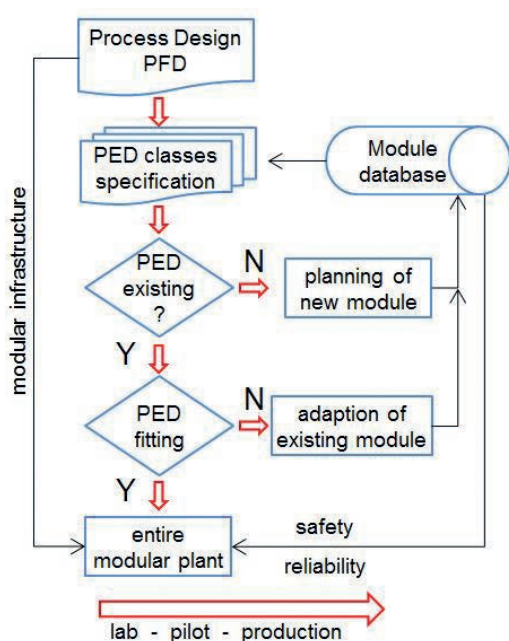
Figure 1: Module-based planning process from PFD to production plant with module database.

Stepwise process development with experience from module database starting from conceptual design and feasibility study, optimization study to long run studies for a robust process leading to production campaigns. A lot of information from two research groups at BCI, TU Dortmund University in close collaboration with INVITE in Leverkusen went into the DECHEMA white paper on Modular Plants (http://dechema.de/2017+2+White+Paper+Modular+Plants.html).

A process module has defined interfaces and well characterized, qualified operating range stored in an information data base. The modular toolbox of plate and tubular reactor, stirred vessel, and columns is the base of devices on different platform levels. This enables a flexible assembly for rapid continuous-flow process development with a wide range of throughput and application (Fig. 2).
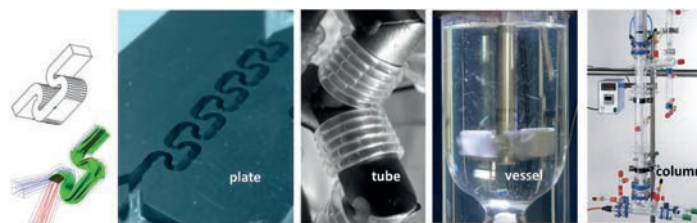
Figure 2: Equipment toolbox from channel element design with simulation results to geometrical realization of miniaturized channels on a plate; coiled tubes with internal bends; stirred vessels, counter-current flow column for separation purposes.

A stage-gate process including conceptual process design and basic engineering phase minimizes the risk of failure and development effort. Detail engineering effort leads to qualified module templates and devices serving a wide process window and enabling multipurpose plants. The development process is shown in Fig. 1. With this setup, the basic engineering happens in the early phase of process development, while detail engineering data is stored in the database. With the current setup, a continuously operating chemical process can be setup in the lab or pilot plant with existing modules in very short time. The scale-up process is quite straight forward with known characteristics of the equipment with their analogues on larger scale.

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Plant and Process Design (APT)

Generation of an Equipment Module Database for Heat Exchangers by Cluster Analysis of Industrial Applications

Martin Eilermann, Christian Post, Dorothea Schwarz, Stephan Leufke, Gerhard Schembecker, Christian Bramsiepe

Module-based plant design opens up the opportunity for the (bio-)chemical industry to reduce lead times, which is crucial for future competitiveness. The time-consuming equipment design step is replaced by selecting the most suitable equipment module from an equipment module database so that engineering work is reused. Although of central importance in module-based plant design, an applicable equipment module database has not been developed yet. Therefore, it is the aim of this work to develop a methodology for the generation of shell and tube heat exchanger modules for an equipment module database.

In conventional planning processes, the equipment is designed individually minimizing total cost with the aid of computer software and under consideration of functional requirements, operating constraints as well as industrial standards. This conventional design process involves several iteration steps. The question is, whether an individually designed apparatus is required for every application, or whether it is possible to cover a group of similar applications with one apparatus. This idea is embraced in the concept of module-based plant design. Equipment modules are designed once such that they can cover a wide range of process conditions and applications. The time-consuming design step is replaced by selecting the most suitable equipment module from an equipment module database. Thus, the lead time can be reduced, which may offer a substantial economic benefit. Overall, it becomes clear that promising approaches in module-based plant design already exist. However, there is a lack of an applicable equipment module database from which suitable equipment modules can be selected.

To consider applications with industrial relevance in the generation of the equipment module database, heat transfer applications provided by Evonik were considered within this work. The heat transfer applications were grouped in a hierarchical clustering analysis according to a set of defining features. For each of these groups a representative heat exchanger was selected. Therefore, a set of shell and tube heat exchangers was generated applying Sobol sampling. From this set a heat exchanger was selected to be the representative, which covers most of the applications inside the considered group of process applications. For that purpose thermodynamic as well hydrodynamic operating constraints were considered. The representative heat exchangers were stored in the equipment module database. Moreover, based on the simulation results the ratio of industrial applications that can be covered by the representative heat exchangers is determined in each step. The results of this work are presented in Figure 1 distinguishing between two cases of applied velocity constraints. If fouling risk is not an issue, the relaxed velocity constraints are adequate.

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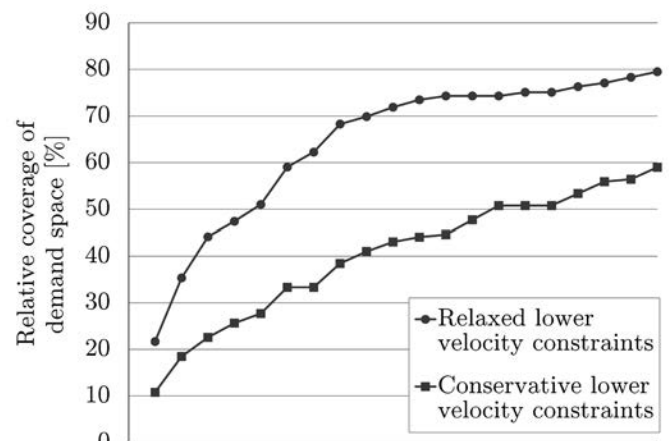
Figure 1: Coverage of the demand space over the number of clusters for conservative and relaxed lower velocity constraints.

With an increased number of clusters and hence an increased number of representative heat exchangers, also the coverage of the demand space increases. Considering the conservative constraints, 17 representative heat exchangers are required to cover 59 % of the industrial applications. As can be seen from Table 1, the process and property data of the applications that can be covered show a great variety.

Process/property	Symbol	Unit	Minimum value	Maximum value
Mass flow rate	$\dot{m}$	$[kg/h]$	380	1 248 740
Heat flow rate	$\dot{Q}$	$[kW]$	5.8	10 987
Specific heat capacity	c_p	$[kJ/kgK]$	0.8	8.7
Density	ρ	$[kg/m^3]$	520	1770
Dynamic viscosity	η	$[mPas]$	0.07	10
Thermal conductivity	λ	$[W/mK]$	0.08	0.8

Table 1: Range of the process and property data for the industrial applications that can be covered by 17 representative heat exchangers considering the conservative lower velocity constraints.

Finally, the equipment module database should be integrated and applied in the module-based planning process.

Discrimination of Single Particles, Agglomerates, and Air Bubbles using a Linear and Non-Linear Classifier

Variable selection with an easy-to-implement qualitative measure to rate image descriptors for classifier generation

Stefan Heisel, Tijana Kovačević, Heiko Briesen, Gerhard Schembecker, Kerstin Wohlgemuth

While particulate products are often characterized by their particle size distribution, no information is given about the agglomeration of particles. To obtain information on the agglomeration degree of a product, image analysis and sophisticated particle classification algorithms like discriminant factorial analysis (DFA) or artificial neural networks (ANN) can be used to discriminate single particles, agglomerates, and air bubbles. Latter have to be considered artifacts when measuring particle suspensions. The accuracy of the classification algorithm generated – the so-called classifier – is highly dependent on the input given like variable subset and training set design. The qualitative measure proportional similarity is used for variable selection for a linear and a non-linear classifier.

Using image analysis, each of the objects detected (Figure 1) can be characterized by a variety of image descriptors, describing qualities like size, roughness, or proportion. As crystalline systems adipic acid/water was used.

single particle   agglomerate   air bubble

Figure 1: Examples for an adipic acid single particle and agglomerate and an air bubble as detected by the imaging sensor.

The quantitative measure proportional similarity (PS, equation 1) is used to rate each of the 19 image descriptors available in terms of how well it can discriminate two populations.

$$PS = \sum_{i=1}^{20} \min(f_{U,i}, f_{V,i}) \quad (1)$$

As can be seen in Fig. 2, PS increases for populations whose similarity for a given image descriptor increases.
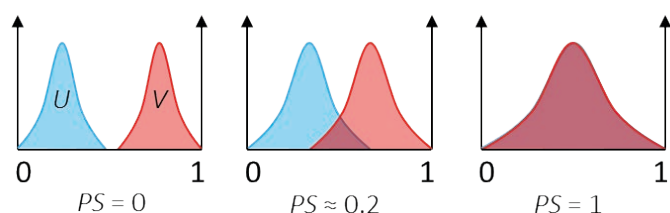
Figure 2: Schematic representation of the populations U and V for a given image descriptor and the resulting PS value.

For creation of a classifier, a set of manually classified objects (equal amount of single particles, agglomerates, and air bubbles) as well as a subset of variables is fed to the classification algorithm which tries to find the pattern within the data given. The accuracy is then tested using a separate test set of manually classified objects. To find a variable subset which results in a sufficiently high accuracy (> 0.9), the image descriptors were ranked according to their PS value from best to worst. Successively, the image descriptors were added to the algorithms:

DFA was used to generate a linear classifier and ANN was used for non-linear classification. For adipic acid, the results can be found below:

For the linear classifier (Figure 3a) at least eight image descriptors and a training set size of 180 objects in total are necessary to reach an accuracy of 0.9 while for the non-linear classifier (Figure 3b) only three image descriptors and a training set size of 90 objects in total are necessary.
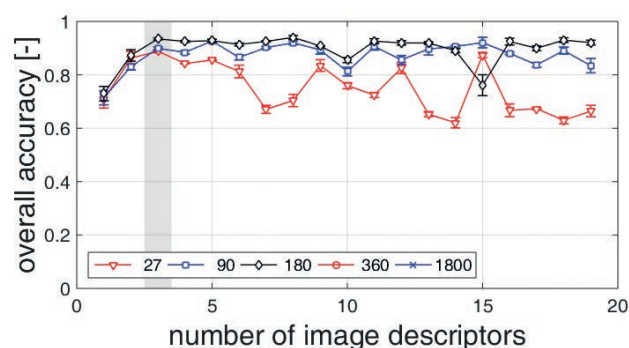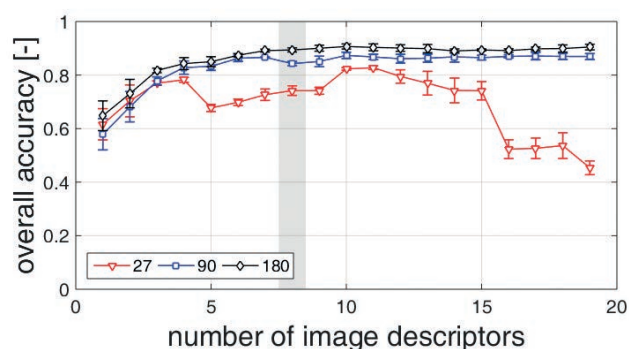
Figure 3a+b: Overall accuracies for the a) linear and b) non-linear classifier using training sets of different size.

In summary, the quantitative measure PS is capable of performing an easy-to-implement method for variable selection. Moreover, it was found that ANN is more accurate than DFA and needs less input in terms of manually classified objects and image descriptors, effectively simplifying the training process.

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Biomaterials and Polymer Science (BMP)

Ultrafast-Swelling, Superabsorbing, Antimicrobial Hydrogels

Cross-linked Ionomers towards interpenetration networks for long-term active antimicrobial coatings

Arne Strassburg, Christian Krumm, Monika Meuris, Joerg C. Tiller

Biocompatible materials with long lasting intrinsic antimicrobial properties are very important for modern medicine. Most antimicrobial materials, such as implants, catheters, and wound dressings contain biocides or antibiotics that are released into the surrounding and deplete eventually. Here, we report on a hydrogel material that is superior to previous coatings, because it can swell about 100 times faster than any other hydrogel and if converted into an interpenetrating polymer network (IPN) it shows antimicrobial properties that might last for a year.

A hemocompatible, antimicrobial 3,4-en-ionene (PBI) derived by polyaddition of trans-1,4-dibromo-2-butene and N,N,N´,N´-tetramethyl-1,3-propandiamine was cross-linked via its bromine end groups using tris(2-aminoethyl)amine to form a fast-swelling, antimicrobial super absorber. This super absorber is taking up the 30-fold of its weight in 60 s and the powder is taking up the 96-fold of its weight forming a hydrogel (Figure 1).
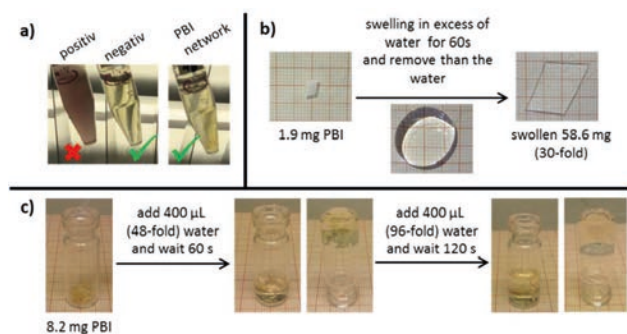
Figure 1: a) Photographs of 15 mL falcon tubes filled with 4 mL growth medium: left) inoculated with $2.5 \cdot 10^4$ *S. aureus* cells/mL incubated at 37 °C overnight, middle) incubated at 37 °C overnight without addition of bacterial cells, and right) 6 mg PBI network treated with 10 µl of *S. aureus* suspension in growth medium (10^7 *S. aureus* cells/mL) for 10 min added to growth medium, incubated at 37 °C overnight. The photographs were taken after 16 h incubation at 37°C and staining with TTC. b+c) Photographs of the rapid swelling of a PBI network film (b) and in small pieces cut PBIN (c) in water.

It fully prevents growth of the bacterium *Staphylococcus aureus*. The PBI network was swollen with 2-hydroxyethyl acrylate and glycoldimethacrylate followed by photopolymerization to form an interpenetrating hydrogel (IPH) with varying PBI content in the range of 2.0 to 7.8 wt %. The nanophasic structure of the IPH was confirmed by atomic force microscopy and transmission electron microscopy. The bacterial cells of the nosocomial strains *S. aureus (S.a.), Escherichia coli (E.c.)* and *Pseudomonas aeruginosa (P.a.)* are killed on the IPH even at the lowest PBI concentration (Figure 1a). The number of the adhered bacterial cells is reduced by the 10^4 to 10^6 – fold after only 30 min of incubation.

The IPHs show minor leaching of the PBI far below the MIC using a new quantitative test for PBI detection in solution. The leaching of PBI into the surrounding never reaches the MIC value of PBI, which is why the bacterial cells are only killed at the surface of the materials. Extrapolation of the determined PBI leaching rate over time suggests that the material is leaching a bacteria-toxic amount of PBI even after a year of washing.

The PBI leaching was shown to be not sufficient to form an inhibition zone and killing bacterial cells in the surroundings of the IPH (Figure 1b), suggesting a seemingly contact-active antimicrobial mechanism.
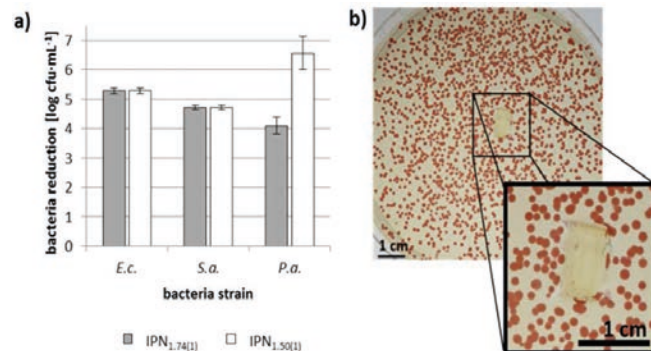
Figure 2: a) Reduction of bacterial cells on the surface of the in water-washed networks IPH$_{1.74(1)}$ (12 d at 37 °C) and IPH$_{1.50(1)}$ (27 d at 37 °C) after an incubation time of 3 h in PBS. b) Image *S. aureus* colonies formed after being sprayed on an agar plate with an embedded IPH$_{1.50(1)}$ network (washed for 7 days with water), incubated at 37 °C overnight and stained with TTC.

The materials were washed for 4 weeks and still showed full antimicrobial activity. Such a hydrogel coating is a promising material as wound dressing, e.g. for burns or infected wounds.

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Telechelic, Antimicrobial Hydrophilic Poly(ethylene imines)

Combination of two modes of action in one biocidal macromolecule

Lena Richter, Montasser Hijazi, Christian Krumm, Joerg C.Tiller

Since the development of antimicrobial agents, such as biocides and antibiotics, lifetime and the state of health have continuously improved especially in affluent societies. The rise of immune and multi-resistant bacterial strains currently threatens this state that might end up in a post antibiotic era. In order to push antimicrobial polymeric biocides to the next level, we have combined two different antimicrobial modes of action in a single molecule.

The characteristics of two different classes of biocidal polymers were combined in one macromolecule by hydrolyzing Gram-positive-selective telechelic poly(2-methyl-2-oxazolines) (PMOx) with quaternary ammonium end groups to the hydrophilic polycation poly(ethyleneimine) (PEI) (Figure 1). The structures of the different PMOx and PEI were proven by ^{1}H NMR spectroscopy. The antimicrobial activity of these conjugates was tested against the Gram-positive bacterial strains *Staphylococcus aureus* and *Streptococcus mutans* as well as the Gram-negative strains *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.
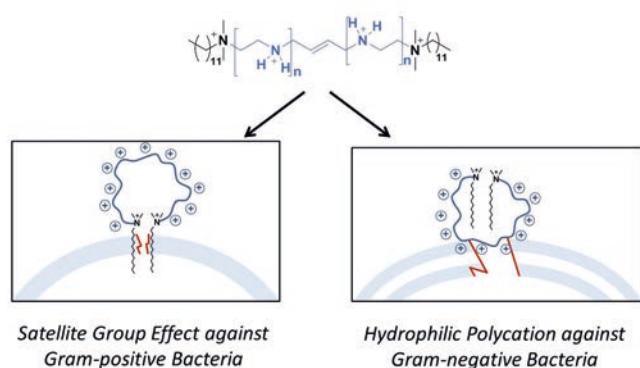
Figure 1: Modes of action of telechelic Poly(ethylene imine) against Gram-positive and Gram-negative bacterial strains.

By rendering the backbone of the telechelic PMOx to the hydrophilic polycation PEI, the antimicrobial activity against *E. coli* improved significantly from 2000 $\mu g \cdot mL^{-1}$ to some 40-160 $\mu g \cdot mL^{-1}$. The activity against the Gram-positive strain *S. aureus* also improved greatly with MIC values for the PEI of some 20-80 $\mu g \cdot mL^{-1}$ (Figure 2).
Since the characteristics of a telechelic biocidal polymer and a hydrophilic polycation are combined in one polymer, it was tested which mode of action dominates against the different bacterial strains. Since it is known to literature that PEI can be deactivated by Ca^{2+} ions, the MIC tests were repeated in the presence of 80 mM of $CaCl_2$.
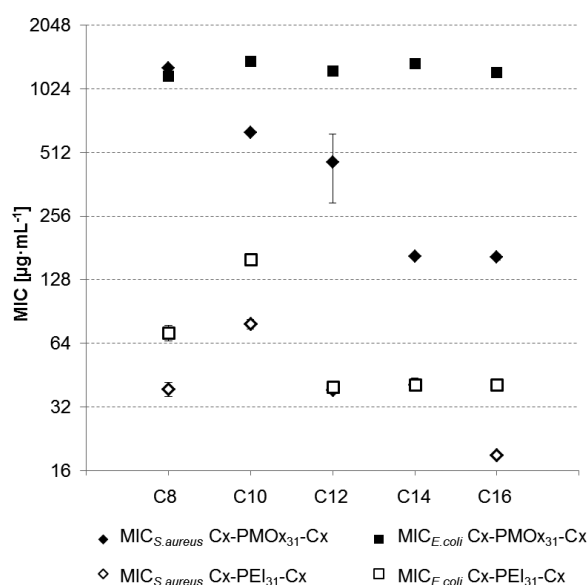
Figure 2: Antimicrobial activities (MIC) of end group functionalized Cx-PMOx30-Cx and Cx-PEI30-Cx against *S. aureus* and *E. coli* dependent on the length of the alkyl chain.

The activity of PEI with octyl and decyl carrying quaternary ammonium groups was deactivated against *E. coli*, while the PEI with longer alkyl chain end groups were less effected by Ca^{2+} ions. This shows that the backbone and the end groups act synergistically. In case of *S. aureus*, the polymers show no calcium-induced deactivation of PEI with longer alkyl chain end groups (C12-C16). This reveals that these telechelic PEIs indeed show a satellite group effect against this bacterial strain. PEIs with a higher molecular weight are dominated by the polycationic backbone. Thus, the polycationic backbone and the quaternary ammonium end groups act synergistically and the modes of action can be balanced by variation of the polymer chain length.

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Penicillin with a Polymer Tail for Combating Resistant Mechanism

Polymer Penicillin conjugates with high activity

Martin Schmidt, Christian Krumm, Joerg C.Tiller

According the World Health Organization antibiotic resistant bacterial strains are one of the greatest health threats to humankind in the 21st century. Today one of the most famous antibiotics, penicillin G is nearly useless because of distribution of resistant bacterial strains. In the most cases the resistant mechanism is based on penicillin hydrolyzing enzymes. Therefore, new methods of antibiotic design are strongly required to defeat bacterial resistance mechanisms. Here we covalently attached penicillin G to poly(2-methyl-2-oxazoline)s in order to achieve a higher stability against these Penicillin hydrolyzing enzymes. The polymer penicillin conjugates (PPC) are promising candidates for antibiotics with lower resistance potential.

The antibiotic penicillin G (PenG) was covalently attached to poly(2-methyl-2-oxazoline) (PMOx), poly(2-ethyl-2-oxazoline) (PEtOx) and poly(2-*iso*-propyl-2-oxazolin (P*i*PrOx) via direct termination of the living cationic polymer chain.

The different polymer antibiotic conjugates shown in Figure 1 were characterized by ^{1}H-NMR spectroscopy and electron spray ionization mass spectrometry.
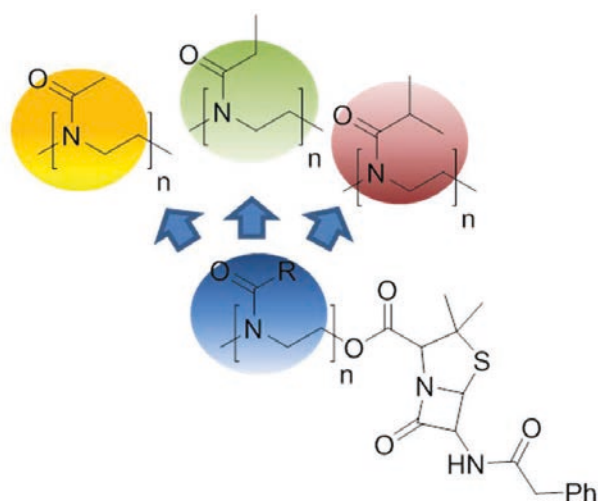
Figure 1: Chemical structure of polymer antibiotic conjugates.

The minimal inhibitory concentrations of these conjugates were determined against *Staphylococcus aureus (S. aureus).* As seen in Figure 2 (black bars), the activity of the different PPC is about 2 orders of magnitude lower than the free antibiotic. The MIC values of different poly(2-oxazoline) derivatives show that the most hydrophilic polymer PMOx affords the highest activity.

ß-lactam hydrolyzing enzymes are the most common bacterial resistance mechanism against penicillin. MIC values against *S. aureus* in presence of the enzyme were determined, accordingly. The results are shown in Figure 2 (white bars). The presence of the enzyme renders the antibiotic PenG inactive, while the respective PPCs are still exhibiting antimicrobial activity. The conjugates also lose their activity by 1 to 2 orders of magnitude in presence of the enzyme.

This indicates that the PPCs exhibit a 20-350-fold higher resistance against the enzyme compared to the free antibiotic.
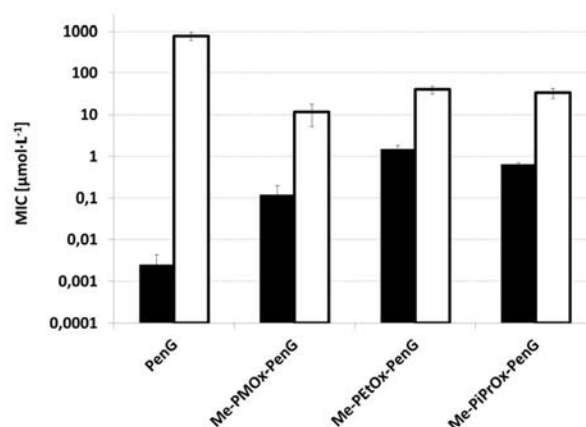
Figure 2: Molar MIC values for the different PPCs against *S. aureus* in comparison to the molar MIC value of PenG (white columns) full bars. The hatch bars present the MIC values of the PPCs and PenG against *S. aureus* in presence of a ß-lactam hydrolyzing enzyme. All measurements were performed in triplicate and the bars are the standard deviation.

The results show that the conjugation of penicillin with poly(2-oxazoline)s is a promising method of modifying these antibiotics, making them more stable against hydrolyzing enzymes.

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Entropically driven Polymeric Enzyme Inhibitors by End-Group Conjugation

A new generic concept for enzyme inhibitors

Montasser Hijazi, Christian Krumm, Joerg C.Tiller

Most pharmaceutically active compounds are enzyme inhibitors. These are typically binding at the active side of the respective biocatalyst. Non-competitive inhibitors do not bind at the active side and are therefore difficult to predict. Here, we present an unusual and new generic approach for the design of non-competitive enzyme inhibitors. To this end, poly(2-methyloxazoline)s are modified with specific not inhibitory functional end groups, which steer the polymers to the enzyme surface, resulting in non-competitive enzyme inhibition.

The concept for the novel enzyme inhibitors is based on a hydrophilic polymer that is driven onto the surface of an enzyme by a specific end group that is not an inhibitor by itself. The polymer is than collapsing on the protein changing the surface polarity, which inhibits the enzyme activity (Figure 1).

Figure 2: Left Inhibition of horseradish peroxidase (HRP) induced by mono- and bifunctional PMOx at varying concentrations (1.25, 2.5, 5, 7.5, 10, 12.5, and 15 mM). Right: Inhibition of HRP induced by 1 mM IDA-PMOx$_{33}$-IDA in different phosphate buffer concentrations. The inhibition was measured with ABTS substrate (10 mM) at pH 5.0 for all polymers.

Figure 1: Schematic representation of the proposed generic concept for enzyme inhibition based on specifically binding anchor groups attached to an inert hydrophilic polymer.

Poly(2-methyloxazoline) (PMOx) was chosen as hydrophilic and biocompatible polymer that has only weak interactions with proteins. 2, 2'-Imino diacetate (IDA) has the potential of binding to bivalent metals that are often found in protein scaffolds. Due to this fact, IDA was selected as specific end group. The enzyme horse radish peroxidase (HRP) was chosen as model enzyme, because it contains two calcium ions in the protein structure and is not inhibited by IDA.

The activity of HRP was investigated by the oxidation of [2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)] diammonium salt (ABTS) with H_2O_2 in the presence of different concentrations of IDA modified PMOx (Figure 2).

The results show that the activity of HRP is fully inhibited at concentrations between 7.5 to 15 mM IDA modified PMOx (see Fig. 2, left). The polymer was found to be a non-competitive inhibitor. Furthermore the binding affinity and thermo-dynamic parameters of interactions of HRP with IDA terminated PMOx was investigated using Isothermal Titration Calorimetry (ITC) measurements (see Fig. 2, right). The titration showed that the addition of the polymer to HRP results in endothermic reaction. This might be caused by attachment of polymer to the enzyme surface, resulting in aggregation which also was confirmed by NMR spectroscopy. This endothermic effect is caused by an entropy-driven release of polymer- and enzyme-bound water molecules.

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Biaxial Orientation upon Uniaxial Stretching

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The development of biaxially oriented polypropylene (BOPP) was one of the most significant improvements in film technology. Nearly 90% of all polypropylene films are biaxially oriented and offer reinforcement in machine as well as transversal direction. Since polymers usually must be stretched simultaneously or successively along perpendicular directions to gain biaxial orientations, biaxial reinforcement is limited to sample geometries with large surface to distance ratios, such as thin films. Here we present a novel route for realizing multiaxial orientations in isotactic polypropylene (iPP) that needs drawing only along one direction and is also applicable for bulky samples.

For realizing multiaxial orientations upon uniaxial stretching we followed the idea to exploit the homoepitaxy of iPP. In the latter polymer specimens self-assembled cross-hatched textures were found, which consist of two sets of lamellae placed at an angle of 100° to each other. This effect is commonly entitled as homoepitaxy. Thus, the homoepitaxial crystallization from the oriented melt might be an appropriate way in order to gain a multiaxial orientation. Unfortunately, there is only a slight increase of the tensile properties upon melt drawing, because entropically driven relaxation of the macromolecules cannot be avoided completely. For this reason we cross-linked iPP to a very low degree (x-iPP) to allow crystallization under constraint conditions, but retain the homoepitaxy. Figure 1 shows the wide angle X-ray scattering (WAXS) of x-iPP crystallized under a strain of 600%.
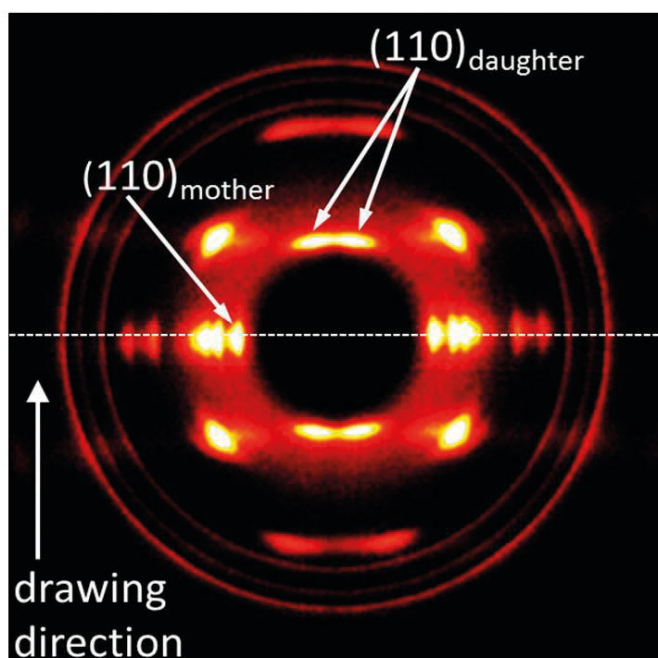
Figure 1: WAXS-pattern of x-iPP drawn to a strain of 600% with the annotation of the signals of the mother and daughter crystals.

The main orientation in drawing direction can be noticed by the crystal reflexes on the equatorial line (mother crystals), but there is also a significant amount of crystals oriented in an angle of 80° and 100°, which is contributed to the homoepitaxy (daughter crystals).

Finally, we investigated the impact of the obtained multiaxial crystal-orientations on the Young's modulus of the iPP-networks under different loading angles. The determined Young's moduli parallel, perpendicular and under 45° to the stretching direction, referred to as E(0°), E(90°), and E(45°), are displayed in Figure 2.
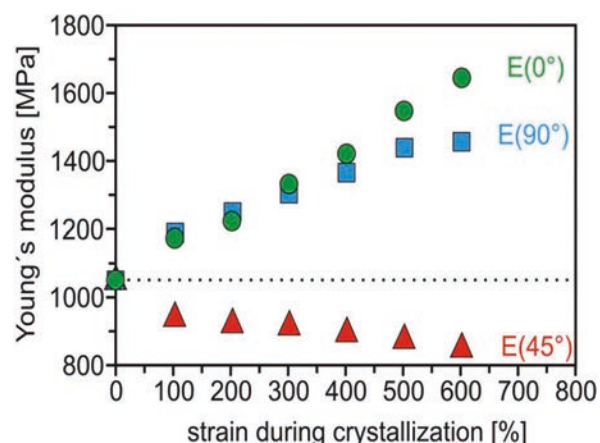
Figure 2: Young's modulus in dependence of the strain in drawing direction (0°), perpendicular (90°) and under an angle of 45°.

It is seen that the occurring multiaxial orientations cause significantly improved Young's moduli parallel (+60%) as well as perpendicular (+45%) to the stretching direction while that under an angle of 45° is slightly decreasing (−20%). Further, the multiaxial orientations and consequentially the Young's moduli can be adjusted within broad ranges by applying different strains during crystallization. In contrast to other techniques for multi or biaxial orienting iPP (e.g., BOPP) the here described method is not limited to thin films but can be efficiently applied also to bulky samples, because stretching is carried out in the molten state.

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Bioprocess Engineering (BPT)

In vitro Protein Synthesis for Biocatalyst Development

Jan Volmer, Lara J. Feliczak, Mattijs K. Julsing, Katrin Rosenthal, Stephan Lütz

In vitro protein synthesis is gene expression with the biological machinery without the use of cells. This cell-free method can be used to produce proteins in a very simple and rapid way. In vitro protein synthesis is especially advantageous in high-throughput applications to screen enzymes, e.g. derived from a gene library, in a short time and to study the influence of genetic modifications on protein activity, stability, substrate, and product specificity. The combination of in vitro *protein synthesis with other modern molecular biology tools such as genome/transcriptome sequencing and gene synthesis will definitely increase the speed of biocatalyst development in industrial biotechnology.*

The synthesis of proteins *in vitro* starting from DNA requires cell components such as ribosomes, enzymes, chaperones, amino acids, as well as energy sources (End et al., 2014). A defined composition of isolated, recombinant elements originating from the translation machinery of *Escherichia coli* turned out to result in the highest protein yields up to now (Kuruma und Ueda, 2015).

We used this protein synthesis system to synthesize a set of four homologous enzymes (cGAS) selected from genome sequences of different eukaryots. Fully synthetic genes were introduced in the *in vitro* protein synthesis system. Protein synthesis was confirmed by SDS–PAGE analyses.

We also investigated *in vitro* protein synthesis in order to rapidly compare the activity of different trans-proline-4-hydroxylases with respect to biocatalytic performance. Trans-proline-4-hydroxylases catalyze the conversion of L-proline into trans-4-hydroxy-L-proline, which is an interesting building block in pharmaceutical industry and is also used in cosmetic and food industry. The trans-proline-4-hydroxylase P4H1of (Falcioni et al., 2013), an engineered P4H1of (P4Hkahof), and the isoenzyme P4H2 were compared.

The enzymes were obtained in concentrations ranging from 0.30-0.59 mg mL^{-1} (Figure 1). The amount of synthesized P4H1of was two-fold higher compared to the mutant and isoenzyme, which shows that *in vitro* expression is dependent on the gene sequence as is also the case for *in vivo* systems.

However, the three enzymes all showed activity in a subsequently performed activity assay (Figure 2). We showed that synthesis of active enzymes was possible in only 4 h based on the presence of the gene as a DNA molecule. The subsequent enzymatic reaction was performed in 15.5 h, which means that results were obtained within 24 h. In comparison, classical *in vivo* protein production including the strain construction and protein isolation takes at least several days.

Figure 1: SDS-PAGE of *in vitro* synthesized proteins: M: marker, 1: reference reaction without DNA template, 2: P4Hkahof (29.7 kDa), 3: P4H2 (31.7 kDa), 4: P4H1of (31.7 kDa).
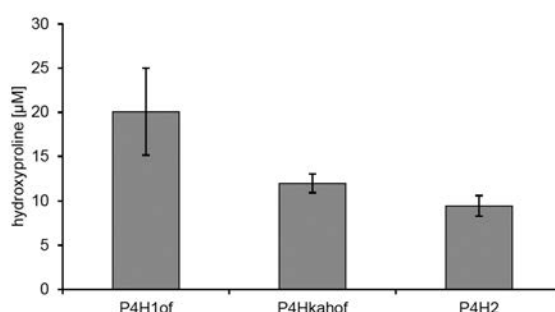
Figure 2: trans-4-hydroxy-L-proline concentrations after 15.5 h incubation with the *in vitro* synthesized trans-proline-4-hydroxylases P4H1of, P4Hkahof and P4H2 and 20 mM L-proline.

In conclusion, we showed the potential of *in vitro* protein synthesis as a tool for rapid production and screening of biocatalysts, which will definitely increase efficiency in biocatalyst development for biotechnological processes.

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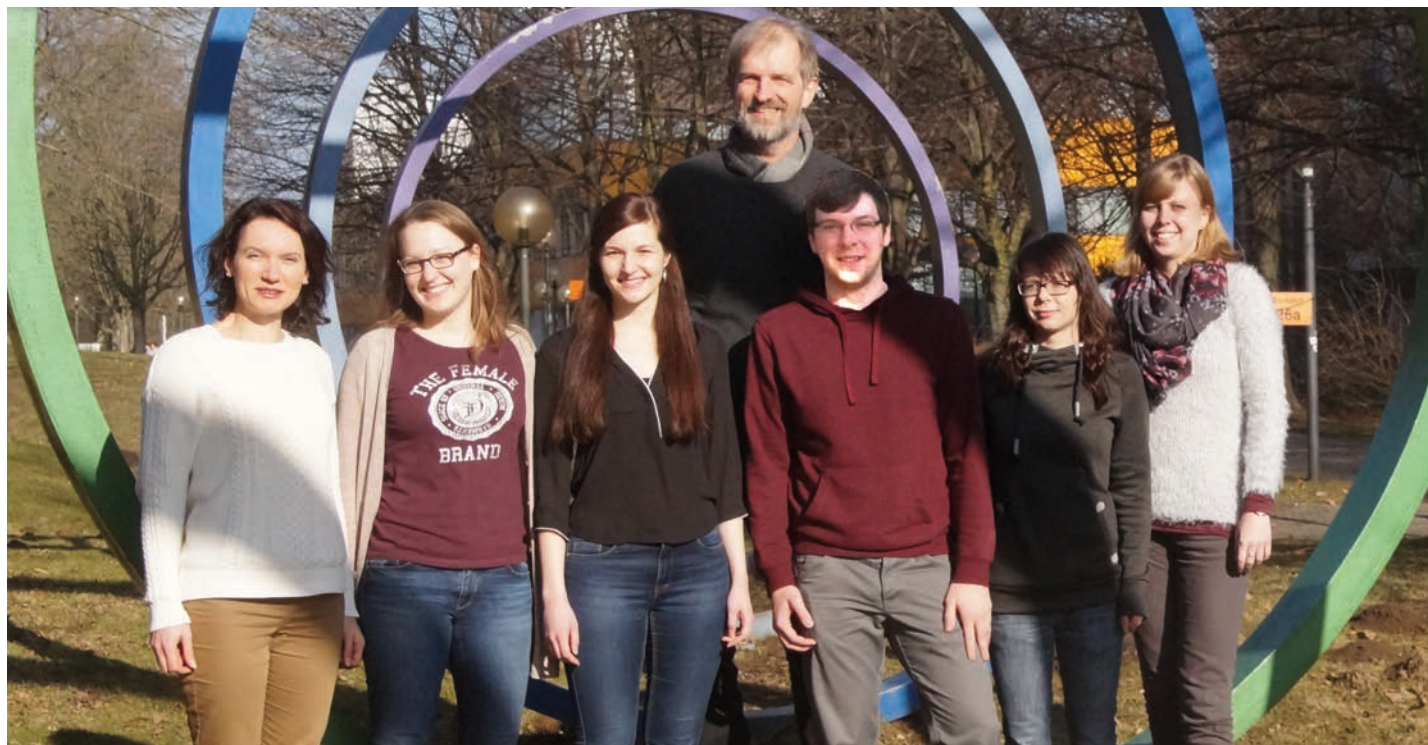
Biochemical Engineering (BVT)

Process Improvement of fermentative Fusicoccadiene Production

Lisa Halka, Rolf Wichmann

Fusicocca-2.10(14)-diene (FCdiene), a fusicoccane, is a tricyclic diterpene which has use in the pharmaceutical industry as a precursor of the anti-cancer drug Fusicoccin A. Chemical synthesis of this diterpene is not economical as it requires 14 steps, partial stereospecific ones. FCdiene is naturally produced at low titers in phytopathogenic, filamentous fungi. However, production of FCdiene can also be achieved via expression of the fusicoccadiene synthase in the yeast Saccharomyces cerevisiae.

Batch and fed-batch cultivations of FCdiene producing *Saccharomyces cerevisiae* abfs were done in shaking flasks and in a 3.1 L KLF 2000 fermenter using a synthetic dropout medium and glucose as sole carbon source. In batch mode two main adjusting screws for the synthesis of FCdiene were identified, pH and DOT.

Figure 1: Lab-scale fermenter.

The results of several cultivations in shaking flask scale indicate that regulating pH while using glucose as sole carbon source decreases FCdiene productivity up to 70 % in comparison to unbuffered fermentations. Buffered cultivations using the KLF 2000 fermenter resulted in lower FCdiene concentrations as well. The results of this investigation indicate higher FCdiene yields with unregulated pH regardless of any buffering system. Additional uncontrolled pH shifts during cultivation may also be advantageous because of decreased risk of culture contamination at low pH (nearly 2.5).

In unbuffered cultivations with changed amino acid concentrations to avoid predicted limitations, FCdiene concentrations up to 270 mg/L were reached and more than 10X greater yields than previously achieved with this strain.

No solubility limit for FCdiene is currently known. At the moment it is unclear if the concentration of FCdiene in culture media surpasses the solubility limit, or whether free fatty acids and other extracellular metabolites contribute to its solubility. No flocculent or second phase was apparent during fermentation and harvesting.

The influence of DOT on glucose cultivations was determined in stirred tank batch fermentations at different stirring frequencies. The highest FCdiene concentration was not found at the highest stirring rate but at values where microaerobic conditions slightly above 0 % DOT were maintained throughout the fermentation.

Microaerobic conditions seem to be the preferred condition for FCdiene production from *S. cerevisiae*, although the exact reason is not readily apparent. It is possible that the terpenoid metabolism in the yeast *S. cerevisiae* is influenced by the microaerobic conditions, or the conditions are favorable for the FCdiene secretion.

But as widely known the crabtree effect occurs in these fermentations, thus a fed-batch fermentation mode with *S. cerevisiae* using glucose as a carbon source has been developed. The aim was an exponential feeding profile which avoids overfeeding of the used yeast culture and increases growth and production. Therefore, an iterative development of a feeding profile was carried out. The cell concentration was increased up to 246 % in comparison to the batch fermentations and the FCdiene concentration increased up to 2.8X within the first 28 h and increased further while extending the fermentation time of the fed-batch fermentation. The production of FCdiene in *S. cerevisiae* did not correlate with growth of the yeast.

The results of these studies indicate there is a potential for economical fed-batch fermentation processes for FCdiene production using this genetically modified *S. cerevisiae*. Yields presented here illustrate 3X improvement over former studies and concentrations show more stable values as batch fermentations. The new feed strategy of glucose would appear to present benefit of favorable terpene production from *S. cerevisiae*.

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Foam Adsorption as a new Generation unit Operation for recovery of Amphiphilic Compounds

Intensification of fermentative production of rhamnolipids by integration of upstream and downstream process

Iva Anic, Arijit Nath, Pedro Franco, Ines Apolonia, Rolf Wichmann

In order to limit the formation of foam during fermentation processes antifoam agents are often added to the fermentation medium. Their separation from the product results in increase of downstream process costs. This issue in downstream processing can be solved with an innovative product capture method called "foam adsorption". The focus of our research is on the development and utilization of this new separation method which is based on the integration of the upstream and the downstream process.

Rhamnolipids (RLs) containing foam is created in the fermentor during aerated fermentation. Instead of suppressing the foam formation, foam is led by the air flow into the adsorption column attached to the gas exhaust line of the fermentor. Due to hydrophobic-hydrophobic interaction between the amphiphilic RLs and hydrophobic adsorbent, the RLs stay adsorbed in the column so that the resulting liquid phase can be recycled back into the fermenter, while the off gas is released out of the system.

Figure 2: Experimental setup of automated adsorption unit: adsorption and desorption process was automatically operated during the fed-batch fermentation.

A fed-batch process for the production of rhamnolipids by *Pseudomonas putida* KT2440 was performed for 60 hours. 95 % of the product was captured in the adsorption columns. Product recovery of 85 % and a purity of 96 % were determined.

Foam adsorption can be integrated in fermentation processes where an amphiphilic product is produced continuously, which has inhibitory effects on the producing cells, or is unstable in the fermentation broth; whereby the product itself is stabilized and enriched in the foam phase.

Figure 1: Schematic representation of the RLs separation principle using the foam adsorption method.

For this purpose five pre-selected, commercially available adsorbents were screened and rated regarding the adsorption capacity and product recovery. High concentration of the amphiphilic compound in the liquid lamella of the foam is favorable, so the adsorption capacity of the selected adsorbent was utilized extremely well with 0.38 g per g adsorbent.

An automated adsorption unit was designed to perform fed-batch experiments on lab-scale. It consists of two adsorption columns packed with C18 modified silica adsorbent operated in parallel during the fermentative production of RLs. Once the maximum capacity of the adsorbent is reached the adsorption column is washed with water and the product is eluted with ethanol.

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Chemical Reaction Engineering (CVT)

Flexible Adjustment of liquid-liquid slug length in Micro-Channels

Linda Arsenjuk, Moritz Asshoff, David W. Agar

The slug length of liquid-liquid flow in micro-capillary reactors has a decisive influence on mass transfer and thus reactor performance. As it depends 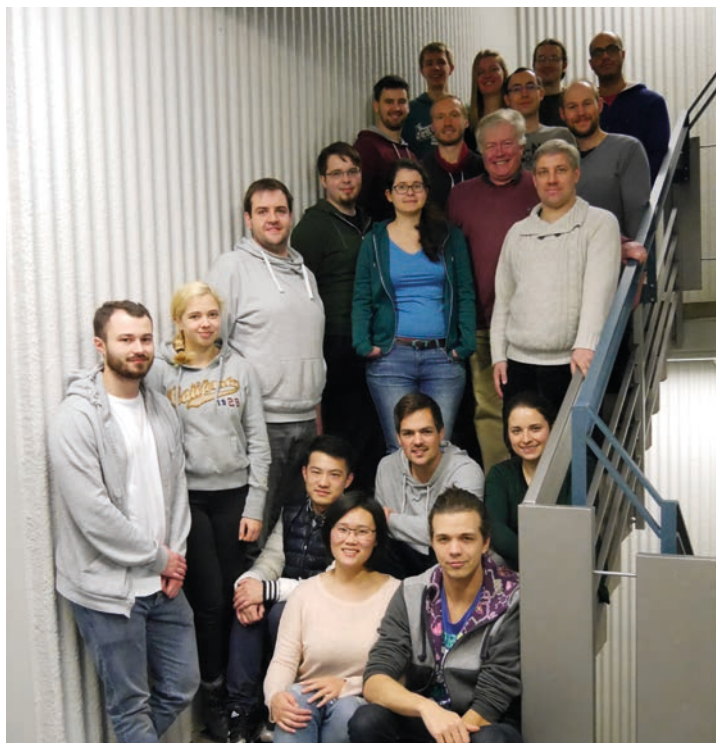on material properties and fluid velocities, it used to be more of a system characteristic, than a controllable variable. A slug generator with variable mixing point geometry is presented which enables stable and reproducible adjustment of slug size, independent of material and system properties.

The implementation of multi-phase reactions in micro-fluidic devices offers a promising approach for process intensification. Short diffusion paths and large surface to volume ratios enhance heat and mass transfer, while low hold-up and system inertia make processes safer and easier to handle.

If two immiscible liquids are contacted in a micro-channel, a flow regime called slug flow occurs under certain conditions. It is characterized by periodically alternating segments of fluid, called slugs. Flow conditions in liquid-liquid slug flow further increase mass transfer through vortex structures in the fluid segments, while axial dispersion is reduced, providing a defined and narrow residence time distribution (Figure 1).
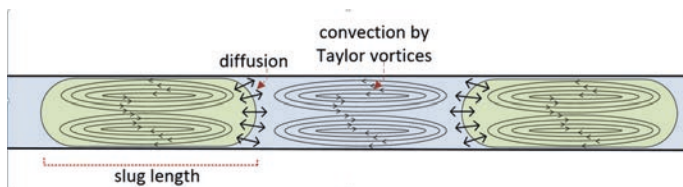
Figure 1: Schematic of liquid-liquid slug flow in a micro-channel.

The resulting slug length is dependent on flow rate, phase ratio and material properties, as well as the geometry of the mixing point of the phases. As it defines the phase interface and impacts the structures of the internal vortices, it has a decisive influence on mass transfer. It is thus desirable to decouple resulting slug lengths from material system and flow conditions, to allow independent adjustment, to a value optimal for the respective application.

For this purpose a slug generator with adjustable mixing point geometry has been designed (Figure 2). The disperse phase is supplied through a concentric metal capillary with a tapered head, while the continuous phase flows coaxially along the outer cylinder. The phases concur in a conical mixing point.
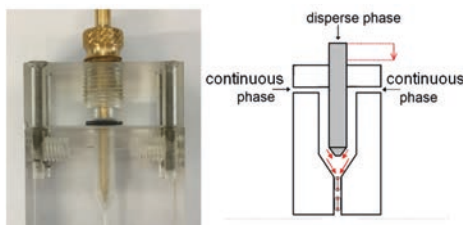
Figure 2: Slug generator with adjustable mixing point geometry and schematic thereof.

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By increasing the insertion depth of the disperse inlet, the volume of the mixing chamber decreases. This reduces the available volume for slug generation and consequently slug size.
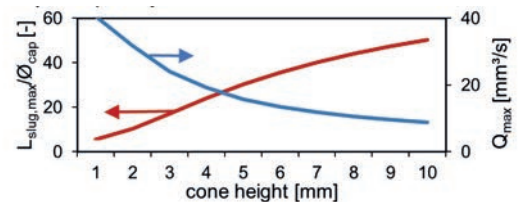
Figure 3: CFD simulated dependence of maximal flow rate Q_{max} and maximal achievable slug length $L_{slug,max}/\varnothing_{cap}$ on height of mixing cone.

With aid of CFD simulations, an operating region of the generator has been identified, where the droplet detachment process is governed by surface forces and thus predominantly dependent on size of the mixing chamber. Boundaries of the operation region, maximum flowrate and maximum achievable slug length, are dependent on the inclination of mixing chamber and thus height of the cone (Figure 3).

Simulated results were confirmed experimentally, for the material systems Kerosene/Water and Dodecan/Water. Stable, adjustable slug generation, with minor influence of material system or flow rate, but strong dependence on mixing point volume was achieved, with $\sigma_{max}<0,17$mm (Figure 4).

The developed slug generator successfully decouples slug length from other material and system influences and thus makes another important reactor parameter accessible for optimization.
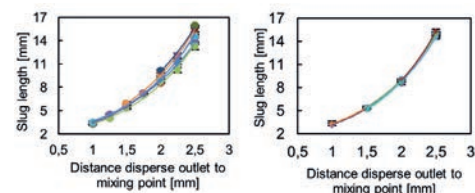
Figure 4: Experimental slug length resulting at different settings of slug generator, velocities ranging from 0.5-14mm/s, left: Kerosene/Water, right: Dodecan/Water.

Selective Partial Oxidation of Hydrogen Sulfide via BrOx Cycle

Maximilian Wiesehahn, Mahsa Moghaddam, Thomas Kembügler, David W. Agar

The research on the bromination-oxidation (BrOx) cycle at the chair of chemical reaction engineering has been applied to hydrogen sulfide (H_2S) among other reactants. The utilization of bromine instead of oxygen to oxidize hydrogen sulfide is preferred in order to avoid the formation of corrosive and toxic sulfur dioxide (SO_2). Instead solid sulfur is formed, which is much easier to handle and the bromine is retrieved in a subsequent oxidation step. As long as the bromine recovery is complete and the formation of brominated side-products is avoided, the BrOx cycle has the potential to be applied for the desulfurization of sour gas.

Typically the neutralization of hydrogen sulfide from natural gas or oil is carried out within a Claus plant, where the highly toxic and corrosive gas is converted into sulfur. Because of the environmental problems, which H_2S would cause, the desulfurization is mandatory. However, multiple plant units are required to ensure complete H_2S conversion and sometimes additional tail gas treatment is necessary. Although the Claus process is well established in today's large scale industrial production, there is still a lot of research going on in this field and the investigation of alternative processes can prove beneficial.

The BrOx cycle is a novel way for removing hydrogen sulfide completely in two exothermic reaction steps. First H_2S is oxidized by bromine and the formed sulfur can be separated off. The second reaction, the oxidation of HBr serves for the regeneration of bromine, thus closing the cycle. Overall, the process generates energy with the products being sulfur and water.
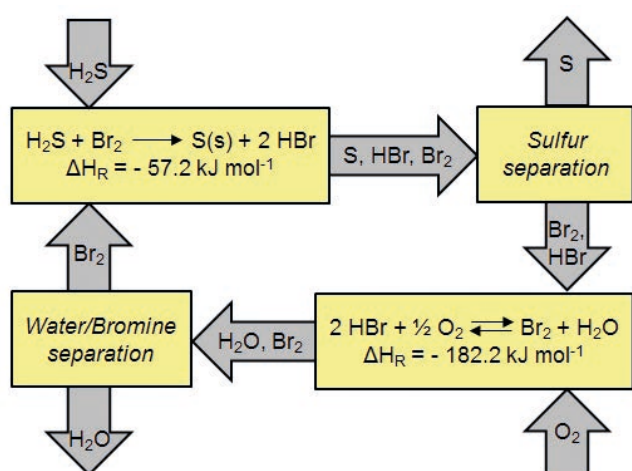
Figure 1: Schematic representation of the BrOx cycle.

The proof-of-principle for the H_2S bromination was provided in a testing plant by reaching HBr yields of up to 77 % at 450 °C. The prospective aim is to reach maximum H_2S conversions by using slight excesses of bromine.

During the H_2S bromination there is also the possibility of the formation of brominated sulfur by-products, like S_2Br_2. Not only would this compound contaminate the sulfur but remove some bromine from the cycle as well, which would make an external feed of bromine a necessity. Because of this, the produced sulfur has been analyzed via EDX on its bromine content with a result of it containing 1 At.-% of bromine at maximum with none of that being chemically bound. Furthermore investigations regarding S_2Br_2 formation and decomposition indicated, that at temperatures above 150 °C - which is far below the reaction temperature - the presence of brominated sulfur species is negligible.

The second reaction, the oxidation of HBr, is strongly exothermic and has negative Gibbs free energy up to very high temperatures, which indicates that the equilibrium conversion will diminish with an increase in temperature (Figure 2). The oxidation can be carried out uncatalyzed at high temperatures or in presence of a catalyst. Experimentally, HBr conversions up to 90 % have been reached in the thermal stage at 830 °C and up to 93 % in a reactor with RuO_2 catalyst at 315 °C. Since thermal and catalytic oxidation are complementing each other, the proposal is to combine those methods and run the thermal process, followed by catalyzed oxidation to reach maximum conversion.
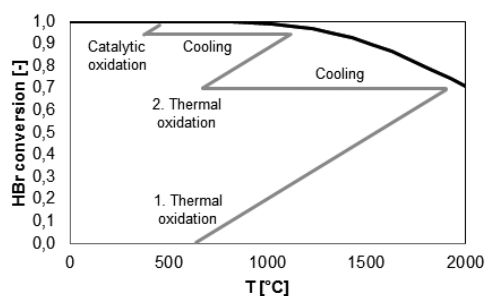
Figure 2: Proposal for a multistage oxidation of HBr.

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Theoretical and Experimental Studies on Reactors for the high Temperature Methane Pyrolysis

Finding new ways to produce hydrogen and energy from fossil fuels without CO_2 emissions

Alejandro A. Munera Parra, I. Schultz, David W. Agar

The question of how clean energy can be provided to an ever increasing population becomes more urgent every year. Last year, theoretical studies on an industrial reactor and experimental work on a novel reactor for the pyrolysis of methane were carried out. The theoretical work focused on the occurrence of multiplicities in moving bed reactors, while the experimental work further developed the concept of a molten metal capillary reactor.

The pyrolysis of methane:

$$CH_4 \rightarrow C(s) + 2H_2, \quad \Delta H^0 = 75.6\ kJ/mol$$
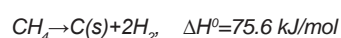
can be carried out in an industrial scale in a moving bed reactor. In order to maximise the heat recovery, a heat integrated moving bed reactor is proposed as shown in Figure 1a with the corresponding simulated temperature and conversion profiles in Figure 1b. Although not extensively known, multiple steady states can occur in moving bed reactors, using continuation methods, these multiplicity regions can be mapped for different parameters in this case, the region for solid to gas flow ratio and inlet temperature is exemplified in Figure 1c.

In addition it can be proved that the multiplicity phenomenon pertains not only to exothermic reactions as most commonly found in the literature but that for endothermic reactions, depending on the way that heat is added to the reactor, multiple steady states can occur due to the interaction between the non-linear heat consumption, the non-linear heat input and the heat feedback due to the countercurrent flow.

This mapping of the regions helps to determine constraints where the reactor should not be operated and helping gain insight in the behaviour of the system.
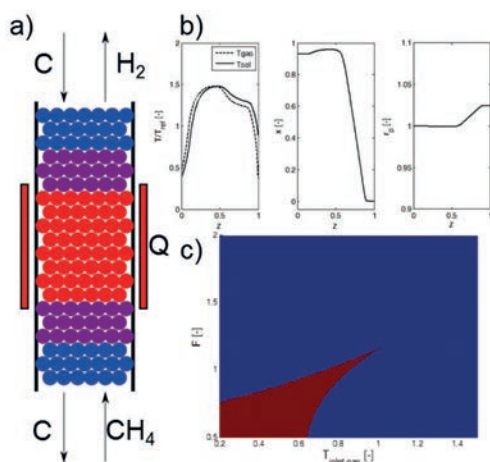
Figure 1: a) Heat integrated moving bed reactor. b) Concentration, particle size and temperature profiles alongside the reactor. c) Region of multiplicities for a standard moving bed reactor.

Figure 2: Top: Carbon deposition in the capillary reactor. Bottom left: slug-flow regime. Bottom right: Galinstan drop at room temperature

The two main hurdles found when carrying out the pyrolysis of methane, are the carbon formation and the need to introduce heat at higher temperatures. The use of liquid media such as molten metals has been used to circumvent both these problems in an elegant way, on the one hand, the liquid media acts as a barrier preventing the carbon deposition at the heat transfer area, as well as a heat transfer medium due to its excellent transport properties. A molten metal capillary reactor operated in slug flow regime (Figure 2b), offers besides the good transfer properties and the formation of a protective film with surface renewal, a sharper residence time distribution in comparison with other reactors found in the literature such as bubble columns. However, operation with pure Tin has shown that carbon deposition (Figure 1a) still occurs when the high temperatures (1200-1300 °C) needed to obtain full conversion are reached. The use of alloys with better wetting properties such as Galinstan (Gallium, Indium, and Tin eutectic) is being studied. In addition Galinstan remains liquid at room temperature as seen in Figure 2c, facilitating its use and allowing trying different pumpless scenarios to feed the reactor.

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Process Dynamics and Operations (DYN)

Application of Iterative Real-time Optimization in an Industrial Pilot Plant

The optimal operating point of a lithiation process in a containerized pilot plant is determined in real-time in the presence of process noise and significant plant-model mismatch

Anwesh Reddy Gottu Mukkula, Sebastian Engell

A lithiation process – a key organic synthesis step – which is performed in an intensified tubular reactor in a con-tainerized pilot plant at INVITE in Leverkusen is optimized using modifier adaptation with quadratic approximation (MAWQA), a state-of-the-art real time optimization (RTO) algorithm developed at TU Dortmund. The iterative model and measurement based optimization scheme drives the process to the plant optimum which is different from the optimum which is obtained from the process model.

It is of great interest to identify the optimal point of a plant and to operate it at this point. Usually, the optimal operating point of a plant is identified by solving a model-based optimization problem. Developing an accurate mathematical model and estimating its parameters require a large amount of time and effort. Sometimes it may not be possible at all to develop an accurate model due to the complex phenomena that take place in the plant.

Modifier adaptation with quadratic approximation (MAWQA) is an iterative optimization scheme which uses the plant measurements to drive the plant to its true optimum in spite of having a plant-model mismatch. In MAWQA, the iterative gradient-modification optimization (IGMO) method is combined with a derivative free optimization (DFO) method to estimate the plant gradients along with an additional surrogate model.

The process under consideration is a lithiation reaction that takes place in a tubular reactor. The reaction mechanism and its kinetic parameters are not precisely known. The overall reaction is depicted in Figure 1.
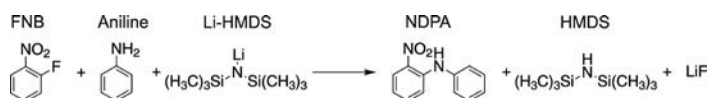
Figure 1: Overall lithiation reaction scheme.

Due to the unavailability of the complete reaction infor-mation, the mathematical model of the process is in-complete and does not represent the behavior of the plant accurately.

The aim of the controller is to operate the process at its economically optimal operating point using the concen-tration measurements from a novel online NMR device that was developed by BAM, Berlin. A challenge for the use of iterative optimization in this process and similar ones is the presence of long measurement delays due to the long piping and the low flow rates between the reactor and the measurement system. Two improved variants of the scheme were proposed to overcome the problems that are caused by the measurement delays by proactive probing of the plant [1, 2].

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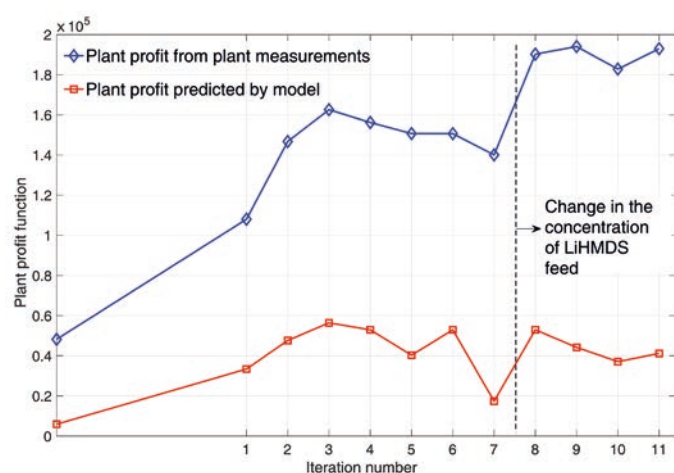
Figure 2: Plant cost over MAWQA iterations in the validation experiment performed at the pilot plant in INVITE, Leverkusen.

Results from experiments:

The evolution of the plant profit during the iterative optimization using the NMR measurements by the MAWQA iterations is shown in Figure 2. The blue line indicates the real plant profit as computed from the measurements whereas red line represents the plant profit as computed from the nominal model which has both structural and parametric plant-model mismatch. After an unknown change of the feed concentration of Li-HMDS, the algorithm improved the plant profit (blue line) significantly. In contrast the plant profit function that was predicted by the model drops as a fixed value for the feed concentration is assumed.

In summary, it was validated that the combination of the NMR measurement with the iterative optimization algorithm MAWQA could drive the plant to an optimal operation despite significant deviations between the plant model and the true plant behavior. MAWQA reacted quickly to changes in the process conditions and responded by making input moves to identify the true process optimum.

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Real-time Optimization of Chemical Processes under Uncertainty - Proof of Concept in a Miniplant

A reliable RTO scheme that can cope with plant-model mismatch has been developed and was applied to the hydroformylation of long-chain olefins in a continuously operated miniplant

Reinaldo Hernández, Sebastian Engell

Real-time Optimization (RTO) is a tool to improve the performance of chemical plants by a model-based optimization of the stationary operating point of the plant. A critical issue in RTO is the quality of the model. The DYN group has developed methods and algorithms to cope with model imperfections in RTO. Here, the application of a recently developed iterative RTO scheme to a homogeneously catalyzed process in a miniplant is described.

The goal of RTO is to optimize the performance of a production process while satisfying environmental, safety, quality and equipment-related constraints. A major challenge in RTO is plant-model mismatch. As a result of using an inaccurate model, suboptimal operation and constraint violations may occur. This is particularly relevant in the case of processes for the production of speciality chemicals where uncertainties related to thermodynamic parameters, reaction kinetics and catalyst activity limit the applicability of model-based optimization.

During the last years, the DYN group has tackled the problem of RTO under plant-model mismatch based on the iterative correction of the nominal optimization problem on the basis of plant measurements in the so-called modifier adaptation (MA) scheme. MA was improved by fitting local quadratic models to the measurements to estimate the plant gradient. Until now, the benefits of modifier adaptation were for the most part demonstrated in simulation studies. Only few published works deal with simple real processes.

In order to validate the potential of iterative real-time optimization based on modifier adaptation, we have applied it to the rhodium catalyzed hydroformylation of 1-dodecene in a thermomorphic solvent system in a miniplant. It makes use of transition metal complex catalysis which is considered as a key technology in green chemistry due to the high activity and selectivity at mild reaction conditions. The processing of this substrate poses similar challenges as the processing of oleochemicals. Hydroformylation is a model reaction due to its similarities to other transition metal catalyzed processes such as hydrocarbonylation, hydroesterification, amination, etc.

For the application, we have developed a reliable iterative Real-time Optimization scheme which is able to also handle measurement noise by integrating methods for automatic steady state identification and robust data reconciliation (see Figure 1). Simulations studies showed that the iterative

optimization is able to drive the plant to optimality despite the presence of model inaccuracies related to catalyst activity, mass transfer, and kinetic parameters. In collaboration with the Technical Chemistry Group, the scheme was implemented in the continuously operated miniplant for the hydroformylation of 1-dodecene.
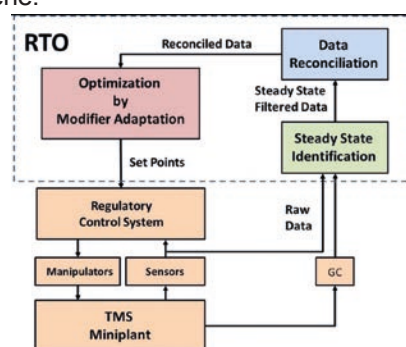
Figure 1: Implementation of the RTO scheme at the miniplant.

Figure 2 shows the yield of the target product (tridecanal) before and after the application of the proposed scheme. First, the optimal conditions that were computed based upon the process model were implemented and then the iterative Real-time Optimization algorithm was started. As it can be seen, a significant improvement of the performance of the process beyond the predictions of the nominal model could be realized. The modifier adaptation with quadratic approximation (MAWQA) scheme is a generally applicable tool to improve process performance even when no accurate process model is available.

Figure 2: Yield of tridecanal in the continuously operated miniplant.

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Economics Optimizing Control of a Pilot-Scale Reactive Distillation Process

Improving the economic performance of a complex chemical process with several degrees of freedom by means of nonlinear model predictive control using economically motivated objectives

Daniel Haßkerl, Clemens Lindscheid, Steven Markert, Sebastian Engell

Dynamic Real-time Optimization (D-RTO) combines nonlinear model predictive control (NMPC) with economic objectives to improve the profitability of chemical processes. Such control strategies have been discussed intensely in the scientific literature, but their application to real processes so far has been limited. We have successfully applied this approach to a very complex real pilot-scale process that is described by a large DAE model. In the past, to use such complex models for online optimization was not feasible, but recently developed computational methods can overcome these limitations. In cooperation with the Chair of Fluid Separations, the successful application of economics optimizing control at a pilot-scale reactive distillation process that realizes the synthesis of ethyl methyl carbonate and of diethyl carbonate in a two-step transesterification reaction could be demonstrated.

Optimizing the plant economics in real-time (RTO) has become an established technique to improve the profitability of large chemical production plants. RTO performs a stationary optimization, the optimal set-points of the process are then implemented by conventional or MPC controllers. A new approach is to combine these two techniques into Dynamic Real-Time Optimization where an economically motivated cost function is optimized over a finite look-ahead horizon based on dynamic process models. To facilitate the development and application of D-RTO schemes, the software platform *do-mpc* [1] was developed in the *dyn* group. *do-mpc* employs efficient solvers and novel methods such as automatic differentiation and efficient line search algorithms. It can be used for simulation studies but also be coupled to real processes. The methods of *do-mpc* were developed further and transferred to a real-time environment that is based on multi-threading so that the state estimation and the optimization algorithm can run in parallel.

The transesterification process to which the D-RTO algorithm was applied can produce two products, ethyl methyl carbonate and diethyl carbonate, depending on the choice of the operating parameters. The process was modelled and studied experimentally in the dissertation of [2]. The so-called EQ-kin model developed in his work provided the basis for the online optimization and state estimation. The instrumentation and automation of the pilot-scale column was improved and online analytics using near-infrared spectroscopy were installed to provide information on the concentrations in the streams leaving the column.

Figure 2: Schematic of the real-time environment and its connection to the pilot-scale plant; threads indicated by arcs.

The model that is used in the controller has approx. 500 dynamic and algebraic state variables that are estimated online from 19 measurements which are available at different sampling rates. The control task is to meet a certain purity of one of t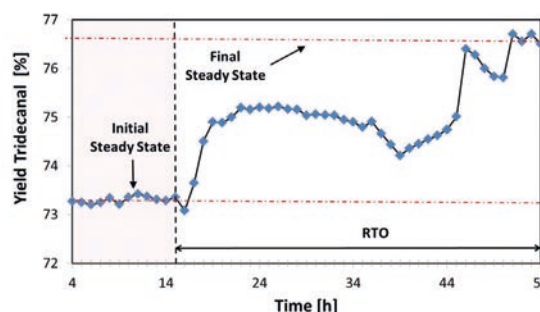he valuable products while maximizing the profit and respecting further process constraints. The optimizing control algorithm steers the plant to its economic optimum and also the product changeover from the production of diethyl carbonate to ethyl methyl carbonate is performed in the most profitable way.
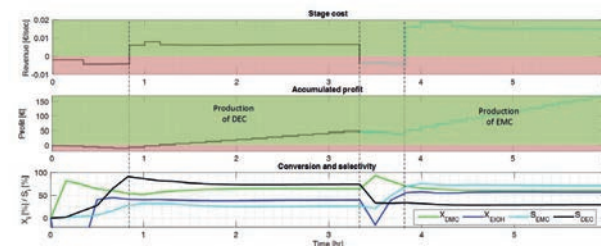
Figure 3: Process variables during the transient changeover from the production of DEC to the production of EMC.

Figure 1: Real-time state estimation (dashed lines: estimated profile, dots: GC measurements); left: initial profile, right: profile after 1 h.

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Solids Process Engineering (FSV)

Scaling Strategies for Twin Screw Extrusion

Preserving the Residence Time Distribution as Crucial Process Parameter

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Hot Melt Extrusion (HME) in a co-rotating Twin Screw Extruder is an established pharmaceutical application. Main advantage next to a continuous processing is the combination of different unit operations within one apparatus. A parameter reflecting all appearing mechanisms is the Residence Time Distribution (RTD). The aim of this study was therefore to identify suitable approaches to maintain the RTD during scaling of HME processes.

Usually a scaling of an extrusion process is performed for geometrically similar machines in order to isolate the process parameters as crucial variables. The typically applied scale-up concepts for HME focus on a constant specific feed load SFL or total specific mechanical energy input SME_{total}. The volumetric approach assumes a constant fill level expressed by the specific feed load SFL as beneficial, which depends on the mass flow $\dot{m}$, material density ρ and the barrel diameter D, while the screw speed n is kept constant for different scales of machine 1 and machine 2.

$$SFL = \frac{\dot{m}}{\rho\, n\, D^3} \xrightarrow{n_1 = n_2} \frac{\dot{m}_1}{\rho_1\, D_1^{\ 3}} = \frac{\dot{m}_2}{\rho_2\, D_2^{\ 3}} \qquad (1)$$

The SME_{total} is the main objective for the energy input approach and is expressed by the torque τ, screw speed n and mass flow $\dot{m}$ of the material. The torque cannot be adjusted independently from the screw speed and mass flow. Typically the screw speed is kept constant.

$$SME_{total} = \frac{\tau\, n}{\dot{m}} \Rightarrow \frac{\tau_1\, n_1}{\dot{m}_1} = \frac{\tau_2\, n_2}{\dot{m}_2} \qquad (2)$$

However, the applied energy can be differentiated in consumed energy for material transport ($SME_{pumping}$), shearing (SME_{shear}) and for the base load (SME_{empty}).

The recently developed balanced energy input approach within this study focuses on the ratio between applied energy for shearing respectively mixing to transport.

$$SME_{balance} = \frac{SME_{shear}}{SME_{total} - SME_{empty}} \qquad (3)$$

Experiments were carried out on co-rotating twin screw extruders (reference: 27 GL; scale down: ZSE 18 HPe) from Leistritz (Nuremberg, Germany) with a L/D of 20 for the processing section. The RTD was measured in-line with an UV/Vis spectroscope (InSpectro X, ColVisTec AG, Berlin, Germany) in transmission and analyzed at a wavelength of 330 nm. A model system containing 95 w% polyvinylpyrrolidone vinylacetate (Plasdone S-630, Ashland, Germany) as polymer and 5 w% theophylline-anhydrat (Fagron, Netherlands) as active pharmaceutical ingredient (API) was used. quinine-dihydrochlorid (Caesar & Loretz, Germany) served as marker for the RTD determination. A

reference point for the evaluation of the scaling concepts was determined by an independent optimization scheme (IOS). The approaches were applied based on the reference point as well as the IOS for the scale down and the RTD measured (Figure 1).
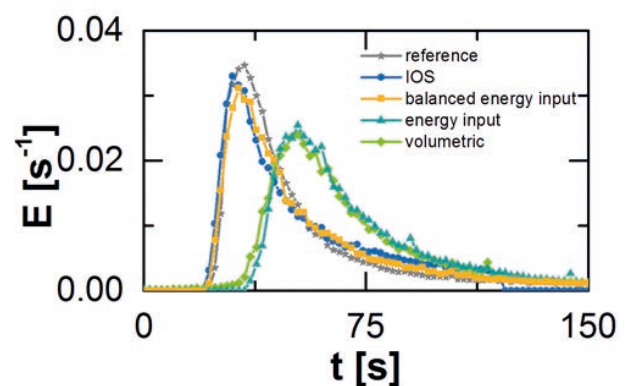
Figure 1: Determined RTDs of scaled and optimized extrusion processes in comparison to the reference for one repetition.

The RTDs are presented by the residence time density function E. This type of function can be compared directly since the overall integral is one by definition. The reference process (circular symbols) is linked to a typical RTD for an extrusion process. The applied approaches can be classified according to the obtained results in two groups. The IOS as well as the balanced energy input approach are suitable to preserve the RTD of the pre-defined reference, while volumetric and energy input approach are not. For these the location of the on-set, peak and off-set of the curve are all shifted to higher values. Basically a second operating point regarding the RTD is observed. Here the overall exposure time to thermal and mechanical stress is enlarged. This might lead to enhanced degradation.

In conclusion, the developed balanced energy approach as well as an independent optimization scheme for extrusion processes have been found suitable to preserve the RTD of HME during scale up. These concepts and the reference have in common a comparable ratio of shear to transport energy input in the same dimension.

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Influence of Slicing Parameters on Properties of 3D Printed Products

Tim Feuerbach, Stefanie Kock, Markus Thommes

Fused Deposition Modeling (FDM) 3D printing is emerging as a pharmaceutical manufacturing process for drug dosage forms and implants. The main incentives are the personalization of drug dosage, the customization of implant geometry and an economic single-unit production. Slicing software generates machine instructions for the printer, based on a digital 3D model to print an object layer-by-layer. The aim of this study was to investigate the influence of individual slicing parameters on specific properties of printed objects. For this purpose, custom slicing software was written in Python due to inaccessible slicing parameters and missing transparency in commercial slicing software.

In the following results, the influence of the slicing parameters *parallel strand distance* and *over-extrusion ratio* on the object properties *dimension and porosity* are presented. The printed objects were cuboids. The cuboid dimensions are represented by cuboid ratios, which are the ratios between the measured dimensions and the set dimensions. The porosity was calculated by determination of the cuboid volume, the cuboid weight and the material density. The parallel strand distance is the distance between two extrudates, which are parallel deposited by the printer nozzle (Figure 1). The over-extrusion ratio describes the applied volumetric flow rate relative to the volumetric flow rate necessary for the intended layer height.
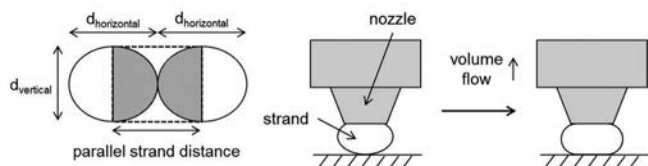

Figure 1: Qualitative depiction of the parallel strand distance (left) and the over-extrusion ratio (right).

Three different deposition strategies have been investigated (Figure 2). In the cross strategy, the strand orientation is altered by 90° in each consecutive layer. In the contour strategy, the strand orientation is similar to the layer contour, while the gap strategy has one strand orientation, but the deposition location is shifted by half a strand width in each consecutive layer.
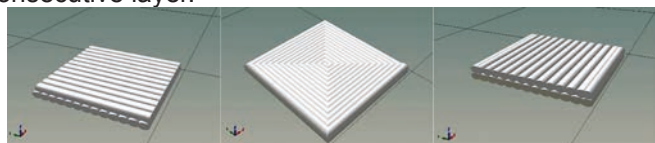
Figure 2: Deposition strategies (from left to right): cross, contour, gap

The cuboids were printed in a custom-built FDM printer with a poly-lactid acid (PLA) filament (RepRap-Austria, Austria), a printing temperature of 200 °C and a layer height of 400 µm. Figure 3 shows decreasing object porosity with decreasing strand distance. The cuboid ratios are showing only small variations for parallel strand distance / nozzle diameter > 1.05. For parallel strand distance / nozzle diameter < 1.05, the cuboid ratios are increasing due to excess material suppressed to the object surfaces.

The horizontal cuboid ratios were > 1 while the vertical cuboid ratios were < 1 due to a flattening of the deposited extrudate strands to an elliptic shape.
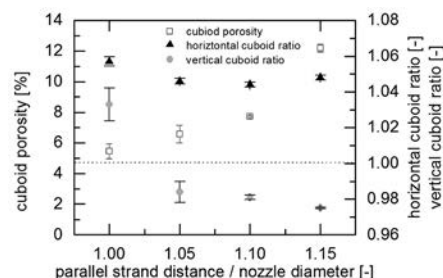
Figure 3: Cuboid porosity and cuboid ratios, dependent on the parallel strand distance for an over-extrusion ratio = 1 (n = 3).

In Figure 4, the cuboid porosities for the three different deposition strategies are compared. The strategies yield different porosity levels for the same slicing parameters. The over-extrusion ratio can be increased to further decrease the cuboid porosity without an increase in cuboid ratios for over-extrusion ratios < 1.26.
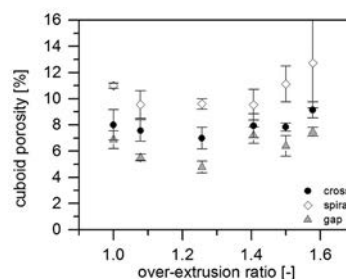
Figure 4: Cuboid porosity, dependent on over-extrusion ratio for a parallel strand distance / nozzle diameter = 1.05 (n = 3).

The strand deposition strategy can be selected to have an optimal strand orientation in the pharmaceutical product, which has a major impact on the mechanical properties of the product. The product porosity can be further adjusted to a desired value by slicing parameters like the parallel strand distance and the over-extrusion ratio, while the object dimensions remain in specification.

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Preparation of Submicron Particles by Spray Drying

Pharmaceutical submicron sized particles by spray drying - production, precipitation and characterization

Adrian Dobrowolski, Ramona Strob, Gerhard Schaldach, Helmut Wiggers, Peter Walzel, Markus Thommes

The preparation of particles in the submicron sized range (0.1-1μm) is of common interest for many different application fields, like chemistry, food and pharmaceutical application. Due to the low water solubility of newly identified drugs, the nanomization of particles is one possibility to increase their bioavailability.

One of the major obstacles for the preparation of new pharmaceutics is the low water solubility of newly identified active pharmaceutical ingredients (APIs). More than 40 % have a low water solubility. The preparation of particles down to the submicron range (0.1-1 μm) and the corresponding increase in the specific surface area directly increases the dissolution rate, thus leads to a higher bioavailability. This is described by the Nernst-Brunner equation. Despite the increased dissolution rate, according to the Ostwald-Freundlich equation, a decrease in particle size down to 1 μm increases the saturation concentration.

So far, different preparation methods for submicron sized particles, like bottom-up and top-down methods exist. Spray drying is a bottom-up technique, were particles are generated from a pure solution. Spray drying has a high potential for the generation of submicron sized particles. It is a simple step process where particle size, shape and morphology can be adjusted by controlled process parameters. In addition, heat sensitive substances can be used due to the moderate drying temperature. Nevertheless, conventional spray drying devices show certain limitations, for the production of submicron sized particles, regarding small droplet sizes and the precipitation of submicron particles.

In this work, a newly designed spray drying device is presented. The spray dryer was designed to ensure a compact structure without redirections (see Figure 1).

Firstly, an aerosol, produced with a pneumatic atomizer, is sprayed into a cyclone droplet separator with a cut-off size of about 2 μm. Thus, only the amount of fine droplets, smaller than the cut-off size is introduced into the drying chamber.

A resulting challenge is the collection of these dispersed particles from a gas flow. The separation in electrostatic precipitators (ESP) is a common technique for air purification purposes where powder particles can be collected rather independently from the particle size. An adapted ESP design is necessary to achieve high separation efficiencies and a robust process.

The ESP design in this work uses the precipitation method of Penney filters which separates charging and collection into two zones. Submicron particles tend to follow the gas flow in appearing turbulences. The setting of a laminar flow in the second zone prevents the appearance of eddies, provides the necessary time for the particles to move to the collection electrode and enhances the efficiency compared to single stage ESPs. Several experiments are conducted with the model substance povidone (Kollidon® K30, BASF, Ludwigshafen, Germany) to examine the ESP and characterize its behaviour in long term tests (see Figure 2). This ESP shows a separation efficiency in a continuous experiment of higher than 99 % for 10 hours for 500 nm particles. These high efficiencies compared to single stage ESPs result in a production rate of 1 g/h.
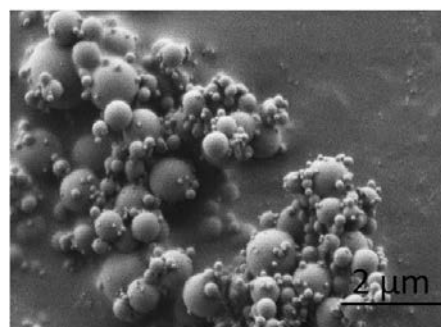
Figure 2: SEM picture of spray dried submicron povidone particles.

Figure 1: Picture of the designed spray dryer for the production of submicron particles.

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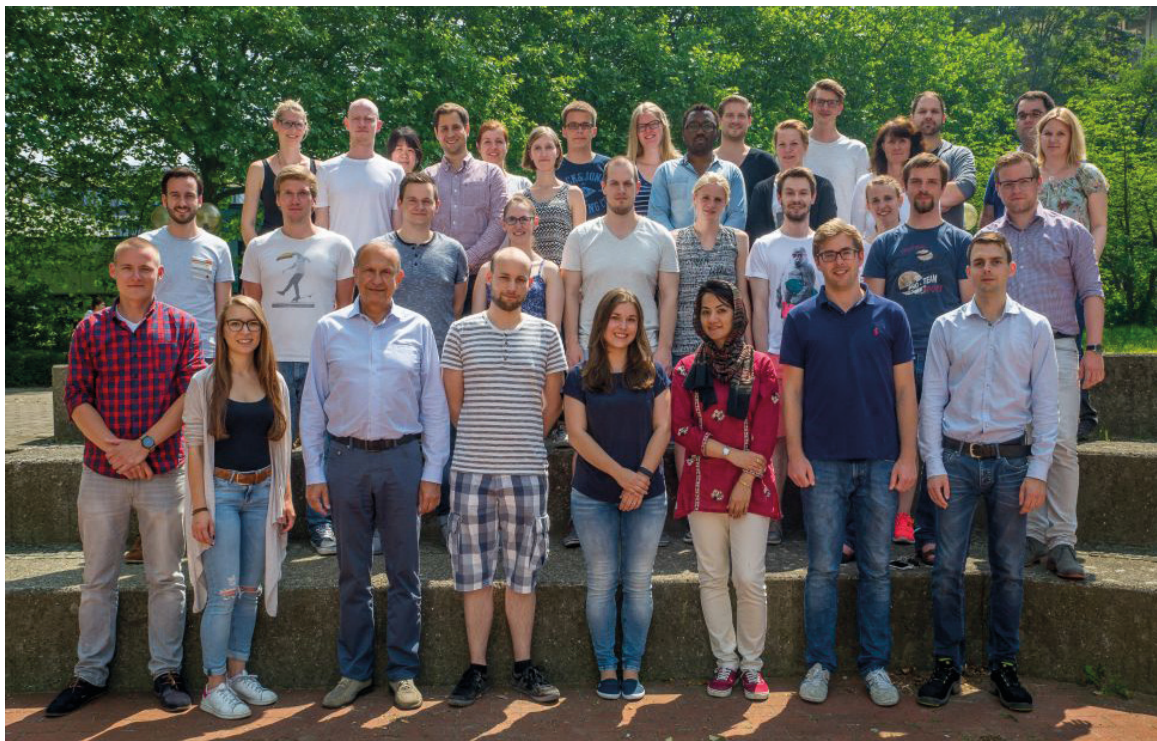
Fluid Separations (FVT)

Additive Manufacturing of Packings for Rotating Packed Bed

Konrad Gładyszewski, Andrzej Górak, Mirko Skiborowski

During the last 30 years HIGEE technology and specifically rotating packed beds (RPBs) have gained considerable interest as compact contacting equipment for process intensification. Through a considerable improvement of mass transfer efficiency, they have the potential for significant volume reductions compared to classical contacting equipment, such as packed columns. The acceleration of the liquid by centrifugal force furthermore enables the use of internals with high packing density and the processing of highly viscous liquids. However, while a wide variety of internals is available for classical columns, including diverse random and structured packing, the range of available packing materials for RPBs is yet very narrow.

While classical manufacturing technologies seem rather of limited suitability in developing tailored packings for use in RPBs (Neumann et al. 2017), the given constraints make them specifically interesting for modern Additive Manufacturing (AM) techniques. Being developed in the 1980s, AM, which is also known as Rapid Prototyping, originated around the same time as RPBs were first introduced at ICI in the UK (Reay et al. 2013). According to the American Society of Testing and Materials (ASTM) AM is "the process of joining materials to make objects from 3D model data, usually layer upon layer, as opposed to subtractive manufacturing methodologies" (F2792-12a). Today, AM has evolved to a mature technology which provides a pathway for inexpensive and flexible manufacturing of specialized components and one-off parts (Engstrom et al. 2014). It allows for computer-assisted design and manufacturing of advanced functional materials, which have been used in all kinds of diverse applications, ranging from medical applications, such as prosthetics and tissue engineering, over drug delivery systems, food and optical applications, applications in art and architecture to the energy and chemical industry (Femmer et al. 2016). Despite the complexity of selecting a specific AM process, the possibility of varying the structure with almost unlimited degrees of freedom makes AM predestined for the design of tailored packing materials. The comparable small packing volume, coming from a range of cubic meters for packed columns to liters in RPBs, as wells as the unique geometrical shape of the required packing, further increase the suitability of a combination of RPBs and AM. Yet, there is no indication of such a combination in open literature. The current investigations demonstrate the possibility of the manufacturing of packing material by means of 3D printing, directly taking into account a pilot scale RPB. In order to illustrate the competitiveness of the approach, first an available metal foam packing

was investigated experimentally, providing basic results concerning hydrodynamics and mass transfer. Afterwards a model of the foam packing was generated and a replica was produced by means of AM using a polymer resin (Figure 1). The generated results indicate the comparability of the different packing materials and demonstrate the suitability of AM as an approach for rapid prototyping in order to generate and test innovative packing materials for RPBs. Future research is dedicated to the development of improved packing structures using the AM approach.
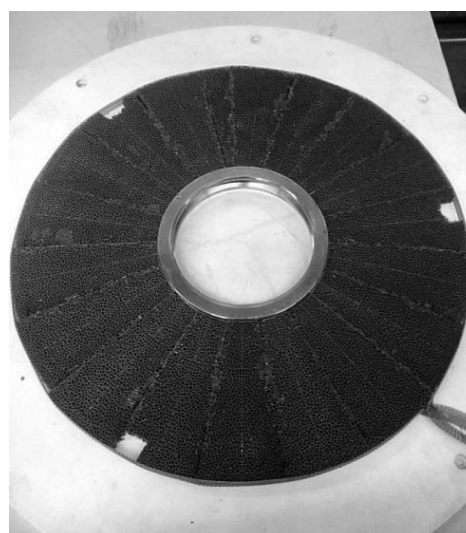
Figure 1: Fully 3D printed packing at Fluid Separations Chair for rotating packed bed.D.S.

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A Systematic Approach towards Synthesis and Design of Pervaporation-Assisted Separation Processes

Bettina Scharzec, Thomas Waltermann, Mirko Skiborowski

Although membrane-assisted processes, such as pervaporation-assisted distillation, are considered as sustainable alternatives to thermal separation processes, they are rarely considered in early stages of conceptual design. In order to enable an identification of promising applications, a systematic approach was developed that includes the synthesis of pervaporation-assisted process variants and applies optimization-based methods for process analysis. It allows for a limitation of the experimental investigations to a necessary minimum and considers competitive reference processes as well as further means for process intensification in the evaluation.

Membrane-assisted hybrid processes, such as the combination of pervaporation (PV) and distillation, provide a tremendous potential for an energy efficient separation of complex and particularly azeotropic multicomponent mixtures. However, the benefits of membrane processes, as e.g. the capability to overcome limitations of other separation techniques are often exploited best when integrated in hybrid processes. Nevertheless, industrial applications are still limited due to a lack of suitable design methods that allow for the consideration of PV-assisted processes in an early stage of conceptual design. Current design methods often require the knowledge of suitable membranes as well as a respective membrane model that, in turn, require an intensive membrane screening. It is of crucial importance to evaluate the potential of a membrane-assisted process prior to any cost- and time-consuming experiments. Further, an appropriate analysis should consider methods for process intensification, such as options for energy integration, for both, membrane-assisted processes and alternative process variants. That allows for a meaningful comparison of the generated configurations regarding the overall potential of each process.

In order to overcome these current limitations, a systematic five-step design approach was developed for the evaluation of the potential of energy intensified PV-assisted processes [1]. An illustration of the proposed methodology is given in Figure 1. Within the first step, the potential feasibility of PV-assisted separation processes is examined by means of thermodynamic insight on different levels of detail. Based on that analysis, suitable process configurations are generated and a proper benchmark process is to be determined. The second step focuses on the evaluation of the PV-assisted process variants under the assumption of a perfect membrane separation by minimizing the total energy demand. That provides an estimate of the maximum benefit obtained by the PV-assisted process prior to any cost- and time- consuming experiment.
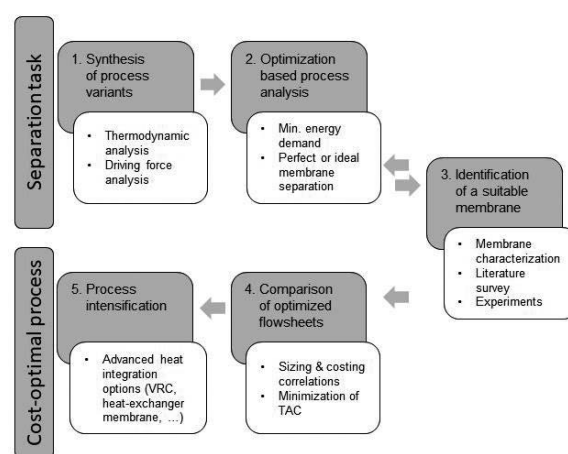
Figure 1: Flowchart for the synthesis and design approach for PV-assisted hybrid processes.

In case of a promising PV-assisted variant, a suitable membrane, as well as a membrane model, has to be determined in the third step. That is achieved either by a literature survey or experiments based on the previous model-based analysis in step two that defines the requirements for the membrane and restricts the experimental design space. In the fourth step, optimized designs of the PV-assisted process variants are determined and compared to the considered reference process in terms of total annualized costs. In the last step, additional means for process intensification are taken into account. For the PV-assisted processes, advanced heat-integrated membrane modules are considered allowing for a nearly isotherm operation resulting in a reduced membrane area as well as costs. In case of a single distillation column, vapor recompression is considered for a direct heat-integration of reboiler and condenser. That final step is essential for a meaningful comparison of the generated process variants.

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Fluid Mechanics (SM)

Filling Flow into Thin Porous Media

Modeling of one-phase and a displacement flow through thin porous media

Konrad Boettcher, Tim Neumann, Peter Ehrhard

If the pores of a porous medium are much smaller than its macroscopic dimensions, the fluid flow through the porous medium can usually considered to be homogeneous. But if the pores are not that small, the influence of the containment onto the flow as well as onto the structure of a porous medium has to be taken into account. The distortion of the pore arrangement near a wall is the so-called wall effect. This effect plays a major role in the filling process of Li-Ion batteries, where an electrolyte has to flow in the porous media of the electrodes and the separator, confined by unpermeable collector foils.

As the propagation speed of the wetting front tends to zero at the end of the process, the Reynolds number is small with Re $\approx 10^{-5}$. Also in recent literature there are several authors proclaiming a low Reynolds number flow regime where the Darcy law, mainly used for describing flows through porous media, is not valid. This so-called Pre-Darcy flow regime starts from Reynolds numbers smaller than Re $\approx 10^{-2} - 10^{-4}$ and has some importance e.g. to the enhanced oil recovery. Finicky experiments are performed to investigate the validity of the Darcy law. Glycerin is used as it is a Newtonian liquid with a high viscosity and easy to handle. It can be shown, that the linear Darcy law holds for all experiments down to a Reynolds number of Re $\approx 10^{-9}$ (see Figure 1). Here, the mean velocity is about 40 nm/s and three days needed to get the last data point. Therefore, it seems as if the Pre-Darcy flow region does not exist and that deviations to the theory are due to other influences like temperature gradients or impurities in the one-phase flow. As the Darcy law holds, the porosity depending on the wall distance in straight reservoirs is examined, showing some differences to the oscillation in cylindrical reservoirs.

To choose a suitable method which correlates the permeability with the porosity ε in the wall-effect domain, the similarity with a characteristic pore diameter is exploited. Several porous media are fixed with epoxy resin, and the porosity and pore diameter is determined in wall-parallel layers.
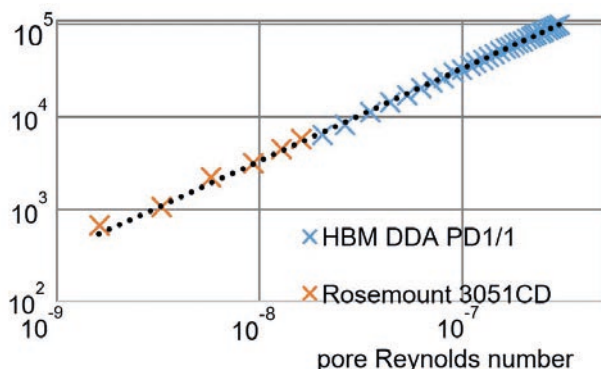

Figure 1: Pressure drop vs. pore Reynolds number for two different pressure sensors.

It is found, that the well-known law by Carman-Kozeny holds in the bulk region of porous media but not in the oscillating region (see Figure 2).
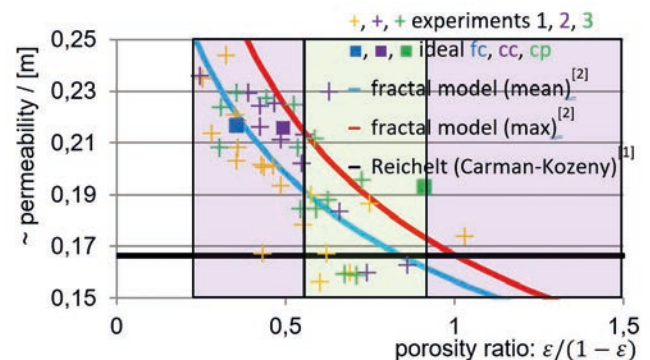

Figure 2: Permeability over porosity ratio: experimental results, mean (blue) and max (red) fractal methods and Carman-Kozeny (black). The latter model is valid only in the bulk (green area) of the porous media but not in the oscillating region (purple).

Here, a fractional law by Cai[2] is applicable. The models are implemented into ANSYS CFX and numerical simulations are performed and shown in Figure 3. They are compared to the experimental velocity profile in a porous medium in a cylindrical domain[3]. The amplitude and position of the minima and maxima are computed quite well.
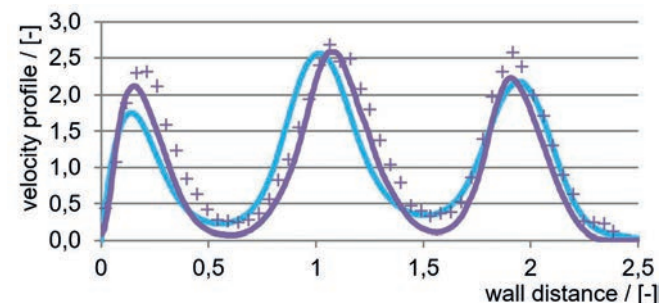

Figure 3: Circumferential averaged velocity in a porous domain: Experimental results[3] and own numerical results (lines).

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Pressure Drop in Fibrous Filters

Jayotpaul Chaudhuri, Peter Ehrhard

Coalescing filtration is a mechanical process which is employed to remove dispersed aerosol particles from a gas stream. This kind of filtration is a depth filtration process and is widely used in process industries to remove particulate matter from exhaust gases or in compressed air applications to filter oil particles introduced during the compression process. Fibrous filters are often used due to low cost, high capture efficiency and low pressure drop. There, droplets are first captured on fibres, then coalesce, and eventually drain out. The performance of a filter medium is judged based on its capture efficiency and pressure drop characteristics. In the present study, numerical simulations using ANSYS CFX are used to predict the pressure drop caused due to air flow through the randomly oriented fibrous filter medium. A fictitious domain approach is used to simulate solid fibres without the need to create a case-specific mesh for different fibre alignment.

Theoretical investigations to predict flows around fibres have started as early as 1930 with 2D flow analysis around a single isolated fibre. The most widely used pressure drop correlation was developed in 1959 using the cell model which also accounts for fibre-fibre interaction. The theoretical approach is only valid for 2D cases and negligible inertial effects. To investigate the influence of inertial effects and the effects of randomly oriented 3D fibres a CFD simulation was setup to measure the Δp. A special fictitious domain approach was used where the fibres are replaced with a region of low permeability. This is advantageous because there is no need to create case-specific meshes as is the case with traditional body-fitted meshes.

The model is extended to a 3D case with multiple fibres, the fibre regions described by a function with five degrees of freedom, namely the gradient angle α, the rotational angle β, and the displacement of the center point coordinates x_m, y_m and z_m; all varied randomly.

The resulting flow field is visualized in Figure 1, where the grey zones signify solid fibres and the colored lines are streamlines of the air. The results of the simulations, both 2D and randomized 3D case can be directly compared with the theoretical cell model, only in the region of low Reynolds number (Re = 0.001). As expected the 2D model gives similar results as the cell model but both are much bigger than the results with 3D randomized fibres.

A possible explanation may be that randomly generated fibre structures yield regions of low solidity, which have a low resistivity to fluid flow; the bulk of the fluid flows through these regions and results in a lower pressure drop. The non-dimensional pressure drop gradient is shown in Figure 2.

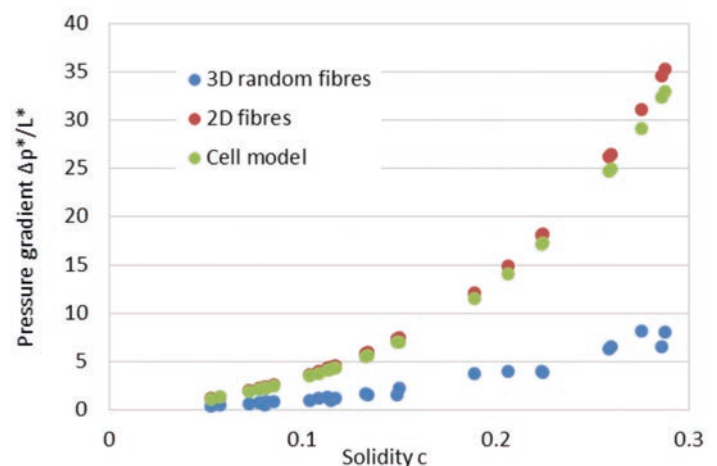Figure 1: Numerical results showing randomly oriented fibres and air streamlines.

Figure 2: Comparison between Happel-Kuwabara, 2D and 3D randomized simulations for Re=0,001.

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Experimental Analysis of Bubble-Entrapment during Droplet Impact on solid Walls

Sabrina Grünendahl, Lutz Gödeke, Peter Ehrhard

Droplet impact on solid walls often leads to the entrapment of thin films of gas underneath the droplet during the spreading process. These films rapidly form small substrate-pinned bubbles by formation of multiple contact lines. These substrate-pinned bubbles are stationary and lead to problems, e.g. spray painting. The resulting film is distorted and optical and mechanical properties do not meet the requirements (see Fig. 2). The process is dependent on both, fluid and solid properties (surface tension, viscosity) as well as application parameters (droplet diameter, impact velocity).

Droplets (d_{drop} = 1.8 – 2.2 mm) are generated by a continuous flow through a thin capillary (d_{cap} = 0.15 – 0.3 mm) and dripping on NBK-7 borosilicate glass substrate wafers. The process is filmed from an axis perpendicular to the droplet trajectory, i.e. side-view, and for transparent substrates from below along the trajectory axis (Figure 1). Due to the rapid formation of the entrapped bubbles, the frame-rates have to be in the range of 20.000 - 35.000 fps.

The obtained pictures allow for diameter and velocity measurements shortly before impact and capture the spreading dynamics after impact. At the same time, we do obtain a series of 10 - 30 pictures that capture the dynamic process of bubble formation. The observed time scale for this rapid process is t_{bubble} = 10^{-1} - 10^{1} ms.

Dimensional analysis leads to a set of dimension-less groups that are used to create a map-of-occurrence (see Figure 3) for substrate-pinned bubbles.
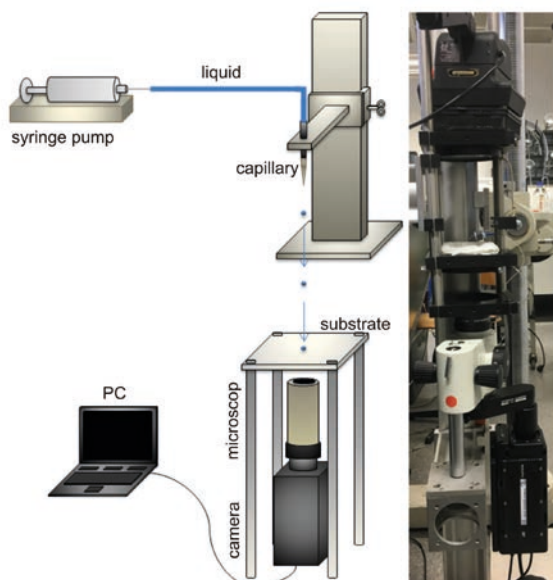

Figure 2: Left side: fluid droplet shortly after impact with substrate-pinned bubbles. Right side: dry film with pinholes and encased bubbles in solidified material. Sterocoll SHT 1.7 % / SXT 0.3 %, Oh = 0.06, Re = 800.

These groups are varied by using mixtures of water and glycerol, thus changing the liquid properties and by changing the capillary-to-substrate distance, thus changing the impact velocity.

Further experiments show, that the diameters of the resulting bubbles and the velocities of corresponding contact lines are dependent on Weber and Reynolds number. The size of entrapped bubbles can be reduced by increasing impact velocity, the characteristic entrapment time t_{bubble} increases with viscosity.
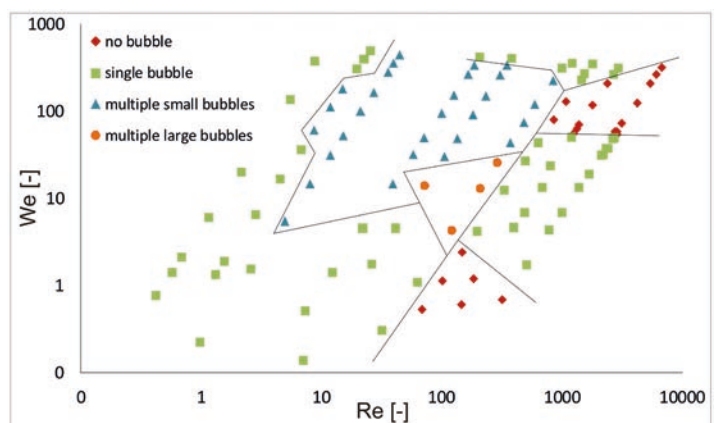
Figure 3: Map-of-occurrence for bubble entrapment displayed as We-over-Re-nomogram. Four major types of bubble formation can be identified (see legend). Lines proportional to Re^{1} correspond to same fluid. Left side: Glycerol, right side: Water, in between mixtures.

Figure 1: Experimental setup, left: schematic, right: laboratory setup with high-speed camera, microscope, light-source and dripping needle.
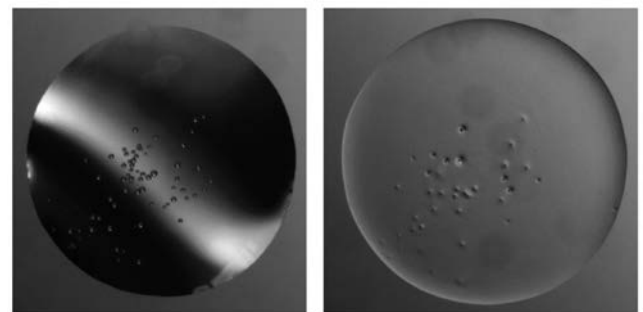
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Technical Biochemistry (TB)

Engineering Yeasts as Platform Organisms for Cannabinoid Biosynthesis

First Reconstitution of the Final Cannabinoid Biosynthesis Pathway in Yeast

Bastian Zirpel, Friederike Degenhardt, Chantale Martin, Oliver Kayser, Felix Stehle

Δ^9-tetrahydrocannabinolic acid (THCA) is a plant derived secondary natural product from the plant Cannabis sativa L. *The discovery of the human endocannabinoid system in the late 1980s resulted in a growing number of known physiological functions of both synthetic and plant derived cannabinoids. Thus, manifold therapeutic indications of cannabinoids currently comprise a significant area of research. Here we reconstituted the final biosynthetic cannabinoid pathway in yeasts. This study is an important step toward total biosynthesis of valuable cannabinoids and derivatives and demonstrates the potential for developing a sustainable and secure yeast bio-manufacturing platform.*

Δ^9-tetrahydrocannabinolic acid (THCA) is a plant derived secondary natural product from the plant *Cannabis sativa L.* with therapeutic indications like analgesics for cancer pain, decreasing intraocular pressure in glaucoma or reducing spasticity associated with multiple sclerosis. Here we reconstituted the late biosynthetic pathway for THCA production from *C. sativa* in yeasts.

In a first approach, the heterologous expression of the native CBGA forming enzyme CBGAS from *C. sativa* was investigated in *S. cerevisiae*, but no functionally active protein was obtained.

Alternatively, the use of the soluble prenyltransferase NphB from *Streptomyces* sp. strain CL190 was tested to replace the native transmembrane prenyltransferase CBGAS. Beside the desired product cannabigerolic acid, NphB catalyzes an *O*-prenylation leading to 2-*O*-geranyl olivetolic acid.
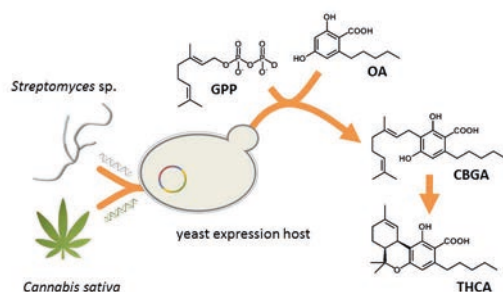

Figure 1: Reconstitution of the final biosynthetic cannabinoid pathway in yeasts.

Based on these results we tried to express both coding sequences *nphB* and *thcas* simultaneously in *S. cerevisiae* to produce THCA. Neither expression of *thcas* and *nphB* driven by the same promoter nor the expression of both enzymes using a bidirectional Gal10/Gal1 promoter system led to formation of sufficient amounts of CBGA which could serve as substrate for THCAS.

In order to improve *nphB* expression we tried to make use of *K. phaffii's* ability to express proteins at high levels upon multi-copy integration of the coding sequences into its genome. Finally, the performed screening for strains with higher NphB activities, in a strain containing a high copy insertion of the *thcas* coding sequence, yielded a *K. phaffii* strain that can produce 82 ± 4.6 pmol L^{-1} OD^{-1} h^{-1} THCA.
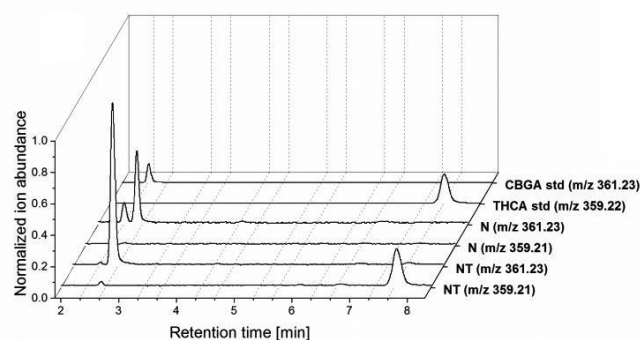
Figure 2: LC–MS analysis of cannabinoids produced with extracts of *K. phaffii* expressing both *nphB* and/or *thcas*. The yeast extracts were incubated with 1mM GPP and OA, respectively. N − assay of lysed yeast expressing only NphB; T − assay of lysed yeast expressing only THCAS; NT − assay of lysed yeast expressing both NphB and THCAS.

We show for the first time that the bacterial prenyltransferase and the final enzyme of the cannabinoid pathway tetrahydrocannabinolic acid synthase can both be actively expressed in the yeasts *S. cerevisiae* and *K. phaffii* simultaneously. While enzyme activities in *S. cerevisiae* were insufficient to produce THCA from olivetolic acid and geranyl diphosphate, genomic multi-copy integrations of the enzyme's coding sequences in *K. phaffii* resulted in successful synthesis of THCA from olivetolic acid and geranyl diphosphate.

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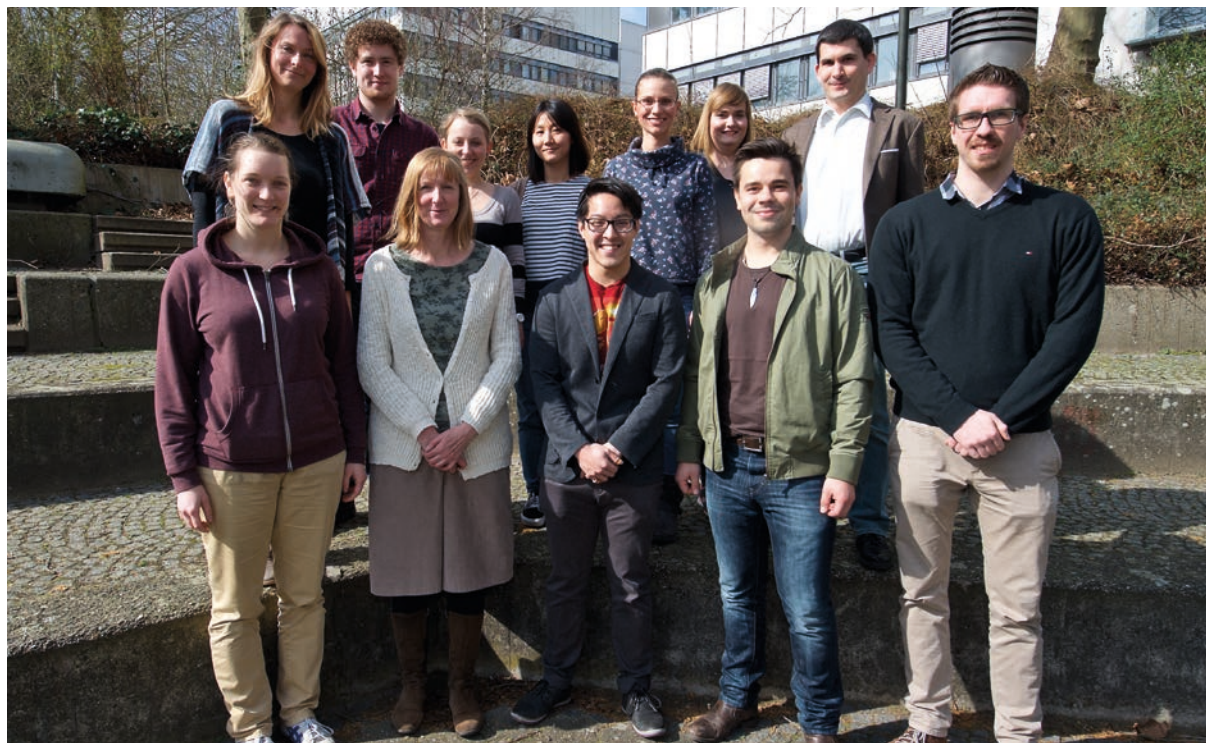
Technical Biology (TBL)

Rewiring Natural Product Biosynthesis

Improving the production of a bacterial lipopeptide by genetic engineering

Florian Baldeweg, Hirokazu Kage, Markus Nett

In biotechnological processes precise expression of metabolic pathway genes is essential for high production of desired products. Here, we developed an orthogonal regulatory circuit for the biosynthesis of the fungicide ralsolamycin and introduced this system into the native producer organism. By combining this genetic engineering approach with procedural improvement, the production of ralsolamycin could be increased by a factor of 70. The facilitated production of this compound set the stage for the determination of its chemical structure.

The natural product ralsolamycin, an inducer of chlamydospore formation in fungi, was previously reported from the soil bacterium *Ralstonia solanacearum*. Although tandem mass data and bioinformatics were used for a preliminary chemical characterization, the full structure of this natural product could not be resolved owing to an extremely low production level (~0.1 mg L-1) under standard laboratory cultivation conditions.
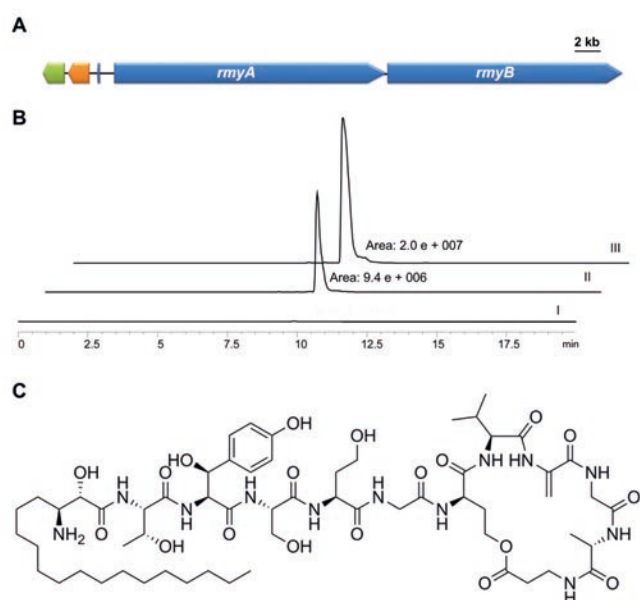

Figure 1: (A) Organization of the ralsolamycin gene locus; core and accessory biosynthesis genes (blue), transporter gene (green), gene of unknown function (orange). (B) Extracted ion chromatograms of ralsolamycin from a negative control (profile I), the wildtype strain (profile II), and the overproduction strain (profile III). (C) Structure of ralsolamycin.

In order to secure sufficient quantities of this compound for further testing, we constructed an overproduction strain by refactoring the regulation of ralsolamycin biosynthesis in the original producer. For this, native promoters and ribosomal binding sites were replaced by synthetic ones, enabling a stringent control of gene expression by defined chemical stimuli. Surprisingly, this approach led only to a modest increase of ralsolamycin production (Figure 1).

Subsequent analyses indicated that the gene overexpression had created bottlenecks in precursor supply, which limited the productivity in batch fermentations. To circumvent this problem, a new optimized production medium was devised. Using this medium, a maximum product concentration of 4.3 mg L^{-1} was achieved with the recombinant *R. solanacearum* strain. This value could be further increased up to 7.0 mg L^{-1} when the production strain was grown in the presence of an adsorber resin. These findings illustrate the importance of integral process development, taking equal account of biotechnological and procedural factors.

Figure 2: ^{1}H,^{13}C HMBC spectrum of ralsolamycin in DMSO-d$_6$.
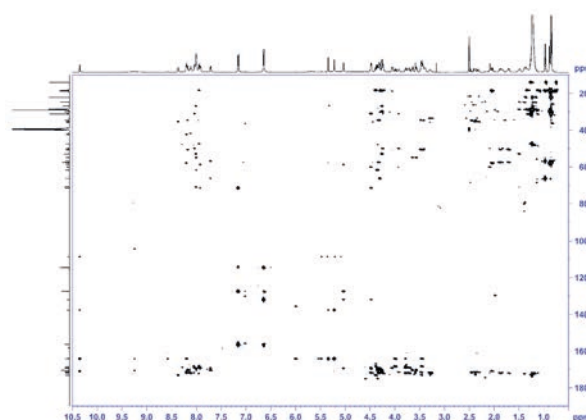
Overall, we generated 200 mg of ralsolamycin in 30-L batch fermentation over 72 h. The obtained material was purified by open column chromatography and reversed-phase HPLC. The structure of ralsolamycin was eventually elucidated following extensive spectroscopic analyses (Figure 2) as well as chemical derivatization.

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Exploration of Novel Biological Resources

Identification of novel bacterial species and evaluation of their biosynthetic potential

Xinli Pan, Hirokazu Kage, Markus Nett

With the advent of genomics, it has become evident that far more microbes than previously anticipated are capable to produce bioactive natural products and other compounds of commercial interest. The genus Herpetosiphon is an illustrative example of a bacterial taxon with notable, yet unexploited biosynthetic potential. Recent analyses of this underexplored microbe led to the discovery of a novel diterpene. Moreover, we obtained new data regarding the taxonomic diversity in this genus.

Bacteria of the genus *Herpetosiphon* occur in a number of soil and freshwater habitats. Furthermore, they are commonly found in the activated sludge of sewage treatment plants. Despite their widespread distribution, information about these filamentous microorganisms (Figure 1) is rather scarce. Some *Herpetosiphon* strains were reported to feed on other soil bacteria. However, it is still unclear whether predation is a common trait in this genus. For the killing of other microbes, *Herpetosiphon* spp. are assumed to resort to a wolf pack strategy, in which a large number of predatory cells congregate in order to lyse the prey by the combined secretion of hydrolytic enzymes. Genomic analyses suggest further that *Herpetosiphon* strains are competent producers of bioactive secondary metabolites. It has even been speculated that a correlation between predation and antibiotic biosynthesis might exist. This would make the genus *Herpetosiphon* a promising resource for antimicrobial compounds.
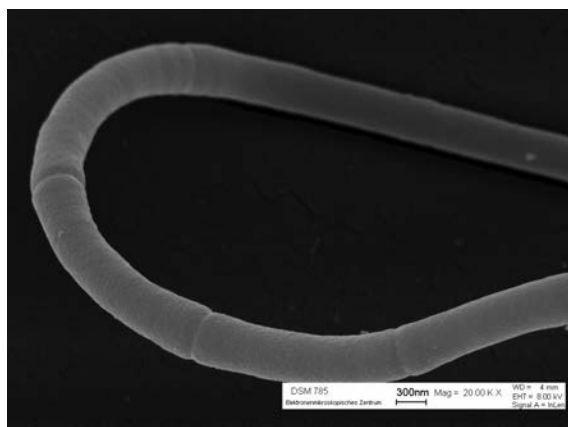

Figure 1: Scanning electron micrograph of a multicellular filament from *Herpetosiphon aurantiacus* DSM 785.

To assess the biotechnological potential of the genus *Herpetosiphon*, several strains were investigated. During our screening, we noted significant differences between the *Herpetosiphon* strains in substrate utilization as well as phenotype, which ultimately led to the recognition of two novel species, *H. gulosus* and *H. giganteus*. Representative strains of both species were fully characterized regarding their phylogenetic position, fatty acid profiles, menaquinone composition and enzymatic activities.

These analyses supported the proposed taxonomic classification as distinct species. Furthermore, we confirmed the predatory behavior of all *Herpetosiphon* strains tested.
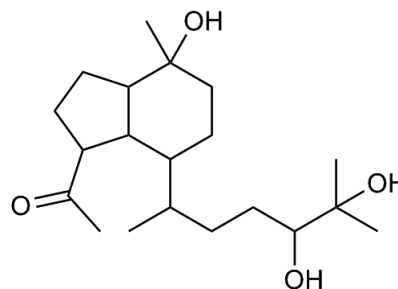

Figure 2: Structure of herpetopanone, which was identified from *H. aurantiacus* DSM 785 using an isotope labeling strategy.

A specific objective of this project was the analysis of isoprenoid biosynthesis in the genus *Herpetosiphon*. Isoprenoids are widely used as pharmaceuticals, flavors and colorants in food, fragrances in perfumes, and biofuels. To identify these compounds in the complex metabolome of a natural product-producing bacterium, we developed a new method, which is based on the feeding of isotopically labeled glucose. The linear oligoprenyl units, which constitute the carbon backbones of isoprenoids, arise from the condensation of activated isoprene units, namely isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). The metabolism of singly ^{13}C-labeled glucose gives rise to a characteristic carbon labeling pattern in IPP and DMAPP. This feature has proven extremely useful to unravel cyclization cascades and carbon-carbon rearrangements in the biosynthesis of some isoprenoids. We anticipated that the resulting mass shifts could also be valuable in the field of natural product discovery. To validate the feasibility of this strategy, we compared the ion chromatograms of *Herpetosiphon* cultures that were grown in the presence or absence of singly labeled glucose. This approach resulted in the discovery of a novel diterpene with a rare octahydro-1*H*-indenyl skeleton (Figure 2). The properties of this compound are currently under investigation.

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Technical Chemistry (TC)

Isomerizing Hydroformylation of Unsaturated Ester Compounds

Development of a new bimetallic tandem catalytic system

Jonas Bianga, Tom Gaide, Kim E. Schlipkoeter, Thomas Seidensticker, Dieter Vogt

The substitution of common polymer precursors from fossil raw materials through some out of renewables is one major issue for the chemical research and industry. Suitable molecules which could be used for such an approach are fatty acid methyl esters because of their long hydrocarbon chains and their relatively low number of functional groups. A wide variety of reactions exist for the implementation of FAMEs as substrate for polymer precursors.

Through the isomerizing hydroformylation it is possible to synthesize *α,ω*-functionalized molecules out of fatty acid methyl esters (FAMEs). In comparison to reactions like the isomerizing methoxycarboxylation in which diesters are synthesized, a formation of bifunctional and asymmetric aldehyde esters is possible in case of using the isomerizing hydroformylation. This facilitates the synthesis of many different polymer precursors trough e.g. an oxidation, a hydrogenation or a reductive amination of this compound. The isomerizing hydroformylation of methyl oleate (Figure 1) is a very challenging reaction. In literature the highest reported yields were limited to 26 % of the linear product. Especially the hydrogenation of the substrate limited the reaction performance. Most approaches focused on the development of a single, auto-tandem catalyst for both reaction steps. In our research we developed a new orthogonal catalytic system, which consists of two different catalysts. One is responsible for the isomerization of the double bond and the other facilitates the linear hydroformylation of the terminal double bond.

Former research in our workgroup showed, that the catalyst system consisting of $Rh(acac)(CO)_2$ and the ligand Biphephos is a very effective system for the hydroformylation part of the reaction.

Very high activities and selectivies can be obtained by the use of this catalyst system in hydroformylation reactions. For the isomerization step another catalyst is necessary. Different metals like Pd, Rh, Ru, Ir, Pt, Co or Ni were investigated. Only a Pd dimer as precursor which was presented before by Gooßen et al. showed a very promising isomerization activity in combination with the hydroformylation catalyst. Because of the instability and the relatively high costs of this catalyst complex, an in situ formation of the catalyst was investigated. The active isomerization species was formed through an addition of PdI_2 and $Pd(^tBuP)_2$ to the reaction mixture. Finally, the new orthogonal catalytic system (Figure 2) led to the highest ever reported yields for the linear selective isomerization hydroformylation of methyl oleate. However, total suppression of the hydrogenation was not achieved in this system.
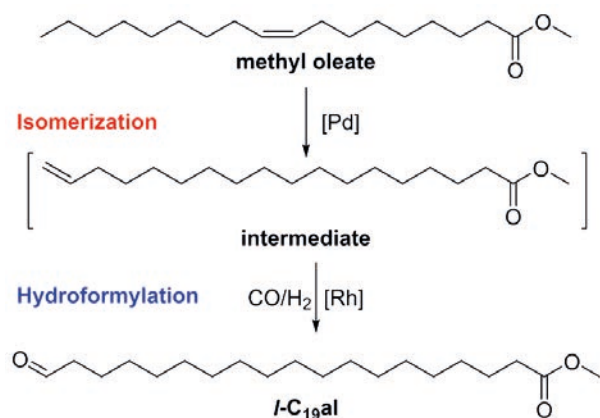

Figure 1: Isomerizing hydroformylation of methyl oleate (1).

For the isomerizing hydroformylation of methyl oleate (1), which is shown in Figure 1, the used catalysts need to fulfill the following requirements under hydroformylation conditions:

- High isomerization activity
- Low hydrogenation activity
- High hydroformylation activity
- High hydroformylation selectivity

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Figure 2: The new developed tandem catalytic system for high linear and high active isomerization / hydroformylation reactions.

In our work, we successfully developed an orthogonal tandem catalytic system for the linear selective isomerizing hydroformylation of methyl oleate in a 100 g scale. Through the new reaction system the highest yields (74 %) and *l/b*-selectivities (91 : 9) to the linear aldehyde ester yet reported were achieved.

Recycling of Homogeneous Catalysts in Reactive Ionic Liquids – Solvent-Free Aminofunctionalizations of Alkenes

First example of a recycling of homogeneous transition metal catalysts in reactive ionic liquids

Michael Terhorst, Thiemo A. Faßbach, Andreas J. Vorholt, Arno Behr, Thomas Seidensticker, Jens M. Dreimann

The recycling of homogeneous transition metal catalysts in amination reactions is a challenging task. Especially on industrial scale, the reuse of the precious metals is economically and ecologically important. The use of a reactive ionic liquid, e.g. dimethyl ammonium dimethyl carbamate, is an elegant solution to combine reactivity and recycling of the catalyst, due to immobilization of the catalyst in the polar carbamate phase.

Methylamines are one of the most important building blocks in the fine chemical industry. Especially the worldwide demand of dimethylamine is high, due to the usage of synthetic unsymmetric tertiary amines as solvents, agrochemicals, or surfactant precursors.

To obtain precursors for surfactants in a straight forward way, we applied β-farnesene in the hydroamination and butadiene in the telomerisation, both in combination with dimethyl amine, which led to the corresponding long chained asymmetric tertiary amines.

As dimethyl amine source, the ionic liquid dimethyl ammonium dimethyl carbamate (dimcarb) consisting of the two gases dimethyl amine and carbon dioxide was used (Figure 1).
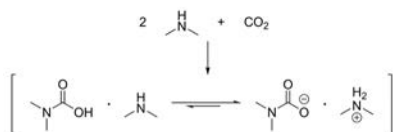

Figure 1: Formation of dimethyl ammonium dimethyl carbamate and equilibrium of ionic and non-ionic form of dimcarb.

Fortunately, this compound is liquid at room temperature and distillable, so that polar by-products will not accumulate in the polar catalyst phase, like in conventional ionic liquids. During the study of the synthesis of surfactant precursors it soon became apparent, that solvent free reaction is possible, which results in high space-time-yields, higher economic impact and the possibility to recycle the catalyst in the reactive ionic liquid. Therefore, the active catalyst species needs to be highly polar, which was achieved by using sulfonated analogues of the used phosphine ligands, to be dissolved in the dimcarb phase.

In case of the hydroamination of β-farnesene, tetrasulfonated 1,4-bis(diphenylphosphino)butane (DPPBTS) was used and a catalyst recycling over 8 runs could be achieved without any loss of activity (Figure 2). Subsequently, an oxidation of the ligand was observed and the reaction performance decreased. Nevertheless, a total turn over number (TTON) of 8724 was accomplished. The catalytic system was also applied to other 1,3-dienes, like β-myrcene and isoprene, whereby these two showed slightly lower overall yields.
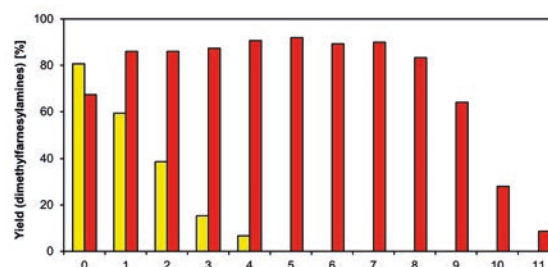

Figure 2: Isolated product yields of the palladium catalyzed hydroamination β-farnesene using the DPPB-ligand (yellow bars) and the tetrasulfonated analog DPPBTS (red bars). Reaction conditions: Pd(tfa)$_2$, 0.1 mol%, metal/ligand = 1/4, $n_{dimcarb}$ = 45 mmol, $n_{\beta\text{-farnesene}}$ = 15 mmol, T = 100 °C, t = 3 h, 500 rpm. Recycling conditions: dimcarb was refilled to 45 mmol (addition of 7.5 mmol), phase separation at room temperature under schlenk technique, addition of 15 mmol β-farnesene, restart of the reaction.

In case of the telomerisation, an even higher performance of the recycling of the catalyst was achieved. With TPPTS (triphenyl phosphine trisulfonate) as ligand no loss of activity over 30 recycling runs (Figure 3) was accomplished. The TTON was at 90712.
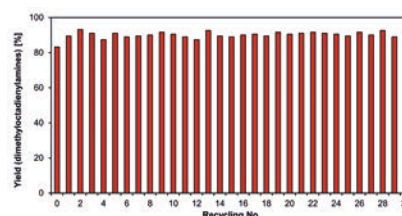

Figure 3: Isolated product yields of the palladium catalyzed telomerization of 1,3-butadiene with dimcarb to N,N-dimethyl octadienylamines. Reaction conditions: Precursor = Pd(acac)$_2$, 0.03 mol% based on 1,3 butadiene, ligand = TPPTS(= triphenylphosphine-trisulfonate), metal/ligand = 1/4, $n_{dimcarb}$ = 30 mmol, $n_{1,3\text{-butadiene}}$ = 38 mmol, T = 80 °C, t = 2 h, 500 rpm. Recycling conditions: Extraction of the product with cyclohexane (2 × 2 mL), dimcarb was refilled to 30 mmol (addition of 11 mmol), addition of 38 mmol 1,3-butadiene, restart of the reaction. TTON defined as converted moles of 1,3-butadiene to the desired products per molecule palladium.

Furthermore, we were able to show, that a recycling of the rhodium catalyst for the hydroaminomethylation of 1-dodecene with dimcarb is promising, although a slight loss of activity was observed due to little leaching of the catalyst.

In conclusion, we were able to show that dimcarb is a very good compound for an application in the recycling of homogeneous transition metal catalysts in amination reactions. We were able to establish three different reactions with very good recycling results.

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Process Development of the Continuously Operated Synthesis of N,N-Dimethylformamide Based on Carbon Dioxide

An evaluation of stability, selectivity and recyclability of a RuCl$_3$ – BISBI catalyst complex

Kai Künnemann, Rene Kuhlmann, A. Prüllage, Arno Behr, Andreas J. Vorholt

The utilization of carbon dioxide, CO$_2$, is currently a hot topic for the sustainable production of chemicals and storage of renewable energy. N,N-*Dimethylformamide (DMF) is an important solvent in the fine chemicals industry and for extractions. The direct synthesis of DMF form CO$_2$ and Dimethylamine with hydrogen was performed in this work with a ruthenium catalyst in a miniplant. Stable operation was demonstrated over a period of 160 hours, demonstrating the feasibility of this approach.*

Due to rising environmental constraints and limitations of fossil resources the chemical industry focuses more and more on the substitution of the usually applied C1-carbon sources like carbon monoxide, methanol, formaldehydes etc. by CO$_2$. In order to compete economically and ecologically against existing processes, carbon dioxide based processes need well-developed reaction systems. In this work, the process development for the homogenously catalyzed hydrogenation of carbon dioxide in presence of dimethylamine to N,N-dimethylformamide (Figure 1) will be demonstrated.

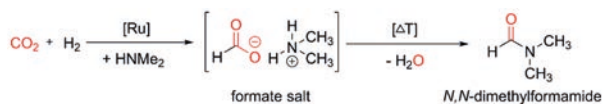
Figure 1: Formation of N,N-dimethylformamide.

Since questions about the substrate and catalyst recycling cannot fully be answered just by batch experiments in laboratory scale, this reaction system was transferred into a continuously operated miniplant (Figure 2) in order to investigate the recycling concept of the catalyst and the reaction behavior regarding both the selectivity and the long-term stability of the catalyst.
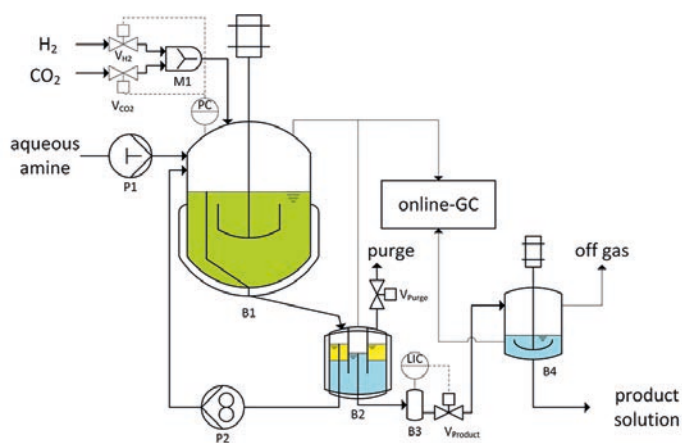

Figure 2: Simplified flow sheet of the continuously operated miniplant for the DMF synthesis.

Various experiments have shown promising results for the reaction systems towards long term stability and selectivity by achieving a stable run-time of 95 h with yields of DMF >40 % (Figure 3). Further investigations of all process streams revealed also that only carbon monoxide is formed as byproduct in very low concentrations (<50ppm).
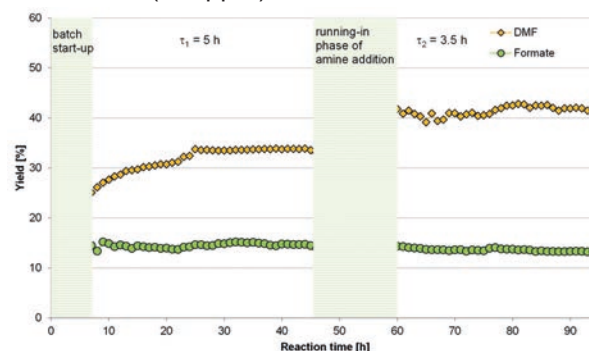
Figure 3: Miniplant results with purge flow regulation. Reaction conditions: Precursor: RuCl$_3$•H$_2$O, Ligand: BISBI, c_{Ru} = 2 mmol/l, c_{BISBI} = 1.6 mmol/l, c_{DMA} = 3.8 mol/l, $m_{DMA\text{-}solution}$: $m_{2\text{-ethylhexan-1-ol}}$ = 1:1, $V_{reactor}$ = 2000 ml, V_{liquid} = 330 ml, t_{batch} = 6 h, $U_{stirrer}$ = 700 1/min, $\tau_{reactor}$ = 3.4 h, $T_{reactor}$ = 140 °C, $T_{separator(B2)}$ = 30 °C, p_{total} = 40 bar, $V_{CO2:VH2}$ = 0.5 : 1, $V_{dimethylamine\text{-}solution}$ = $V_{recycle}$ = 33 ml/h, $V_{dimethylethanolamine}$ = 24 ml/h.

Especially the gas composition had a major impact on the activity of the catalyst. A defined ratio of CO$_2$ to amine increased the yield from 14 % to 34 % at an even lower residence time. Furthermore, the catalyst leaching was low with 0.3 wt.%/h in average and had no measurable influence on the activity during the investigated time frame, even at temperatures up to 160 °C. A subsequent product isolation via distillation was successfully realized and showed moreover no product decomposition.

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Selective Product Crystallization for Sustainable Recycling of Homogeneous Catalyst

Norman Herrmann, Andreas J. Vorholt, Thomas Seidensticker

Conversion of renewable raw materials by homogeneous transition metal catalysis can play a great role in the chemical industry of the future, both from a sustainability and economic point of view. The crux lies in the recovery of the homogeneously dissolved catalyst. In this context, a simple process for selective product crystallization was developed that enables the catalyst used in the product to be recycled for high-purity products. The renewable methyl-10-undecenoate obtained from castor oil used here supplies economic diesters with methoxycarbonylation and linear alcohols in reductive hydroformylation for ester alcohol synthesis.

Environmental awareness and sustainability are becoming increasingly important in the chemical industry. One important aspect in this context is the implementation of renewable resources in chemical processes. The homogeneously catalyzed hydro-formylation of unsaturated long-chained oleo compounds is a promising strategy for adding value to renewable resources. Unfortunately in this context, the recycling of the homogeneous catalyst is a great challenge. This is particularly true in carbonylation reactions of oleobased compounds, since these often suffer from high boiling points and/or high degrees of functionalization. Often distillation cannot be used because at the elevated temperatures that are required. Extraction is also not of interest because a large amount of extractant must be used to separate the catalyst. One approach for catalyst recovery at mild conditions is the crystallization of the product and subsequent separation of the catalyst and the solid product. The principle is to cool down the reaction solution slowly in certain temperature intervals. After precipitation of the product, the catalyst solution is separated via filtration. This technique is gentle in terms of thermal stress to the product, the catalyst and the applied ligands (Figure 2 and 3).

A palladium/ DTBPMB complex was used as catalyst for the methoxycarbonylation. This reaction system gave a high n-selectivity (95 %). The yield of the isolated linear diester after crystallization is 95 %.
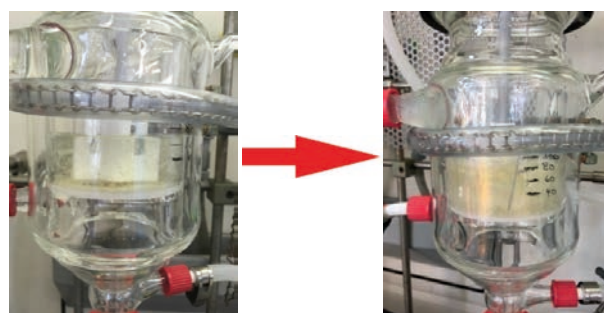
Figure 2: Reaction mixture before, Figure 3: Reaction mixture after crystallization.

The hydroformylation/ hydrogenation reaction was operated with two different catalysts, whereas the hydroformylation was catalyzed by a rhodium/ Biphephos complex and the subsequent hydrogenation was catalyzed by a ruthenium/ tetracyclone complex. This reaction system resulted in high *n*-selectivity (82 %). The yield of the isolated linear alcohol after crystallization was 82 %. By crystallization of the product most of the catalyst remained in the reaction solution and was recycled for further reactions.

Figure 1: Homogeneously catalysed synthesis of polymer precursors from the renewable methyl 10-undecenoate and catalyst recycling by selective product crystallization.

To show the feasibility of this approach, the above-mentioned methoxycarbonylation of methyl-10-undecenoate was investigated, as well as the tandem hydroformylation/ hydrogenation reaction applying the same substrate (Figure1).

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Micelle-Like Polymer Particles – Phase Transfer Agents in Aqueous Hydroformylation of 1-octene

Daniel Peral, D. Stehl, B. Bibouche, H. Yu, J. Mardoukh, R. Schomäcker, R. von Klitzing, Dieter Vogt

For the industrial application of homogeneous catalysts efficient separation and recycling are important issues. The use of water soluble catalysts in aqueous biphasic catalysis is a proven concept for catalyst recovery in the Ruhrchemie-RhônePoulenc hydroformylation process. However, this is only applicable for water soluble substrates. In order to apply the concept also for higher alkenes, micelle-like polymer particles have been used as phase transfer agents and catalyst carriers for anionic ligands in aqueous multiphase hydroformylation reactions. High reaction rates and efficient catalyst recycling were demonstrated, showing the high potential of this approach.

Colloidal, micelle-like polymer particles have been synthesized - constituting a non-polar cross-linked polystyrene core, a polyethylene glycol shell (making them water soluble) and are functionalized with cationic ammonium salts which can attract anionic ligands.
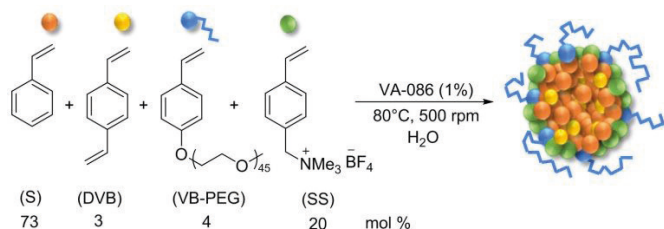

Figure 1: Molar composition and reaction conditions for the synthesis of the polymer particle suspensions by emulsion polymerization.

The particles were characterised by dynamic light scattering (DLS), atomic force microscopy (AFM), transmission electron microscopy (TEM), scanning electron microscopy (SEM) and zeta potential (ζ) measurements.
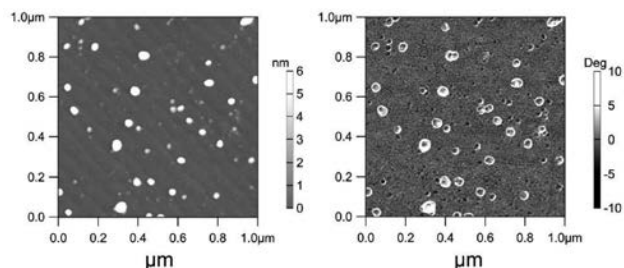

Figure 2: AFM images of polymer particles. Height image (left) and phase image (right).

These polymer particles were designed to act as microreactors in aqueous biphasic catalytic reactions. The particles are suspended in the aqueous catalyst phase where they electrostatically attract any ionic ligands (e.g. the common TPPTS-ligand). The particles were applied as phase transfer agents in aqueous multiphase rhodium-catalysed hydroformylation of 1-octene (scheme 1 below).
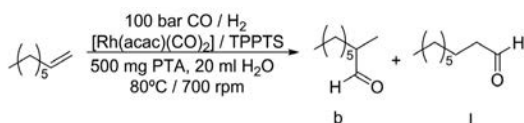
Scheme 1: Multiphase hydroformylation of 1-octene.

The reactions were performed in high pressure autoclaves fitted with mechanical gas-inlet stirrers, temperature control, dropping funnels and mass flow control units. Only branched and linear aldehydes were detected in the GC analysis after the reaction, obtaining around 72 % linear aldehydes. The organic phase was further analyzed by ICP-OES showing the amount of rhodium to be below 0.5 ppm. Recycling experiments of the aqueous catalyst/particle phase was then performed three times (Table 1 below).

Run	Conversion (%)	Chemosel. (%)	l: b	TOF at 10% conv. (h^{-1})
1	74.6	>99	2.6	272
2	91.9	96.4	2.5	476
3	92.7	82.7	2.5	462
4	98.5	85.9	1.7	381

Reaction conditions: 0.03 mmol [Rh(acac)(CO)$_2$], 0.18 mmol TPPTS, 150 mmol 1-octene, [C]:[L]:[S] = 1:6:5000, 15 mmol n–dodecane as standard. 500 mg of LX5, 20 ml H$_2$O. 80 °C, 700 rpm, 100 bar CO:H$_2$ (1:1), 22 h.

Table 1: Recycling experiments of the multiphasic hydroformylation of 1-octene using latex particles.

The reaction progress of the recycling experiments is shown in Figure 3 below.

Figure 3: Yield of aldehyde vs. time in the aqueous multiphase hydroformylation of different alkenes.

Further work to optimize the system is underway, with particular focus on recyclability, conversion and selectivity – parameters which are important for industrial application of a process.

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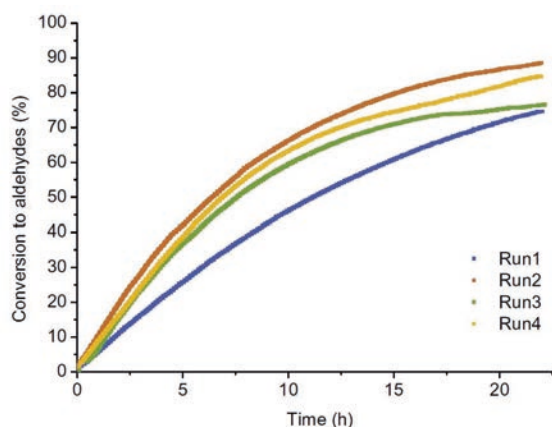# Continuously Operated Hydroamination – Toward High Catalytic Performance *via* Organic Solvent Nanofiltration in a Membrane Reactor

Implementation of a stable polymeric membrane for *in-situ* separation of the homogeneous catalyst

Dennis Vogelsang, Jens M. Dreimann, D. Wenzel, Andreas J. Vorholt

The continuous operation of the palladium catalysed hydroamination is still a challenging task. Herein, we present the high performance of a membrane reactor by the implementation of ambitious hydroamination reaction of β-myrcene with morpholine. Via application of a proper poly ether−ether−ketone (PEEK) membrane, operation at elevated temperatures was possible in an integrated reaction/separation unit. By application of model-based predicted reaction conditions, a drastic increase of the turnover number from 460 to 5135 compared to a batch process was achieved. The desired geranyl amines as target products were obtained in very good yields higher than 80%, while an excellent conversion of β-myrcene above 93% was reached in a long-time stable process.

The palladium-catalysed hydroamination of β-myrcene with morpholine is a value adding well-studied reaction to form allylic amines in a 100% atom economic way (Figure 1). The industrial relevant terpenyl amines1 can be applied as intermediates in Takasago process to produce (-)-menthol.
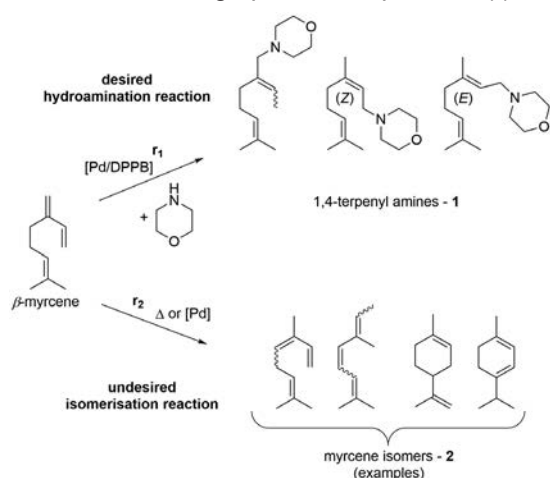

Figure 1: Reaction pathways of the hydroamination reaction of β-myrcene and morpholine. (r_1=hydroamination, r_2=isomerisation); For simplification only examples of double bond isomers are shown.

Still, the continuous operation of the hydroamination is a challenging task. The applied palladium catalyst is prone to precipitation by changing the reaction conditions, which limits the number of suitable catalyst recovery methods.

One concept to increase the productivity of the homogeneous transition metal without having a strong influence on the reaction conditions is the usage of organophilic solvent nanofiltration (OSN).

In the present study, a polymeric poly-ether-ether-ketone-membrane was applied in a dead-end filtration membrane reactor. To evaluate the optimal process conditions, the continuous operation was implemented in three steps. First, the kinetics of the hydroamination reaction and relevant membrane characteristics were determined under optimized reaction conditions. Afterwards, these results were incorporated in a reactor/separator model to predict the process behavior. With this, catalyst replenishment was adjusted resulting in stable continuous operation (Figure 2).
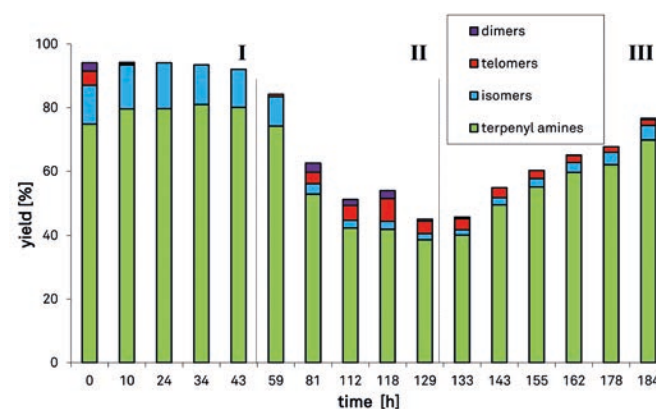
Figure 2: Interval I: (predicted optimal conditions): c(β-myrcene) = c(morpholine) = 0.17 mol/L, c(Pd(tfa)$_2$) = 6.86·10^{-5} mol/L, c(DPPB) = 5.56·10^{-4} mol/L, T=100 °C, 500 rpm, feed = 9.9 g/h; interval II ligand omitted): c(β-myrcene) = c(morpholine) = 0.17 mol/L, T = 100 °C, 500 rpm, feed = 9.9 g/h; III = I; all results were determined via GC-FID-analysis.

The desired geranyl amines were obtained in yields and selectivities higher than 90% over a time period of one week. Via utilization of Organic Solvent Nanofiltration the turn-over-number (TON) of the catalyst could be drastically increased to 5135 compared to the batch process with 460. By this process intensification, the continuous hydro-amination could be more feasible for industrial application.

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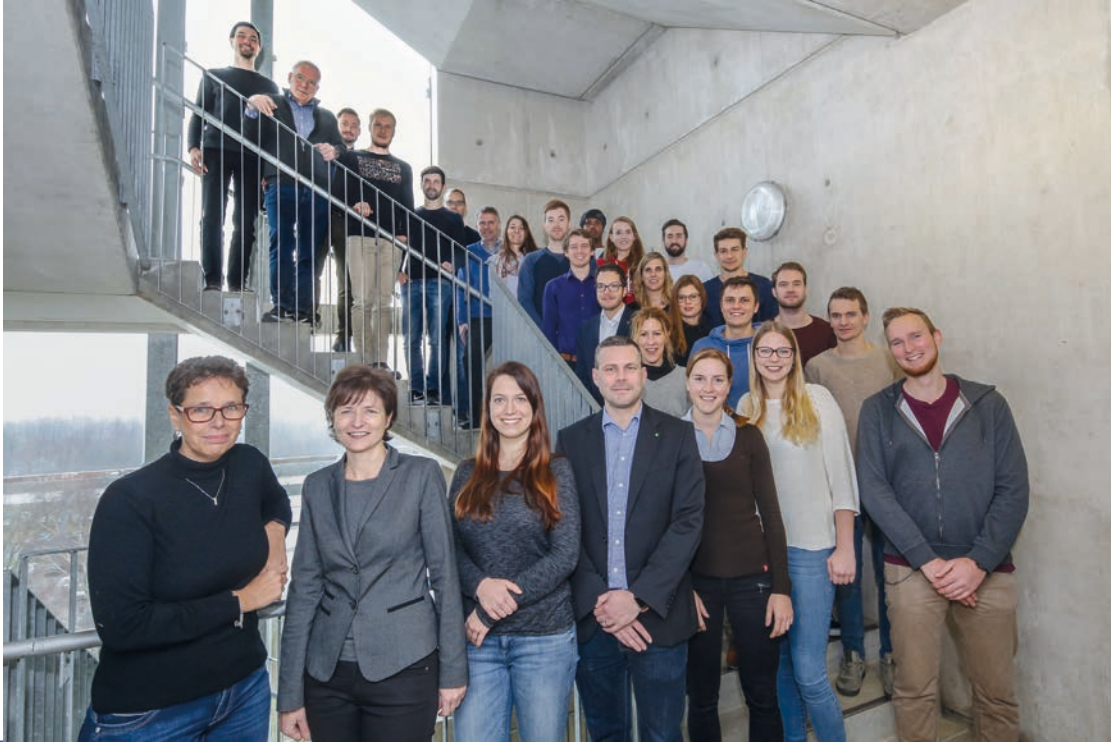
Thermodynamics (TH)

Modeling Mixtures of Long-Chain Hydrocarbons and Water Using PC-SAFT

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Modeling and measuring the very low mutual solubility in binary n-alkane + water mixtures is very challenging. Consequently, experimental data regarding mutual solubilities of these components scatter remarkably. In this work, the PC-SAFT equation of state has been applied to successfully model liquid-liquid equilibria of binary n-*alkane + water mixtures. Excellent agreement between modeling results and available experimental data has been achieved for the liquid-liquid equilibria even describing the minimum of* n-*alkane solubility in water as a function of temperature. These results could further be used to predict mutual solubilities in binary methyl ester + water mixtures.*

In petrochemical plants like refineries and steam crackers, process water or steam inevitably gets in contact with crude oil or hydrocarbons. If water exceeds its solubility limit in hydrocarbons, e.g. *n*-alkanes, corrosion of plant equipment can be caused. Furthermore, wastewater streams are polluted with *n*-alkanes which need to be removed for environmental reasons. Hence, knowledge of the mutual solubility in *n*-alkane + water mixtures is indispensable.

In the past, several thermodynamic models have already been applied to model the mutual solubility in these systems without achieving a satisfying description of the phase behavior. In this work, the homo-segmental Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) was applied for the modeling. The results are depicted in Figure 1 along with experimental data from literature. It can be seen that the solubility of water in the organic phase monotonically increases with temperature and only slightly depends on the chain length of the *n*-alkane. In contrast, the solubility of the *n*-alkanes in the aqueous phase exhibits a minimum as function of temperature and significantly varies with the chain length of the *n*-alkane.
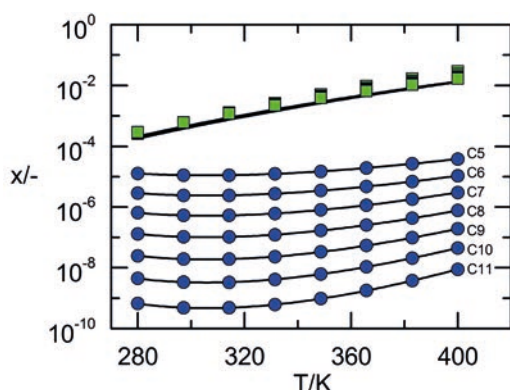
PC-SAFT achieves a remarkably good description of the solubility of the *n*-alkane in the aqueous phase for all *n*-alkanes from *n*-pentane to *n*-undecane including describing the minimum as function of temperature, whereas the models used in the literature so far predict a continuous decrease in solubility for decreasing temperature. Beyond that, the solubility of water in the organic phase is also predicted very well. These modeling results could also be used within a new hetero-segmental approach of PC-SAFT to predict the mutual solubilities in binary methyl ester + water mixtures. For this, the long-chain ester was modeled as comprising a universal functional head domain and an *n*-alkylic residue modeled as an *n*-alkane. Hence, the interactions between water and the *n*-alkylic residue were described using the aforementioned modeling approach of *n*-alkane + water mixtures. As an example, the mutual solubility in the binary methyl hexanoate + water mixture could be predicted without any parameter fitting as shown in Figure 2.

Figure 1: Mutual solubilities of water and *n*-alkanes (*n*-pentane to *n*-undecane). Lines: modeling results with PC-SAFT. Symbols: experimental data where squares represent the solubility of water in the organic phase and circles show the solubility of the *n*-alkanes in the aqueous phase (J. Phys. Chem. Ref. Data 33 (2004) 549-577).
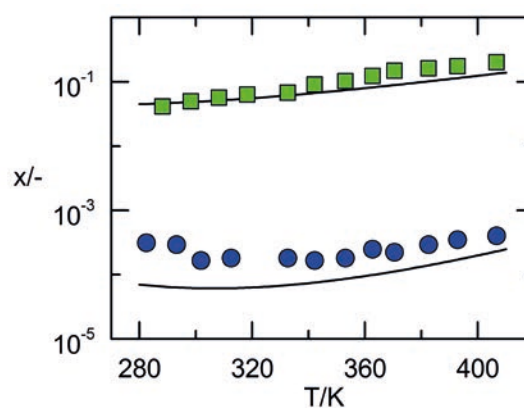

Figure 2: Mutual solubilities of water and methyl hexanoate. Lines: predictions with PC-SAFT. Symbols: experimental data where squares represent the solubility of water in the organic phase and circles show the solubility of methyl hexanoate in the aqueous phase.

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Selecting Best Polymeric Excipients for Amorphous Solid Dispersions

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The formulation of so-called amorphous solid dispersions (ASDs) is an established technique to improve the oral bioavailability of poorly-water-soluble active pharmaceutical ingredients (APIs). In an ASD, an amorphous API which usually shows a higher solubility than its crystalline form is embedded in excipient(s) (e.g. amorphous polymers) to inhibit API crystallization. The excipient selection for long-term physically-stable, crystal-free ASD formulations usually requires time- and resource-consuming stability studies at relevant storage temperatures and relative humidities (RHs). This work shows that thermodynamic modeling can be used to determine suitable excipients and excipient compositions therewith reducing cost-intensive stability studies to a minimum.

The low water solubility of many active pharmaceutical ingredients (APIs) is a main bottleneck in the development of oral solid dosage forms. The aim of dissolving the API in amorphous excipients by generating so-called amorphous solid dispersions (ASDs) is to stabilize the higher-soluble amorphous form of the API. ASDs are thermodynamically stable if the API content is lower than the API solubility in the excipients. Supersaturated ASDs are kinetically stabilized as long as the storage temperature is sufficiently lower than the glass-transition temperature (T_g) of the ASD. Thus, the physical stability of ASDs in terms of API-crystallization inhibition can be concluded from the phase diagram which contains solubility curve and T_g curve.

In this work, the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT), and the Kwei equation were applied to model the solubility curve and the T_g curve, respectively, of naproxen and paracetamol ASDs at 0 %, 60 % and 75 % RH. Hydroxypropyl methylcellulose acetate succinate (HPMCAS), poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA 64) and poly(vinylpyrrolidone) (PVP) as well as blends of these polymers were considered as excipients. For validation of the modeling results, ASD formulations were prepared via hot-melt extrusion or spray drying and stored for up to 24 months at standard conditions (25 °C/0 % RH; 25 °C/60 % RH; 40 °C/75 % RH). The samples were monitored periodically for API crystallization by polarized-light microscopy and powder X-ray diffraction.

At 0 % RH, the modeling revealed decreasing solubilizing and kinetically-stabilizing abilities of the applied polymers in the order PVP > PVPVA64 > HPMCAS. The physical stability was also predicted to decrease with increasing HPMCAS content in the API/polymer-blend ASDs. The predicted impact of RH generally correlates with the hydrophilicity of the polymers: PVP > PVPVA64 > HPMCAS.

Figure 1 shows as an example the predicted phase diagrams for paracetamol/polymer ASDs at 75 % RH.
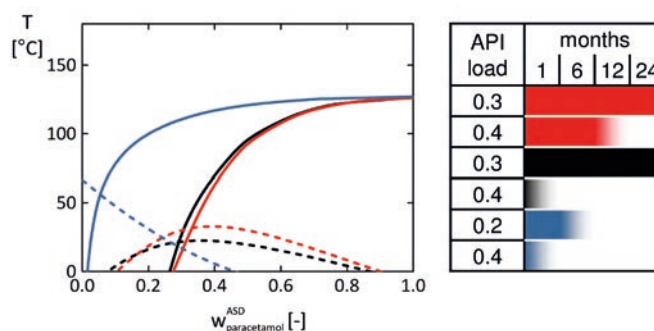

Figure 1: Physical stability of paracetamol ASDs with PVP (red), PVPVA64 (black) and HPMCAS (blue). left: Phase diagrams at 75 % RH. The full lines represent the solubility lines calculated using PC-SAFT. The dashed lines represent the T_g calculated using the Kwei equation. The x-axis refers to the API content in the water-free ASDs. right: Experimental results of stability studies at 40 °C/75 % RH. The lengths of the bars indicate the number of months after which first crystals were observed. Full bar indicates the ASD was still crystal-free at the end of the studies.

As to be seen, PVP and PVPVA64 ASDs with 30 wt% paracetamol remained stable at 40°C/75 % RH for 24 months, while the PVP and PVPVA64 ASDs with higher paracetamol loads (≥40 wt%) and the HPMCAS ASDs (≥20 wt % paracetamol) crystallized within one to twelve months. This agrees with the predicted phase diagrams; at 40 °C the 30 wt% PVP and PVPVA64 samples are located to the left of the solubility lines, while all other samples are supersaturated (to the right of the solubility line).

Same as the presented example, stability results of all investigated systems agreed very well with the modeled phase diagrams. Thus, PC-SAFT and the Kwei equation can be applied as an early tool for excipient selection in the design of ASD formulations.

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Crystallization Kinetics in Pharmaceutical Formulations

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Most recently marketed polymer-based pharmaceutical formulations are thermodynamically instable; their long-term stability is basically impaired by crystallization of the incorporated active pharmaceutical ingredient. Robust detection and quantification of crystal formation- especially at temperatures and humidities relevant for long-term storage tests - are essential for understanding the crystallization phenomena. In this work, the moisture-induced crystallization kinetics was investigated just by measuring the kinetics of water-sorption from humid air. By combining these experiments with thermodynamic predictions of the water sorption in amorphous versus crystallized formulations, the amount of crystallized nifedipine could be in-situ determined as function of time just by weighing the ASD samples and without any calibration.

The bioavailability of poorly water-soluble active pharmaceutical ingredients (APIs) is significantly improved by dissolving the amorphous API in a suitable polymer. Several formulations based on this approach have been marketed recently. In most of these formulations, the API loading exceeds the equilibrium solubility of the API in the polymer. The API will therefore crystallize as function of time, meaning the end of shelf life of the formulation. Knowledge of the API crystallization kinetics in such systems is essential to find suitable polymeric excipients and sufficiently long-term-stable API/polymer compositions.

Time-dependent water sorption measurements in nifedipine/ poly (vinyl acetate) formulations revealed that the water content in the formulation changes even during storage at constant storage conditions (40 °C / 75% relative humidity (RH)). Results of sorption measurements in formulations with different nifedipine loadings are shown in Figure 1.
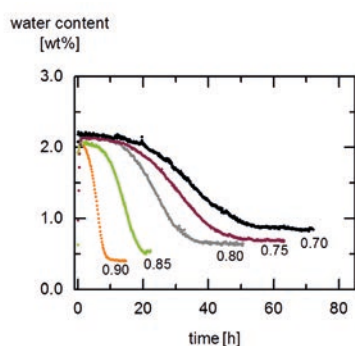

Figure 1: Measured water sorption as function of time in nifedipine/ poly (vinyl acetate) formulations with indicated nifedipine loadings stored at 40 °C / 75% RH.

As can be seen in Figure 1, the water content increased almost instantaneously upon exposure to RH to a value of approximately 2.1 wt % followed by a decrease after a few hours finally reaching a second plateau. X-ray measurements confirmed that initially amorphous formulations crystallized during these sorption measurements.

Using Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) the observed water-sorption behavior of the amorphous (at the beginning) and crystallized (at the end) formulations was predicted almost quantitatively.

Thus, the amount of nifedipine crystals could be directly obtained by combining the experimental results from Figure 1 with PC SAFT water-sorption predictions (Figure 2).
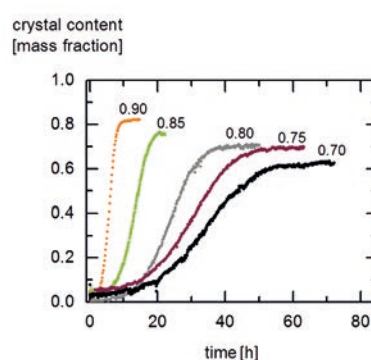
Figure 2: Nifedipine crystallization kinetics in nifedipine/ poly (vinyl acetate) formulations with different nifedipine loadings calculated from the measured water-sorption data (Figure 1) combined with PC-SAFT water-sorption predictions.

Figure 2 shows that the crystal content was predicted to be zero at the beginning of the experiment and increased sigmoidally upon further storage. Obviously, a high API content in a formulation accelerates the crystallization kinetics (12 hours in formulations containing 90 wt % nifedipine vs. 60 hours in those containing 70 wt %).

This robust new approach allows for easy, reliable and in-situ determining the crystallization kinetics in pharmaceutical formulations and thus estimating their shelf life.

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Excipients for High-Concentration Biopharmaceutical Formulations

How thermodynamics can aid in the choice for the right excipients

Miko Schleinitz, Gabriele Sadowski, Christoph Brandenbusch

Biopharmaceuticals, especially therapeutic proteins such as monoclonal antibodies (mAbs) are the fastest growing segment in the pharmaceutical industry. However, most of these proteins show a poor aqueous solubility limiting their application to intravenous administration over several hours to deliver the required dosage (> 100 mg). "High Concentration Protein Formulations" (HCPFs) can solve this problem and lead to formulations with concentrations allowing for delivery of the required dosage in a single injection (self-administration). However, identification of these HCPFs is commonly based on heuristic decisions and "trial-and-error" screening approaches. Within this work, we developed a physical sound method to identify HCPFs with the aid of thermodynamic modeling.

HCPFs are commonly achieved by addition of suitable excipients (e.g. salts, sugars, amino acids, surfactants), which are approved by the Food and Drug Administration (FDA), to aqueous protein solutions. Even though many excipients described in recent literature fulfill the requirements of enhanced solubility and solubility of the biopharmaceutical in solution, no general approach exists to identify suitable excipients. Furthermore, the "state-of-the-art" development of HCPFs and the selection of excipients are almost solely based on heuristic approaches hindering transferability of the results to other biopharmaceuticals or formulations. Furthermore consideration of negative influences induced by the excipients (e.g. protein agglomeration) upon excipient selection is so far not possible in advance. To solve this challenge, we developed a physically-sound method (using both, experiments and thermodynamic modelling) to identify suitable excipients based on intermolecular interactions.
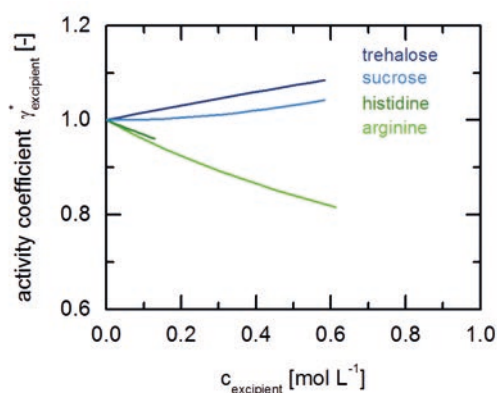

Figure 1: Activity coefficients of sugars and amino acids as a function of excipient concentration.

The suitability of an excipient was first predicted based on its thermodynamic behavior in aqueous buffer solution expressed by its activity coefficient.

If the latter is below 1, the excipient prefers to be surrounded by other excipients (instead of water molecules) thus leaving more water molecules for the hydration of the biopharmaceutical (see Figure 1) which is beneficial.

Thus, an initial excipient screening can already be performed without the knowledge on the biopharmaceutical itself, and limited amount of experimental data. Afterwards, osmotic virial coefficients were taken into account to access the protein-protein interactions in the presence of the excipients (second osmotic virial coefficient, B_{22}) as well as the protein-excipient interactions (cross virial coefficient, B_{23}).

Based on these values, which can be measured by light-scattering experiments as well as predicted using an in-house model, the aggregation propensity of the biopharmaceutical was accessible (Fig. 2).
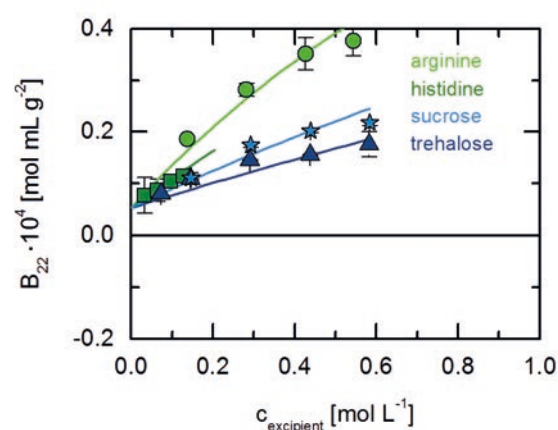
Figure 2: Second osmotic virial coefficients B_{22} of a monoclonal antibody as a function of sugar or amino acid concentration.

Results on optimal formulations were then evaluated by long-term stability studies. Critical parameters are both aggregate formation / loss in monomer content as well as solubility of the biopharmaceutical.

This method will simplify the future of biologics formulation development and increase the understanding of the mechanisms behind the stabilization of biopharmaceuticals by excipients and excipient mixtures.

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Reaction Equilibria and Reaction Kinetics of an Enzyme-Catalyzed Reaction

Experimental and Theoretical Study on the Influence of Additives on Reaction Equilibrium and Reaction Kinetics

Anton Wangler, Gabriele Sadowski, Christoph Held

Reaction equilibrium and reaction kinetics are two key parameters in biotechnological process design. While reaction conditions (T, pH, concentrations) usually only moderately influence the equilibrium position and reaction kinetics, the influence of additives such as PEG or salts (e.g. Na$_3$Cit) is known to be much stronger. In this work, the influence of the additives PEG and Na$_3$Cit on the reaction equilibrium and reaction kinetics of the acetophenone reduction catalyzed by ADH 270 was studied. The experimental results showed a very beneficial effect of the additives on reaction kinetics while the reaction equilibrium was shifted to the reactant side. The observed effects were explained by molecular interactions between the reacting agents and the reaction medium. These were expressed and quantified via activity coefficients of the reacting agents, which allowed even predicting the additive influence on reaction kinetics and reaction equilibrium.

New developments in downstream processing, e.g. the addition of possible phase formers (inert additives) for in situ product removal from aqueous broth constantly improve the process design in biotechnology. While leading to more efficient product purification, the presence of additives also affects reaction yield and reaction kinetics. This was addressed in the present work for an alcohol dehydrogenase (ADH 270) – catalyzed reaction:
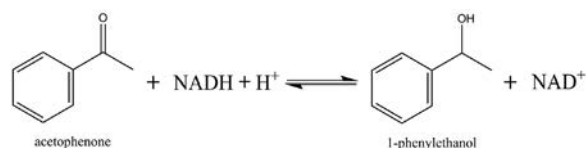

Figure 1: Reaction scheme of the reduction of acetophenone to 1-phenylethanol by a modified alcohol dehydrogenase ADH 270.

The reaction yield is connected to the thermodynamic equilibrium constant K_{th} that only depends on temperature and pressure as:

$$K_{th} = K_{exp}K_\gamma = \frac{x_{NAD^+} \cdot x_{1-PE}}{x_{NADH} \cdot x_{ACP} \cdot x_{H^+}} \frac{\gamma_{NAD^+} \cdot \gamma_{1-PE}}{\gamma_{NADH} \cdot \gamma_{ACP} \cdot \gamma_{H^+}} \quad (1)$$

In Eq. (1), x and γ are the mole fractions and activity coefficients of the reacting agents at equilibrium. The kinetics of an enzyme-catalyzed reaction is characterized by the maximum reaction velocity r_{max} and the Michaelis constant K_M, which is an important factor for determining substrate affinity to the enzyme. The Michaelis-Menten equation for a two-substrate reaction based on substrate activities a_i is:

$$r = \frac{r_{max} \cdot a_{NADH} \cdot a_{ACP}}{K_{IA} \cdot K_{M,ACP}^a + a_{NADH} \cdot K_{M,ACP}^a + a_{ACP} \cdot K_{M,NADH}^a + a_{NADH} \cdot a_{ACP}} \quad (2)$$

where K_{IA} and K_M^a are the inhibition constant and the activity-based Michaelis constants of ACP and NADH, respectively.

Addition of inert additives to the reaction mixture will impact the activity coefficients and thus the equilibrium position and the reaction kinetics, while K_{th} and K_M^a remain constant,

as long as the stability of the enzyme upon addition of the additives is still ensured. The tremendous influence of the considered additives (PEG and Na$_3$Cit) on equilibrium position and reaction kinetics is illustrated in Figures 2 and 3. For both additives the reaction equilibrium was significantly shifted to the reactant side (Figure 2 left). Regarding reaction kinetics, K_M of acetophenone increased, while K_M of NADH decreased upon addition of PEG to the neat reaction mixtures (Figure 2 right). This behavior could be explained by molecular interactions between reacting agents and the reaction medium. For quantification, the activity coefficients of the reacting agents were predicted using ePC SAFT, which allowed for accurately predicting the equilibrium position and the Michaelis constants. This further shows that activity-based constants are general and additive-independent values that are crucial for process design in biotechnology.

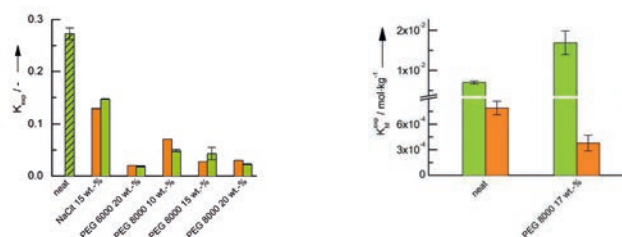Figure 2 left: Comparison between predicted equilibrium compositions K_{exp} (orange) and the respective experimental values (green) of the acetophenone reduction; T = 303 K, pH = 8.

Figure 2 right: Comparison of between experimental Michalis constants K_M of acetophenone (green) and NADH (orange); T = 303 K, pH = 8.

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New Experimental Melting Properties for Predicting Amino-Acid Solubility

The combination of new experimental melting properties and the modeling using PC-SAFT allows quantitative predictions of amino-acid solubility in water

Yeong Zen Chua, Hoang Tam Do, Christoph Schick, Dzmitry Zaitsau, Christoph Held

Predicting the solubility of solid compounds requires their melting properties. Measuring the melting temperature and the enthalpy of fusion of biological compounds by calorimetry is often not possible due to the decomposition during heating. To overcome this problem, fast scanning calorimetry (FSC) was used to measure the melting properties of glycine and L-alanine. These new melting properties were used to predict the solubility of an amino acid in water by using the modeling framework PC-SAFT. At first, the solubility-independent thermodynamic properties such as osmotic coefficients and mixture densities of these amino acids in water were used to fit the pure-component PC-SAFT parameters and one binary parameter. The predicted solubility of amino-acid in water was found to be in quantitative agreement over a broad temperature range. The combination of FSC and PC-SAFT provides access for predicting solubility of biomolecules which decompose before melting.

The production and purification of amino acids is still realized through crystallization which is the state-of-the art unit operation. The solubility of amino-acid is essential for crystallization because it determines the product yield and purity as well as the choice of the solvent in the process. The experimental measurement of solubility is time-consuming and expensive, especially according to the high number of influences on solubility (temperature, pH-value, type and concentration of co-solutes and co-solvents). The prediction of solubility using thermodynamic models is therefore desired and can be realized by

$$x_i^{L,sat} = \frac{1}{\gamma_i^{sat}} \cdot \exp\left\{ -\frac{\Delta_{fus}H_m}{R}\left(\frac{1}{T} - \frac{1}{T_{fus}}\right)\right\} \qquad (1)$$

where $x_i^{L,sat}$ the solubility, γ_i^{sat} the activity coefficient of component i at its solubility, T_{fus} and $\Delta_{fus}H_m$ the melting temperature and molar fusion enthalpy, respecitvely. The PC-SAFT parameters for the amino acids were taken from the literature. The binary interaction parameter k_{ij} was fitted to experimental osmotic-coefficient data at T = 298.15 K and p = 1 atm (Figure 1).

The melting properties of L-alanine and glycine were determined using fast scanning calorimetry (FSC) to $\Delta_{fus}H_m$ = (21 ± 4) kJ·mol^{-1} and T_{fus} = (569 ± 7) K for glycine, and $\Delta_{fus}H_m$ = (22 ± 5) kJ·mol^{-1} and T_{fus} = (608 ± 9) K for L-alanine. Based on these melting properties, amino-acid solubility was predicted with PC-SAFT (Figure 2) and validated with experimental data from different authors.
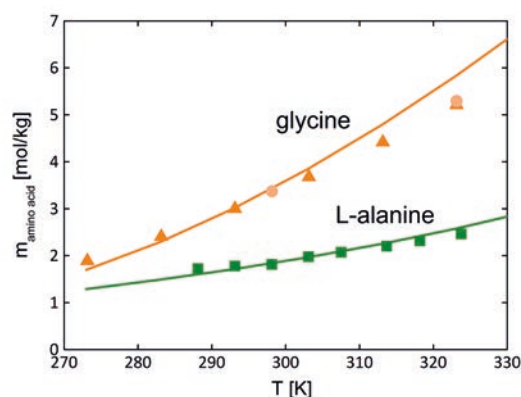
Figure 2: Solubility of glycine and L-alanine in water vs. temperature. Symbols represent experimental data (glycine: triangles, circles and L-alanine: squares). Lines represent PC SAFT predictions.

As to be seen, the prediction and experiments are in agreement over a wide temperature range. The combination of FSC and PC-SAFT allows an accurate prediction of amino-acid solubility in water which opens the door for the future for predicting solubility of molecules which decompose before melting.
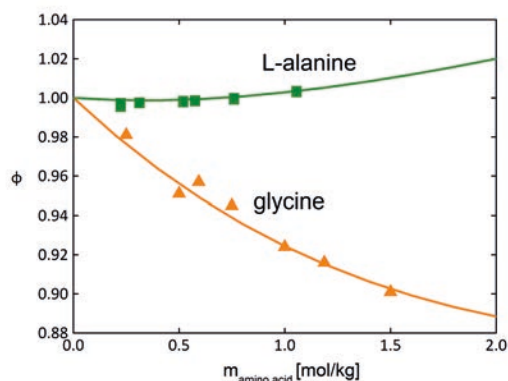

Figure 1: Osmotic coefficients Φ of glycine + water and L-alanine + water solutions at T =298.15 K and p = 1 atm. Symbols are experimental data (glycine: triangles and L-alanine: squares) and lines are PC-SAFT modeling results.

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