

# Intensification of Kinetic Studies for a Multi-step Reaction in a Milli-structured Plate Reactor by using Model-based Design of Experiments

Lucas Schaare<sup>ab\*</sup>, Rafael Kuwertz<sup>b</sup>, Joachim Heck<sup>b</sup>, Mirko Skiborowski<sup>a</sup>

<sup>a</sup>Hamburg University of Technology, Institute of Process Systems Engineering, Am Schwarzenberg-Campus 4, 21073 Hamburg, Germany

<sup>b</sup>Ehrfeld Mikrotechnik GmbH, Mikro-Forum-Ring 1, 55234 Wendelsheim, Germany  
[lucas.schaare@tuhh.de](mailto:lucas.schaare@tuhh.de)

In the context of process intensification, milli-structured plate reactors provide significant advantages over conventional reactors in terms of heat and mass transfer as well as process safety. The ART<sup>®</sup> plate reactor PR37 of Ehrfeld Mikrotechnik GmbH offers excellent heat transfer, narrow residence time distributions and high mixing efficiency, while simultaneously allowing an effective scale-up to industrial applications due to its modular set up. This does not only enable the realization of novel process windows exceeding the limits of conventional reactors, but also provides optimal prerequisites for kinetic modelling due to the well-defined process conditions, providing key information regarding process design and optimization.

The integration of the ART PR37 with Model-based Design of Experiments (MBD<sub>oE</sub>) allows for an intensification of kinetic studies, combining the well-defined operating conditions with a rapid and targeted identification of kinetic models. In the current study this combination is applied to successfully identify the kinetics of a multi-step aromatic nucleophilic substitution reaction with low experimental effort, saving time and resources compared to conventional factorial Design of Experiments.

## 1. Introduction

The optimal Design of Experiments (DoE) is a non-trivial task, especially for complex systems with nonlinear dynamics. Poorly designed experiments may yield inadequate information and can cause a waste of time and resources, and even misleading or wrong conclusions. Therefore, it is crucial to purposefully plan experiments in order to get high quality experimental data with a maximum of information. Statistical DoE methods such as full or fractional factorial designs are regularly used in industrial R&D processes and familiar to most experimental chemists. DoE uses relatively simple correlations and linear regression to model the effects of single factors and their combinations on dependent variables, such as conversion or yield. While the resulting information allows for a simple characterization of the response surfaces, the nonlinear behavior that is underlying most chemical or biochemical reaction networks is not necessarily well presented. Optimal Model-Based Design of Experiment (MBDoE) methods are explicitly developed to exploit the structure of mechanistic nonlinear and dynamic process models. These methods have secured huge attention in almost all fields of studies, particularly in biochemical disciplines (Franceschini and Macchietto, 2008). The application of MBDoE is especially suitable for continuous flow reactors which offer excellent prerequisites for fast and efficient experiments under well-defined process conditions enabled by an enhanced heat and mass transfer (Fath et al., 2020). The combination of MBDoE with flow reactors supports quick development, modification and statistical validation of linear or nonlinear, and static or dynamic models. The main benefits of MBDoE in comparison to statistical design methods are the use of prior model information, especially exploiting known model structure, the possible application to complex systems, i.e. nonlinear, dynamic and multi-dimensional systems, as well as the consideration of different objective functions, e.g. for model discrimination and parameter estimation, which enable numerical optimisation frameworks (Yu, 2018).

In any case, the main purpose of MBDoe is to optimally design experiments that return the highest information content for the identification of a suitable model. In the context of reaction kinetics, MBDoe is mainly applied for model discrimination and parameter estimation. The aim of model discrimination is to distinguish between different model structures and select the most suitable model. Design criteria for parameter estimation aim to improve the accuracy for the parameter estimation of a given model. Due to the fact, that prior information is given about the reaction order of the kinetic model to be dealt with in this study, the focus is to design experiments which help to precise the accuracy of the parameter estimation. The objective criteria for designing optimal experiments to improve the parameter estimation is mostly based on the Fisher Information Matrix (FIM), which is derived from the sensitivity matrix taking into account the partial derivatives of the model response with respect to the model parameters. In case no explicit solution of the derivative is obtainable, the parameter sensitivities can be calculated numerically, e.g. with the complex step approximation (Martins et al., 2003). In the current work, a MBDoe based on the D-optimality criteria is applied for parameter estimation, aiming to minimize the volume of the confidence ellipsoid for the estimated parameter errors.

## 2. Materials and methods

### 2.1 ART plate reactor PR37

In order to combine intensified reactor equipment and experimental design, the current work focuses on the kinetic investigation of a multi-step reaction in the ART plate reactor PR37 from Ehrfeld Mikrotechnik GmbH, which is designed as an integrated heat exchanger and reactor. The ART PR37 has a modular design and can integrate up to 10 reactor plates. The process channel is characterized by a meandering, periodically diverging/converging structure which promotes the formation of secondary flows leading to an intensification of transport processes. The utility channel is located below and contains a tubular grid that improves the cross-mixing of the tempering medium and thus the heat transfer. Four different type of plates are available (PL37-08, PL37-3, PL37-6 and PL37-12) which have similar geometry and only differ in the depth of the process channel and the respective cross-sectional area. This allows a straight forward scale-up of the process, which is even transferable to the production scale ART plate reactor PR49 (Rave et al., 2019). The reactor plates are stacked up in a frame and braced by tension rods. Due to its robust design made of stainless steel (SS 316 L) or Hastelloy (C-22), the reactor is suitable for the processing of aggressive media with pressures up to 20 bar on the process side and to 10 bar on the utility side, as well as temperatures between -60 and 200 °C. The reactor has been investigated systematically in terms of heat and mass transfer, demonstrating high heat transfer coefficients of about  $5 \text{ kW m}^{-2} \text{ K}^{-1}$  at moderate Reynolds numbers (Rave et al., 2020) and micromixing times below 0,1 s for Reynolds numbers higher 150 (Rave et al., 2022). This demonstrates the excellent suitability of the ART reactor for strongly exothermic reactions and fast, mixing-sensitive reactions. Moreover, it was found, that narrow residence time distributions close to an ideal plug flow are achieved for Reynolds numbers above 100 (Schaare et al., 2021), providing the basis for the kinetic study in this work.

### 2.2 Reaction system

In order to analyse the proposed combination of the milli-structured plate reactor and MBDoe, kinetic studies are performed in the ART PR37 for the nucleophilic aromatic substitution reaction ( $S_NAr$  reaction) between 2,4-difluoronitrobenzene (component 1) with pyrrolidine (component 2) in ethanol. This multistep reaction consists of two parallel and consecutive reactions. The reaction scheme is shown in Figure 1.

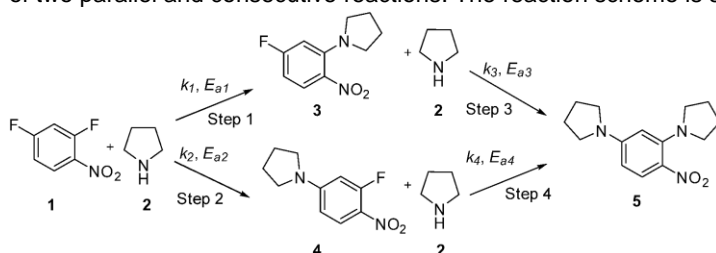


Figure 1: Nucleophilic aromatic substitution reaction of 2,4-difluoronitrobenzene (1) with pyrrolidine (2).

During the reaction, the fluorine atoms of the 2,4-difluoronitrobenzene (1) are substituted by pyrrolidine (2) forming hydrogen fluoride as side product. In the first substitution steps, ortho- (3) and para-substituted (4) intermediates are formed, which react in another substitution of pyrrolidine to the final bi-substituted product (5). According to the kinetic investigations of Hone et al. (2017), all four reaction steps of the  $S_NAr$  reaction can be assumed as second order kinetics. Based on the previous characterization of the ART reactor (Rave et al.,

2022), an ideal plug flow can be assumed for the reactor in the considered operating window allowing for a direct modelling of the reaction kinetics.

The two reactants 2,4-difluoronitrobenzene (99%) and pyrrolidine (99%) are purchased from Sigma-Aldrich as well as the base triethylamine (99,5%) and the internal standard for the HPLC-analysis N,N-dimethylbenzamide (99%). The solvent ethanol (99,8%, denatured) and hydrochloric acid (1 N standard solution), which is used as quench, are purchased by Carl Roth.

### 2.3 Experimental setup and procedure

The experimental set up of the ART PR37 for the kinetic studies is divided into a reaction and a cooling sequence. The reaction sequence consists of a series connection between plate PL37-3 and PL37-6 resulting in a reaction volume of approximately 40 mL. Below these two plates an insulation plate is installed. This insulation plate separates the reaction plates from an additional plate PL37-3 which is used as cooling plate in order to quench the reaction. With the help of the insulation plate, two thermally-decoupled zones are realized. The schematic setup of the pilot plant is shown in Figure 2.

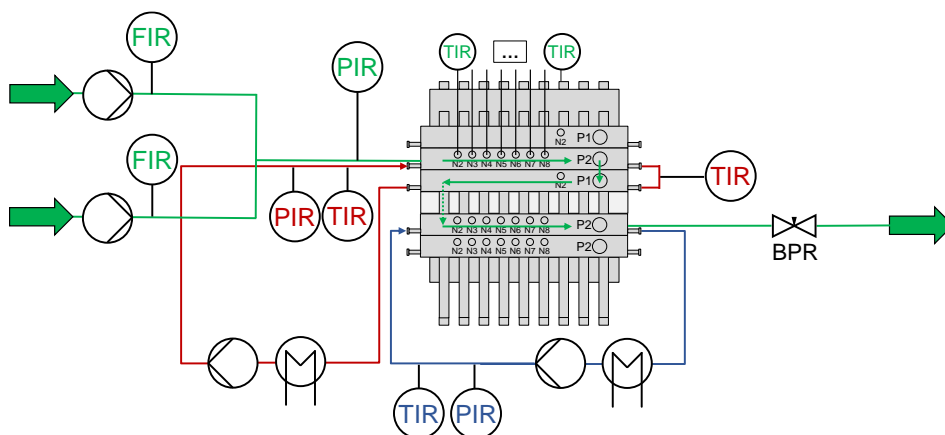


Figure 2: Schematic scheme from the pilot plant of the ART plate reactor PR37.

The two reactant solutions, introduced in Section 2.2, are fed into the reactor using gear pumps. The mass flow and density of the streams are measured using a Coriolis mass flow meter. The utility for the reaction sequence is controlled by a heating circulator supplied with thermal oil. A centrifugal pump is used to enhance the utility flow rates for an improved heat transfer. The utility stream for the cooling plate is supplied with tap water with a temperature of approximately 16 °C. In this way an efficient thermal quench of the reaction is achieved in the thermally-decoupled cooling plate after the two reaction plates. Additionally, a back-pressure regulator is used at the reactor outlet allowing to keep ethanol, which is used as solvent, in liquid state at temperatures above boiling point. The process and utility channels are equipped in total with 12 thermocouples. All measured values are continuously monitored on a computer using FieldPoint modules and LabVIEW providing a full insight into the process. The sampling is done at the outlet of the cooling plate with HPLC vials and an additional chemical quench with hydrochloric acid.

The experiments are conducted according to two different experimental plans. Three factors are varied in the experiments: temperature, pyrrolidine concentration and residence time. The concentrations of 2,4-difluoronitrobenzene is kept constant as well as the concentration of triethylamine and the internal standard N,N-dimethylbenzamide. In the first set of experiments, a face-centered central composite (CCF) design of these three factors is used. The temperature for this design plan is set between 50, 75 and 100 °C. The pyrrolidine concentration is varied between 0.05, 0.25 and 0.5 M. The minimum residence time is 0.5 min. The maximum residence time depends on the minimum required Reynolds number of 100 allowing an ideal plug flow to be assumed in the ART reactor, which means that the maximum residence time depends on the density and the operating temperature, respectively. Therefore, the maximum residence time is identified individually by means of the developed correlation for the residence time distribution (Schaare et al., 2021) and ranges between 2 and 3 min. The CCF design plan consists of 15 experiments in total.

In the second set of experiments, a MBDoE is applied based on four initial experiments from the CCF design plan. The subsequent experiments are determined in an iterative MBDoE approach with successive refinement of the kinetic parameters after each experiment, due to the nonlinearity of the reaction kinetic model. The initial set of experiments includes two experiments under moderate conditions at low concentration and temperature and two experiments under extreme conditions at high concentration and temperature.

Subsequent experimental conditions are determined by the MBD<sub>oE</sub> considering the D-optimal criteria. After each additional experiment, a nonlinear regression is performed to update the parameter estimates, before repeating the cycle again, until a satisfactory parameter accuracy is achieved. The latter is quantified by the 95% confidence intervals of the respective parameters. The experiments designed based on this method are described in detail in Section 3.2.

### 3. Results and discussion

#### 3.1 Factorial Design of Experiments

The experimental data of the CCF design plan is fitted to the kinetic parameter of the reaction scheme shown in Figure 1. The nonlinear regression is performed as non-linear curve-fitting problem using *lsqcurvefit* in MATLAB, with the trust-region-reflective algorithm. The estimated rate constants and the corresponding 95% confidence intervals based on the experiments from the DOE are given in Table 1.

Table 1: Kinetic parameter estimation for the factorial design plan

Rate Step	$k_0$ [L/mol/s]	$E_A$ [kJ/mol]
1	$0.158 \pm 5\%$	$49.5 \pm 5.3\%$
2	$0.0242 \pm 14\%$	$48.9 \pm 11\%$
3	$1.55 \cdot 10^{-6} \pm 6900\%$	$76.2 \pm 2100\%$
4	$4.36 \cdot 10^{-4} \pm 370\%$	$62.6 \pm 140\%$

The kinetic parameters for the first two rate steps are estimated with a high accuracy and confidence intervals below 15%. It is noticeable that the rate constant for reaction step 1 is significantly higher than for step 2, while the activation energies are approximately the same. This implies that component 3 is formed significantly faster than component 4. Unlike the first two rate steps, the kinetic parameters of the two consecutive reactions to form the bi-substituted product are practically not identifiable, indicated by the large confidence intervals. In order to analyze the kinetic parameter estimation in more detail, Figure 3 (a) shows the molar composition of the outlet concentration for the experiments in dependency of the Damköhler number  $Da$ . The Damköhler number is a function of the input design parameters and represents a measure for the relative reactivity.

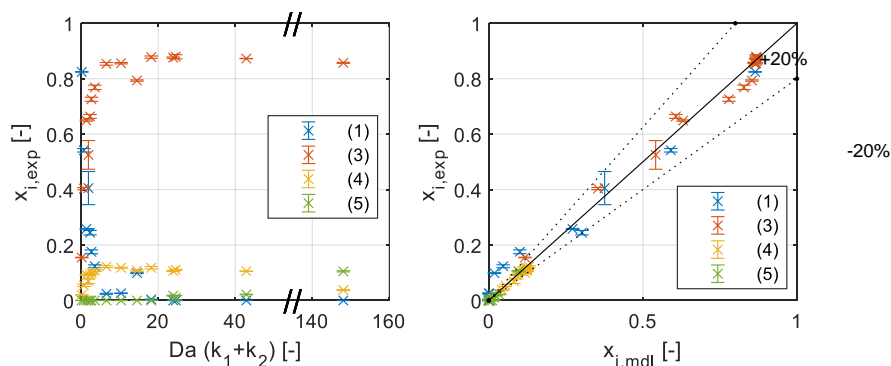


Figure 3: (a) Molar composition for the reactor outlet concentration of component (1), (3), (4) and (5) as function of the Damköhler number and (b) parity plot showing experimental vs. modelled molar composition.

Figure 3 (a) shows that component 3 is formed in excess compared to component 4 reaching a maximum selectivity of about 90% at low  $Da$ . This confirms the estimated rate constants for step 1 and 2. While the molar composition of component 3 remains approximately constant with increasing  $Da$ , component 4 is reduced under extreme conditions resulting in a formation of component 5. This indicates that rate step 4 is significantly faster than rate step 3 which is negligible small under the given conditions. The high uncertainties for the estimation of these rate steps are caused by the fact that the formation of component 5 is very small and only in one experiment at the highest  $Da$  a selectivity of close to 10% is reached. It is important to note that despite the high uncertainty, the model provides a good approximation of the experimental values as indicated in the parity plot in Figure 3 (b). Only at low composition of component 1 noticeable deviations above the 20% lines are found, which relate to higher inaccuracies of the HPLC at these concentrations. However, due to the limited data on the consecutive reactions it can be concluded that the estimated kinetic model is capable to accurately predict the first two rate steps, while the prediction of the consecutive reactions is highly uncertain, limiting the extrapolability of the model. Therefore, in the next step the design concept of MBD<sub>oE</sub> is used to improve the quality of the kinetic model especially in regards of the consecutive reactions.

### 3.2 Model-Based Design of Experiments

Based on the initial four experiments extracted from the CCF, a first estimation of the kinetic parameters is performed. Next a D-optimal MBDoe is performed in order to find the next best experimental conditions providing a high level of information. Since the inlet concentration cannot be adjusted continuously during operation and the feed solutions need to be prepared in advance, only residence time and temperature are considered as variables, determining D-optimal experiments for low concentration of pyrrolidine at 0.05 mol/L and at high concentration of 0.5 mol/L. These two respective experiments are performed in each MBDoe iteration with a successive refinement of the kinetic parameters by nonlinear regression.

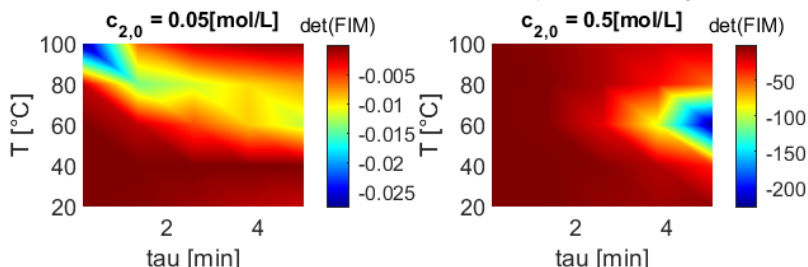


Figure 4: D-optimal design criteria determined from the initial experiments as function of the residence time and the temperature at constant inlet concentration of component (2) for (a) 0.05 mol/L and (b) 0.5 mol/L.

Figure 4 exemplarily illustrates the objective function of the D-optimal criterion objective for the first optimally planned experiment, based on the initial experiments, evaluated for varying residence time and temperature for (a) low and (b) high pyrrolidine concentration. For low pyrrolidine concentration a local optimum occurs at low residence time and high temperature, while at high pyrrolidine concentration, the optimum occurs at high residence time and a temperature of 60 °C. Consequently, these two experiments are performed during the first MBDoe iteration. Three MBDoe iterations are performed, resulting in a total of ten experiments, including the initial four CCF experiments. Thus, the MBDoe approach is conducted with 1/3 less experiments compared to the full CCF design. Figure 5 shows the estimated kinetic parameters and the corresponding confidence interval for each iteration.

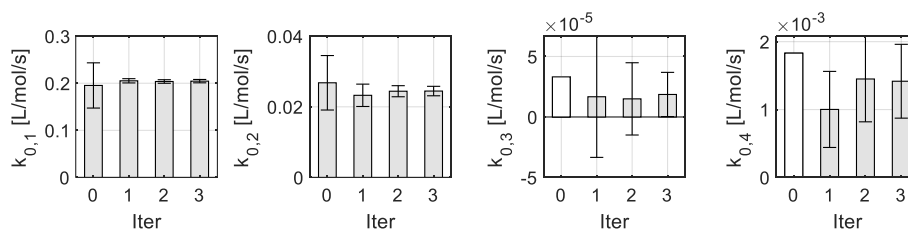


Figure 5: Kinetic constants and their corresponding confidence interval as function of the iteration for Model-Based Design of Experiments.

Apparently, the confidence intervals are effectively reduced in each iteration of the MBDoe. For example, the confidence interval for rate constant  $k_{0,2}$  is improved from 40% for the initial experiments to 5.5% with the additional three experiments, while an accurate estimate of rate constant  $k_{0,1}$  is determined after the first iteration. Also,  $k_{0,3}$  and  $k_{0,4}$ , which are practically unidentifiable with the CCF design, are determined with confidence intervals below 100%. The estimated rate constants after the last MBDoe iteration are summarized in Table 2.

Table 2: Kinetic parameter estimation for the Model-Based Design of Experiments

Rate Step	$k_0$ [L/mol/s]	$E_A$ [kJ/mol]
1	$0.204 \pm 1.7\%$	$50.5 \pm 1\%$
2	$0.0245 \pm 5.5\%$	$53.2 \pm 2.8\%$
3	$1.86 \cdot 10^{-5} \pm 98\%$	$67.8 \pm 34\%$
4	$1.42 \cdot 10^{-3} \pm 38\%$	$45.0 \pm 21\%$

Compared to the rate constants calculated with the CCF design (Table 1), especially the reaction constants for the consecutive reactions are determined with significantly higher accuracy, despite the fact that considerably fewer experiments are carried out. Nevertheless, rate step 3 is significantly slower than rate step 4 with a high activation energy and therefore almost negligible in the studied temperature range. This results in the remaining high uncertainty for the kinetic parameters for rate step 3. The effect of the improved experimental design is

illustrated best by means of the (pointwise 95%) confidence bands of reaction step 2 and 4 in Figure 6. The reaction rates  $k_2$  and  $k_4$  as well as the respective confidence bands are plotted as function of the temperature for the kinetic models, as derived from the CCF, the MBDoe and a simple intuitive study, where one-factor-at-a-time (OFAT) is investigated in 20 experiments. In the OFAT approach, the residence time is varied during the experiments while the concentration and temperature are kept constant.

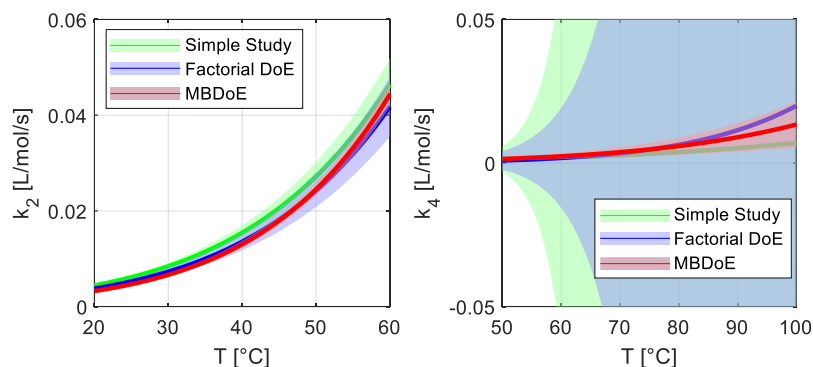


Figure 6: Reaction rate (a)  $k_2$  and (b)  $k_4$  as function of the temperature for a simple design plan, the factorial Design of Experiments and the Model-Based Design of Experiments.

While there are only little differences between the model results, with a noticeably smaller confidence band for the MBDoe, for reaction rate  $k_2$ , the advantage of the MBDoe becomes significant for modelling  $k_4$ . Only the MBDoe provides a confined confidence band, while the confidence bands for the other experimental plans extend largely, demonstrating the improved parameter identifiability using MBDoe.

#### 4. Conclusions

This work illustrates that the integration of MBDoe with the well-defined ART reactor allows to identify the kinetics of a multi-step reaction with less experimental effort comparing to a static DoE. Especially, the rate constants for the consecutive reactions are determined with significantly improved accuracy despite a smaller number of experiments. After showing the high potential of applying MBDoe in the ART reactor for the efficient identification of kinetic models via offline experiments, future work aims at the realization of a closed-loop system, in which the reactor is linked with online analytics and an automated process control system. With this setting, MBDoe will enable a fully automated platform for model identification.

#### References

- Fath V., Lau P., Greve C., Kockmann N., Röder T., 2020, Efficient Kinetic Data Acquisition and Model Prediction: Continuous Flow Microreactors, Inline Fourier Transform Infrared Spectroscopy, and Self-Modeling Curve Resolution, *Organic Process Research & Development*, 24, 1955–1968.
- Franceschini G., Macchietto S., 2008, Model-based design of experiments for parameter precision: State of the art, *Chemical Engineering Science*, 63, 4846–4872.
- Hone C.A., Holmes N., Akien G.R., Bourne R.A., Muller F.L., 2017, Rapid multistep kinetic model generation from transient flow data, *Reaction chemistry & engineering*, 2, 103–108.
- Martins J.R.R.A., Sturdza P., Alonso J.J., 2003, The complex-step derivative approximation, *ACM Transactions on Mathematical Software*, 29, 245–262.
- Rave A., Kuwertz R., Fieg G., Heck J., 2019, Characterization of a Modular, Scalable Millistructured Plate Reactor, *Chemie Ingenieur Technik*, 91, 602–606.
- Rave A., Kuwertz R., Fieg G., Heck J., 2020, Modeling and experimental investigation of the spatial heat transfer in a plate reactor with meandering millichannels, *Chemical Engineering and Processing - Process Intensification*, 150, 107860.
- Rave A., Schaare L., Fieg G., 2022, Investigation of micromixing in the ART plate reactor PR37 using the acetal cleavage method and different mixing models, *Chemical Engineering and Processing - Process Intensification*, 181, 109134.
- Schaare L., Rave A., Kuwertz R., Heck J., Fieg G., Skiborowski M., 2021, Hydrodynamics, heat transfer, and mixing in a millistructured plate reactor, 15th International Conference on Chemical and Process Engineering, 2021
- Yu H., 2018, Optimal experimental design and its applications to biochemical engineering systems, PhD thesis, University of Strathclyde.