Inline Spectroscopy-Based Optimization of Chemical Reactions Considering Dynamic Process Conditions

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The demand for sustainable energy sources, like biomass, solar energy, hydro and wind power, is connected to challenges like energy storage and fluctuating energy supply. Regarding the second challenge, industry has to evolve their existing processes from steady state processes to dynamic ones. This work is concerned with the conception of an inline spectroscopy-based optimization routine for chemical reactions under dynamic process conditions, which implements the search for a well applicable optimization algorithm. The studied reaction to reach this goal is a nitroaldol condensation.

Keywords: Continuous plug-flow reactors, Dynamic process conditions, Energy transition, Inline spectroscopy, Optimization

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1 Introduction

The exploitation of fossil resources leads to their diminish-
ment [1], which causes the demand to alternatively pro-
duced energy in a sustainable manner [2, 3]. An alternative is the utilization of renewable energies like biomass, solar energy, hydro and wind power [4–7]. Another aspect caus-
ing the energy transition are the anthropogenically caused CO₂ emissions from fossil fuels combustion [8–10]. One of the EU goals for 2030 is to increase the share of renewable energies to 32 % of the final energy consumption [11]. The transition to renewable energies is a promising environmen-
tally friendly and sustainable solution that is nonetheless related to challenges like energy storage [12–18] or fluctuating energy profiles [19–21]. The amount of achievable renewable energy is affected by instabilities of natural origin like weather dependencies. The solar radiation, e.g., consists of direct and diffuse radiation and depends on factors like the sun path, weather, and air pollution [22].

Industrial chemical processes are mostly carried out and optimized under steady state conditions, which means each parameter is controlled and fixed to a certain value. To conduct processes using renewable energies, the industry has to face uncontrollable dynamic conditions and their impact on the productivity and other important aspects such as process management. Also, the ordinary optimization procedures must be renewed or modified. The unsteady conditions can easily be simulated with parts of the automated setups on a lab scale. A continuous plug-flow reactor is capable of such dynamic process conditions and is characterized by advantages like a simple construction, the possibility for automation, and an increased safety [23–28]. For fast process parameter fluctuations, offline analytics are not sufficient enough as the measurement results might not correlate with actual process conditions. An alternative for faster response is the utilization of inline analytics [29]. This work is concerned with the conception of an inline spectroscopy-based optimization routine for chemical reactions under dynamic process conditions and the search for a well applicable optimization algorithm.

2 Strategy for the Optimization Routine

The strategy for an optimization routine under dynamic process conditions consists mainly of four steps. The general overview of the strategy is shown in Fig. 1. It starts with a parameter screening of a suitable reaction in a continuous plug-flow reactor. It is important to receive system answers as fast as possible while working with unpredictable or fast fluctuations of process conditions. The possibility of fast response allows early identification of malfunctions in the system. Besides, the gained results at dynamic process conditions are only significant when they correspond with actual process conditions. Therefore, an ultraviolet-visible (UV-vis) inline probe is implemented into the continuous plug-flow reactor. As model reaction, one has to be chosen, where substrate and product are UV-active. The investi-

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Ammonium acetate-catalyzed nitroaldol condensation is a Henry reaction followed by a condensation reaction carried out in acetic acid as depicted in Fig. 2 [30]. Except for substrate (1) and product (3) all other reagents and by-products are not UV-active and do not affect the measurement. The product (3) belongs to the category of Michael acceptors [31] and is an attractive reactant due to the electron-withdrawing nitro group [32]. Michael acceptors can be used in many reactions, e.g., in an asymmetric Michael addition reaction for synthesizing biologically active compounds [31, 33–34]. Derivatives of Michael acceptors are also used for medical purposes [35].

Figure 1. Strategy routine for the optimization of chemical reactions under dynamic process conditions, divided into four main (1–4) and two secondary steps (5,6).

Which parameter will be screened depends on the reactor. In this study, the investigated parameters are catalyst concentration, residence time, and temperature. The screening process serves to identify a suitable parameter working range. Some specific limitations given by the setup devices have to be considered, e.g., flow rate. Screened parameters that are out of the suitable range, e.g., due to too long reaction times or low conversion can be excluded from the working range. The results of parameter screening and limitation will be used in the second step.

The second step consists of the dependency investigation between the process parameters and the target value using the design of experiments (DoE) approach [36, 37] within the previously determined working range. It starts with the choice of a design order. Designs with first order, also called two-level designs, are used for the description of linear behavior with linear models. Second-order designs (three-level designs) are used for the investigation of nonlinear behavior with quadratic models. In case of no existing information about the type of parameter interactions with the target value, it is reasonable to apply a quadratic model. The linear approach is not sufficient for the identification of nonlinearity [36]. To exclude any missing information related to the investigated nitroaldol condensation, the second-order design is chosen as an extensive study. There are different quadratic models like the Box-Behnken or central composite design. The Box-Behnken design is characterized by a specific technique to reduce the experimental effort [38–40]. The central composite design is augmented with star points for curvature estimation of the response surface [41–43]. The evaluation of the results with a DoE software leads not just to information about parameter interactions but also to information regarding optimal process conditions that can be derived from the resulting hyper surface plot. These results will be used for the evaluation of optimization algorithms.

The third step consists of the implementation of different optimization algorithms into the control system of the continuous setup. The focus of this project is on optimizations carried out under dynamic reaction conditions, which means that the established optimization algorithms cannot be used in their original form. In ordinary optimization procedures, all process parameters can be adjusted and a new operating point will be set just in the case of a reached steady state. The optimization can be carried out with different types of algorithms, which differ in their searching range like local [44] or global algorithms [45, 46]. A well-known example for a local algorithm is the simplex algorithm. There are already a few modifications of the original one, like Nelder-Mead simplex [47], modified simplex [48], or the super-modified simplex [49, 50]. A representative for global optimization algorithms is the stable noisy optimization by branch and FIT algorithm (SNOBFIT) [51]. These algorithms have one objective function, so that only one variable chosen by the operator can be optimized. In a dynamic system, fluctuations will affect the standard optimization routines. However, before considering the effect of the fluctuation, the shape of the fluctuation itself should be considered. It is obvious that the simulations for fluctuation profiles should stay close to naturally occurring courses. For example, for the construction of a fluctuating parameter profile, the knowledge and measurements of the solar irradiation course collected over years can be applied. In this study, the general course of the solar irradiation will be transformed into a temperature course profile and applied, e.g., in form of a digital signal course. The parameter for the course transformation is given by the used setup. Consequently, the temperature can be used as an independent parameter. The digital signal course is chosen to allow the preservation of necessary residence times in a continuously operating plant. Considering the independent temperature profile, the optimization

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can be carried out under realistic dynamic process conditions. An advantageous property for the algorithm modification is the ability of an algorithm to memorize. Based on previous results, the property could be used to direct the algorithm into a specific direction with the goal to reduce the optimization time.

In the last main step, after the modification of applied algorithms, the optimization times of a complete optimization cycle and the final results will be compared and evaluated with respect to their application under dynamic process conditions. The results can also be compared with those gained from experiments under steady state conditions. After constructing and proving the optimization routine for processes under unsteady conditions, the routine could be transferred to reactions, which are carried out under realistic unstable conditions like in photochemical reactions under sunlight irradiation.

Fig. 1 is extended by two further steps. In general, it is important to use a second analysis method to verify the quality of gained results. For the chosen reaction system, offline nuclear magnetic resonance (NMR) spectroscopy has proven to be a suitable reference method to monitor substrate and product. Furthermore, this method allows the identification of side products. Except from limitations of the reaction setup and from parameter screening, the second analytical method can as well contribute to define applicable parameter ranges suppressing side reactions.

The optimization in a continuous plug-flow reactor extended by inline spectroscopy provides much information on the investigated system in a short time. The gained data can be used for further investigations like kinetic studies and be compared with results from experiments carried out in a batch reactor. In addition, this would not just help to gain deeper knowledge of the reaction system but also to evaluate the efficiency of both reactor types.

### 3 First Results

The presented nitroaldol condensation is identified as a suitable reaction due to its aromatic components, which allows measuring the substrate (1) and the product (3). As stated above, the first optimization step consists of a parameter screening to determine limitations. The used parameter range table is given in Tab. 1, which includes different temperatures, residence times, and catalyst concentrations.

The temperature range of 403–428 K (above the boiling point of acetic acid at ambient pressure) can be chosen due to the application of a back pressure regulator (BPR) in the continuous setup. The installation of a BPR is necessary to avoid the boiling of the reaction solution, which would influence the flow properties and lead to a discontinuous absorbance measurement. Furthermore, the application of a BPR allows the temperature variation at a stable continuous flow. The used BPR works at 5.2 bar. The allowed temperature at 5 bar is up to 452 K. [52]

As mentioned before, the temperature can be used as a fluctuating parameter in the optimization process. The difficulty of a wide temperature range is the long cooling time to reach the minimal temperature. Long cooling times are related to the refrigerated circulator, which is used as a heating component of the setup. Hence, long cooling times are unsuitable for a fluctuating application. Experiments at low temperature require long residence times realized by low flow rates, which are sensitive to pulsations caused by a piston pump. The pulsation leads to an unstable continuous flow. In addition, long reaction times lead to low time-space yields. To investigate the general influence of the catalyst concentration on the reaction, the range of ±40 % of the initial value was chosen.

The temperature and residence time influence on the conversion of the substrate (1) is shown in Fig. 3. At
elevated temperature, the residence time affects the conversion less than at low temperature. At a residence time of 30 min, the conversion changes about 5% for all temperatures in the range of 403 to 428 K. Additionally, a decreasing conversion is observed at high temperature and long residence time due to catalyst decomposition, which is identified using NMR spectroscopy as a reference analysis method. Short residence time leads to low conversion even at the highest temperature of 428 K.

The assumption of catalyst decomposition is based on the formation of broad NMR signals at extreme process conditions and a pH value change. The initial pH value of the reaction solution is 2.67 at room temperature. After the reaction at the temperature of 428 K and the residence time of 60 min, the resulting pH value is 2.23. The absorbance of the substrate and the product at a certain concentration are influenced by varying pH values. [53]

An autoclave experiment using ammonium acetate dissolved in acetic acid showed the formation of acetamide. The NMR result matches literature data in dimethyl sulfoxide-d$_6$ (DMSO-d$_6$) [54]. Due to the changing pH value, the used calibration has to be adjusted for occurring pH values. To enable the pH value measurement, the setup has to be equipped with a pH probe. The knowledge of the pH value will be used for the estimation of the exact absorbance and, therefore, the concrete concentration of substrate (1) and product (3).

Since the reaction rate is influenced by the rate of catalyst decomposition, a reasonable range to exclude fast catalyst decomposition is at mild temperatures and long residence times. Hence, the variation of the catalyst concentration is carried out in the range of 408–418 K. The maximum conversions are shown in Fig. 4 at different catalyst concentrations and temperatures with the corresponding residence times. The highest conversion achieved from previous experiments is 76% at 408 K and 60 min. Varying the catalyst concentration led to a maximum conversion of 77% at 408 K and a residence time of 60 min with a catalyst concentration of 1.58 mol L$^{-1}$. The conversion decreases for all shorter residence times at the temperature of 408 K. For lower catalyst concentrations, the trend remains the same. At 413 K and 1.58 mol L$^{-1}$, the maximum conversion occurs at lower residence time than at 408 K. At the residence time of 60 min, there is a decrease of the conversion, which is in accordance with the decomposition of the catalyst at longer residence times and higher temperatures. Further increasing of the temperature up to 418 K causes the shift of the conversion maximum to even lower residence time but also to lower conversion. The change of the catalyst concentration from 1.13 to 1.58 mol L$^{-1}$ does not lead to a significantly higher conversion. Thus, this result indicates setup limitations like reactor volume. In general, the residence time is influenced by the catalyst amount at higher temperatures. The obtained trends using UV-vis spectroscopy are confirmed by NMR data.

**Figure 4.** Maximum conversion $X$ of $p$-anisaldehyde (1) achieved at different catalyst concentrations $c$ (cat) and temperatures $T$ with the corresponding residence times $t$ (conditions: $c$ (1) = 0.45 mol L$^{-1}$, $c$ (2) = 0.90 mol L$^{-1}$). The results are calculated using UV-vis data.

### 4 Conclusion Related to the First Step

The investigated nitroaldol condensation has proven suitable as a reaction example for the development of an optimizing routine using UV-vis inline spectroscopy. The substrate and product can be identified by UV-vis analysis. All other reagents and side products are not UV-vis-active. The variation of the parameters temperature, residence time, and concentrations led to the determination of a suitable process range. In addition, the parameter screening was also used to determine the parameter limitations related to the undesired decomposition of the catalyst, which results in a decrease of the conversion for harsh parameters. These results were confirmed by the NMR data. In general, the utilization of a second analysis method was useful to identify by-product formation.

### 5 Outlook

After finishing the first step out of four, the investigation of parameter dependencies can be carried out using DoE in the next step. The first and second step will deliver all necessary information about the chosen reaction system, which will be used for the characterization of implemented algorithms. The implementation of different algorithms is the third step in the strategy for the optimization routine under dynamic process conditions. The efficiency comparison of the algorithms will be the last step. Furthermore, the
algorithms can be applied for reactions under steady state conditions as well and be compared with those under fluctuations to estimate the effect of running a process under dynamic conditions.

**Symbols used**

\[ c(1) \text{ [mol L}^{-1}\text{] concentration of p-anisaldehyde} \]

\[ c(2) \text{ [mol L}^{-1}\text{] concentration of nitromethane} \]

\[ c(\text{cat}) \text{ [mol L}^{-1}\text{] catalyst concentration} \]

\[ T \text{ [K] temperature} \]

\[ X \text{ [%] conversion} \]

**Greek letter**

\[ \tau \text{ [min] residence time} \]

**Abbreviations**

BPR back pressure regulator

DoE design of experiments

NMR nuclear magnetic resonance

SNOBFIT stable noisy optimization by branch and FIT

UV-vis ultraviolet-visible

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