SUPPORTING INFORMATION

Self-Optimising Processes and
Real-Time-Optimisation of Organic Syntheses in a
Microreactor System using Nelder-Mead and Design of Experiments

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A. Experimental Procedure

A.1. Analytical IR spectra and integration method

Analytical IR spectra and details on the integration method are exemplarily provided in Figure S1. The evaluation of the characteristic IR band is based on a calculation of absorption height. This is illustrated in Figure S1 for benzaldehyde **1** as starting material (decreasing band at $1680-1720$ cm^{-1}) and n-benzylidenebenzylamine **3** (increasing band at $1620-1660$ cm^{-1}).
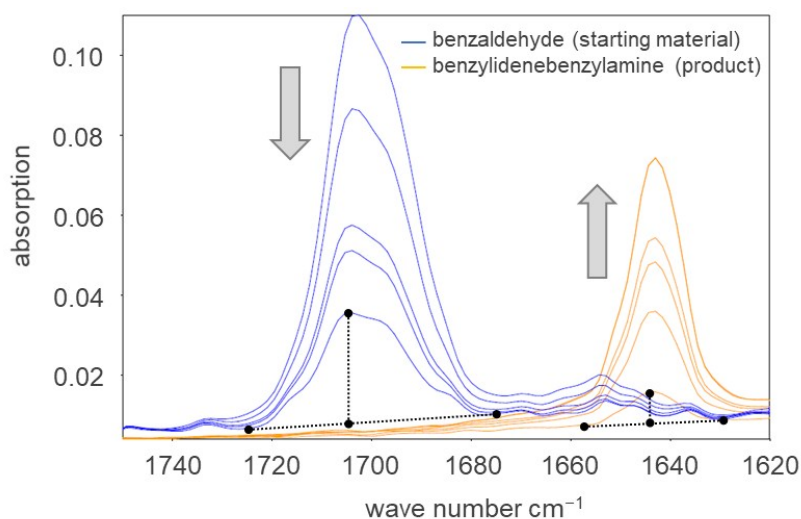
Figure S1. Exemplary analytical IR spectra of benzaldehyde **1** and n-benzylidenebenzylamine **3** at different concentrations.
Legend: ⋯⋯ integration method based on calculation of absorption height.
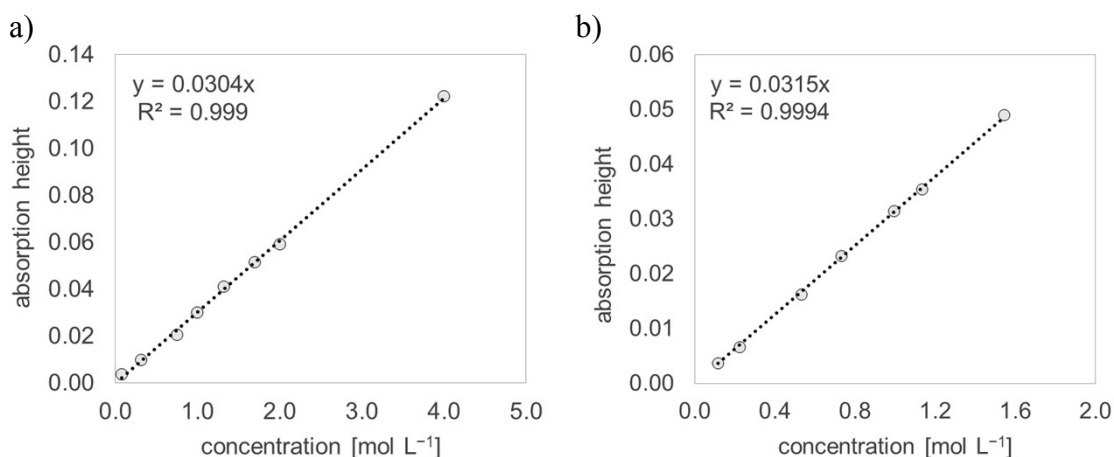
Figure S2. Calibration curves. a) Benzaldehyde **1**. b) n-Benzylidenebenzylamine **3**. Each experimental data point was determined by five repeated measurements, with every measurement consisting of 32 scans. Standard deviations were calculated for all data points. Averaged across data points, it amounted to 4 %.

A.2. Workflow of optimisation procedure

Figure S4 illustrates a schematic workflow of the optimisation procedure. The presented self-optimising system integrates a flow microreactor with automatised devices (pumps and thermostats) and real-time reaction monitoring through inline FT-IR spectroscopy. Pumps and thermostats are controlled via a laboratory automation system (HiTec Zang GmbH, Germany); FT-IR measurements by OPUS, a spectroscopy software from Bruker, United States. The system is equipped with a real-time optimisation procedure. Two optimisation strategies were tested: the modified Simplex algorithm and Design of Experiments. Both optimisation strategies are applied within the same experimental setup, only their experimental sequences differ. In case of the modified Simplex algorithm, real-time optimisation works as feedback in flow. During DoE optimisation, defined experimental plans are executed. Either fully automated experimental sequence is coded in MATLAB. However, MATLAB does not only control the optimisation strategies, but calculates the objective function and transfers values for pumps and thermostats through communication with the laboratory automation system as well. Besides, the laboratory automation system controls pumps and thermostats, communicates with OPUS via an OPC interface, and transfers analytical results to MATLAB.

The optimisation procedure starts by defining the experimental setup including the objective function, reactor volume, experimental space, and number of variable parameters. One of three different objective functions can be chosen: maximum product concentration, maximum production quantity, and minimum costs per product unit. The whole system is completely automatised, whereby also remaining volumes of starting materials are calculated permanently. Hence, the optimisation procedure stops autonomously whenever one of the starting materials is depleted. The procedure can then be restarted at this point. After defining the experimental setup, the MATLAB sequence continues by proposing the experimental conditions. In case of the Simplex algorithm, a randomly chosen initial simplex is generated, see details on this approach in main document's chapter "numerical evaluation of optimisation methods, start simplex set to axes". In contrast, if DoE optimisation is performed, defined experimental plans are executed, and all experimental conditions are transferred to the laboratory automation system in sequence. Then, the calculated values are transferred to pumps and thermostats. It should be noted that MATLAB operates with stoichiometric ratios and residence times, whereby the laboratory automation system works with volumetric flow rates, so that values must always be translated. When experimental conditions are applied in pumps and thermostats, a waiting time until reaching constant reaction temperature and steady-state conditions is estimated. Meanwhile, IR spectra are continuously monitored, and OPUS performs a defined integration method of the characteristic product band. These values are transferred to the laboratory automation system via an OPC interface in real

time. As soon as steady-state is reached (IR value remains constant), the laboratory automation system transfers the actual IR value to MATLAB, where the objective function is calculated based on this result. Thereafter, all related experimental conditions are documented.

In case of the Simplex algorithm, optimisation works with feedback in flow. Thus, once the reaction is finished and the experimental sequence has conveyed the reaction results to the optimisation algorithm, new experimental conditions are proposed, aiming to maximize or minimize the objective function. This process is repeated iteratively until eventually converging to a local optimum, without any human intervention. Simplex optimisation stops after executing the previously defined maximum number of experiments, or when the value of the objective function varies only within a defined range anymore (local optimum is found). During Simplex optimisation, it may happen that experimental conditions are proposed that lie outside the experimental space. In that case, the related iteration step is skipped and new experimental conditions are suggested, until Simplex proposes conditions that lie within the allowed experimental space once again (Figure S3).
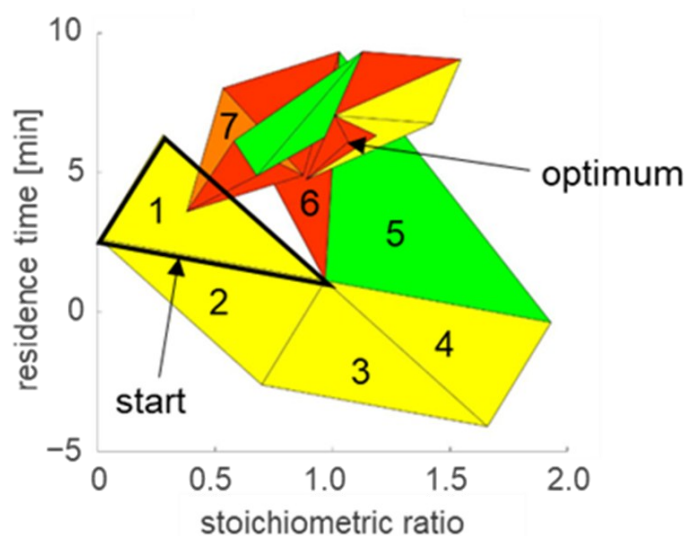

Figure S3. Simplex optimisation of two variable parameters with product concentration as objective function: Simplex progress. Legend: colouring of simplexes corresponds to simplex movement: yellow – reflection, green – expansion, red – contraction, orange – contraction with change of movement direction (negative residence times are not physically appropriate, Simplex responds to such values by suggesting new experimental conditions).

In case of DoE optimisation, defined experimental plans are executed, whereby experimental conditions are transferred to the laboratory automation system one by one. After a first DoE run, used to screen the whole experimental space, a response surface model is calculated, and optimal conditions are determined. Based on these conditions, a second DoE run is established around the optimal value of the first DoE run. This new experimental plan then contains the optimum of the first DoE as central point. Its size is

defined through a variable delta that reduces the plan to 20 % of the size of the first DoE. Subsequently, the second DoE is performed, and another surface response model is built to refine the search for a global optimum.

The presented self-optimising system is designed as transferable modular concept. Optimisation strategies can easily be changed, and are all performed in a fully automated manner. This allows for considerable flexibility of the system, whilst ensuring high reproducibility and safety.
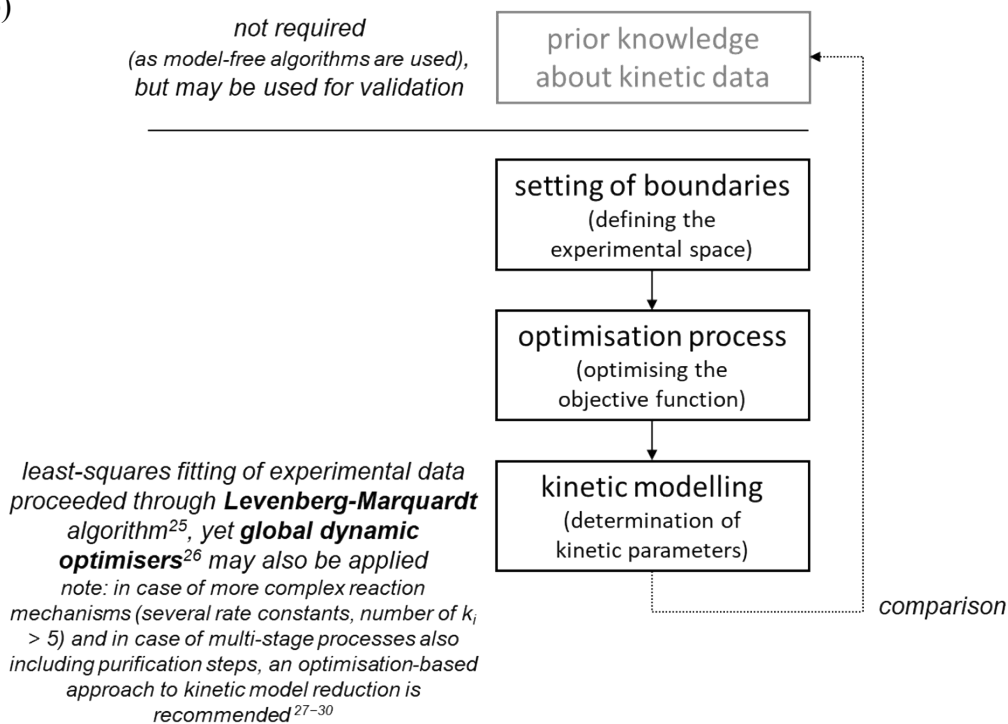
a)
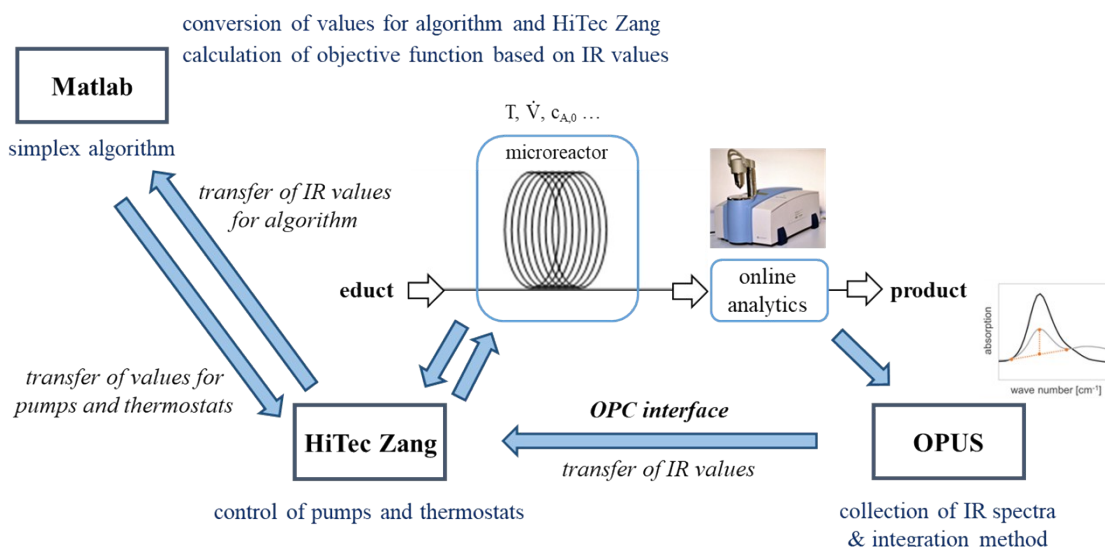
b)

Figure S4. Schematic workflow of optimisation procedure.

A.3. Modified Simplex Algorithm

The Nelder−Mead Simplex Algorithm[1] is a gradient-free, direct search optimisation method. During optimisation, input variables (e.g., stoichiometric ratio, residence time, and reaction temperature) are transformed into an output variable to be optimised (e.g., product yield, productivity, and costs), whereby a given chemical reaction is treated as a black-box. The method proceeds by exploring the experimental space with n-dimensional simplexes, where n is the dimension of the particular optimisation problem, hence the number of input variables. The simplexes are constructed and permanently replaced in order to steer the process towards optimal reaction conditions. In the beginning, an initial simplex consisting of a convex polytope with $n+1$ vertices, where each vertex represents an experiment, is developed. Thus, a simplex in one dimension constitutes a line, whereas in two dimensions, it is represented by a triangle, in three dimensions, it is represented by a tetrahedron, and hyperpolyhedrons characterise multiple dimensions[2–5].

Optimisation then proceeds through ranking the $n+1$ vertices of the simplex according to their objective function values. The worst result is replaced by a new vertex that is supposed to deliver a better result, while creating a novel simplex. By changing multiple variables at a time and in an iterative fashion, it is possible to steer the process to a region within the experimental space that results in the optimum response. As soon as the objective function value cannot be enhanced anymore, a local optimum is found[4–8].

The original basic algorithm is the simplest form of Simplex optimisation, since it is only based on a reflection movement to replace poor results. In contrast, the modified algorithm allows a greater range of motions by adding expansion and contraction movements. Optimisation efficiency can thus be improved, facilitating faster simplex development and reducing the number of experiments needed to identify optimal conditions. Figure S5 schematically displays possible movements of the modified Simplex algorithm, including reflection, expansion, and contraction[3, 5–7].

However, Simplex optimisation comes with the drawback of being only a local search technique. The Simplex method always converges to a local optimum, which does not necessarily correspond to the absolute one. To overcome this drawback, it is recommended to apply different initial simplexes during the optimisation process[5, 6, 8, 9].
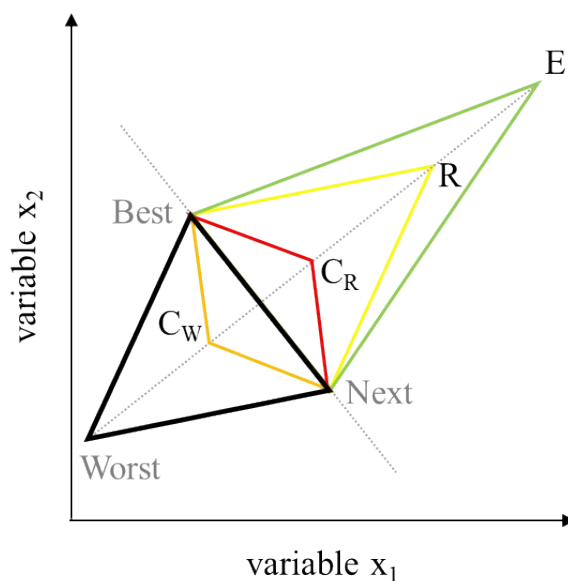
Figure S5. Movements of Modified Simplex Algorithm: reflection, expansion, and contraction. Legend: *R* – reflection point, *E* – expansion point, C_W – contraction point without change in movement direction, C_R – contraction point with change in movement direction.

A.4. Design of Experiments

The technique of 'Design of Experiments' is a statistical approach to multidimensional reaction optimisation[10–12]. As result of DoE optimisation, the effect of each variable, and potential interactions between variables on the objective function are determined. Multidimensional DoE optimisation enables evaluation of a large number of reaction parameters in a relatively small number of experiments depending on the chosen experimental design. Hence, experiments are planned intelligently so that finally a response surface model can be built as mathematical expression displaying the whole experimental space and allowing for identification of optimal conditions[11, 13].

Selection of experiments is based on the following three steps[13–16]:

1. Definition of objective function and optimisation goal, e.g., yield, productivity, costs.
2. Selection of variable parameters: After identifying variable parameters that influence the objective function, the experimental space has to be defined. When specifying parameter ranges, it should be noted that, if factor ranges are too small, optimum conditions could lie outside the area of study. However, factor ranges should neither be oversized since otherwise the reaction could not work anymore. Number of experiments strongly depends on number of variable parameters. Thus, to reduce time and costs, only those parameters should be included that have a real impact on the objective function.

3. Choice of DoE strategy and experimental design: The experimental design specifies the arrangement of experimental points within the experimental space. Based on this experimental plan, experiments are performed during DoE optimisation.

DoE strategies are generally grouped in screening and response surface designs[12, 14]. Screening designs aim at exploring the entire experimental space, while simultaneously identifying those factors that wield the largest influence on the response. This strategy is most effective when applied at the beginning of a study, when little knowledge about a process is available, helping to minimize the efforts required to identify optimal reaction conditions in a second step. In contrast, response surface designs are mainly applied within optimisation procedures, such as central composite (CCD) and Box–Behnken design[17, 18]. Both strategies are based on experimental plans whose experimental runs are uniformly distributed around a central point. Especially the multidimensional optimisation of continuous variables, e.g. (stoichiometric ratio, residence time, and reaction temperature) thereby becomes possible. Finally, response surface designs aim at describing the experimental space through a nonlinear mathematical model[12, 13, 19, 20].

Based on this model, a response surface can be expressed as function of the variable factors. This polynomial equation can be written with (Eq. 1) and without (Eq. 2) interactions between the parameters[21–23]:

$$f(x,y,z) = a_0 + \left(a \cdot x^2 + b \cdot y^2 + c \cdot z^2\right) + (d \cdot x + e \cdot y + f \cdot z) + (g \cdot x \cdot y + h \cdot x \cdot z + i \cdot y$$

$$(1)$$

$$f(x,y,z) = a_0 + \left(a \cdot x^2 + b \cdot y^2 + c \cdot z^2\right) + (d \cdot x + e \cdot y + f \cdot z) \qquad (2)$$

These mathematical models allow for interpreting functional relations between response and experimental variables, and for predicting optimal reaction conditions[10, 16, 24].

B. Numerical Evaluation of Optimisation Methods

B.1. Kinetics of theoretical reaction model

Performances of modified Simplex algorithm and Design of Experiments as optimisation strategies were evaluated using a theoretical chemical model reaction (eq. 3).

$$c_A + c_B \rightarrow c_P \rightarrow c_{SP} \tag{3}$$

In a second order reaction, starting materials **A** and **B** form the desired product **P**. However, in a consecutive reaction, product **P** is transformed into undesired side product **SP**.

Differential equations describing the reaction kinetics of this model reaction are as follows:

$$\frac{dc_A}{dt} = R_A = -k_1 \cdot c_A \cdot c_B \tag{4}$$

$$\frac{dc_B}{dt} = R_B = -k_1 \cdot c_A \cdot c_B \tag{5}$$

$$\frac{dc_P}{dt} = R_P = k_1 \cdot c_A \cdot c_B - k_2 \cdot c_P \tag{6}$$

$$\frac{dc_{SP}}{dt} = R_{SP} = k_2 \cdot c_P \tag{7}$$

with calculation of reaction rate coefficient k_i based on reference temperature T_{ref}:

$$k_i(T) = k_{i,ref} \cdot \exp\left[-\frac{E_{A,i}}{R_{ideal}} \cdot \left(\frac{1}{T} - \frac{1}{T_{ref}} \right) \right] \tag{8}$$

Table S1 lists the reaction parameters of the described theoretical model including the chosen experimental space (minimum and maximum values of all variable parameters) and kinetic data of both, the main and the side reaction.

Table S1. Reaction parameters (experimental space and kinetic data) of the theoretical model reaction.

Parameters	Minimum value	Maximum value
Reaction temperature T [K]	230	300
Residence time τ [s]	0	600
Stoichiometric ratio of starting materials $\dfrac{c_A}{c_B}$	0.1	1.5
Reaction rate coefficient of main reaction $k_{1,\text{ref}}$ [L mol^{-1} s^{-1}]	0.01	
Activation energy of main reaction $E_{A,1}$ [kJ mol^{-1}]	60	
Reaction rate coefficient of side reaction $k_{2,\text{ref}}$ [s^{-1}]	0.001	
Activation energy of side reaction $E_{A,2}$ [kJ mol^{-1}]	80	
Reference temperature T_{ref} [K]	273	
Initial concentration $c_{B,0}$ [mol L^{-1}]	1	
Initial concentration $c_{P,0}$ [mol L^{-1}]	0	
Initial concentration $c_{SP,0}$ [mol L^{-1}]	0	

Concentration profiles of all involved components of the theoretical model reaction are exemplarily presented in Figure S6 for a constant reaction temperature of −8 °C and a stoichiometric ratio of starting materials amounting to 1.5.
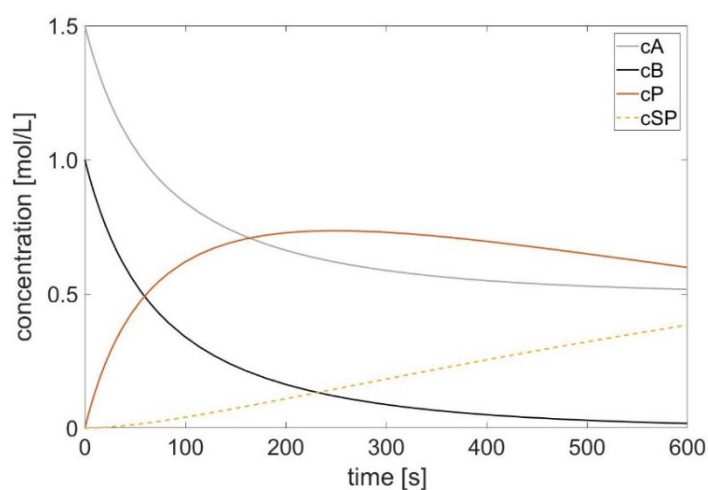

Figure S6. Concentration profiles of theoretical model reaction's components, exemplarily presented for a reaction temperature of −8 °C and a stoichiometric ratio of starting materials of 1.5.

B.2. Numerical evaluation of Simplex Algorithm

Different opportunities to construct start simplexes during Simplex optimisation were numerically evaluated. One of them was a maximum start simplex which constitutes a start simplex that was placed over the whole reaction space. With two variable parameters (temperature, and residence time), maximum start simplex results in four possible configurations. The corner points of these start simplexes are listed in Table S2. In contrast, with three variable parameters (temperature, residence time, and stoichiometric ratio of starting materials) 16 possibilities arise, but only four of them where investigated as described in Table S3.

Table S2. Corner points of tested maximum start simplexes with two variable optimisation parameters.

Corner points	1	2	3	
Simplex option No.1	1	600	600	[s]
	27	−43	27	[°C]
Simplex option No.2	1	600	1	[s]
	27	−43	−43	[°C]
Simplex option No.3	1	600	600	[s]
	−43	27	−43	[°C]
Simplex option No.4	1	600	1	[s]
	−43	27	27	[°C]

Table S3. Corner points of tested maximum start simplexes with three variable optimisation parameters.

Corner points	1	2	3	4	
Simplex option No.1	0.1	1.5	0.1	1.5	[mol L^{-1}]
	1	600	600	1	[s]
	−43	27	−43	27	[°C]
Simplex option No.2	0.1	1.5	0.1	0.1	[mol L^{-1}]
	1	600	600	1	[s]
	−43	27	−43	27	[°C]
Simplex option No.3	0.1	1.5	0.1	0.1	[mol L^{-1}]
	1	600	600	600	[s]
	−43	27	−43	27	[°C]
Simplex option No.4	0.1	1.5	0.1	1.5	[mol L^{-1}]
	1	600	600	1	[s]
	−43	27	−43	−43	[°C]

B.3. Numerical evaluation of Design of Experiments

In order to evaluate the performance of Design of Experiments as optimisation strategy, different experimental designs were compared, among them Central Composite Design, full and fractional factorial, and Box Behnken Design. The quality of all calculated optimal solutions based on the resulting surface response models was examined. This was done through determining the optimal reaction conditions from all surface response models and their corresponding optimal product yields. The optimal parameter combination was then transferred to the kinetic model of the theoretical reaction to indicate real product yield. The results are compared in Figure S7 for all three experimental designs, with and without consideration of parameter interactions, respectively.
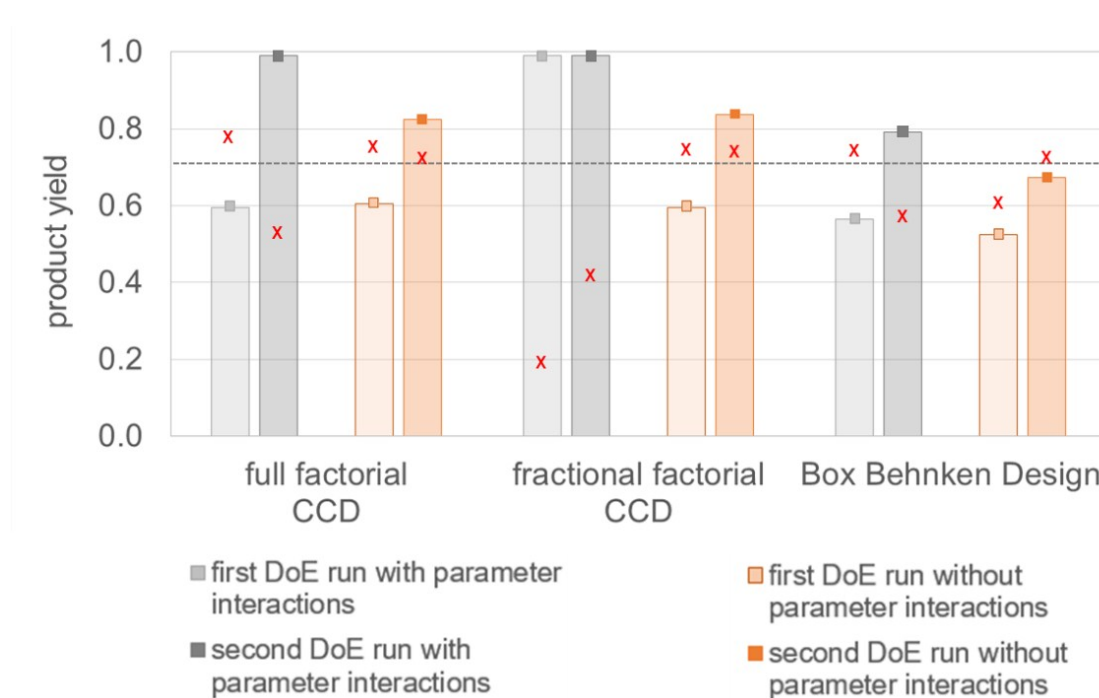

Figure S7. Results of numerical evaluation of different DoE strategies. Calculated product yield from resulting surface response model (with and without consideration of parameter interactions) is displayed and compared to real value received from kinetic model.
Legend: ---- quality criterion of product yield >70 %
x – real value for product yield from kinetic model at conditions resulting from DoE optimisation.

As parameter interactions are included, both, full and fractional factorial CCD, result in maximum product yields of nearly 100 % and represent real yield (predicted by the kinetic model) only poorly. In other words, high discrepancies between surface response model and kinetic model occur. It has to be noted that those high yields amounting to nearly 100 % are theoretical values that cannot be reached in reality as far as the model reaction is concerned. Instead, they result from a mathematical expression of the surface

response model. In fact, the mathematical equation could even lead to yields greater than 100 %, but the program used prevents such values.

In contrast, Box Behnken design demonstrates a superior performance compared to CCD when parameter interactions are implemented. This becomes apparent as the calculated product yield values that result from the surface response model are more realistic. However, deviations from real yield as indicated by the kinetic model nonetheless amount to around 30 %, and are too large in magnitude to be used for a reliable optimisation procedure.

In order to estimate relevance and meaningfulness of the inclusion of parameter interactions, surface response models were calculated without consideration of parameter interactions for all three experimental designs. It can be shown that involvement of parameter interactions has a considerable impact on surface response modeling. Without parameter interactions, optimal theoretical yields do not accomplish unrealistic values of around 100 % anymore, and discrepancies between surface response model and kinetic model are diminished for all experimental designs. Therefore, especially regarding chemical reactions, parameter interactions should rather be excluded, as neither physical nor chemical justifications exist for including terms of parameter interactions within response surface models.

Under these circumstances, fractional factorial CCD demonstrates a good performance in predicting optimal and reasonable values for product yield, while simultaneously reducing the number of experiments needed.

C. Experimental Evaluation of Optimisation Methods

C.1. Theoretical results for production quantity and costs per kg of product

As proof of concept, the reaction of benzaldehyde **1** with benzylamine **2** to form n-benzylidenebenzylamine **3** was experimentally investigated. Three different optimisation goals were experimentally evaluated, e.g. maximum product concentration, maximum production quantity, and lowest possible costs. As the underlying kinetics are known[25], theoretically expected optimisation results can be calculated.

Figure S8 displays the theoretical results of production quantity as function of residence time and stoichiometric ratio (two variable parameters).
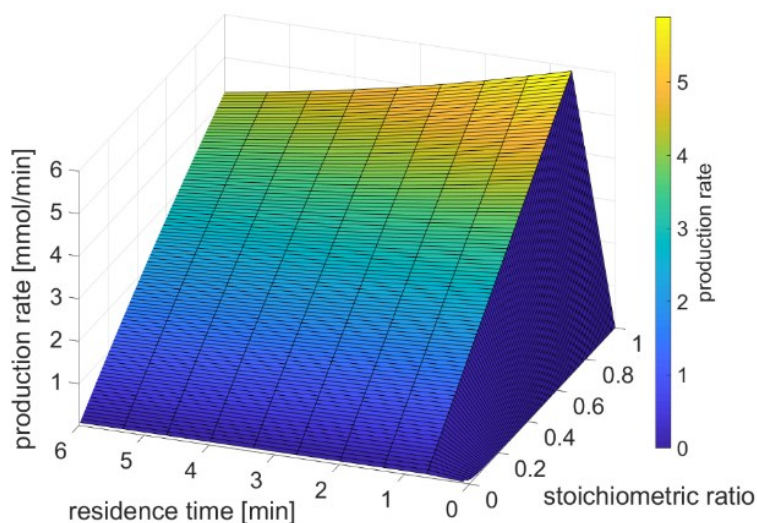

Figure S8. Theoretical values for production quantity as function of stoichiometric ratio and residence time.

The theoretically expected optimal result regarding a maximum production quantity amounts to 5.8 mmol min^{-1}, and is obtained at a stoichiometric ratio of 1.0 and a residence time of 0.8 min.

Minimum costs per kg of product were approximated using a cost function (eq. 9) consisting of a term describing raw material costs and a fixed costs portion. Fixed costs were estimated to amount to 30 % of the raw material costs that occur at an output rate of 8.2 g h^{-1}, which is in line with cost estimates that are commonly used in industrial contexts.

$$\text{costs per kg of product} = \frac{\text{costs for starting materials} + \text{fixed costs}}{\text{kg of product}} \tag{9}$$

Raw material costs amounted to 44 € mol^{-1} for Benzaldehyde **1** and 23 € mol^{-1} for Benzylamine **2**. The theoretical results of costs per kg of product are illustrated in Figure S9 as function of residence time and stoichiometric ratio (two variable parameters).
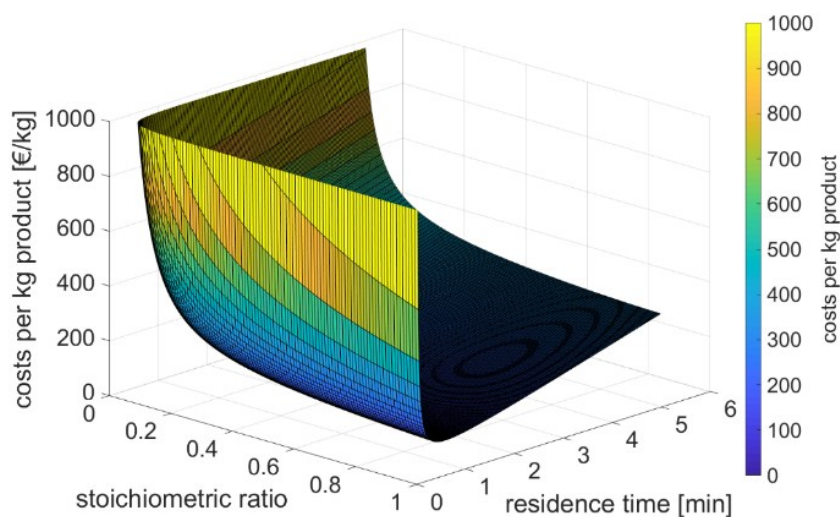

Figure S9. Theoretical values for product costs as function of stoichiometric ratio and residence time.

The theoretically expected result regarding minimum costs amounts to 129 € kg^{-1}, and is obtained at a stoichiometric ratio of 1.0 and a residence time of 0.6 min.

Comparison of absolute values of determined minimum costs per kg of product

It should be noted that minimum costs per kg of product constitute relative values rather than absolute ones. Nevertheless, if the absolute values resulting from Simplex and DoE optimisation are compared, slight discrepancies can be recognized.

Simplex and DoE optimisation are based on different approaches to identify optimal reaction conditions. Hence, the Simplex method proceeds by constructing Simplexes that are permanently replaced in order to steer the process towards optimal reaction conditions. In contrast, the results of DoE optimisation are obtained from surface response models, thus from a mathematical expression describing the experimental space.

The theoretically expected minimum costs amount to $129 \, €\, kg^{-1}$, and are obtained for a stoichiometric ratio of 1.0 and a residence time of 0.6 min. Therefore, minimum costs arise at rather small residence times that lie close to the lower boundary of the experimental space (the chosen microreactor setup allows to investigate residence times ranging from 0.5 to 6 min). Exploring experimental points that are located close to the lower or upper boundary poses challenges in case of both optimisation strategies. Concerning DoE optimisation, the surface response model can be extrapolated to those boundary values. Conversely, as soon as the Simplex algorithm constructs a Simplex that lies too close to the boundary, it responds to these values by suggesting new experimental points (that lie further away from the boundary). Therefore, in case of Simplex optimisation, it is challenging to obtain absolute values of minimum costs per kg of product.

C.2. Multidimensional Simplex optimisation of three variable parameters

During multidimensional optimisation of three variable parameters, stoichiometric ratio, residence time, and reaction temperature were optimised. Exemplary for maximum product concentration as optimisation goal, the simplex progress and the progress of the objective function over the number of iterations are displayed in Figure S10.
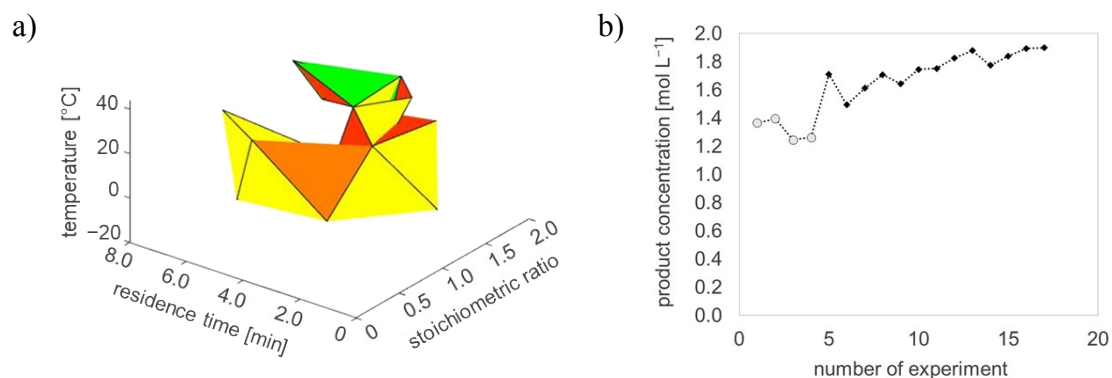

Figure S10. Multidimensional Simplex optimisation of three variable parameters with product concentration as objective function. a) Simplex progress. Legend: yellow – reflection, green – expansion, red – contraction, orange – contraction with change of movement direction. b) Progress of objective function over number of experiments. Legend: ○ values of start simplex.

C.3. Influence of varying start simplexes on Simplex optimisation result

The influence of varying start simplexes on the result of Simplex optimisation was studied. Hence, initial values were chosen randomly, and six repetitions of the same optimisation procedure, only with different start simplexes, were conducted. Details on the investigated start simplexes and all individual results are provided in Figure S11.
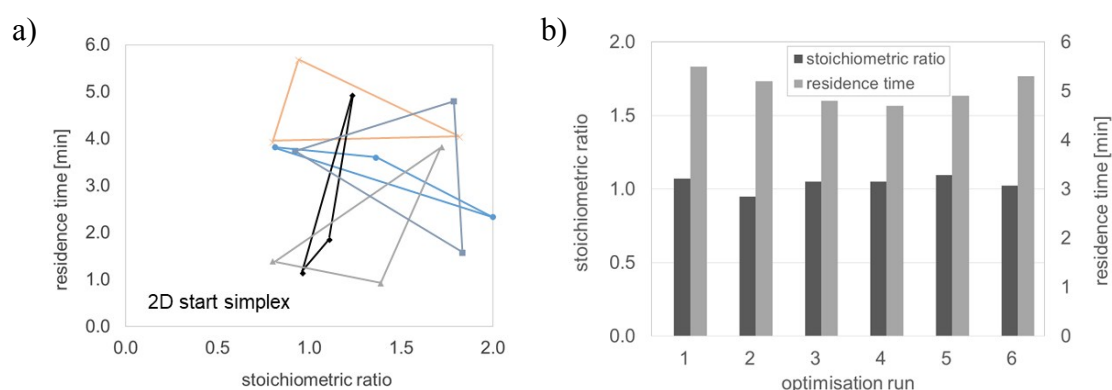

Figure S11. Influence of varying start simplexes to optimisation result. a) Initial values of two-dimensional start simplexes. b) Results for all optimisation runs regarding their determined optimal values for stoichiometric ratio and residence time.

C.4. Optimisation using Design of Experiments

The reaction of benzaldehyde **1** with benzylamine **2** was used as proof of concept to experimentally investigate Design of Experiments as optimisation strategy. During multidimensional optimisation of two respectively three variable parameters, two different optimisation goals were examined: maximum product concentration and minimum costs per kg of product.

In terms of product concentration as objective function, the surface response models obtained by the first and second DoE run, while optimising three variable parameters (stoichiometric ratio, residence time, and reaction temperature), are exemplarily provided in Figure S12 and Figure S13.
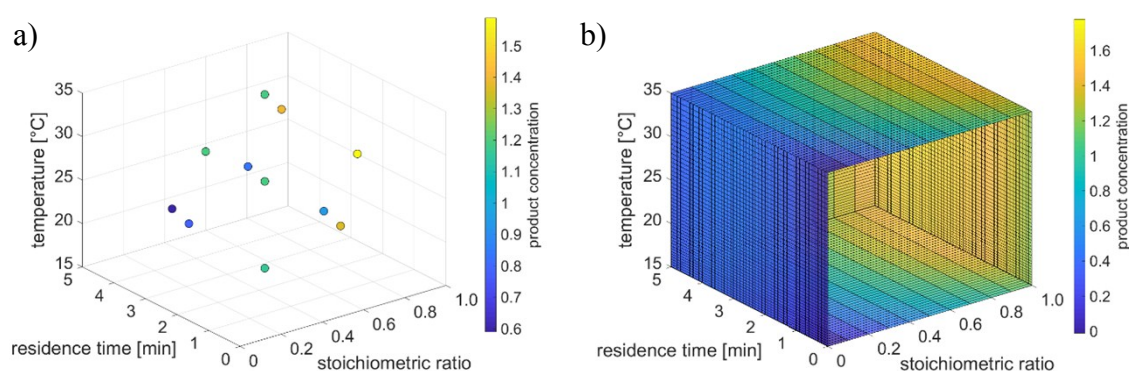

Figure S12. Optimisation of product concentration with three variable parameters using DoE, results for first DoE run.
a) Experimental data points, colour scheme represents product concentration as function of variable parameters (stoichiometric ratio, residence time, and reaction temperature).
b) Resulting surface response model (displayed with cut surfaces).

Figure S13. Optimisation of product concentration with three variable parameters using DoE, results for second DoE run.
a) Experimental data points, colour scheme represents product concentration as function of variable parameters (stoichiometric ratio, residence time, and reaction temperature).
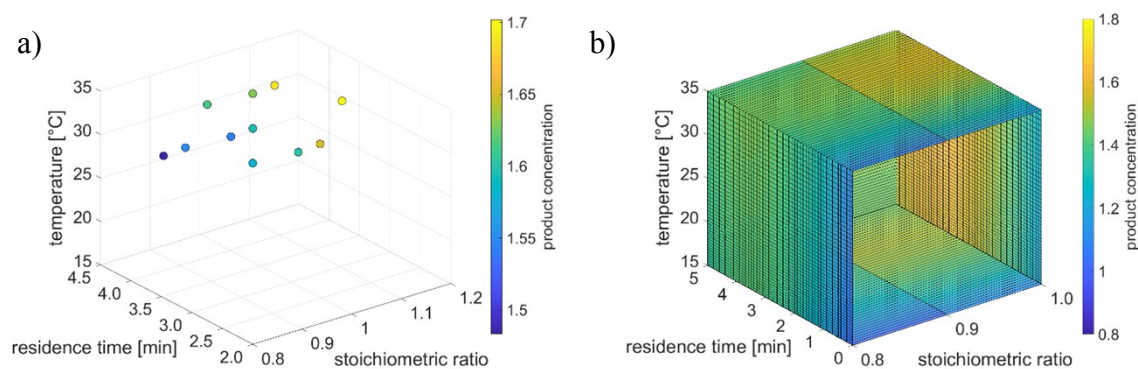b) Resulting surface response model (displayed with cut surfaces).

In terms of minimum cost as optimisation goal, the surface response models obtained by the first and second DoE run, while optimising two variable parameters (stoichiometric ratio and residence time), are exemplarily provided in Figure S14. Besides, the surface response models obtained by the first and second DoE run, while optimising three variable parameters (stoichiometric ratio, residence time, and reaction temperature) are displayed in Figure S15 and Figure S16.
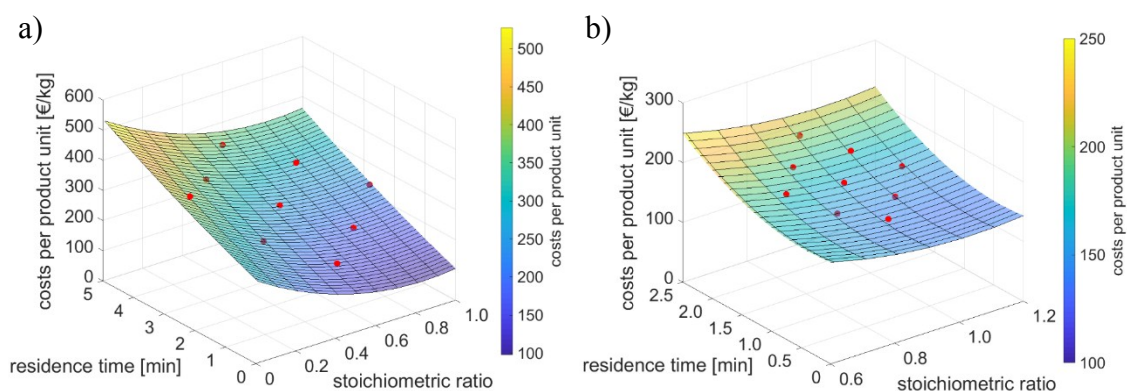
Figure S14. Optimisation of costs per kg of product with two variable parameters using DoE.
a) First DoE run for screening of whole experimental space.
b) Second DoE run to refine optimisation.

Figure S15. Optimisation of costs per kg of product with three variable parameters using DoE, results for first DoE run.
a) Experimental data points, colour scheme represents product concentration as function of variable parameters (stoichiometric ratio, residence time, and reaction temperature).
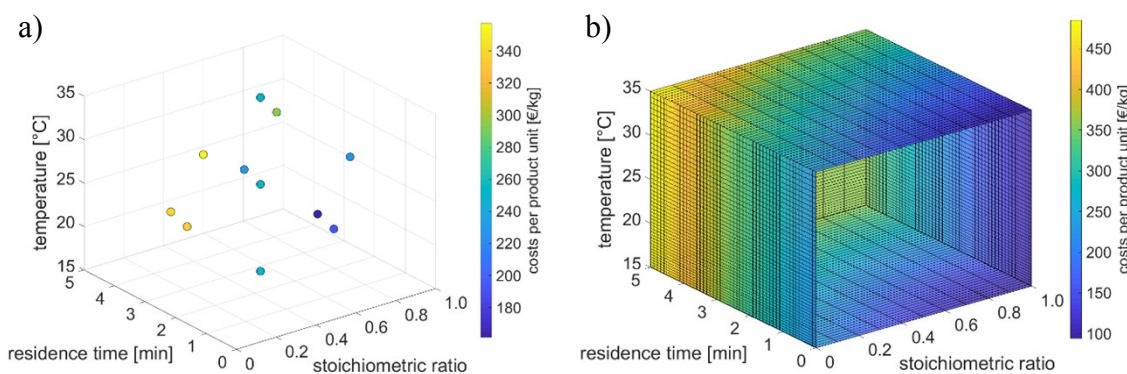b) Resulting surface response model (displayed with cut surfaces).

Figure S16. Optimisation of costs per kg of product with three variable parameters using DoE, results for second DoE run.
a) Experimental data points, colour scheme represents product concentration as function of variable parameters (stoichiometric ratio, residence time, and reaction temperature).
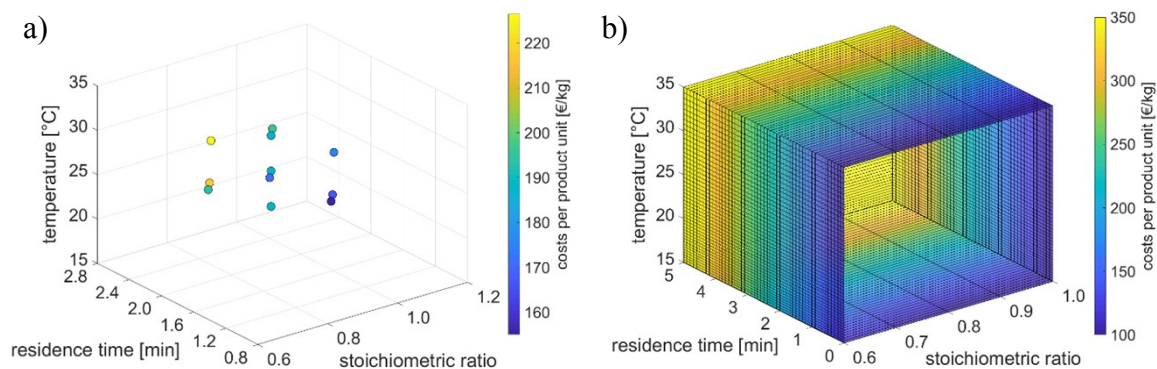b) Resulting surface response model (displayed with cut surfaces).

Finally, the overall measuring accuracy of DoE optimisation was determined. For this purpose, the optimisation procedure with product concentration as objective function was repeated six times at the centre point of the first CCD run and its outer point, both for two and three variable parameters. Results are displayed in Table S4.

Table S4. Reproducibility of DoE optimisation strategy.

Relative standard deviations	Optimisation of two variable parameters	Optimisation of three variable parameters
Centre point	0.3 %	0.3 %
Outer point	0.9 %	0.2 %

In all cases, relative standard deviations amount to values lower 1 %. Hence, DoE optimisation offers high reproducibility.

D. Real-Time Optimisation

D.1. Disturbance of the chemical process through breakdown of temperature control

To study the third type of disturbance, a breakdown of temperature control, real-time optimisation was extended to cover three variable parameters: stoichiometric ratio, residence time, and additionally reaction temperature. A breakdown of temperature control was then simulated. Hence, at optimal conditions for the reference case (stoichiometric ratio of 1.0, high residence time of around 4 min, and reaction temperature of 38 °C, resulting in a maximum product concentration of around 1.8 mol L^{-1}) three sharp temperature decreases were induced. The first disturbance led to a reaction temperature of 15.4 °C, the second one to 15.2 °C, and the third to 14.7 °C.

Based on previously obtained kinetic data[25], the temperature dependence of the reaction can be derived. Therefore, a decrease in product concentration is to be expected in the event of a temperature control breakdown. However, as illustrated in Figure S17, the value of the objective function decreases only slightly, and already reaches its previous level again during the next iteration cycle. This indicates that the process is hardly vulnerable to malfunctions in temperature control. A severe temperature control breakdown merely causes a longer waiting time until the optimal reaction temperature of 38 °C is reached once again. In contrast, the stoichiometric ratio and residence time remain completely unaffected, in line with expectations.

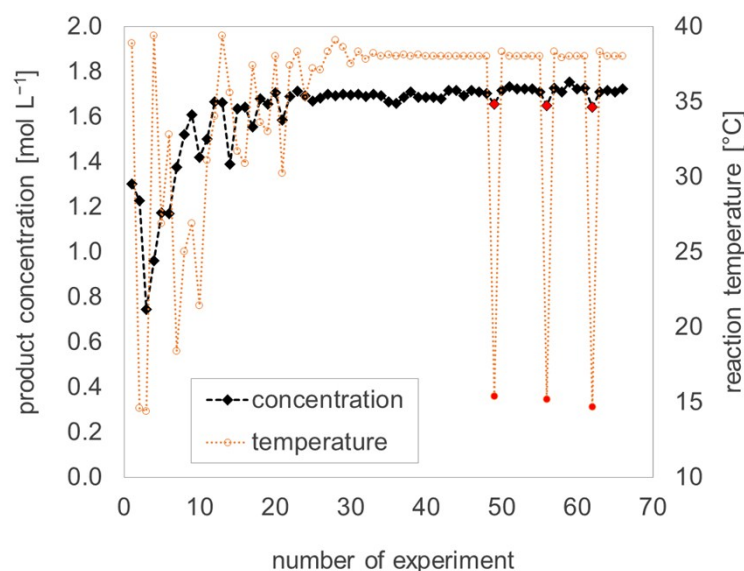**Figure S17.** Real-time response of Simplex algorithm towards breakdown of temperature control (reference case: concentration of starting materials benzaldehyde **1** and benzylamine **2** amounting to 4 mol L^{-1}, optimal reaction conditions at a stoichiometric ratio of 1.0, a high residence time of around 4 min, and a reaction temperature of 38 °C).
Legend: ◊ event of breakdown of temperature control.

D.2. Disturbance of chemical process through inaccurate dosage of starting materials

An inaccurate dosage of starting materials was induced through simulating a defect of the syringe pump: Thereby, the flow rate of one of the starting materials was halved. It should be noted that the actual flow rate consisted of half of the flow rate that was transmitted to the Simplex Algorithm. Hence, a recalculation of actual flow rates was necessary.

Once again, the disturbance was simulated on the basis of an initial situation featuring equal initial concentrations of both starting materials (concentration of benzaldehyde **1** and benzylamine **2** amounting to 4 mol L^{-1} respectively) and accurate flow rates. Once the process had identified optimal reaction conditions (stoichiometric ratio of 1.0 and high residence time of 4 min at a constant reaction temperature of 25 °C, resulting in a maximum product concentration of 1.8 mol L^{-1}), the inaccurate dosage of one of the starting materials was induced. Table S5 provides an overview of the investigated disturbances.

Table S5. Overview of disturbances of the chemical process through inaccurate dosage of starting materials (benzaldehyde [1], benzylamine [2]).

Inaccurate dosage of starting materials	Expected new stoichiometric value	Stoichiometric value reached after real-time optimisation	Number of experiments required to offset disturbance
halved flow rate of [**1**]	2.0	2.0	9
halved flow rate of [**2**]	0.5	0.5	8

Exemplarily for a disturbance through halving the flow rate of benzaldehyde **1** (initial concentrations of benzaldehyde **1** and benzylamine **2** are held constant at 4 mol L^{-1}), Figure S18 illustrates the progression of simplexes during real-time optimisation.
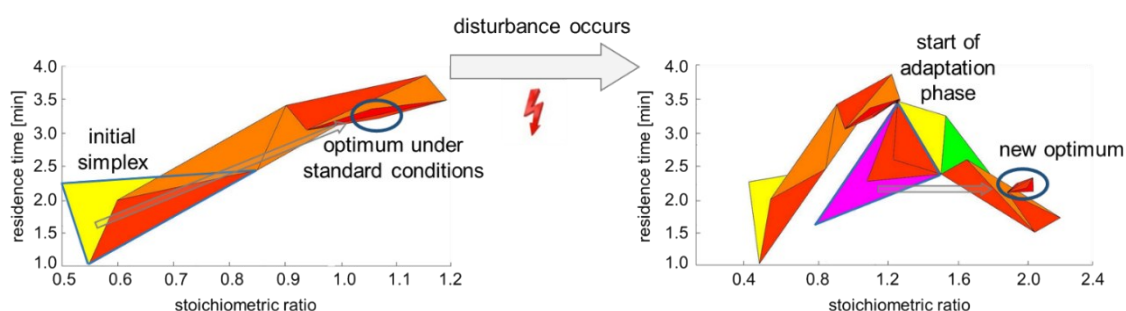

Figure S18. Simplex progress during real-time optimisation.
a) Progress under standard conditions (initial concentrations of benzaldehyde **1** and benzylamine **2** amounting to 4 mol L^{-1} respectively, both starting material with accurate flow rates).
b) Simplex response towards inaccurate dosage of benzaldehyde (flow rate of benzaldehyde **1** is halved).
Legend: colouring of simplexes corresponds to simplex movement: yellow – reflection, green – expansion, red – contraction without change in movement direction, orange – contraction with change in movement direction, purple – start of adaptation phase after disturbance has occurred.

Simplex size increases as soon as an inaccurate dosage of benzaldehyde **1** affects the objective function in an adverse manner, and the algorithm consequently attempts to offset this impact through converging to a new optimal stoichiometric ratio. Hence, a stoichiometric ratio of 2.0 yields a much better result compared to a stoichiometric ratio of 1.0 that proved ideal for the initial situation. This is in line with expectations.

However, it should be noticed that simplexes seem to navigate towards lower residence times after the disturbance is induced. This deviates from real conditions, as the Simplex algorithm overestimates flow rates. As mentioned before, the actual residence times are higher than the displayed ones (after simulating a defect of the syringe pump), and have to be recalculated.

Figure S19 illustrates the progression of the objective function (product concentration) during real-time optimisation with inaccurate dosage of benzaldehyde **1**, and the related parameter combinations.
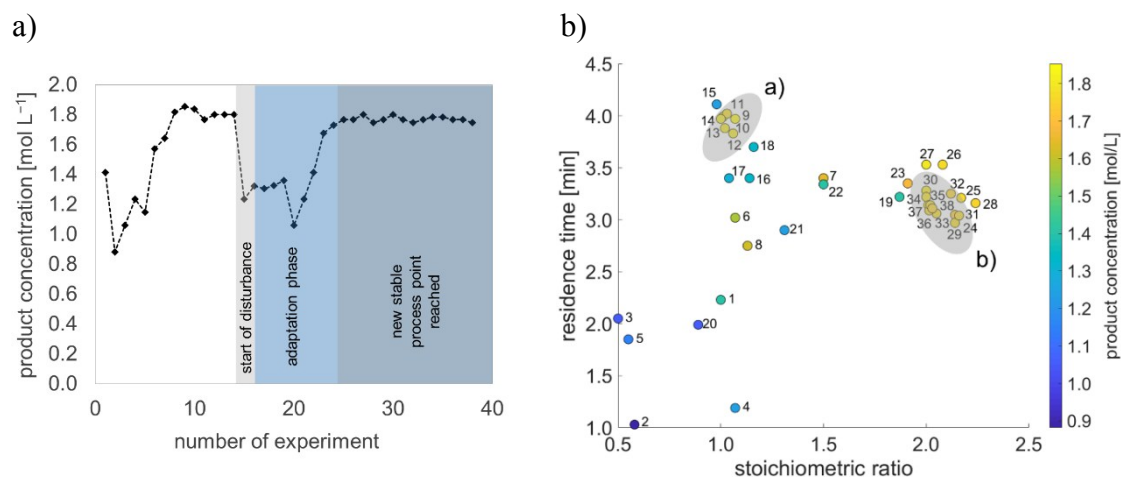

Figure S19. Disturbance of the chemical process through inaccurate dosage of benzaldehyde **1** (flow rate of benzaldehyde **1** is halved).
a) Real-time response of Simplex algorithm towards inaccurate dosage process (product concentration resulting from individual experimental runs).
b) Product concentration as function of stoichiometric ratio and residence time. Legend: at *a)* optimal reaction conditions for reference case, at *b)* Simplex response to disturbance through halving benzaldehyde's flow rate, resulting in optimal reaction conditions once again.

As soon as the disturbance occurs through halving the flow rate of benzaldehyde **1**, the product concentration decreases sharply, and increases again when real-time optimisation intervenes. This rebound in product concentration up to the initial situation's value is accompanied by an increase of the stoichiometric ratio from 1.0 to 2.0, as outlined in Figure S19. However, it should be noted that the resulting new optimal residence times are slightly lower than those of the initial situation, even after recalculation.

Two examples of inaccurate dosage of starting materials were evaluated: halved flow rate of benzaldehyde **1,** and halved flow rate of benzylamine **2**. In both cases, the Simplex autonomously discovers the new optimum stoichiometric ratio, always corresponding to the expected values.

E. Comparison of modified Simplex algorithm and Design of Experiments

For both optimisation strategies, Table S6 provides an overview of the overall measurement times needed to complete an optimisation cycle. Moreover, different optimisation goals and multidimensional optimisation of two or three variable parameters are compared.

It should be noted that the actual measurement times strongly depend on the respective residence time, and thus on the reaction kinetics. Hence, the relation between the number of experiments and overall measurement time is not linear, but rather depends on whether experimental points with high or low residence time are investigated. The next measurement did not commence until steady-state conditions and a constant reaction temperature had been re-established. Re-establishing a constant reaction temperature is especially crucial when it comes to optimisation with three variable parameters (including temperature as variable parameter). In comparison, the optimisation workflow itself proceeded quite fast (<1 s), since it only consists of permanent communication between MATLAB, HiTec Zang, and OPUS in the background.

Table S6. Overall measurement times and number of experiments required to find optimal reaction conditions for Simplex and DoE optimisation, with different optimisation goals, and two or three variable parameters.

Optimisation strategy	Overall measurement time [h]	Number of experiments
Simplex optimisation		
objective function: *product concentration* **two** variable parameters	4.3	25
objective function: *product concentration* **three** variable parameters	5.5	20
objective function: *costs per kg of product* **two** variable parameters	1.5	22
objective function: *costs per kg of product* **three** variable parameters	2.9	22
DoE optimisation		
objective function: *product concentration* **two** variable parameters	2.8	18
objective function: *product concentration* **three** variable parameters	4.7	22
objective function: *costs per kg of product* **two** variable parameters	2.0	18
objective function: *costs per kg of product* **three** variable parameters	3.3	22

In case of product concentration as objective function, DoE optimisation had always been completed faster than the Simplex optimisation (even though Simplex optimisation needed fewer experiments in case of three variable parameters). This was due to the fact that the Simplex algorithm soon converged to high residence times, as the value of the objective function increased drastically with increasing residence time. By contrast, the experimental plans of the DoE optimisation were always evenly distributed over the entire experimental space. Therefore, experimental plans included both, low and high residence times. Thus, DoE also involved testing lower residence times to calculate surface response models, resulting in shorter measurement times.

However, when searching for lowest possible costs per kg of product, Simplex optimisation succeeded faster than the DoE optimisation (even though Simplex optimisation needed more experiments in case of two variable parameters). The Simplex algorithm soon converged towards low residence times, whereas DoE optimisation was now been slowed down by its experimental plans that had been evenly distributed throughout the entire experimental space. Thus, it also involved testing higher residence times to derive the surface response models.

Overall, it can be stated that a three parameter optimisation always required longer measurement times compared to an optimisation with two variable parameters. This difference was caused by an additional waiting period, during which the reaction temperature was resettling on a constant (particular) level once again. Nevertheless, all optimisation problems were successfully solved within one working day.

F. Parallel determination of kinetic data

In Figure S20, the experimental data points that were investigated during the classical approach for kinetic modeling under nonsteady-state conditions are compared with the experimental data gained during Simplex optimisation with two variable parameters (stoichiometric ratio and residence time). Experimental data from Simplex optimisation was used for a parallel determination of kinetic data.

Figure S20. Comparison of experimental data points investigated during classical kinetic modeling approach and during Simplex optimisation with parallel determination of kinetic data. Reaction temperature is held constant at 25 °C, stoichiometric ratio and residence time are varied.

In Figure S21, the experimental data points that were investigated during the classical approach for kinetic modeling under nonsteady-state conditions are compared with the experimental data gained during DoE optimisation with two variable parameters (stoichiometric ratio and residence time). Experimental data from DoE optimisation was used for a parallel determination of kinetic data.

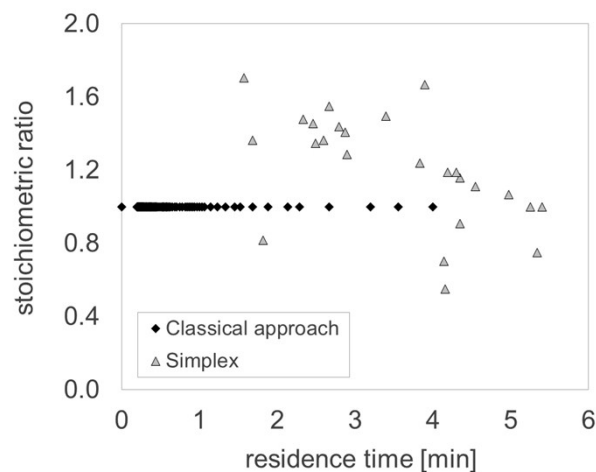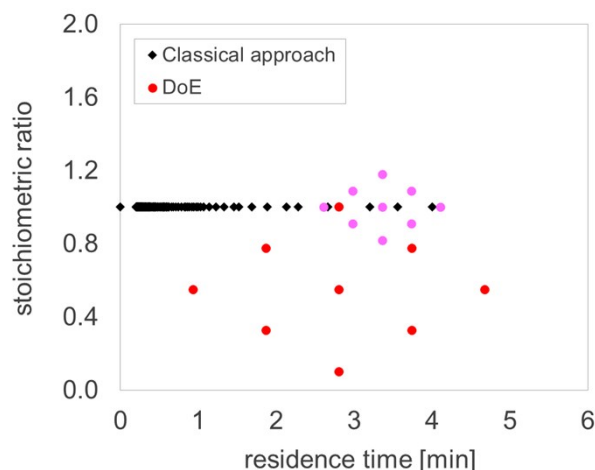**Figure S21.** Comparison of experimental data points investigated during classical kinetic modeling approach and during DoE optimisation with parallel determination of kinetic data. Reaction temperature is held constant at 25 °C, stoichiometric ratio and residence time are varied.
Legend: ● First DoE run. ● Second DoE run.

In case of the classical approach, concentration profiles had been acquired as function of residence time. This had been done at a constant reaction temperature and a defined stoichiometric ratio of starting materials (benzaldehyde **1** : benzylamine **2** amounting to 1.0). Subsequently, the reaction's temperature dependence had been examined. Kinetic data had been determined through fitting the experimental results to a kinetic model. This model described the reaction rate as a function of the concentration of starting materials. Therefore, the least squares method had been used to perform a curve fit based on a calculation of rate coefficient k_{ref} at a defined reference temperature T_{ref} amounting to 25 °C and activation energy E_A.

During multidimensional Simplex optimisation, all involved variable parameters were iterated frequently, resulting in diverse parameter combinations. By the same token, especially the stoichiometric ratio was varied frequently (during Simplex optimisation), since it constituted a variable parameter with high impact on product concentration. In case of maximum product concentration as optimisation goal, short residence times were investigated only to a lesser extent compared to high residence times. This was also true for optimisation with three variable parameters, where lower reaction temperatures have hardly been investigated. Hence, the simplex algorithm quickly converged to parameter combinations that ensured high product concentration. In the final stages of Simplex optimisation, only slight changes in the parameter values arose. Instead, the process was driven towards long residence times, high reaction temperatures, and a stoichiometric ratio near 1.0.

Nomenclature

1	[-]	benzaldehyde
2	[-]	benzylamine
3	[-]	n-benzylidenebenzylamine
c_j	[mol L^{-1}]	concentration of compound j
C_R	[-]	contraction point with change in movement direction
C_W	[-]	contraction point without change in movement
E	[-]	expansion point
$E_{A,i}$	[kJ mol^{-1}]	activation energy of reaction i
k_i	[L mol^{-1} s^{-1}] [s^{-1}]	reaction rate coefficient of reaction i
n	[-]	dimension of optimisation problem
R	[-]	reflection point
Rj	[mol L^{-1} s^{-1}]	reaction rate of compound j
R_{ideal}	[J mol^{-1} K^{-1}]	ideal gas constant
t	[s]	time
T	[K]	temperature
T_{ref}	[K]	reference temperature

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