# Enhanced process development using automated continuous reactors by self-optimisation algorithms and statistical empirical modelling

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## ARTICLE INFO

## ABSTRACT

Reaction optimisation and understanding is fundamental for process development and is achieved using a variety of techniques. This paper explores the use of self-optimisation and experimental design as a tandem approach to reaction optimisation. A Claisen-Schmidt condensation was optimised using a branch and fit minimising algorithm, with the resulting data being used to fit a response surface model. The model was then applied to find new responses for different metrics, highlighting the most important for process development purposes.

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## 1. Introduction

Traditional univarient optimisation of a chemical reaction involves the systematic and sequential optimisation of each individual reaction parameter until an optimum is found. While the execution is simple, the data will not account for interactions between reaction parameters.[1] Design of experiments (DoE) conversely uses statistical calculations to screen reactions and generate a polynomial model over a constrained area of experimental space. The model can highlight the key parameters and interactions that affect changes in the desired response, as well as predicting new responses depending on the model's design. The methodology is commonly utilised in the pharmaceutical industry, particularly for reactions with poor yield, inconsistent output or unexpected results upon scale up.[2] DoE is a very powerful tool and it can show where improvements in operating conditions can be made to deliver a more consistent and reliable product with respect to the optimisation target.

One of the disadvantages of DoE arises when there are a large number of parameters requiring optimisation. The number of experiments required for a design increases substantially with an increasing number of experimental parameters. Often this number can be too large to explore the system efficiently, so a fractional factorial design is implemented to reduce the number of experiments. The disadvantage with this approach is that at least one parameter is confounded with an interaction, thus increasing the complexity of the model analysis. It is also very important that the correct limits are chosen for each parameter to ensure that there are no sudden changes in response and a good polynomial fit can be achieved. Furthermore, additional experiments might be required to verify a response, deconvolute interactions or determine the robustness of optimum conditions.

Self-optimisation is a technique that could remove the problems associated with DoE whilst still obtaining the important information about key parameters and interactions. A self-optimising reactor combines on-line analysis with an adaptive feedback loop and minimising algorithm to autonomously execute reactions, obtain the respective yields and ultimately optimise a chemical process without user intervention.[3–8] The algorithm typically generates a cluster of points around an optimum, therefore increasing the robustness of proposed optimal conditions.

The recent popularity of self-optimisation is increasing but its use in industrial chemical processes is severely limited.[9] A continuous self-optimising reactor will benefit from the numerous advantages of flow reactors including high surface area to volume

ratios, safer operation of hazardous materials, improved mixing, faster kinetics and easier access to automated processes.[10–13]

The main disadvantage with self-optimisation is that new experiments need to be physically executed to optimise for a new target or different chemical compound. If DoE has already been carried out, new models for different responses can be calculated without complication or increased experimentation.

This paper attempts to combine these two optimisation techniques in parallel. A self-optimisation experiment will rapidly generate optimum conditions and scatter across the chemical space through an exploratory algorithm, whilst a response surface model (RSM) will permit the prediction of new responses using the experimental data.

## 2. Results and discussion

Self-optimising reactors have been designed using a variety of analytical techniques including IR[14–16] and NMR spectroscopy[17], mass spectrometry[16,18], gas[19–22] and liquid[23,24] chromatography. In this paper, a feedback-controlled flow reactor, equipped with an at-line HPLC system, is used to provide fast separation and quantification of the desired compounds. Through the combined implementation of a variable wavelength UV detector and microvolume sample injector, automated optimisations were executed at the mesoscale with the direct injection of reaction mixture into the HPLC column, thus negating the need for dilution prior to analysis. The optimisation target was the minor product of a Claisen-Schmidt condensation between acetone (**1**) and benzaldehyde (**2**) to form the desired product, benzylideneacetone (**3**) (Scheme 1).[25] Strict control over the reaction parameters was required to prevent **3** reacting to form dibenzylideneacetone (DBA) (**4**) and acetone polymerization, both of which caused clogging in the reactor.

A gradient HPLC method at 254 nm was developed to quantify compounds of interest. While adequate separation between species was achieved, preliminary HPLC calibrations resulted in a non-linear response for **2** and **3** at the reference wavelength of 254 nm. UV spectra of both compounds were obtained to determine the wavelengths at which each species could be quantified, without saturating the detector (Fig. 1). The HPLC method was
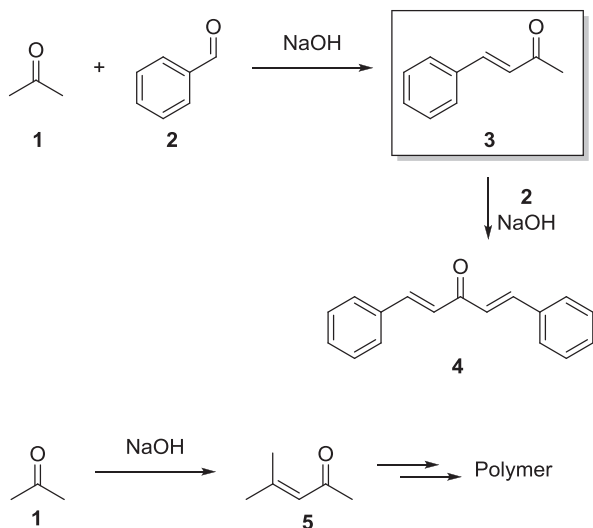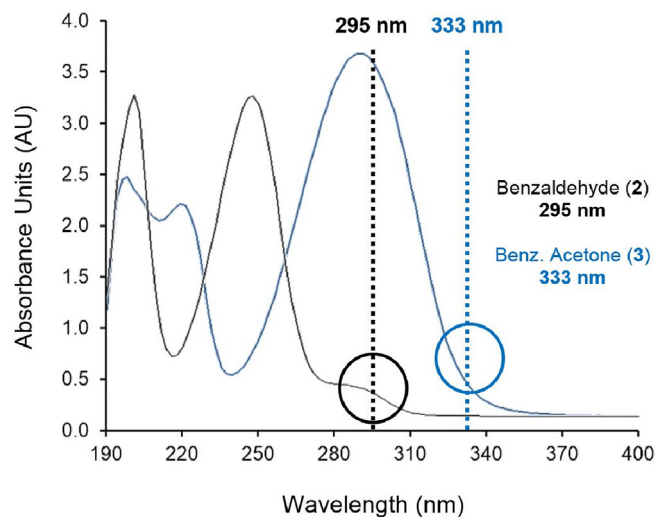


**Fig. 1.** UV absorption spectra of benzaldehyde (**2**) and benzylideneacetone (**3**) in ethanol between 190 and 400 nm. Dashed lines indicate wavelengths selected for variable wavelength HPLC method.

consequently modified to momentarily switch to 295 nm and 333 nm, when compounds **2** and **3** were respectively eluted, to ensure the detector would not be saturated during optimisation. This new method allowed linear calibrations of species **2**–**5**.

All components were monitored and controlled via a bespoke MATLAB based software package (reactor setup is shown Fig. 6). The flow rates of the three reagent pumps and reactor temperature were varied to maximise the yield of **3**. Table 1 displays the optimisation limits for the four reaction variables. Acetone flow was controlled relative to **2** to ensure it was always in excess, while the temperature was limited to 80 °C after initial experiments exhibited polymer formation beyond this. While previous literature and preliminary experiments can be used to constrain the experimental space and speed up the optimisation process, the algorithm is also capable of optimising within the entire operating range of the equipment being utilised. This capability is particularly advantageous when no prior knowledge of a chemical process is available.

The algorithm used for the optimisation was SNOBFIT, a constrained branch and fit function that locates optima by fitting polynomials to the response of experimental data points.[26] During an optimisation it focuses on locating optimal conditions, whilst simultaneously exploring empty space to prevent premature termination at local optima. In the event of multiple optima within a chemical system, the algorithm is capable of exploring both regions of experimental space within a single experiment.

The optimisation cycle was repeated until a total of 70 experiments had been executed. The results (Fig. 2) indicate that an optimum yield of 66.0% was achieved at a benzaldehyde (**2**) flow rate of 0.4 mmol/min, with 7 molar equivalents of acetone and a reactor temperature of 35.8 °C. The catalyst concentration of 0.25 M is also displayed in molar equivalents relative to benzaldehyde to ease comparability between runs. Because the catalyst concentration was regulated in mmol/min (Table 1), the algorithm minimised the flow rate of benzaldehyde to 0.4 mmol/min, whilst maximising the catalyst flow rate to 0.25 mmol/min, to achieve this maximum equivalence. While the cluster of high yield experiments surrounding the optimum were all executed at maximum NaOH equivalence, there are other experiments exhibiting yields of around 60%, with much lower NaOH equivalents, which suggests that catalyst concentration may not be the most significant yield limiting factor in this reaction. Following the data points along the



**Scheme 1.** Claisen-Schmidt condensation between acetone (**1**) and benzaldehyde (**2**) to form the desired benzylideneacetone (**3**) and undesired benzylideneacetone (**4**). Acetone can also undergo self-condensation to form mesityl oxide (**5**), as well as the subsequent polymer.