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An Automated Microfluidic System for Online Optimization in Chemical Synthesis

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Abstract:

An automated, continuous flow system for the online, multivariable optimization of a chemical reaction is presented. Time and material required for an optimization trial are minimized by performing reactions in an integrated silicon microreactor and incorporating an HPLC for inline monitoring of the reaction performance. We use the system to optimize two different reactions to describe the potential impact of this system for reaction development. First, we demonstrate the broad operation capabilities by incorporating several feedback algorithms to optimize a weighted objective function involving the yield and the throughput of a Knoevenagel condensation reaction. After illustrating how system operations can be adapted for individual reactions, we perform a multiparameter optimization to maximize the yield of benzaldehyde in the oxidation pathway of benzyl alcohol to benzaldehyde to benzoic acid. A significant feature of the automated system is the ability to perform "black-box" optimization where no *a priori* information of the reaction parameters is required.

1. Introduction

Finding the optimal operating conditions for complex reaction networks that are encountered in pharmaceutical and fine chemistry applications can be an arduous task. Search procedures for identifying reaction temperature, time, and reagent concentrations that maximize the desirable product yield are complicated by poorly understood side reactions and interactions among reaction variables. Traditionally, batch techniques used for determining the optimal conditions require considerable amounts of labor and expensive starting material.[1] Furthermore, results from batch experiments can be constrained by mass and heat transfer limitations, making the scale-up of reaction results difficult. Alternatively, the efficiency and speed of the optimization procedure are improved through the use of integrated microreactors.

Attributed to enhanced mass and heater transfer rates, improvements of reaction yield in microreactors over conventional bench-scale equipment have been demonstrated for a wide range of applications,[2−6] including pharmaceutical,[7] fine chemical,[8,9] and chemical and biochemical screening.[10,11] Since the continuous flow operations and the submilliliter volume of microreactors permit rapid sequential experimentation, these devices are ideal tools for optimization[12,13] and kinetic investigations.[14] Additionally, the incorporation of physical sensors and spectroscopic equipment enables precise monitoring of experimental conditions and reaction progression, respectively.[15,16] Combining these features with the appropriate feedback control and logic algorithms enables automation of experimental conditions.[17,18]

For the pharmaceutical industry, the combination of continuous flow and automated operations enables researchers involved in lead compound generation to quickly identify promising drug candidates and to scale the reaction to manufacturing. Reductions in time and material costs associated with reaction screening have been demonstrated for the synthesis of cycloadducts,[19] pyrazoles,[20] and Ciprofloxacin analogues.[21] Recently, multidimensional screening, where reactions are evaluated by varying reaction conditions as well as reagent compounds, has been demonstrated as a method for investigating transformations

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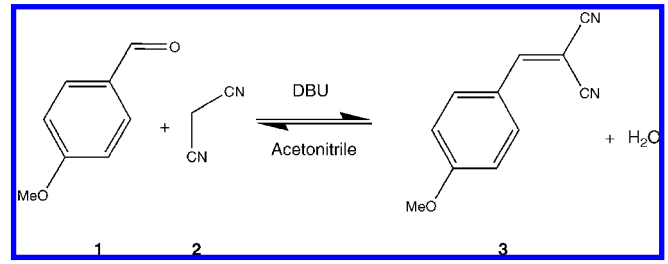
of densely functionalized bicyclo[3.2.1]octanoid scaffolds.[22] Once a candidate reaction has been selected, numerous experiments aimed at determining the continuous operating and optimal conditions are performed.

The efficiency and the speed of these reaction optimization experiments are also improved through the use of automated continuous-flow reactor systems,[23] as has been illustrated in several demonstrations. In one approach, a specified set of experimental conditions are performed in an automated manner and the results are analyzed off-line.[24] Based upon this reaction data, a new set of experimental conditions are proposed and the procedure is repeated until the optimal conditions are determined. Alternatively, the set of automated experimental conditions can be determined through response surface modeling and optimal experimental design frameworks.[25,26] While these automated systems are ideal for scanning a selection of predetermined experimental conditions, these approaches are less efficient in terms of the number of experiments required to locate the optimal conditions.

Incorporating an inline analytical detection method with an optimization algorithm significantly improves the reaction optimization procedure, as demonstrated by Krishnadasan and co-workers for the controlled synthesis of Cadmium Selenide (CdSe) quantum dots.[27] This automated microfluidic system used a CCD spectrometer to measure the fluorescence emission of the nanoparticles and adjusted the temperature and the precursor flow rates to maximize the emission at a specified wavelength. The Stable Noisy Optimization by Branch and Fit (SNOBFIT) method was the optimization routine employed in this system and is also one of the methods used in the current work. The microreactor system described herein was developed for the optimization investigations of small molecule synthesis. The automated experimental protocol was established and validated for inline HPLC analysis. This analytical techniqe provides a convenient method of extracting multicomponent information, can be used to quantify a wider range of reaction types than inline spectroscopy alone, and is a preferred detection method in many synthesis laboratories. A combination of local and global search techniques were used in the automated microreactor system to briefly illustrate the range of algorithms that could be implemented and to highlight the costs and benefits of these different approaches.

The reversible, condensation reaction involving *p*-anisaldehyde **1** and malononitrile **2** catalyzed by 1,8-diazabicycl-[5.4.0]undec-7-ene (DBU) was selected as the first model reaction (Scheme 1).[28] Using three different feedback algorithms, the system maximized the weighted objective function, f_1 (eqs 1a−1e), by varying reaction temperature and residence time within a constrained parameter space. This objective function, which is a combination of the production throughput ($Q_{exp}Y_{exp}$) and the yield (Y_{exp}), biases the system to look at shorter residence times without sacrificing yield.[29] For reversible reactions, this approach searches for equilibrium conditions that can be achieved on smaller time scales. Algorithms used to optimize this reaction included the Nelder−Mead Simplex,[30] the Steepest Descent Method using design of experiment (DoE) techniques for response surface modeling,[31] and the Stable Noisy Optimization by Branch and Fit (SNOBFIT).[32] Implementing these algorithms demonstrated the robustness of this system and the ability to easily incorporate future algorithms aimed at optimizing complex reaction schemes and multistep organic syntheses or precisely estimating the kinetic parameters of a reaction.

Scheme 1. **Knoevenagel condensation was performed in the automated microfluidic system with various optimization approaches to demonstrate the ability to implement numerous feedback methods into the system operations**



$$f_1 = \max_{T,\tau} \frac{Q_{exp}Y_{exp}}{Q_{max}Y_{max(theory)}}Y_{exp} \quad (1a)$$

Q_{exp}:Experimental flow rate (1b)

Y_{exp}:Experimental product yield (1c)

Q_{max}:Maximum flow rate, set by constraints on parameter space (1d)

Y_{max}:Maximum theorectical yield, 100% (1e)

The oxidation of benzyl alcohol to benzaldehyde by chromium trioxide with further oxidation to benzoic acid was selected as the model reaction for multiparameter optimization (Scheme 2).[33,34] For this reaction, the system varied temperature, residence time, and the inlet concentrations of the reagents to maximize the benzaldehyde **5**

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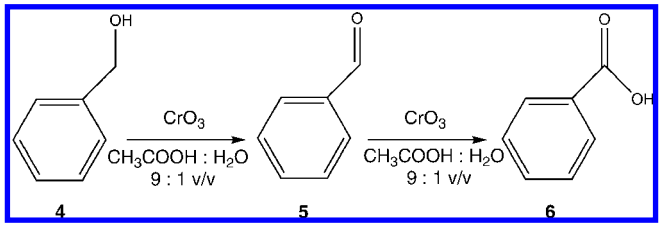
Scheme 2. **Oxidation of benzyl alcohol and benzaldehyde was used to demonstrate multiparameter optimization with the automated microfluidic system**



yield. Although alternative oxidation pathways that produce only the intermediate **5** in excellent yields have been developed[35−40] and implemented in continuous-flow microreactors,[41−43] the challenging features of maximizing the yield of **5** in Scheme 2, given the highly oxidative environment created by the acidic solvent,[44] serve to demonstrate convincingly the advantages associated with the automated microfluidic continuous-flow reaction system.

2. Experimental Methods

2.1. Automated Microfluidic System Components. A schematic of the microfluidic system used in this investigation is shown in Figure 1a. The system consisted of five syringe pumps (Harvard Apparatus, PHD 2000), and serial communications between the central computer (Dell, OptiPlex GX270) and each pump were accomplished with daisy chain connections (Harvard Apparatus, 9 pin D-sub, 2 ft daisy-chain interconnects). Reactions were performed in a silicon microreactor that was designed with a serpentine mixing zone, a reaction zone, and a quench zone (Figure 1b). An optional, 101-channel silicon micromixer[45] designed on interdigitated mixing principles[46] was included downstream of the microreactor for reactions that required dilution before analysis. Online monitoring of the reaction was achieved by using an actuated 6-way valve (Rheodyne, MXP7900) to inject reaction samples into the HPLC system (Waters, 1525 binary pumps, Nova-Pak C18 4 μm, 3.9 mm $\times$150 mm column, 2996 PDA detector, Empower software). Optimization algorithms were written in Matlab scripts (release 2007a, Mathworks) and interfaced with in-house LabVIEW programs (v7.1, National Instruments) to adjust experimental parameters such as syringe pump flow rates and reaction temperature. A compact fieldpoint system (National Instruments, cFP-2020 controller, cFP-AI-100 analog input module, cFP-RLY-425 relay module) was used for data acquisition and process control.

2.2. Microreactor Technology. The silicon reactor (Figure 1b) was fabricated using standard lithography and deep reactive ion etching (DRIE) techniques.[47] The channels were etched 400 μm deep and consisted of three zones: a mixing zone with 200 μm $\times$ 400 μm channels to promote mixing, followed by a reaction zone with 400 μm $\times$ 400 μm channels to act as a residence time unit, followed by an 8 μL quench zone to terminate the reaction on chip. The reactor was coated with silicon nitride and capped with Pyrex to create a chemically inert environment that is suitable for numerous chemistry applications. Details of the integrated compression packing scheme (Figure 1c) are provided in the Supporting Information.

2.3. Inline Monitoring. Previous works have relied on inline spectroscopy for monitoring of the reaction progress.[17,18,27,48,49] Recently, the benefits of incorporating inline ATR-IR with continuous-flow reactors have been demonstrated for a variety of chemical syntheses.[50] Though such inline methods can increase the experimental throughput of the system, organic synthesis typically requires a method that can distinguish between regio- and stereochemically different compounds.[51] Furthermore, slight differences between the reactant and the product structures can be difficult to quantify with spectroscopic measurements alone. For these reasons, an HPLC was integrated with the automated microfluidic system for inline detection. Reaction samples were loaded into the HPLC system through a 6-way valve that was activated by a contact closure through the relay module. Isocratic HPLC methods were created and operated using Empower software. Two analog outputs from the photodiode array, corresponding to the absorbance values at two specified wavelengths, were also configured using Empower. After specifying the retention time for each analyte, a baseline absorbance value for each wavelength was computed by averaging the absorbance signal at 10−30 s before analyte elution. HPLC methods were developed to ensure that the analyte peaks were sufficiently separated at the specified wavelengths to avoid biasing this baseline measurement. Chromatograms were created by recording the absorbance signals that surpassed a threshold absorbance value around the specified retention times. Numerical integration functions in LabVIEW (Numeric Integration VI) and Matlab (trapz) were used to integrate a chromatogram, and the resulting area measurement was related to the analyte concentration through a calibration curve.

2.4. Automation and Feedback Control Systems. All experimental hardware and data measurements were interfaced with in-house LabVIEW programs. Within the main LabVIEW program, Matlab scripts were developed to regulate the temperature controller, to execute the optimization algorithm, and

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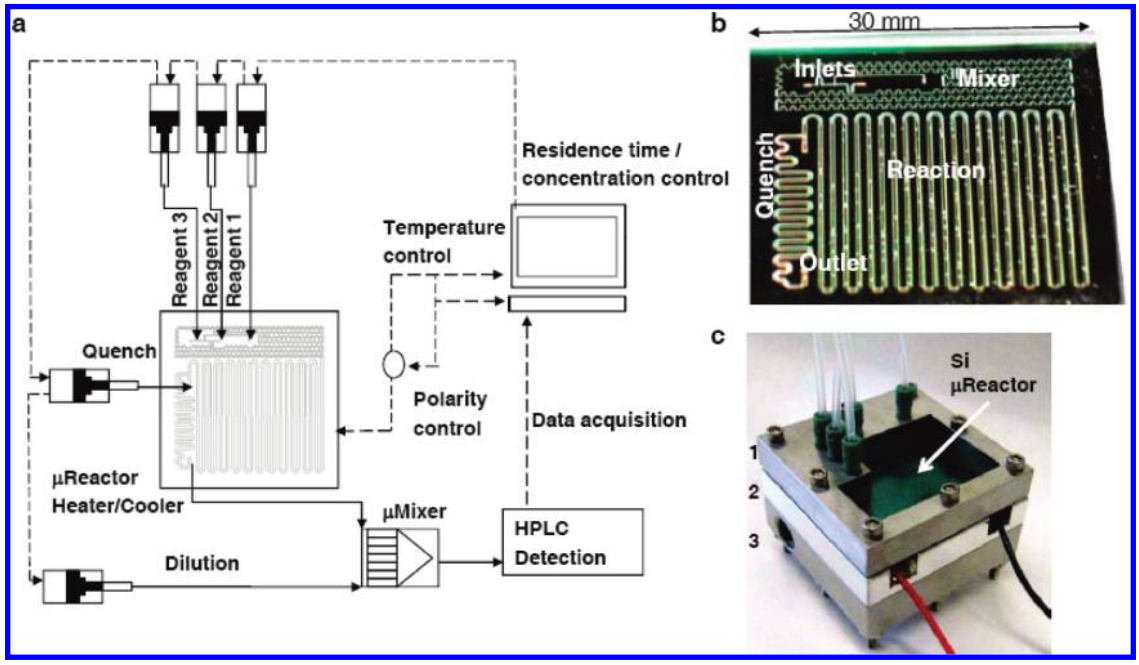

Figure 1. **(a) Schematic of automated microfluidic system consisting of syringe pumps, microreactor, micromixer, HPLC, and computer with associated LabVIEW interface hardware. (b) Microreactor used in optimization study with mixing, reaction, and quench zones. (c) Packaging scheme for the microreactor included fluidic connections in the top plate (1), a recessed plate (2) to house the microreactor and TE device, and baffled heat exchanger (3) for sufficient heat removal and additional temperature control.**

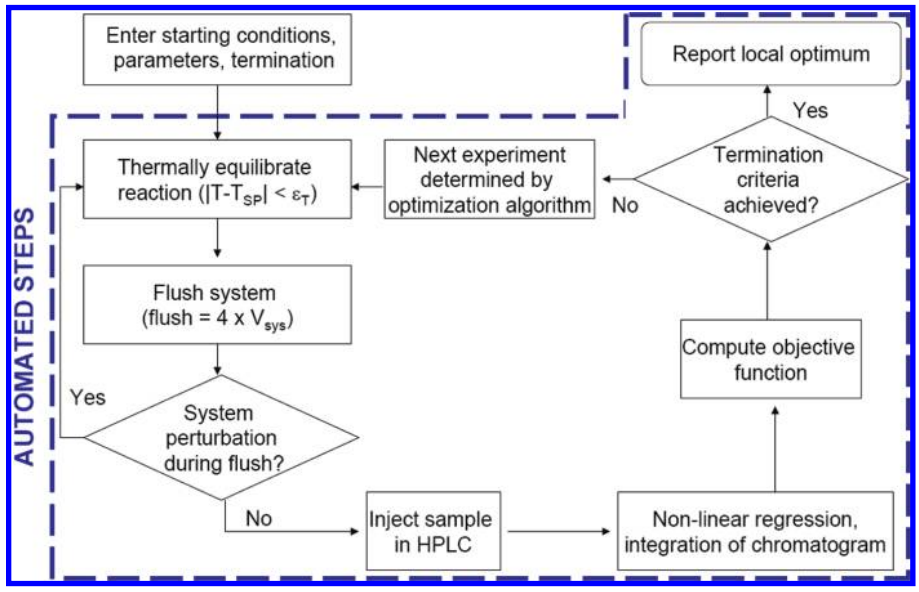

Figure 2. **Flowsheet description of operations implemented into automated microfluidic system.**

to perform advanced mathematical operations such as nonlinear regression and solving multiple equations simultaneously. Syringe pumps (Havard PHD 2000) were used to control the residence time and reactant concentrations. A pulse width modulated (PWM) approach with a proportional-integral-derivative (PID) controller on the duty cycle provided reaction temperatures within 1.5 °C of the set point temperature. The reaction temperature was monitored with a K-type thermocouple (Omega, 5TC Series) that was placed on the backside of the silicon microreactor and secured using thermally conductive silicone paste (Omega). A separate control algorithm on a double pole, double throw switch (Potter Brumfield, KUP-11D15−24) controlled the direction of the current through the TE element, offering a means to heat or cool the reactor without discontinuity in operations. In combination with the cooling capabilities of the integrated compression packaging scheme, this control strategy provided reaction temperatures between −30 and 120 °C and increased the experimental throughput of the system by decreasing the lag time between sequential experiments as the system thermally equilibrated.

The experimental procedure that was developed, validated, and implemented into the operations of the automated microfluidic system is shown in Figure 2. First, the necessary criteria for the optimization and control methods were inputted into the program. After providing this information, the process became completely automated and user intervention was

obviated. Each experiment began by thermally equilibrating the microreactor—defined as the absolute difference between the reaction temperature and the set point temperature (T_{SP}) being less than a specified tolerance, nominally 3 °C. The system was then flushed adequately, generally four system volumes (V_{sys}), to ensure steady-state data collection. A sample was then injected into the HPLC system, and the chromatographic data were recorded with the LabVIEW hardware. The area of the chromatogram was computed to determine the concentration of the different components. After using these measurements to calculate the objective function, the optimization algorithm determined the next sequential experiment in the procedure or terminated if appropriate. As described, this methodology provided reproducibility equal to the reproducibility of the HPLC detection.

2.5. Optimization Algorithms. Selecting the most appropriate algorithm for reaction optimization without knowledge of the kinetics or the mechanism is difficult because the response surface for typical objective functions, such as yield or selectivity, can be simple and monotonic or highly corrugated depending upon the complexity of the individual reaction steps. Obtaining the so-called global solution to the latter type of reaction system is particularly challenging because many optimization algorithms are designed to converge upon local optima. Determining the global solution becomes more challenging when search variables that have highly nonlinear effects on the reaction outcome, such as pH and solvent composition,[52] are included in the reaction optimization problem. Methods exist to locate the global solution for these challenging systems[53−55] but require extensive knowledge of the reaction that is seldom available or is prohibitively difficult to experimentally ascertain due to limited research resources. Furthermore, these approaches are not necessarily efficient when the local optimum is the global solution, as is common for many reactions of pharmaceutical interest.[56−60] For these reasons, our optimization investigations used black-box algorithms that appear efficient for most experimental optimization applications.

Because no single technique is unanimously accepted as an efficient and effective means of experimental reaction optimization, we designed a microreactor system that could operate with a variety of algorithms. The optimization methods, or variations thereof, that were developed and implemented in the automated microfluidic system represent neither a comprehensive list of the algorithms that could be applied with the system nor a selection of approaches that guarantee fast convergence for black-box experimental optimization. Two local search methods, the Nelder−Mead Simplex Method and the Steepest Descent Method with response surfacing modeling, were implemented to demonstrate the ability to rapidly optimize a chemical synthesis. A global search technique, SNOBFIT, was also implemented to illustrate the potential to use the microreactor system for the optimization of highly nonlinear reaction systems. The operational details of these algorithms are discussed in the Supporting Information.

2.6. Experimental Methods for Knoevenagel Investigation. A 10 mL solution containing *p*-anisaldehyde (200 mM), malononitrile (200 mM), and naphthalene (100 mM) as an internal standard was prepared in acetonitrile. A second 10 mL solution containing DBU (80 mM) was prepared in acetonitrile. Each solution was loaded into a 10 mL SGE syringe, mounted on a single syringe pump, and connected to an inlet of the microreactor. The third microreactor inlet was plugged. By mounting both reaction solutions on the same syringe pump, the inlet concentrations of each reagent were half that of the prepared solution. Because the two-dimensional optimizations that were performed with this model reaction used only temperature and residence time as variables, these inlet concentrations remained constant throughout the experiments. The reaction was quenched with a 10 mL solution of trifluoroacetic acid (1000 mM) in acetonitrile. This solution was loaded into a 10 mL SGE syringe and mounted on a syringe pump that was programmed to flow at the same rate as the DBU solution.

A 6-way actuated valve with a 2 μL sample loop was used to inject reaction samples into the HPLC for analysis. Adequate and reproducible analyte separation was observed with an isocratic HPLC method using 0.7 mL/min of methanol and 0.3 mL/min of 0.1% (v/v) formic acid in water. The reaction yield was measured using a response factor and the ratio of absorbances of 2-*p*-anisylidenemalononitrile at 400 nm to naphthalene at 250 nm.

2.7. Experimental Methods for Oxidation Investigation. Reaction solutions (50 mL) containing benzyl alcohol (30 mM) and chromium trioxide (30 mM) were prepared in 90% v/v acetic acid/water. Each solution was loaded into a 25 mL SGE syringe and mounted on a syringe pump. To operate at different reactant concentrations and residence times independently, a third syringe pump was used to adjust the flow rate of a 90% v/v acetic acid/water solution. A bulk solution of sodium bisulfate (200 mM) in water was prepared, loaded into a 60 mL B.D. plastic syringe, and mounted on a syringe pump. Sodium bisulfite reduces Cr(VI) to Cr(III) and eliminates oxidation of the aromatic species once the solution exits the reactor.[61] Effective quenching was observed when the sodium bisulfite flow rate was set to be twice that of the CrO_3 flow rate. Water was loaded into two 60 mL B.D. plastic syringes, mounted on a syringe pump, and added to the reactor outlet stream to dilute the reaction mixture before HPLC detection. A 101-channel interdigitated micromixer was used to ensure fast, thorough mixing of these two streams before sample injection.

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A 6-way actuated valve with a 10 μL sample loop was used to inject reaction samples into the HPLC for analysis. Adequate and reproducible analyte separation was observed with an isocratic technique using 1.05 mL/min of water and 0.45 mL/min of acetonitrile. The concentrations of benzaldehyde and benzoic acid were measured using absorbance data at 248.5 and 226 nm, respectively.

For the model oxidation system, reaction parameters that were controlled by the automated system and varied during optimization trials included reaction temperature (T), the residence time (τ), the reactor inlet concentration of benzyl alcohol ([$PhCH_2OH$]°), and the molar equivalence of chromium trioxide (CrO_3 equivalence). Although the multidimensional optimization presented in the current work was limited to these four reaction variables, the same approach can clearly be extended to include other reaction variables, such catalyst loading, ionic strength, pH, and solvent composition.

2.7.1. Automated Calibration. Reaction yield and selectivity for the oxidation investigation were calculated using a calibration curve to relate the area of the chromatogram to the concentration of the analyte. The monotonous process of formulating a calibration curve for the reaction species of interest was automated by loading the syringe pumps with different reagents and adjusting the flow rate of each pump. A mixture containing benzaldehyde (10 mM) and benzoic acid (10 mM) in 90% v/v acetic acid/water was loaded into a syringe (25 mL SGE) on one pump, and water was loaded into a syringe (25 mL SGE) on a different pump. These two streams entered the interdigitated micromixer, and the combined stream was sampled by the HPLC. In this manner, precise calibration curves were quickly created.

3. Results and Discussion

3.1. Knoevenagel Optimization Results. Multiple two-dimensional optimization procedures were performed using the Knoevenagel condensation example reaction to demonstrate the versatile range of operations that could be implemented into the automated system. Each optimization procedure varied the temperature (T) and residence time (τ) to maximize the objective function specified by eq 1a within the feasible space enclosed by box constraints given by eq 2a,b. For the Simplex Method and Steepest Descent Method, the optimization initiated from 70 °C and 180 s, while the SNOBFIT Method required no initial condition information.

$$40°C \leq T \leq 100°C \quad (2a)$$

$$30s \leq \tau \leq 300s \quad (2b)$$

Results from each optimization procedure are shown in Figure 3. The algorithmic parameters used in each optimization trial, the objective function values, and the reaction yields obtained in each optimization procedure are provided in the Supporting Information.

From the specified starting point, the Simplex Method maximized the objective function by methodically selecting experiments at higher temperatures and lower residence times. After attempting to select experiments outside of the feasible space, the simplex contracted in order to hone in on the optimum. This contraction corresponds to the cluster of experiments between temperatures of 85 and 95 °C at residence times between 30 and 100 s in Figure 3a. As the Simplex Method continued to select experiments near the minimum residence time constraint, the simplex collapsed on this value (30 s) and the method performed a one-dimensional optimization search by varying only temperature. As determined by the Simplex Method, the optimum for the objective function was located at a temperature of 99 °C and a residence time of 30 s.

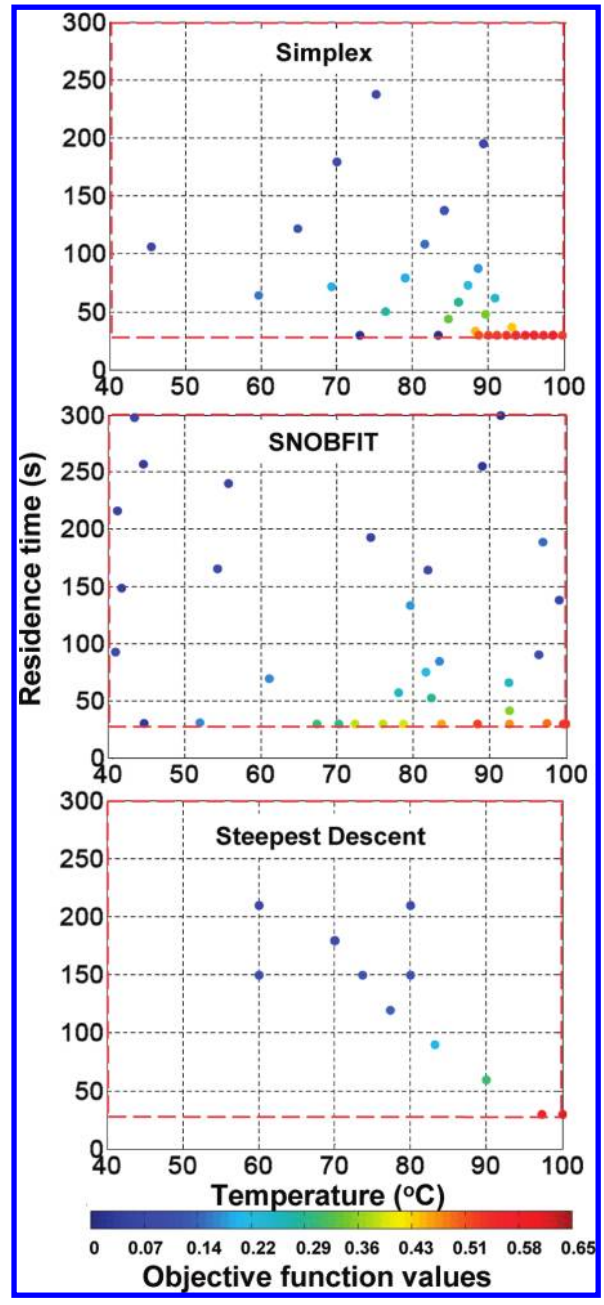

Figure 3. **Optimization results for Knoevenagel example using Simplex Method, SNOBFIT, and Steepest Descent Method. Objective function values, as defined by eq 1a, are denoted by the color bar and range from 0 (poor) to 0.65 (good). Boundaries on the reaction variables are denoted by red dashed lines.**

As shown by Figure 3b, the local fitting feature of the SNOBFIT algorithm preferentially selected experiments at low residence times and higher temperatures. After performing 36 automated experiments, the SNOBFIT method also located the

Table 1. **Summary of optimization results for Knoevenagel reaction**

Algorithm	Total experiments	Optimal conditions		Objective function value	Yield at optimum	Total time (h)
		T (°C)	τ (s)			
Steepest Descent	13	100	30	0.60	77%	~4.5
Simplex	30	99	30	0.58	76%	~8
SNOBFIT	36	99	30	0.54	74%	~11

optimum of the objective function near the vertex of the feasible space, with a temperature 99 °C and a residence time of 30 s. Additionally, because the SNOBFIT method performed experiments in unexplored regions of the parameter space, more confidence that these conditions correspond to the global maximum was gained.

For the specified objective function and inputted parameters, the optimum was located in the fewest number of required experiments using the Steepest Descent Method. As shown in Figure 3c, the program performed a two level factorial with three repeats at the center. Because the algorithm determined that quadratic curvature was not present in the response surface (see Supporting Information), the program calculated the gradient and progressed towards experiments at higher temperatures and lower residence times. After attempting to select an experiment outside of the feasible region, the program selected the final experiment at the vertex of the constraints. The program terminated at this point, since the objective function at the active constraints was higher than any value obtained within the interior of the parameter space. This process is similar to gradient based optimization techniques for linear problems.

A summary of the optimization results and the time required to complete each optimization trial are given in Table 1. It is important to note that the parameters of the individual algorithms were not customized to find the optimal conditions in the fewest number of experiments. Therefore, one should not draw conclusions on the convergence or efficiency of these algorithms and their applications to experimental optimization. Rather, the intent of implementing multiple algorithms is to demonstrate how numerous feedback techniques can be imbedded into a high throughput experimental apparatus for fast reaction optimization.

3.2. Oxidation Optimization Results. A four-dimensional optimization using the Simplex Method was performed where values of the temperature, residence time, [$PhCH_2OH$]°, and CrO_3 equivalents were varied to maximize the benzaldehyde yield. A starting point of 50 °C at 1.0 min residence time, with [$PhCH_2OH$]° = 8 mM and 1.0 equiv of CrO_3 was selected as the starting point for the optimization investigation. The automated microreactor system performed 46 sequential experiments to determine the local optimum of benzaldehyde yield at 80% (Figure 4). The range of values that the algorithm investigated are shown in Table 2, with the optimal conditions corresponding to T = 88 °C, τ = 48 s, [$PhCH_2OH$]° = 8.2 mM, and 0.65 equiv of CrO_3.

The results indicated that the reaction was enhanced at higher temperatures with shorter reaction times. Traditionally, however, this reaction is performed at longer residence times and at lower temperatures to prevent subsequent oxidation of the aldehyde to the carboxylic acid.[62] However, the increased control over reaction conditions in microreactors allowed the reaction to be performed at more aggressive conditions. With a throughput rate of approximately 1 experiment per 10 min, a rate which includes the time for system equilibration and sample analysis, this reaction example also demonstrated the system's potential to quickly determine the optimal conditions using minimal amounts of reaction material. Results from these optimization trials provided additional insight into the chemistry. At the optimal conditions, the CrO_3 equivalents were less than the yield of benzaldehyde formed, which suggested that more than one state of chromium can oxidize the aromatic reagents. In fact, it has been reported that both Cr(VI) and Cr(V) play a role in the oxidation of the alcohol.[61] This ability to draw conclusions of the reaction behavior from the numerous experiments performed by the automated system provides an additional advantage of this system. Finally, the optimal yield was not associated with the optimal selectivity (see Supporting Information), indicating that some benzaldehyde must be sacrificed to form benzoic acid to increase conversion of benzyl alcohol to benzaldehyde. Further extensions of this system could be accomplished by incorporating selectivity into the objective function, but the weighting between yield and selectivity would be highly dependent on the application.

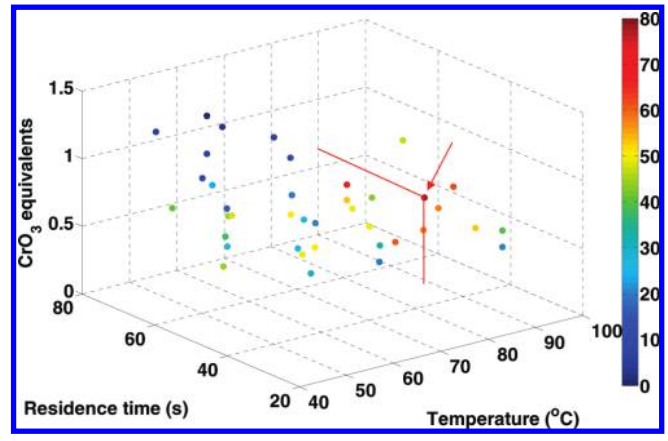

Figure 4. **Benzaldehyde yield measured during four-dimensional optimization by Simplex algorithm. Inlet reactor concentrations of benzyl alcohol are not shown in this graph in order to present the benzaldehyde yield data in the clearest possible form but are located in the Supporting Information.**

Table 2. **Range of values for each reaction parameter varied during four-dimensional optimization**

Reaction parameter	Min.	Max.
Temperature (°C)	50	94
Residence time (s)	25	79
[$PhCH_2OH$] × 10^{-3} (M)	6.7	9.3
CrO_3 equivalence	0.25	1.37

(62) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990.

4. Conclusions

The concept and methodologies for multivariable, online reaction optimization in a highly integrated microreactor system have been presented. A variety of different optimization algorithms have been implemented to demonstrate the broad operational capabilities of the microfluidic system. Local and global optimization search techniques can be applied, and the parameters of these algorithms can be adjusted in an effort to reduce the number of required experiments to locate the optimum. Black-box optimization approaches have been explored in this effort to create a microfluidic system suitable for reaction optimization when kinetic information is limited. Moreover, the ability to perform a high throughput of sequential experiments indicates that automated optimization in integrated microfluidics could be applied to rapidly establish libraries of reaction data by optimizing a specific reaction for several different objection functions or by optimizing the same class of reactions with different substrates and solvents.

Approaches similar to those of this work can be used with microseparators to optimize workup operations, which give way to the use of automated microfluidic systems for online optimization of multistep, microchemical processes. Because the conditions that optimize a single unit operation may not correspond to those conditions that optimize the complete synthesis, the ability to efficiently investigate the interactions between the various components in automated microchemical networks will lead to significant improvements in process development. When integrated with statistical and optimal experimental design techniques, these systems offer the opportunity to quickly determine the reaction rate expression and accurately estimate the kinetic parameters. This reaction modeling information can be applied for the scale-up of reaction conditions as well as implemented in model predictive control strategies to maintain synthesis quality.

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Supporting Information Available

Description of fluidic packaging scheme, details of the operations for the optimization techniques, algorithm parameters and 2-D optimization results obtained for Knoevenagel reaction, Nelder−Mead Simplex parameters used in multiparameter optimization of oxidation reaction, benzaldehyde yield and selectivity measurements for 4-D optimization search, exemplary chromatograms from reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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