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Adaptive Process Optimization for Continuous Methylation of Alcohols in Supercritical Carbon Dioxide

Richard A. Bourne,*,† Ryan A. Skilton,† Andrew J. Parrott,† Derek J. Irvine,‡ and Martyn Poliakoff*,†

†School of Chemistry and ‡Department of Chemical and Environmental Engineering, The University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

ABSTRACT: A self-optimizing continuous flow reactor has been developed using the Super-Modified Simplex algorithm. This system, coupled with online gas chromatographic analysis enables automated optimization via a feedback control loop without user intervention. This has been applied to the methylation of 1-pentanol in supercritical carbon dioxide using dimethyl carbonate and methanol with γ-alumina catalyst to give 98% and ~68% yield of pentyl methyl ether respectively. This was accomplished by variation of four reaction parameters; Temperature, Pressure, CO_2 Flow rate, and the Ratio of methylating agent.

There is increasing interest in continuous or flow reactors for making pharmaceutical or fine chemicals.[1−3] The attractions of this approach include the option of running sequential reactions, the straightforward integration of chemical or physical sensors, accessing a wider operating window than with batch reactors, and a simpler, more obvious route to scale up. Flow reactors also lend themselves to a higher degree of automation as displayed, for example, in the H-cube continuous flow hydrogenation reactor.[4]

Our research group has specialized in the development and automation of continuous reactors using supercritical CO_2 ($scCO_2$), as the solvent. Examples include hydrogenation,[5,6] hydroformylation,[7] oxidation,[8] photooxidation,[9,10] and acid-catalysed reactions, particularly etherification.[11−13] Although these reactions have been largely carried out on a small scale, one hydrogenation reaction, the hydrogenation of isophorone, was scaled up[14] to 1000 tons per annum. Most of our reactions have been optimized manually for maximum yield, but manual optimizations are often relatively laborious, and not all reaction variables were optimized due to time constraints.

Nevertheless, a major advantage of optimizing for yield is that the maximum conversion to the desired product is obtained within the limitations of the reactor system. This usually reduces the need for purification which can often be a wasteful process.

Overall, optimizing for yield can reduce the environmental impact of a process, whilst also reducing the cost associated with production.[15−20] Traditionally, the experimenter varies a single factor at a time, and measures the effect that this has on the yield.[19,21,22] Only after the first factor has been optimized is another factor varied. Not only is this time consuming, but the interdependence of factors can be overlooked, preventing a full optimization from being reached, even though the yield has been increased.[23] Optimization of supercritical reactions is particularly tedious because the tunable density of the solvent adds an extra variable to be optimized compared to more traditional solvents. Whatever the solvent, automation of a flow reactor removes much of the tedium of optimization. More importantly, automation opens up the possibility of developing self-optimizing reactors.

Such self-optimizing continuous reactors consist of a reactor with automated process control and an integrated online analytical technique coupled to a feedback algorithm. The system then acts as an autonomous unit where reactants are pumped in and the process is optimized automatically, resulting in a system which delivers products under optimized conditions, with the optimization process greatly accelerated compared to manual optimization.

A series of recent publications have described some examples of such self-optimizations. For example, Krishnadasan et al.[24] generated nanoparticles using a microreactor system where flow rates and temperature were controlled by computer and an online-fluorimeter was used to determine the optimal composition of nanoparticles produced. An automated feedback loop using the sequential application of the Stable Noisy Optimization by Branch and Fit (SNOBFIT) algorithm was used to generate new reaction conditions leading to optimal production of nanoparticles with the desired emission wavelength.

McMullen et al. have used a similar approach with microreactors with online high-performance liquid chromatography (HPLC),[25] for the optimization of a Heck reaction,[22] Knoevenagel condensation and the oxidation of benzyl alcohol. In their system the Nelder and Mead Modified Simplex (NMSIM) algorithm[26] was used to generate new conditions to complete the feedback loop.[22]

Very recently, we described the development of an automated self-optimizing reactor for acid-catalysed reactions in CO_2, Figure 1.[27] This reactor is a self-contained unit, where the reactants flow in, the reaction is optimized by the Super-Modified Simplex algorithm (SMSIM, see below) within the control software, and product flows out. We showed that the reactor was capable of carrying out a three-parameter self-optimization (Temperature, Pressure, and Flow rate of CO_2) for (a) the dehydration of ethanol over (γ)-alumina and (b) the production of pentyl-methyl ether from 1-pentanol and dimethyl carbonate (DMC), Scheme 1, on a scale that was considerably larger than the previous demonstrations of self-optimization described above.

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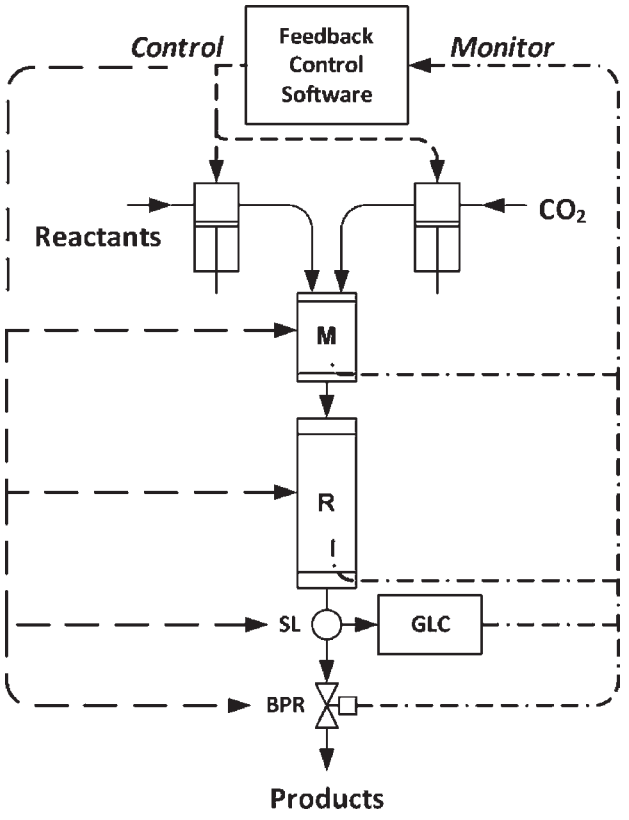


Figure 1. Schematic diagram of the self-optimizing reactor, where M is a preheater and mixer, R is the reactor, SL is the sample loop, GLC is the online gas−liquid chromatograph, and BPR is a back-pressure regulator. The control software runs on a standard PC. See Experimental Section for full details.

In this paper we extend our approach to a four-parameter optimization, applying it again to the etherification of 1-pentanol in $scCO_2$, and compare the effectiveness of MeOH and DMC as methylating agents. First, we report the results of the optimization, and then we describe our implementation of the software in more detail than was possible in our original communication.[27]

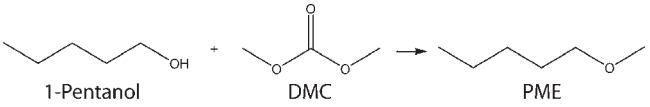
RESULTS AND DISCUSSION

The etherification of 1-pentanol has been optimized with four parameters: (i) the Temperature of the preheater and the γ-alumina catalyst bed, (ii) the Pressure, (iii) Flow rate of CO_2, and (iv) the Molar ratio of the 1-pentanol:methylating agent (MA, either DMC or MeOH). Varying this ratio was achieved by using two HPLC pumps; one pump delivered a constant flow of a 1:1 molar ratio mixture of 1-pentanol and MA, while the other pump delivered a flow of pure MA at a rate that could be varied by the software.

Analysis of the reactor output was performed by online gas−liquid chromatography (GLC), the results from which were used to calculate the yield of PME with respect to 1-pentanol; these results were then fed into the feedback loop described below.

Figure 2 shows that the SMSIM algorithm rapidly optimized the DMC system to >90% yield of PME in ∼10 measurements and then proceeded to optimize the system further to ∼98% yield where the optimization was terminated because the covariance limit had been reached, Table 1. The full optimization with DMC required 47 measurements and took just under 25 h to complete. By comparison, the MeOH system required 125 measurements and ran for 74.3 h, most probably due to the optimal conditions being further from the starting point. Even so, the maximum achievable yield of PME was only 68% with MeOH (Table 2 and Figure 2). This confirms the conclusions of our previously published study[11] that DMC is a more effective methylating reagent than MeOH.

Scheme 1. Methylation of 1-pentanol by DMC to yield PME



It can be seen from these results that the four-parameter optimization was successful for both MeOH and DMC in the direct methylation of 1-pentanol, with DMC giving much higher yields of PME than MeOH. Furthermore, DMC has the advantage that it reacts at a lower temperature, 246 °C, rather than 328 °C, albeit at a slightly higher pressure, 175 bar compared to 140 bar for MeOH (see Figure 3).

AUTOMATED OPTIMIZATION

To automate adaptive optimization techniques, it is necessary to implement feedback control. This requires commands to be sent to the control equipment as well as being able to monitor the current conditions. Each control device of the flow reactor (CO_2 pump, organic reagent pumps, temperature controllers, etc.) is fitted with an RS-232 serial communication module linked to a standard desktop computer. Monitoring of reactor temperature and pressure is performed using a PicoLog data logger connected to k-type thermocouples and RDP pressure transducers (Figure 1). Custom software, written in the Matlab programming environment is used to coordinate the control of the rig. Communication between the software and each control element of the rig was achieved by incorporating the serial communication protocols provided by Jasco,[28,29] Eurotherm,[30] and VICI Valco[31] into the software itself. Within this control and monitoring system, customizable feedback loops permit automated optimization reactions (Figure 4):

Our work employs the Super Modified Simplex algorithm (SMSIM).[33] This adaptive algorithm is used to follow the response surface of a number of factors to locate an optimum. In practical terms, this means changing various reaction conditions (temperature, pressure, etc.), and measuring the response at those conditions to determine the location of the next experiment. Once the response, which in this paper is the yield, at a set of conditions has been measured, the algorithm is able to calculate a location for another experiment, which should result in a higher yield. This process continues, increasing the yield of the reaction until a predefined stopping criterion is reached. The SMSIM algorithm was originally introduced by Routh et al.[33] as an advanced form of the Modified simplex developed by Nelder and Mead;[26] both of these algorithms are commonly used in analytical techniques to optimize chromatographic methods, etc.[26,34−37] The modifications in the SMSIM allow the simplex to follow the response

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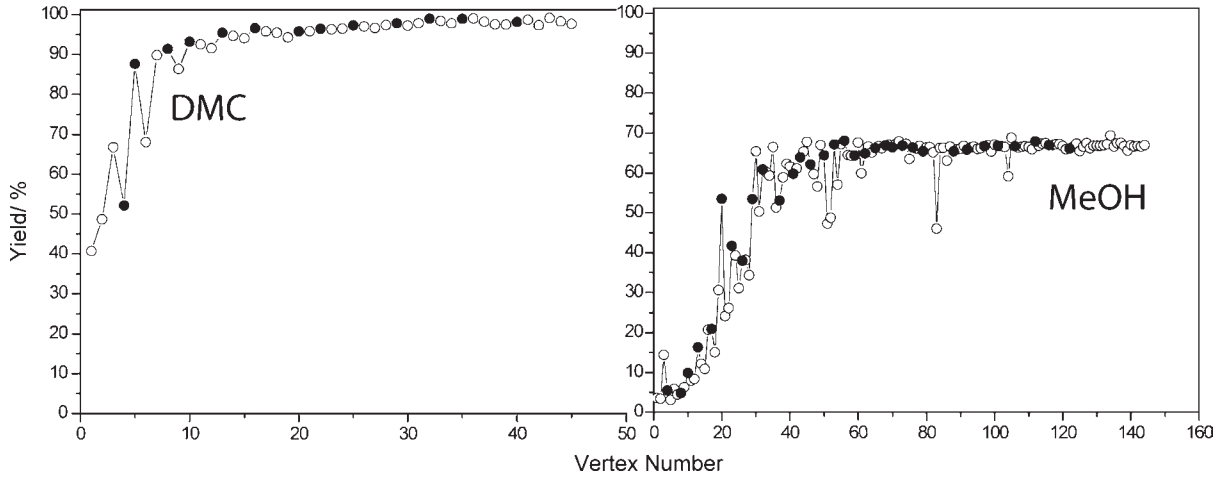

Figure 2. Change in yields of 1-pentyl-methyl ether, PME, during the SMSIM optimization of 1-pentanol + DMC, and of 1-pentanol + MeOH, with four parameters: Temperature, Pressure, CO_2 Flow rate, and Ratio of 1-pentanol:methylating agent. Filled points represent vertices that were retained in the simplex. The optimization was terminated when the covariance of the responses of a simplex were below 0.6%.

Table 1. Initial parameters (conditions 1−5) and optimal conditions for the methylation of 1-pentanol using DMC following optimization using the SMSIM algorithm[a]

condition	CO_2 flow rate/mL min^{-1}	temperature/ °C	pressure/bar	[DMC]:[1-pentanol]	yield/ % PME
1	1.00	200	150	1.57	40.7
2	1.24	200	150	1.57	48.6
3	1.12	229	150	1.57	66.7
4	1.12	209	163	1.57	52.0
5	1.12	209	153	4.29	87.6
optimal	**1.57**	**246**	**175**	**10.94**	**98.7 ± 0.3**

[a] Yield calculated using GLC analysis and an internal normalization method.

Table 2. Initial parameters (conditions 1−5) and optimal conditions for the methylation of 1-pentanol using MeOH following optimization using the SMSIM algorithm[a]

condition	CO_2 flow rate/ mL min^{-1}	temperature/ °C	pressure/ bar	[MeOH]:[1-pentanol]	yield/ % PME
1	1.00	200	150	4.9	2.7
2	1.24	200	150	4.9	2.4
3	1.12	229	150	4.9	1.1
4	1.12	209	163	4.9	4.1
5	1.12	209	153	10.5	1.5
optimal	**0.94**	**328**	**140**	**7.2**	**67.8 ± 0.2**

[a] Yield calculated using GLC analysis and an internal normalization method.

surface more closely, and to accelerate across it when appropriate, resulting in fewer iterations to reach the optimum,[23] and in a more tightly defined optimum than either the basic simplex or NMSIM algorithms[33] (see Figure 5).

A simplex is a geometrical figure, with $F + 1$ vertices, where F is the number of variable factors being investigated. Each vertex represents the coordinates of an actual experiment, e.g. 200 °C and 150 bar. In Figure 6, a simplex with two variable factors (a triangle) is used to describe the simplex mechanism. To carry out such an optimization, one needs three sets of user-defined conditions to define the vertices of the first simplex. These vertices are then ranked according to the response measured. The vertex which had the best response is labeled **B**, and the vertex with the worst is labeled **W**. All other vertices are labeled according to the proximity of their response to the response of the worst (next worst (**N**), etc.) see Figure 6. A measurement is then carried out at the midpoint position (**P**), calculated as the average of all the vertices, apart from the worst. The position of the reflection vertex, **R**, is calculated using (eq 1), in the reflected position of **W**, where α is the reflection coefficient, which equals 2 in the SMSIM algorithm, (Figure 6).

$$\mathbf{R} = \alpha\mathbf{P} + \mathbf{W}(1 - \alpha) \quad (1)$$

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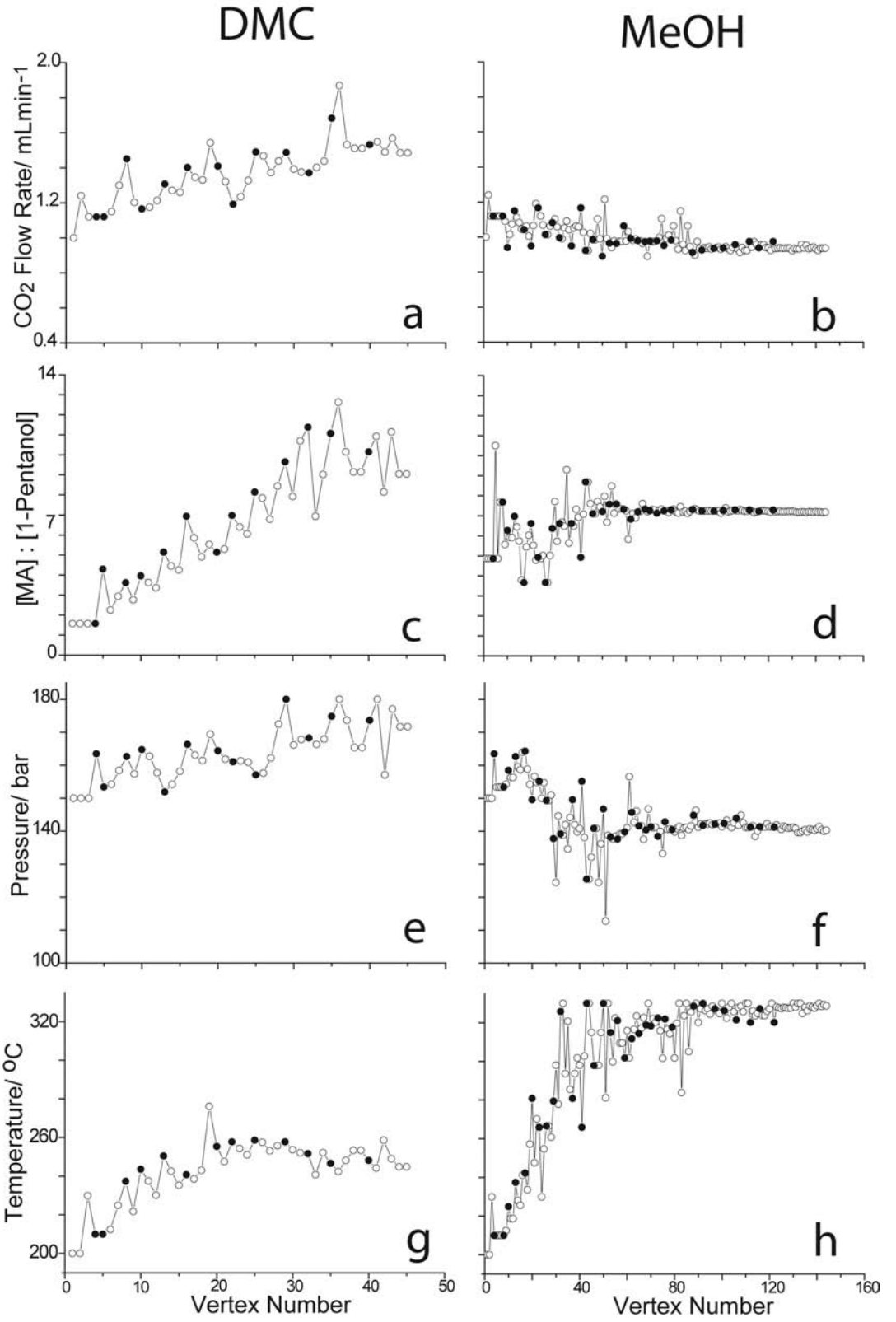

Figure 3. Comparison of yield of PME and variation of conditions during a SMSIM optimization of 1-pentanol for either DMC (left) or MeOH (right). Filled points are vertices that were retained by the simplex. (a,b) Variation in CO_2 flow rate. (c,d) Variation in the ratio of methylating agent to 1-pentanol. (e,f) Variation in pressure. (g,h) Variation in temperature.

Once **R** has been defined, an experiment is performed at these conditions and the response determined. A key feature of the SMSIM algorithm is that a further point is identified before a new simplex is constructed. This is done by constructing a second

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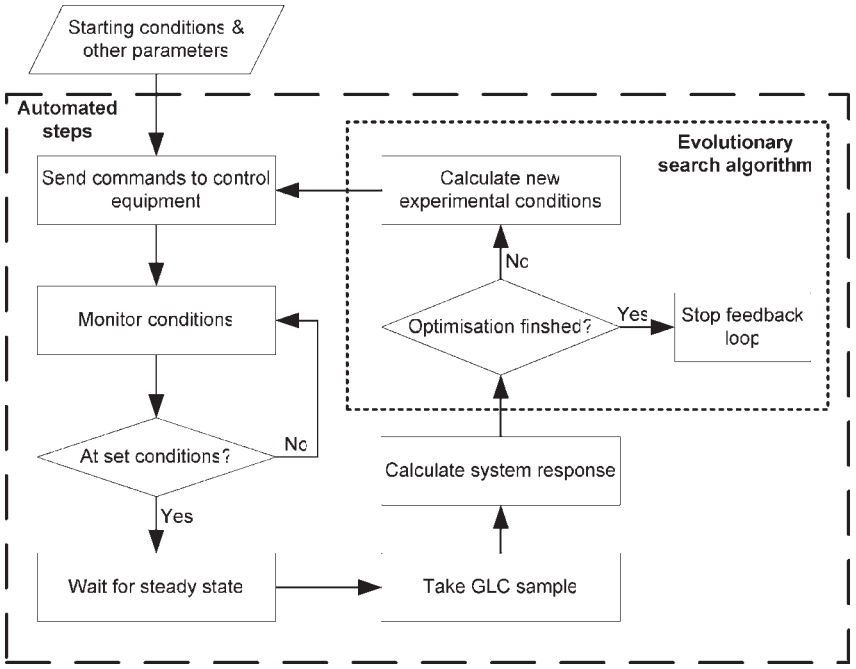

Figure 4. Schematic of the feedback loop procedure for optimization of a continuous flow reactor system.[32] Commands are sent to equipment using automated RS232 control software to set reaction parameters. Conditions are tested using a custom algorithm which checks that the absolute difference between actual values and the set value is less than an offset value (e.g., 3.5 °C or 5 bar) and that the range within the actual values over the last 2 min is less than a predefined noise value (e.g., 2 °C or 2 bar). The reactor is left to equilibrate to steady state for 20 min following this step. The system response was determined by calculating the yield by GLC peak integration using GC solution. The values for system response and the values for each factor (i.e., the set conditions) are then passed to the particular evolutionary search algorithm being used, which calculates whether the optimization should be stopped. If this calculation shows that the optimization should continue, then new conditions are calculated and passed back to the main feedback control loop, and the optimization process is repeated.

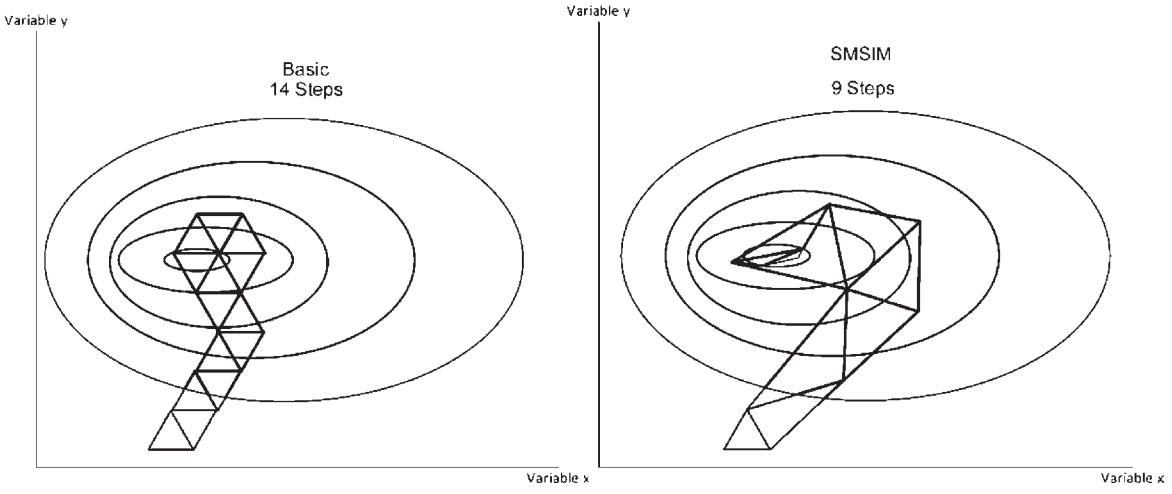

Figure 5. Example of the basic simplex (left) and SMSIM (right) following a response surface until optimum region is reached. The basic algorithm uses a fixed size of simplex. By contrast the simplexes from SMSIM can expand or contract to match the shape of the response surface more closely, and to locate the optimum more precisely.

order polynomial at **WPR**, to calculate the optimum expansion factor (Y_{opt} eq 2), where w, p, and r are the responses of the system at **W**, **P**, and **R**, respectively.

$$Y_{opt} = \frac{w - p}{w - 2p + r} + 0.5 \qquad (2)$$

The optimum vertex (**O**), calculated from eq 3, is located a distance Y_{opt} from **W**, along line Y, (Figure 6).

$$\mathbf{O} = Y_{opt}\mathbf{P} + \mathbf{W}(1 - Y_{opt}) \qquad (3)$$

The response of **O** is measured, and in general, the response of **O** is greater than that of **R**. A new simplex is

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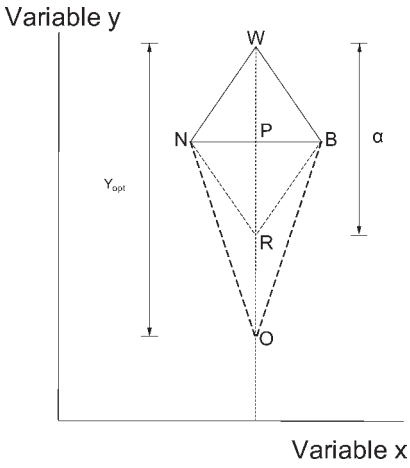

Figure 6. The vertices in the initial simplex (solid line) are ranked according to their response (**B**, **N**, and **W**). The midpoint (**P**) of all the vertices apart from the worst (**W**) is then calculated. The position of the reflect vertex (**R**) is then calculated, at a distance α from **W**, through **P** to give the line, *Y*. A polynomial fit is used to determine the optimum expansion coefficient (Y_{opt}) along this line. The optimum vertex (**O**) is then plotted a distance Y_{opt} from **W** through **P**. If the response at **O** is greater than that of **R**, the new simplex is formed with **O** and the vertices from the previous simplex, excluding **W**. This allows the SMSIM algorithm to follow the response surface more closely than the basic algorithm, which can only form a new simplex of a fixed size.

Table 3. Predefined boundary limits of the system defining the reaction space within which the simplex can safely operate

system limits	minimum value	maximum value
temperature	100 °C	330 °C
pressure	70 bar	180 bar
CO_2 flow rate	0.4 mL min^{-1}	2 mL min^{-1}
methylating agent flow rate	0 mL min^{-1}	2 mL min^{-1}

formed with **O**, and the vertices from the previous simplex, excluding **W**, (Figure 4).

The procedure is repeated using this new simplex. New simplexes are generated continuously by this process, until some user-defined termination criteria are met. In these experiments the first simplex is automatically generated based on the boundary limitations and "best guess" initial starting conditions provided by the operator.[32] By measuring the response, and determining the new experimental conditions in this way, the SMSIM algorithm is able to locate the optimum conditions for a reaction, within the boundaries determined by equipment limitations (see Table 3). Different criteria determine how the simplex reacts when a system boundary is encountered, a detailed description of which, and other exceptions to the procedure outlined above, can be found in the tutorial by Morgan et al.[23] In our software, Y_{opt} is set to a maximum value of 3, and a minimum of −1, in accordance with common practice.[23] In addition, Y_{opt} is set to be at least ±0.3 from either **W** and **P**, as recommended by Routh et al.[33]

CONCLUSIONS

In this work we have demonstrated the use of a self-optimizing reactor, which incorporates online analysis, reactor control and an evolutionary search algorithm to effectively optimize the methylation of 1-pentanol by variation of four reaction parameters (98% yield), leading to a more successful optimization than with three parameters (70% yield). The use of DMC and of MeOH as alkylating agents were compared, and it was shown that DMC gave the product at higher yield and at substantially milder conditions. We are now applying this adaptive technique not only to optimize reaction yield but also to optimize the productivity and efficiency of our reactor system by optimizing for space-time yield and *E*-factor respectively. In addition, we are applying the technique to other classes of reaction.

EXPERIMENTAL SECTION

CAUTION! The experiments described in this paper involve the use of high pressures and require equipment with the appropriate pressure rating.

Figure 1 shows a schematic of the supercritical flow reactor, and the associated feedback loops. CO_2 (BOC gases, food fresh grade) is pumped by a programmable HPLC CO_2 pump (Jasco PU-1580-CO2). All organic solutions were pumped by HPLC pumps (Jasco PU-980). The premixer and reactor were both heated using cartridge heaters within aluminium heating blocks controlled by programmable heating controllers (Eurotherm 2216 L). The premixer and reactor were 10 mL 316 stainless steel tubes (156 mm × 12 mm OD) filled with sand in the premixer, and the catalyst (NWA-150 (γ)-alumina (supplied by SI group; powder, 150 m^2/g surface area and containing trace impurities of SiO_2, Fe_2O_3, and Na_2O)). The system pressure was controlled by a Jasco BPR (Jasco BP-1580−81), and monitored by pressure transducers in both HPLC pumps and the BPR. Analysis of reactor output was measured by an online Shimadzu GC-14B, using an AllTech SE-30 column (30 m, 0.25 mm ID, 0.25 μm FT). In a typical experiment, system parameters and starting conditions are input to the custom control program, the HPLC pumps are supplied with the required organic solution, and a complete leak test is carried out using Snoop leak detection fluid. Once the simplex program is started, the automated optimization program will take samples of the reactor flow, using the GLC to measure the response, and changes the conditions accordingly. Commercially available DMC (Alfa Aesar, 99%) and 1-pentanol (Sigma-Aldrich, 99%) were used in all experiments without further purification.

AUTHOR INFORMATION

Corresponding Author

*Richard.Bourne@Nottingham.ac.uk; Martyn.Poliakoff@Nottingham.ac.uk

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REFERENCES

(1) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675.
(2) Jas, G.; Kirschning, A. *Chem.—Eur. J.* **2003**, *9*, 5708.
(3) Kockmann, N.; Gottsponer, M.; Zimmermann, B.; Roberge, D. M. *Chem.—Eur. J.* **2008**, *14*, 7470.

(4) Jones, R.; Godorhazy, L.; Szalay, D.; Gerencser, J.; Dorman, G.; Urge, L.; Darvas, F. *QSAR Comb. Sci.* **2005**, *24*, 722.
(5) Bourne, R. A.; Stevens, J. G.; Ke, J.; Poliakoff, M. *Chem. Commun.* **2007**, 4632.
(6) Stevens, J. G.; Bourne, R. A.; Twigg, M. V.; Poliakoff, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8856.
(7) Meehan, N. J.; Sandee, A. J.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P.; Poliakoff, M. *Chem. Commun.* **2000**, 1497.
(8) Chapman, A. O.; Akien, G. R.; Arrowsmith, N. J.; Licence, P.; Poliakoff, M. *Green Chem.* **2010**, *12*, 310.
(9) Bourne, R. A.; Han, X.; Poliakoff, M.; George, M. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 5322.
(10) Han, X.; Bourne, R. A.; Poliakoff, M.; George, M. W. *Green Chem.* **2009**, *11*, 1787.
(11) Gooden, P. N.; Bourne, R. A.; Parrott, A. J.; Bevinakatti, H. S.; Irvine, D. J.; Poliakoff, M. *Org. Process Res. Dev.* **2010**, *14*, 411.
(12) Hyde, J. R.; Licence, P.; Carter, D.; Poliakoff, M. *Appl. Catal., A* **2001**, *222*, 119.
(13) Walsh, B.; Hyde, J. R.; Licence, P.; Poliakoff, M. *Green Chem.* **2005**, *7*, 456.
(14) Licence, P.; Ke, J.; Sokolova, M.; Ross, S. K.; Poliakoff, M. *Green Chem.* **2003**, *5*, 99.
(15) Walters, F. H.; L. R. P., Morgan, S. L.; Deming, S. N. *Sequential Simplex Optimization: A Technique for Improving Quality and Productivity in Research, Development, and Manufacturing*; CRC Press Inc: Boca Raton, 1991.
(16) Montgomery, D. C. *Design and Analysis of Experiments*; John Wiley and Sons, Inc: Hoboken, 2005.
(17) Harre, M.; Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **1999**, *3*, 304.
(18) Davies, I. W.; Welch, C. J. *Science* **2009**, *325*, 701.
(19) Long, D. E. *Anal. Chim. Acta* **1969**, *46*, 193.
(20) Laird, T. *Org. Process Res. Dev.* **1998**, *2*, 339.
(21) Araujo, P. W.; Brereton, R. G. *Trac-Trends Anal. Chem.* **1996**, *15*, 63.
(22) McMullen, J. P.; Stone, M. T.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7076.
(23) Morgan, E.; Burton, K. W.; Nickless, G. *Chemom. Intell. Lab. Syst.* **1990**, *8*, 97.
(24) Krishnadasan, S.; Brown, R. J. C.; Demello, A. J.; Demello, J. C. *Lab Chip* **2007**, *7*, 1434.
(25) McMullen, J. P.; Jensen, K. F. *Org. Process Res. Dev.* **2010**, *14*, 1169.
(26) Nelder, J. A.; Mead, R. *Comput. J.* **1965**, *7*, 308.
(27) Parrott, A. J.; Bourne, R. A.; Akien, G. R.; Irvine, D. J.; Poliakoff, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3788.
(28) *Jasco Model BP-2080 Reference Manual for RS-232C Communication Protocol.* http://www.jasco.co.uk.
(29) *Jasco Model PU-2080 Series Intelligent HPLC Pump RS-232C Communication Protocol Reference Manual.* http://www.jasco.co.uk.
(30) *Eurotherm Series 2000 MODBUS and EI-BISYNCH Digital Communication Handbook.* http://www.eurotherm.com/.
(31) *VICI Valco Instruments Co. Inc. Two Position Microelectric Valve Actuator -Technical Note 413.* http://www.vici.com/support/tn/tn413.pdf.
(32) Parrott, A. J. Ph.D. Thesis, The University of Nottingham, Nottingham, 2011.
(33) Routh, M. W.; Swartz, P. A.; Denton, M. B. *Anal. Chem.* **1977**, *49*, 1422.
(34) Morgan, E.; Burton, K. W.; Nickless, G. *Chemom. Intell. Lab. Syst.* **1990**, *7*, 209.
(35) Shavers, C. L.; Parsons, M. L.; Deming, S. N. *J. Chem. Educ.* **1979**, *56*, 307.
(36) Horstkotte, B.; Duarte, C. M.; Cerda, V. *Trac-Trends Anal. Chem.* **2010**, *29*, 1224.
(37) Silva, H.; Alvares-Ribeiro, L. *Talanta* **2002**, *58*, 1311.