Towards dial-a-molecule by integrating continuous flow, analytics and self-optimisation

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The employment of continuous-flow platforms for synthetic chemistry is becoming increasingly popular in research and industrial environments. Integrating analytics in-line enables obtaining a large amount of information in real-time about the reaction progress, catalytic activity and stability, etc. Furthermore, it is possible to influence the reaction progress and selectivity *via* manual or automated feedback optimisation, thus constituting a dial-a-molecule approach employing digital synthesis. This contribution gives an overview of the most significant contributions in the field to date.

Key learning points
1. Scope of analytical possibilities under flow conditions
2. Advantages and possibilities of self-optimisation
3. Novel process design and control strategies based on real-time acquisition of data and information
4. Spectroscopy applied to process chemistry

Introduction

Continuous-flow chemistry is gaining interest in industry and research laboratories due to the inherent efficiency of the reactor configuration which is superior to batch reactors. Flow reactors offer enhanced mixing, heat-exchange and productivity than batch equivalents.[1] This has led to the development of a new area of research at the intersection between chemistry and chemical engineering. The efficient and safe conditions that result from managing reactions under continuous-flow means that it is possible to undertake chemical reactions under non-conventional conditions. Such reactions can involve highly reactive reagents and exothermic processes, which might lead to runaway reactions. A good example of this is the flash chemistry concept developed by the group of Yoshida,[2] where the extremely short residence times, in the order of milliseconds enables selective alkylation and C–C coupling reactions through intermediate lithiation reactions eliminating the need of protecting groups. This synthetic strategy is only possible due to the unique features of flow chemistry. A number of reviews have been published highlighting the advantages of these technologies

and therefore this contribution will not focus on covering the basics of flow chemistry.[1,3–5] Continuous flow technologies are closely linked to the development of supported catalysts that further increase the efficiency of the transformations.[6,7] Another aspect that has received increasing attention is the need of integration of separation and purification steps into the automation processes.[4,8]

The process automation associated with flow chemistry is the base for further integration of chemistry and engineering. The precise, automated and digital control over reaction conditions, such as temperature, residence time and compositions allows the introduction of the concept of digital chemistry, where programmable synthetic sequences can be realised by means of automated synthetic platforms. In this way, it becomes possible to undertake the synthesis of complex chemicals and materials, often requiring multi-step transformations, by integrating chemical and engineering design. Recently, Richmond *et al.* described the employment of a continuous-flow chemical platform applied to chemical discovery.[9] This is the first example of a complex inorganic cluster (polyoxometalate) discovered employing a fully automated flow synthetic platform. The integration of real-time analytics is crucial to realise this shift in synthesis. This is because, by monitoring the reaction progress as it occurs, *i.e.* the analytical time scale is below the overall reaction time scale, it is possible to obtain important information about the synthetic processes. This could be in terms of catalytic activity, selectivity,

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deactivation, *etc.* Traditionally, this has been made by varying one parameter at a time, what is time and resource consuming, and represents a limited way of exploring the reaction parameter space, which can easily miss the optimal conditions. A subsequent step consists of integrating algorithms that autonomously analyse the data, structure and extract the relevant information, and generate a knowledge-base. This knowledge can then be employed to feedback the system in order to achieve predefined requests, such as property optimisation, drug discovery, structure–activity relationships, formulations, *etc.* The combination of rational Design of Experiments (DoE) with black box self-optimisation algorithms can help increasing the speed of exploration of complex parameter spaces, thus enhancing the probability of discovery of new advanced compounds[9] and chemical reactions.[10]

Furthermore, the rapid generation of data and information of the process allows influencing it by modifying the inputs (composition, temperature, residence time, *etc.*) thus achieving precise control over the outcome of the process. Enhanced control will not only enable self-optimisation, but also to rapidly adapt and determine key information about the system like kinetic and thermodynamic parameters, yield, selectivity, *etc.* In this way, the integration of real-time analytics can be applied for process control, enabling tailored actuations adjusted to concrete reaction conditions and to account for deviations due to problems associated with axial dispersion of flow.

An accurate definition and distinction between in-line, on-line and *in situ* was presented by Browne *et al.*[11] In-line refers to a platform configuration whereby the analytics are connected in-series to the reactor and all of the reaction

mixture is analysed right after leaving the reactor. This configuration minimises the time-lag between reaction and analysis. Nevertheless, in reaction systems where kinetics are relatively low or high data density is not a crucial requirement, chromatography techniques (HPLC and GC) are viable alternatives that offer large amounts of information.[12,13] These techniques facilitate the analysis of the results due to the separation process, which is advantageous over in-line techniques, where the high-speed of data acquisition often comes at the expense of problems to process and extract quantitative data.

In this way, it is possible to develop algorithms that influence, control and explore complex reaction landscapes in an autonomous and automated way, thus closing the gap between discovery and application. The combination of these three technologies (automated flow chemistry, real-time analytics and algorithms) perhaps could even lead to the idea of synthesising virtually any molecule with minimal human interaction. The ability to 'Dial-a-Molecule' is still far from reach, but in principle could be achieved using the type of approaches we will describe here. As previously mentioned, due to the numerous reviews covering the area of continuous-flow chemistry this contribution will focus on a selection of relevant contributions in the field of in-line analytics and the emerging area of feedback algorithms.

UV-Vis spectroscopy

One of the earliest examples of in-line reaction monitoring was reported by Lu *et al.* who employed UV-Vis spectroscopy coupling fibre optics to a microfluidic device to monitor a

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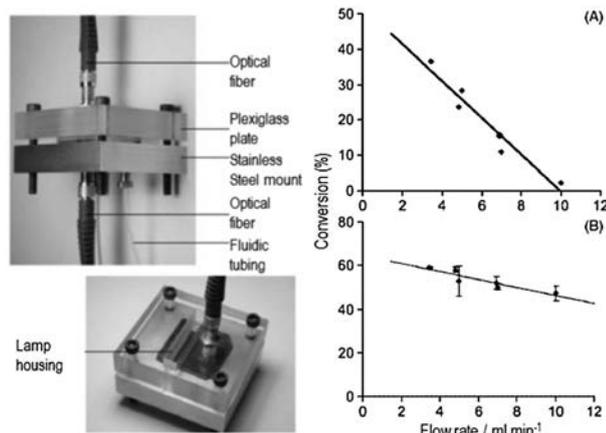
Fig. 1 Left: Pictures of the microreactor designed and fabricated for photochemical transformations with integrated fiber optics for reaction monitoring by UV-Vis. Right: Conversion values observed for benzopinacole as a function of the flow rate by in-line UV-Vis (A) and HPLC (B). Reproduced from ref. 14 with permission from The Royal Society of Chemistry.

photoreaction synthesis of benzopinacol.[14] In this contribution, two manufacturing techniques were combined to fabricate microreactors based on silicon and quartz, thus being suitable for photochemical reactions employing UV light (λ = 365 nm). (Fig. 1, left). The chips were manufactured by timed deep reactive ion etching (DRIE) of silicon wafers. A measuring point was integrated in the chip design, where fiber optics were placed and connected to a light source and a detector. A reduction in the conversion was observed with increasing flow rates, due to the reduction in residence time inside the reactor. The results were validated by HPLC. The authors found that the quantum efficiency increased at high flow rates. Furthermore no evidence of process integration was demonstrated, *i.e.* the analytics were run separately to the synthetic process.

The development of integrated platforms, where the analytics are controlled by a single platform represents a step forward towards realising the grand challenge of DaM. This concept has been recently applied to the synthesis of nanoparticles with strong localised surface plasmons of resonance (LSPRs). This has been employed also for the real-time monitoring of the synthesis of gold nanoparticles.[15] By developing fully automated and pre-programmed synthetic sequences that were run by a fully automated platform (Fig. 2), it was suggested that this approach could constitute a type of digital synthesis for nanochemistry. In this way the digital sequences are transformed into dynamically controlled variations in a property of interest, and characterised in real-time, employing in-line analytics to detect in real-time the properties of the nanomaterials.[16] A systematic increase of the ionic strength of the reaction media was generated employing two pumps, one containing the reducing citrate and the second with a mixture of citrate and borate buffer. Upon increasing the ionic strength, an aggregation of the citrate stabilised nanoparticles was observed, by a red shift of the LSPR and a strong reduction in intensity. The HRTEM of samples made from collecting the output solution was employed to confirm the in-line results. The process was proven to be switchable by a

progressive reduction of the ionic strength. This reduction led to a blue shift of the LSPR, returning eventually to the original state. Thus the combination of an automated platform and the exploration of novel surfactant type ligands, derived from the isonicotinamide (see Fig. 2f), led to the discovery of a novel morphology of hyperbranched nanoassemblies (Fig. 2d). An increase in the length of the aliphatic chain seemed to contribute to a larger degree of branching.

Raman spectroscopy

The use of non-invasive spectroscopic techniques that can yield a high level of spectroscopic information to monitor reaction progress, and the properties of materials and molecules synthesised under continuous-flow, has received a great deal of attention. In most cases, confocal Raman microscopy has been generally employed for the monitoring of organic reactions under continuous-flow.[17–20] A significant challenge to the integration of Raman in continuous-flow set-ups is the need to develop custom flow cells and analytical probes.

In an early example, the synthesis of molecules containing an imine functional group was monitored under continuous-flow in a microfluidic chip, with channel dimensions of 400 μm in width and 20 μm in depth.[17] The chips were placed under a confocal microscope that was focused on different points of the chip to monitor the progress of the reaction as a function of the residence time. An increase of the stretching C=N band and a decrease of the C=O band were observed with the increase of the distance to the mixing point due to an increase in the residence time. However, no quantitative values of conversion and yield were reported, due to the absence of a calibration curve.

More complex catalytic reactions were monitored and quantitatively characterised under continuous-flow employing confocal Raman was reported by Cao *et al.*[18] The selective oxidation of benzyl alcohol with oxygen employing a catalyst made of Au–Pd supported on TiO_2 was studied. A silicon–glass micro-packed-bed reactor was employed in a tailor-made gasket that was placed under a confocal Raman microscope. By monitoring the evolution of the carbonyl band C=O at 1700 cm^{-1} the effect of different parameters was established. This allowed the rapid optimisation of the reaction conditions, leading to a conversion of 95.5% with a selectivity of 78%. There is no process integration, since the process and the data collection were independently run.

A step forward in this regard was reported by Mozharov *et al.*,[20] who developed a novel method to characterise kinetic parameters and optimisation of microfluidic reactions employing an in-line configuration of the Raman detection point without the need to move the measurement probe. The method is based on setting a low flow rate F_1 for a sufficiently long period. Afterwards the flow rate is increased by one order of magnitude to F_2, thus rapidly pushing all the reagents with different residence times towards the detection point. A crucial aspect for the validity of this method is that the measurement time is smaller than the residence time within the analytical cell, or
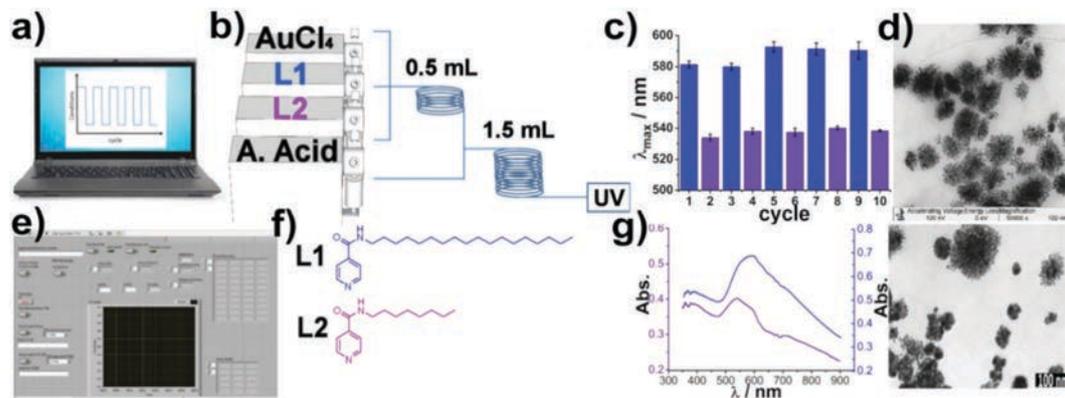
Fig. 2   Digital synthetic platform for the discovery of nanomaterials. (a) Representation of the digital programming of a synthetic sequence. (b) Schematic of the platform. Three pumps are employed to pump the gold precursor and different ligands tested. The mixture is introduced into a tubular flow reactor. Afterwards, the reaction mixture is combined with a weak reducing agent (ascorbic acid) and flown through a second tubular reactor that is connected to a UV-Vis flow-cell. A fraction collector is placed at the end of the platform to collect the nanomaterials synthesised. (c) Values of the LSPR obtained in different cycles, alternating L1 (odd cycles) and L2 (pair cycles). (d) TEM images corresponding to the hyperbranched nanomaterials. The image above corresponds to the nanoparticles stabilised with L1 (up) and L2 (down). (e) Screenshot of the front panel of the Labview vi. (f) Ligands employed to stabilise hyperbranched nanoparticles. (g) Example of extinction spectra obtained in odd and pair cycles. Adapted from ref. 16 with permission from The Royal Society of Chemistry.

measuring point. Thus, this system was designed to adapt the flow processes to the analytics, thus signalling an initial degree of integration. By employing this method a five-time fold reduction in time and a ten-fold reduction in reagent consumption was achieved for a Knoevenagel condensation.

Fast kinetic reaction determination in highly exothermic reactions has been reported combining silicon glass microreactors and Raman spectroscopy.[21] The model reaction was a Michael reaction of 3-piperidino propionic acid ethyl ester from piperidine and ethyl acrylate. In this reaction, water acts as a catalyst and therefore the weak response of water in Raman is a distinctive advantage over IR based techniques. Two methods for kinetics measurements in-line were employed and compared to a traditional off-line GC method. Initially, the spectra were analysed at multiple points of the reactor under steady-state conditions. In their studies, the authors found that to undertake a time-conversion series of experiments of at least 10 points, a reduction from 3 hours in the traditional method to 20 minutes in the multipoint analysis and 3 minutes with the gradient analysis is needed. The application of Raman microspectroscopy plays a fundamental role in this approach, since it allows a multipoint analytics at different points of the reactor.

Despite the usefulness and potential of this technique, its inherent low sensitivity remains an important barrier to its widespread application. The use of nanoparticles which have a resonance with the incident light, a phenomenon called Surface Enhanced Raman Spectroscopy (SERS) due to combined electric and chemical mechanisms, has been employed as an strategy to increase the sensitivity of the analysis by several orders of magnitude.[22] Cecchini et al. employed silver nanoparticles suspended in droplet based microfluidic devices and analysed by Raman its aggregation and the analytical response of the system to the dye tracer Malachite Green. The increase in sensitivity allowed the fast and precise examination of droplets in a microfluidic environment
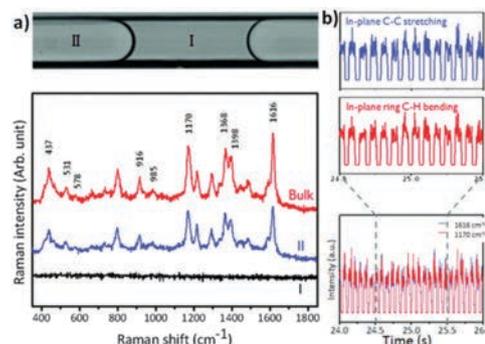

Fig. 3   Development of an analytical method based on surface enhanced resonant Raman spectroscopy employing silver nanoparticles to analyse individual droplets at superior time resolution. Adapted with permission from ref. 23. Copyright 2011 American Chemical Society.

with submillisecond time-resolution and two times higher spatial resolution than previously reported (Fig. 3).[23] By comparing the background to a signal corresponding to a dye affected by the aggregation the SERRS effect could be observed within single droplets, achieving a resolution able to yield resolved submillisecond spectra, thus being theoretically able to analyse droplets generated at high frequency (in the order of kHz).

Despite numerous reports employing in-line Raman for the characterisation of chemical and biochemical processes there are no reports integrating this analytical technique in automated platforms. Hence, there is an untapped potential to take full advantage of this technique in integrated platforms.

IR spectroscopy

Infrared spectroscopy is a very powerful technique to monitor organic transformations in real-time. This is because it is a
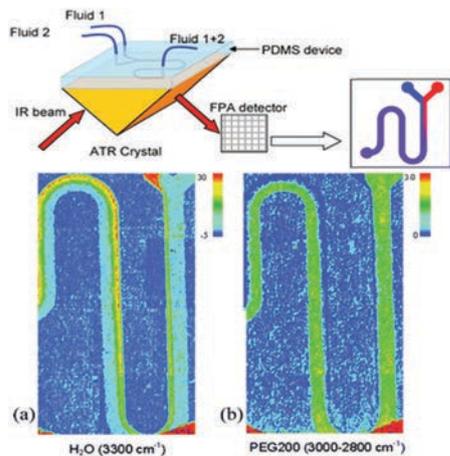
Fig. 4 Up: Scheme of the microfluidic device coupled to an ATR–IR cell for IR imaging along the channels. Below: IR imaging of the mixture of (a) H$_2$O and (b) PEG200. Reproduced from ref. 25 with permission from The Royal Society of Chemistry.
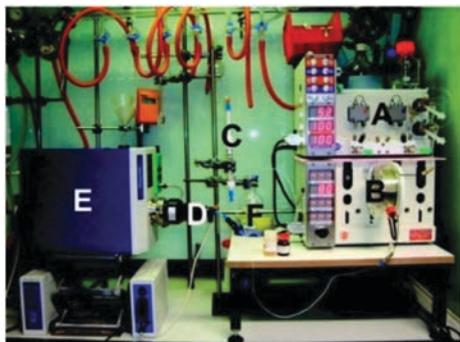

Fig. 5 Continuous-flow reactor set-up with integrated ATR–IR analytics. A Vapourtec series reactor including HPLC pumps (A), a reactor coil (B), a packed bed column (C), the analytical flow cell (D) and the ReactIR spectrometer (E). Reprinted with permission from ref. 26. Copyright 2010 American Chemical Society.

non-invasive technique and it can offer a much larger amount of spectroscopic information about the reactions monitored compared to UV-Vis. Early examples of the use of custom ATR for reaction monitoring and spectroscopic studies in the liquid phase employed bespoke ATR cells.[24] Coupling ATR-IR to micro-fluidic devices has enabled the development of IR imaging devices, capable of mapping the distribution of different species along the reactor channels (see Fig. 4).[25]

The development of commercial flow-cells (e.g. ReactIR from Mettler-Toledo) facilitates the access of this technique to non-specialists, thus enabling their facile integration in the synthetic platforms. Recently, Ley and collaborators[26] reported the employment of a commercial ATR-IR cell (React IR) with integrated software capabilities that enable in-line monitoring of chemical reactions and the employment of the data obtained to control and actuate the system (Fig. 5).

This application of in-line IR spectroscopy represents a significant step forward towards realising truly integrated platforms. This is because the technique allows transient states to be analysed, correcting deviations from ideal flow due to axial dispersion. It is also possible to monitor the formation of intermediate and/or hazardous species, and the synchronisation of complex multi-step synthetic processes.[27] In this way, the in-line analytics can be employed, not only to characterise the reaction outcomes, but also to actuate pumps to adapt the conditions to the variability introduced by the platform architecture or external factors (Fig. 6).

Fig. 7 shows an example of the monitoring of a fluorination employing an ATR-IR flow-cell. The combination of a tubular reactor and a chromatographic column for separation introduces a lag time between the detection of reagent and products. Additionally it was observed the radial dispersion of the concentration of all species due to imperfect mixing. By employing multiple compact fiber optical probes it was possible to monitor chemical transformations at multiple points, thus enormously improving process control, safety and allowing for optimisation of each step.[28]
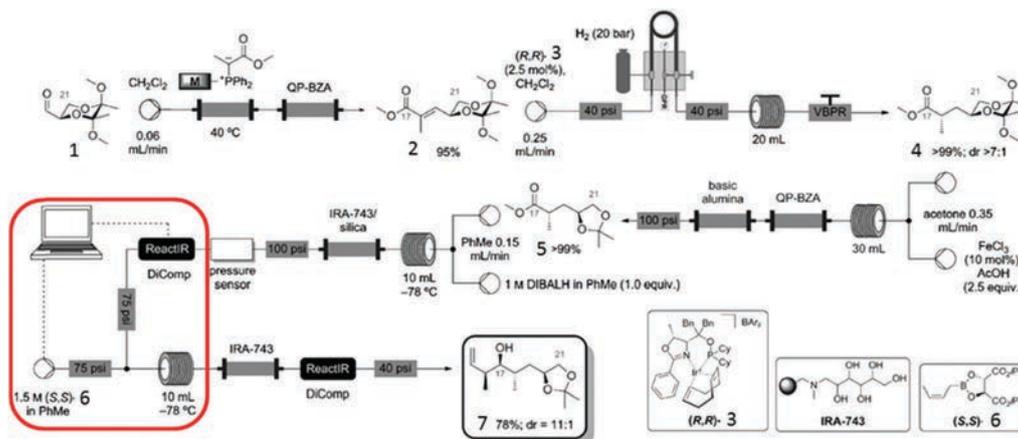

Fig. 6 A multi-step synthetic sequence of an allylic alcohol shown as number 7. Supported catalysts and reagents are combined to synthesise and purify a complex product in a multi-step sequence. In-line IR spectroscopic data (red square) are employed to correct the effect of the axial dispersion of an intermediate due to non-ideal flow patterns across a packed bed reactor and tune the addition of a subsequent reagent to optimise the mixing profile. Adapted from ref. 27 with permission. Copyright 2014 Wiley.
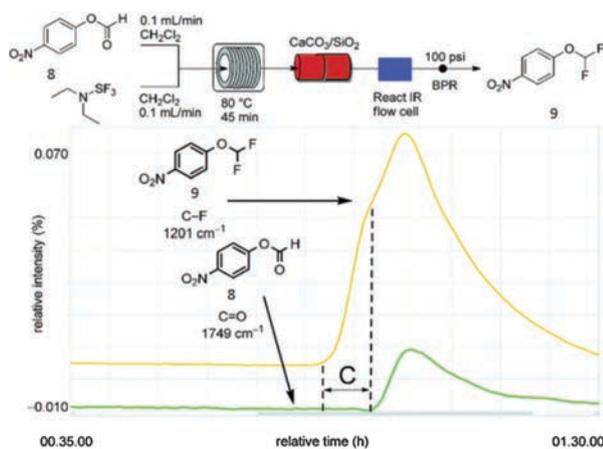
Fig. 7   Ester fluorination with DAST under continuous-flow monitored by flow-IR. Up: Reactor and reaction scheme. Down: Relative intensity of the product 9 and unreacted ester 8 as a function of time. *C* represents the time delay between the detection of both compounds due to the chromatographic retention. Adapted with permission from ref. 26. Copyright 2010 American Chemical Society.

The integration of in-line IR with 3D-printed "reactionware" was proved to be a very efficient way to monitor and control the organic synthesis of imines,[15] and for multi-step synthetic sequences.[29] The integrated platforms were controlled with tailored Labview control programs (Vis) that controlled the compositions, the residence time, and the analytics encapsulated within a single platform. This approach allowed to quickly close the loop between reactor design and application, by very quickly evaluating the performance of a reactor design in a continuous-flow platform. The amount of data generated in real-time, coupled with the efficiency of flow chemistry, allowed for the determination of reaction kinetics in a faster and more efficient way than it is possible under classical batch conditions. Jensen *et al.*[30] have recently developed a methodology to establish full kinetic models of organic reactions. By combining ramping sequences of the flow rate with a step-wise increase of temperature in a microfluidic continuous-flow set-up equipped with an IR detector it was possible to quickly characterise kinetic sequences at different temperatures for the Paal–Knorr reaction between 2,5-hexanedione and ethanolamine in dimethyl sulfoxide. The small dimensions of the device (channel width of 400 μm) resulted in a low axial dispersion of the reaction mixture. Fig. 8 presents a schematic representation of the concept, where a constant flow rate gradient was employed to quickly acquire information related to the studied reaction much quicker than with a one experiment at a time classical approach. The flow rate ramps are repeated at increasing temperatures to obtain a full kinetic data including kinetic parameters from the Arrhenius equation.

Mass spectrometry

Early examples of bespoke platforms and microfluidic devices for mass spectroscopy detection were focused mostly on analytical
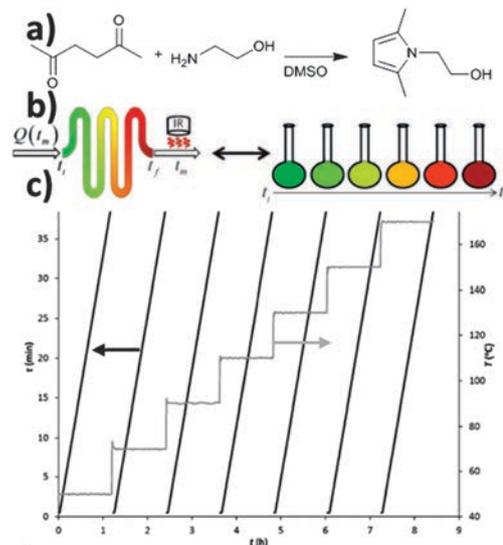

Fig. 8   The treatment of a low dispersion microfluidic device as a series of batch reactors monitored by in-line ATR-IR allows for a quick determination of kinetic parameters. (a) Scheme of the Paal–Knorr employed as benchmark reaction. (b) Representative scheme of the time-series concept employing flow-rate gradients. (c) Example of a flow-rate, time and temperature series. Adapted from ref. 30. Copyright Wiley.

applications, such as electrophoresis.[31] The high sensitivity of mass spectrometry, together with the highly controlled reaction conditions available under continuous-flow, is an ideal combination for detailed studies of organic and organometallic transformations in terms of mechanisms, and to dynamically characterise reaction intermediates 'on the fly'.[32]

The Sandmeyer cyclization reaction for the formation of isatins was studied in detail by Silva *et al.* employing simple microfluidic devices connected to ESI-MS.[33] By employing ESI-MS and ESI-MS/MS a number of short lived intermediates were transferred to the gas phase and detected for the first time, thus helping to confirm the reaction mechanism. The development of compact lab scale ESI-MS devices facilitated the integration of such devices in continuous-flow platforms in a laboratory scale. Browne *et al.*[11] elegantly demonstrated the potential of compact ESI-MS (Microsaic MD3500) to monitor reaction intermediates from a continuous flow reactor at representative temperature and pressure conditions (500 psi) employing a 6-way valve to sample 5 μl aliquots of reaction mixture. The reaction studied was the diazotization of anthranilic acid to benzene followed by a Diels–Alder condensation with furan. A number of intermediates, including an explosive diazotised intermediate, and several competitive reaction pathways were identified and the reaction conditions were optimised based on the MS data collected.

Advanced polymerisation processes based on RAFT polymerisation of acrylates were monitored employing a microfluidic device coupled to an ESI-MS detector.[34] After careful calibrations of the different possible products the authors could track the addition of each individual monomer and correlate the residence time of the reaction as a function of the input, thus indicating the potential of this approach to control complex
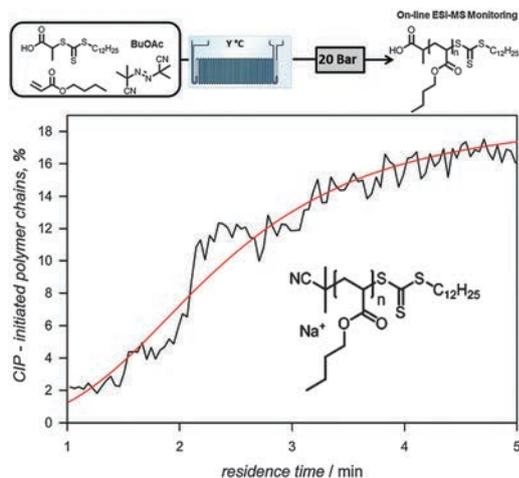
Fig. 9 On-line monitoring of the RAFT polymerization process. Up: Schematic representation of the polymerisation. A set of reagents. Down: Fraction of CIP-initiated polymer chains as a function of time in the RAFT polymerization of nBA at 100 °C in the microreactor. Adapted from ref. 34 with permission of The Royal Society of Chemistry.
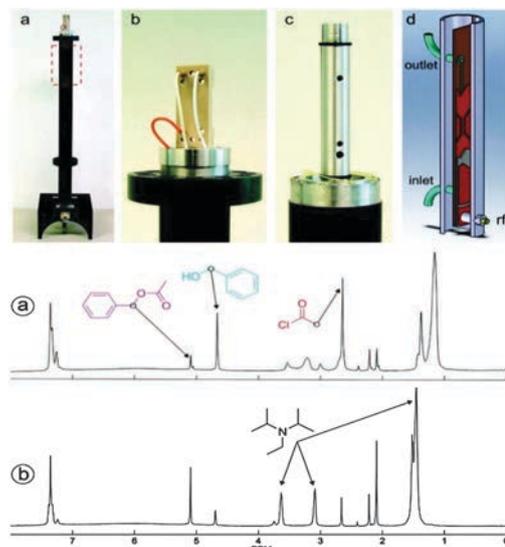

Fig. 10 Custom made microfluidic NMR flow cell and representative ^{1}H NMR spectra. Up: Images corresponding to the cell and the holder: (a) the microfluidic probe with the position of the NMR chip marked by the dashed line; (b) microreactor holder mounted on top of the probe; (c) holder of the stripline; (d) schematic representation of the microfluidic chip in the NMR holder. Down: Representative spectra corresponding to the acetylisation of benzyl alcohol in the presence of DIPEA at (a) 9 s and (b) 3 min. The band corresponding to the product increase with the time. Adapted from ref. 37 with permission from The Royal Society of Chemistry.

chemical syntheses. Furthermore, it was possible to monitor the formation of oligomers with controlled fractions of monomers (Fig. 9).

Nuclear magnetic resonance

Nuclear magnetic resonance is perhaps the most powerful spectroscopic technique available to characterise organic molecules. It is a technique routinely employed in research laboratories and industrial environments. However, the need of high field NMR machines equipped with flow cells[35] or specialist manufacturing techniques for microfluidic coils[36,37] is a strong limitation to its widespread application in research laboratories and industrial environments.

Bart et al.[36] developed a high resolution microfluidic probe (Fig. 10) based on a planar coil design, the stripline, that can work with commercial glass microchips (Micronit). This design has superior sensitivity than traditional coils and therefore represents an ideal tool to monitor reactions in microfluidic devices with sub-Hz resolution. As a proof of principle acetylation of benzyl alcohol in the presence of N,N-diisopropylethylamine (DIPEA) in a 1:1:1.2 stoichiometry was conducted (see Fig. 10, down). The reaction was successfully monitored, showing a conversion of 70% at a residence time of 3 minutes. The resolution of the spectra allowed for a fine analysis of the reaction sample. The broadening of the DIPEA and a shift at different residence times indicated a partial protonation of the base employed in the reaction (see Fig. 10, down). To demonstrate the potential of this technique in metabolomics, a sample of human cerebrospinal fluid at a concentration of 1.21 mM was characterised in the microchip with a detection volume of 600 nL.

Another example of miniaturised NMR has been reported by Gomez et al.[37] Their contribution was the first to combine microstructured NMR probes with microliter continuous-flow

microwave assisted organic reactions. This is very interesting because it can potentially lead to a synergistic interaction between the increase in reaction kinetics often observed under microwave irradiation and the rapid reaction characterisation available with NMR. Thus, the reaction conditions can be rapidly optimised. A planar micro-coil was employed, generating a 300 MHz (^{1}H Larmor Frequency) field at 7.05 T. A Diels–Alder condensation was investigated as a benchmark reaction, and the conversion was quickly characterised at different residence times and temperatures.

Very recently, the same group has elegantly reported a method to determine kinetic parameters (reaction order, rate constant and Arrhenius parameters) of chemical reactions from a single non-isothermal flow experiment with minimum consumption of resources (< 10 μmol) and time (ca. 10 minutes).[38] This was achieved by in-line NMR monitoring of a reaction performed in a commercially available microfluidic synthetic platform (Labtrix start). The data were collected before, at the onset and during the steady state operation regime and fitted to a model. Despite the impressive reaction capabilities, there is a need of a high field superconductive NMR to accurately apply this method.

Low field NMR spectroscopy applied to continuous-flow reaction monitoring offers a cost effective alternative to overcome these limitations. Despite its inherent lower resolution, the permanent magnets are much more suitable than high field super-conducting magnets for process and laboratory environments. Furthermore, processes can be monitored employing non-deuterated solvents, thus eliminating problems associated

with kinetic isotopic effects. Dalitz *et al.*[39] have published a comprehensive review on the use of low field NMR for process monitoring. It is worth mentioning that in most cases, a "by-pass" configuration was employed, where a sample of a continuous-stirred tank reactor is extracted at controlled intervals, pumped through the detector and then returned to the reactor.

In an early contribution and employing such by-pass configuration, Nordon *et al.*[40] employed a 29 MHz NMR to characterise an homogeneous esterification reaction and heterogeneous water–toluene mixtures. They reported difficulties in obtaining reliable data in heterogeneous phases due to imperfect mixing in the reactor. Other factors affecting the results are temperature and high flow rates that prevent complete magnetization of the reagents.

The technology has evolved in recent years to produce highly sensitive NMR magnets based on the Halbach design employing individual magnet blocks arranged in a cylindrical fashion with additional rectangular blocks that can be adjusted to manually correct the inhomogeneities of the magnetic field due to the imperfection of the magnetic blocks.[41] This has led to the development of benchtop NMR machines (*e.g.* Spinsolve from Magritek) that have been adapted to flow platforms (see Fig. 11). The group of Professor Bluemich demonstrated in an early example, how a NMR magnet could be placed under a fumehood and employed for the monitoring of a transfer hydrogenation reaction between acetophenone and isopropanol. Later, the same group employed a commercially available Spinsolve machine to monitor the 1H signal of organic reactions under continuous-flow.[42] By studying a transfer hydrogenation catalysed by an Iridium complex, the limits of detection and quantification were found to be 3 and 10 mmol L^{-1} for a temporal resolution of 10 s. A signal loss at increasing flow rates due to the incomplete polarization of the sample and to the replacement of excited spins with polarised ones in the detector was observed.

In our contribution to the field we have recently reported the integration of Spinsolve into a fully automated synthetic platform (Fig. 11).[43] A benchtop NMR with ability to acquire ^{1}H, ^{13}C, 2D-NMR (HSQC, COSY, *etc.*) and ^{19}F was equipped with an in-house developed glass flow-cell and connected to a synthetic rig consisting of a set of programmable syringe pumps, a static mixer and a tubular reactor. An interface between the Spinsolve was created employing a TCP/IP connection, thus enabling a full and remote control over the apparatus. This allowed developing an interface with Labview that controls the whole platform. The platform was employed to monitor reaction kinetics by monitoring the ^{1}H change from the aldehyde and the imine bands at different flow rates. At lower flow rates, higher values of conversion were observed, and the reaction could be modelled according to a second order reaction order, which is in agreement with previous reports.[15] The possibility of characterising reaction products by ^{13}C, and multinuclear analyses (COSY and HSQC) was also demonstrated. The use of NMR in a fully automated platform enables the monitoring and characterisation of processes of novel reaction features based on real-time information. This was demonstrated by characterising the conversion and stereoselectivity of a Diels–Alder condensation of
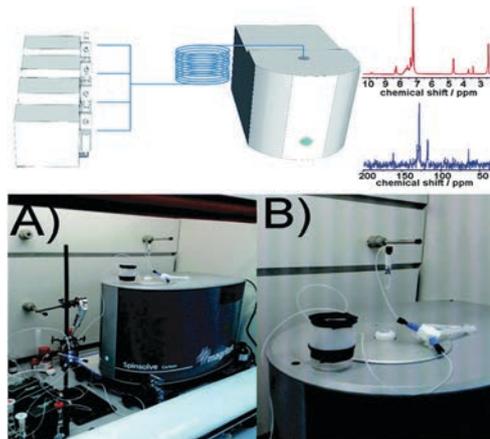

Fig. 11 Low field benchtop NMR adapted as in-line analytics in a continuous-flow platform. Up: Schematic of the synthetic platform and examples of ^{1}H and ^{13}C acquired in flow. Down: Pictures of rig: general view (A) and details of the benchtop NMR (B). Reprinted from ref. 43. Published by The Royal Society of Chemistry.

acrolein and cyclopentadiene by increasing the amount of the catalyst Sc(OTf)$_3$. This reaction can generate two isomers, the *endo* and the *exo*. One is the thermodynamically favoured and the other is kinetically controlled. Depending on the choice of catalyst and reaction conditions, a different ratio can be obtained. By monitoring the decrease of the carbonyl band corresponding to the acrolein and the increase in the bands corresponding to each monomer, it was possible to simultaneously monitor the formation of both isomers. In a separate experiment, a Select-fluor based fluorination was monitored by ^{1}H and ^{19}F NMR. A monofluorinated product was observed in both spectra. Hence, it was demonstrated that flow NMR enables to obtain an unprecedented amount of chemical and structural information from a single integrated platform (Fig. 12).

Intelligent algorithms

To date, it has been shown that the combination of continuous-flow platforms with in-line analytics is highly advantageous because it synergistically combines the high process efficiency typically associated with flow chemistry with high speed chemical, structural and process related data acquisition. Faster data acquisition enables a very detailed monitoring of chemical processes and the fast optimisation of the reaction conditions, thus minimising the time and waste generated in optimising the synthetic transformations. The rapid and facile generation of high volumes of data enables the employment of statistical techniques for process analysis, like "Design of Experiments" (DoE), where the effect of multiple parameters are studied simultaneously to rapidly understand their influence on the process. Furthermore, the integration of flow and analytical platforms to undertake complex chemical transformations has the added advantage to facilitate process control employing the data generated during the course of the transformation to modify the input parameters (typically residence times,
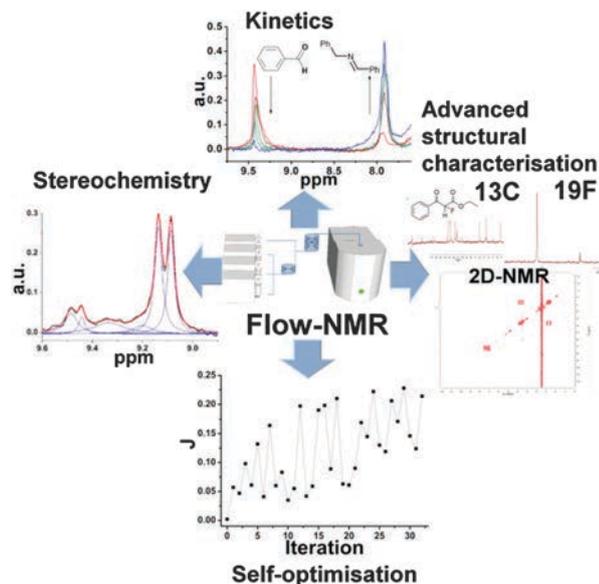
Fig. 12 Summary of the multiplexed analytical capabilities of in-line flow-NMR. Reprinted from ref. 43. Published by The Royal Society of Chemistry.
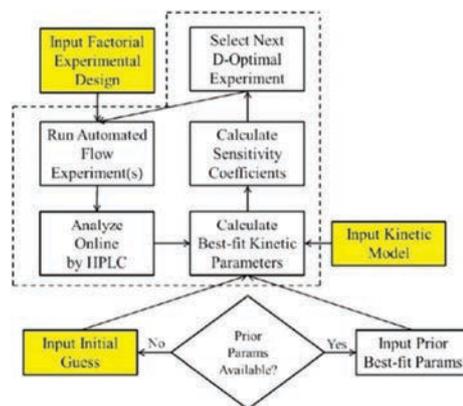

Fig. 13 Flow diagram for the kinetic parameter estimation under continuous-flow conditions. Reprinted with permission from ref. 44. Copyright 2012 American Chemical Society.

temperatures, pressure, *etc.*) in order to optimise the user-defined output of the transformation (*e.g.* yield, selectivity, productivity, *etc.*). The next evolutionary step consists of the integration of feedback optimisation algorithms, capable of autonomously interpreting the data generated in real-time to both identify the regions of the parameter space that maximise or minimise the outputs of interest. In this way, the minimal human intervention enables closing the experimental loop required to optimise processes and to maintain the optimum conditions through process control techniques. In this way, the autonomous systems can account for unforeseen changes in the inputs, like physico-chemical variability in the feedstocks.

The simplest possible algorithm consists of employing a systematic exploration of the parameter space in a combinatorial fashion. This was applied to chemical discovery by McNally *et al.*[10] and was coined "accelerated serendipity". In this work, an automated platform was employed to undertake a large number of random reactions to increase the probability of discovering an emerging property or an unexpected event. The adequate selection of the parameter space is key to increase the chance of discovery. In the relatively new field of photoredox catalysis, the automated platform combined a pool of reagents in pairs in a 96 well plate with fixed amounts of Ir catalysts. The platform was connected to a GC-MS that analysed each reaction outcome and the peaks of substantial intensity were analysed and the mass compared to the National Institute of Standards and Technologies (NIST) database. This high-throughput platform allowed performing 1000 experiments per day by a single operator. A new coupling reaction to produce acyclic and cyclic benzylamines was discovered employing this methodology. Once the discovery was established, the authors undertook a systematic study of the scope of the reaction to a number of substrates, they proposed a mechanism and a commercial pharmaceutical was synthesised employing the new methodology.

Despite the impressive potential of the accelerated serendipity, the process is based on random combinations, following a combinatorial chemistry approach. The employment of intelligent algorithms that employs the experimental data feedback to the system, thus autonomously and intelligently deciding subsequent experiments helps to explore the parameter space in a faster way, thus reducing the time and resources required to achieve a desired result, such as maximum yield and/or selectivity or the rapid determination of kinetic models for scale-up.

Reizman and Jensen reported a method for the rapid estimation of kinetic parameters in a complex network of parallel reactions. This system employed an automated set-up, design of experiments, and maximum likelihood estimation through an iterative process shown in Fig. 13.[44] Their method allowed for the statistically-based development of models for multiple reactions, thus allowing the optimization in a rational fashion yielding reliable information for scale-up. The network studied was the nucleophilic aromatic substitution of morpholine onto 2,4-dichloropyrimidine. The assumptions of the model were that the reactions are second order and the reactor is a plug-flow reactor (PFR), thus having ideal mixing.

A user-defined model was proposed, where 5 different reagents were involved. On-line HPLC coupled to a microfluidic reactor was employed to monitor the concentration of the 5 reagents at different residence times, temperatures and concentrations. The experimental conditions were determined by design of experiments (DoE). Statistical analysis of the data allowed estimating the kinetic parameters applying least square fitting. By employing this approach a reduction of 50% in the kinetic parameter uncertainties was observed with a consumption of less than 5 g of dychloropyrimidine.

Another approach to have an intelligent analysis of the reaction parameter space is the employment of black-box feedback optimisation algorithms. These algorithms have the advantage of not needing *a priori* information, because they employ experimental data to decide the subsequent experiments in the search for optimal responses across the parameter space. Derivative-free local (*e.g.* Simplex) and global (*e.g.* genetic

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algorithms, SNOBFIT, *etc.*) algorithms have been applied to solve chemical problems.[45]

A continuous-flow microfluidic platform combined with in-line analytics to monitor the emission spectra of nanoparticles was also reported by Krishnadasan *et al.*[46] A self-optimization algorithm based on the stable noisy optimization by branch and fit (SNOBFIT) that controlled the temperature and flow rates of the different reagents was employed to intelligently control the formation of quantum dots, employing the emission spectra of CdSe nanomaterials as the basis for the optimisation.

The authors defined a fitness function that integrates in a single objective called the dissatisfaction coefficient (DC), a two characteristic parameter found in the emission spectra, the wavelength and the intensity of the spectra. The closer these two parameters get to a desired value the lower the DC. A single objective weighted fitness function made of these two parameters was employed and the algorithm was programmed to minimise DC. Fig. 14 shows an example of the landscape profile of the variation of the flow rates of each reagent.

An automated platform coupled to an on-line HPLC to self-optimise a Heck reaction between activated aryl chlorides and alkenes was reported by McMullen *et al.*[12] They employed a local search algorithm, the simplex, to direct the feedback control optimisation system. After 19 automated experiments, the conditions were optimised, requiring small amounts of reagents. Furthermore, the reaction was scaled up 50-fold employing the optimal conditions determined by the microreactor system to yield 114 kg per year of product.

McMullen and Jensen also reported the self-optimisation of a Knoevenagel reaction and a selective oxidation of benzyl alcohol to benzaldehyde employing CrO_3.[47] Fig. 15 shows a scheme of the automated platform and images of the silicon microreactors employed. The selection of the most suitable algorithm is not trivial, because the response surface is dependent on the studied system. In this study, the performance of three algorithms, the simplex, SNOBFIT and steepest descent,

Fig. 15 (a) Scheme of the automated platform integrating a microfluidic system consisting of syringe pumps, a microreactor, a micromixer, HPLC, and a PC. The platform was controlled with a LabVIEW interface. (b) Silicon microreactor used for the self-optimization including mixing, reaction and quench zones. (c) Image corresponding to the assembled microreactor with fluidic connections in a top plate (1), a recessed plate (2) to house the microreactor and temperature controller, and (3) a baffled heat exchanger for heat removal and temperature control. Reprinted with permission from ref. ref. 47. Copyright 2010 American Chemical Society.

were compared to determine the minimum number of steps or iterations required to achieve an optimal result. It was found that for the Knoevenagel reaction the steepest descent algorithm was 2.3 and 2.8 times faster than the Simplex and the SNOBFIT, respectively, in achieving a user-defined optimum. In the case of oxidation a four dimensional optimisation employing the Simplex algorithm revealed that shorter residence times at higher temperatures were the optimal, as opposed to traditional conditions. This is due to the ability of the micro-reactors to efficiently mix the reagents and to dissipate the heat generated during the reaction.

Shortly after, Poliakoff's group reported a self-optimisation platform for supercritical carbon dioxide ($scCO_2$) applications.[13,48] They employed initially the super modified simplex algorithm (SMSIM) to optimise synthetic protocols of relevance from the green chemistry point of view, like methylations employing dimethyl carbonate (DMC) under continuous-flow employing $scCO_2$ as the solvent. The samples were analysed by GC, thus introducing a lag time between the analysis and the generation of the subsequent reaction conditions. In a later contribution, in-line IR was employed to analyse the reaction progress in a faster and more efficient way.[49] This step led to a reduction of one order of magnitude in time and amounts of reagents required to optimise the methylation of 1-pentanol with DMC (Fig. 16).

The employment of in-line analytics for self-optimisation is therefore a very efficient approach to reduce the amount of waste generated and to reduce the time required to achieve an optimal result. Very recently, a self-optimising platform based on in-line NMR has been recently reported.[43] As a proof of principle, a modified simplex algorithm was employed to self-optimise under continuous-flow conditions the acid catalysed synthesis of an imine (Fig. 17). The parameters studied were flow rate and composition of two reagents and a catalyst under defined constraints. The residence time was limited between 2 and 10 minutes. The lower limits were selected for practical
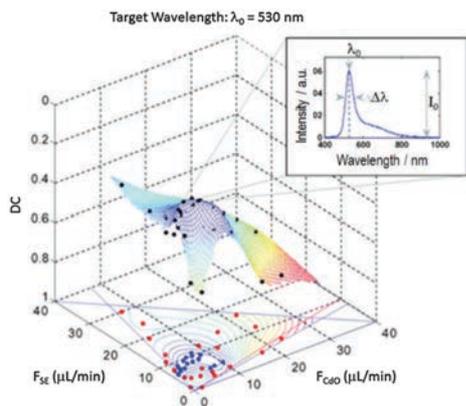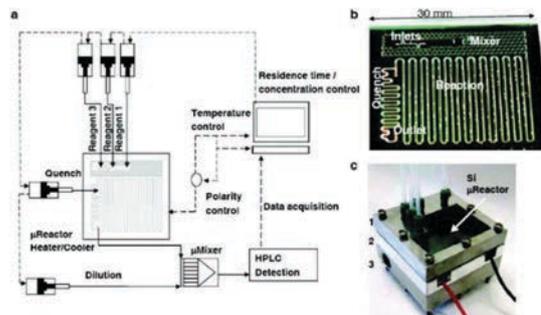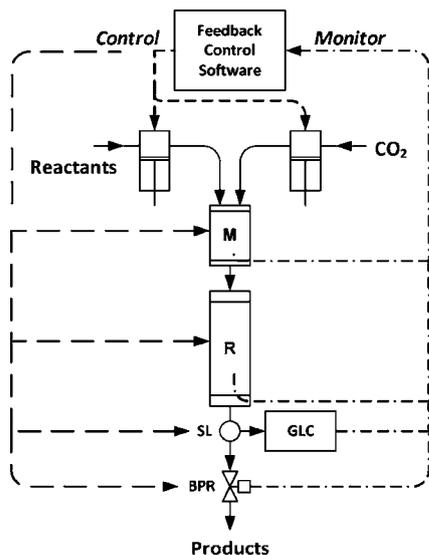

Fig. 14 Fitness landscape of the synthesis of CdSe QDs modifying the flow rates of both reagents. Red and blue dots correspond to fitness values that are greater or smaller than the median value of 0.26. The region corresponding to the optimum can be observed by a pronounced minimum. Reproduced from ref. 46 with permission from The Royal Society of Chemistry.

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Fig. 16 Schematic of a continuous-flow self-optimisation rig. The reactants and CO_2 are pumped to a pre-heater and mixer (M) and into the reactor (R). A sample loop (SL) collects the product stream and sends it to the on-line gas–liquid chromatograph (GLC). The back-pressure regulator (BPR) maintains the system pressure. Reprinted with permission from ref. 13. Copyright 2011 American Chemical Society.
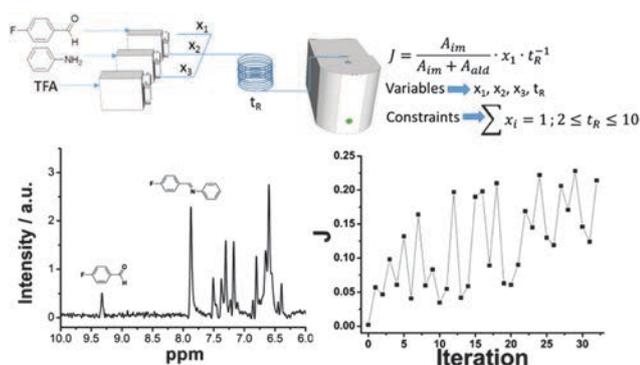

Fig. 17 Self-optimisation platform employing in-line NMR. An acid catalysed imine synthesis was selected as a benchmark reaction to validate the platform. Ref. 43. Published by The Royal Society of Chemistry.

reasons to avoid large backpressure from the pumps and to prevent a loss of signal in the detector due to incomplete magnetisation. As previously discussed, NMR is the most powerful spectroscopic analytical technique and the coupling to a continuous-flow self-optimisation platform will lead to the development of an array of applications based on different and complementary analyses.

The development of new algorithms with enhanced efficiency, able to reduce the number of experimental iterations to reach the optimal result is particularly important in chemical systems, where experimentation is difficult due to challenging experimental conditions or a high dimensionality of the optimisation problem requires an excessive amount of iterations. A novel algorithm based on a combination of Gaussian Process surrogate models and evolutionary algorithms, called the multi-

objective active learner (MOAL) algorithm was applied to the multi-objective semi-batch optimisation of emulsion polymerisations.[50]

Conclusions

The progress in recent years in the field of continuous-flow chemistry has contributed to develop highly efficient and automated synthetic rigs. The key advantages inherent to continuous-flow, such as enhanced mixing, heat transfer and extremely precise control over pressure and temperature has led to a plethora of applications reported in the literature in recent years. Building on this, the development of in-line analytical techniques based on spectroscopic signals have been employed to monitor and characterise synthetic transformations in real-time. This step enables the integration of intelligent algorithms to control the synthetic platforms in order to maximise or minimise a set of objectives, like yield, selectivity, waste generated, *etc.* In this way the need of user supervision is minimised through the synthetic process. The combination of these three technologies will contribute to the overall philosophy of dial-a-molecule. The scope for integration of multi-step synthetic sequences and multiple parallel analytical tools for applications in complex synthetic continuous-flow rigs is enormous. For example it has even be possible to construct an autonomous robot to evolve oil droplets in a fully automatic platform, and this represents the first platform to robotically embody chemical evolution.[51] This is an emerging field in the interface between chemistry, physics, engineering and mathematics with a huge scope for innovation.

Acknowledgements

Notes and references

1 J. Wegner, S. Ceylan and A. Kirschning, *Adv. Synth. Catal.*, 2012, **354**, 17–57.

2 A. Nagaki, K. Imai, S. Ishiuchi and J.-i. Yoshida, *Angew. Chem., Int. Ed.*, 2015, **54**, 1914–1918.

3 J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8849–8869.

4 R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins and S. V. Ley, *Angew. Chem., Int. Ed.*, 2015, **54**, 144–148.

5 R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 7502–7519.

6 U. Hintermair, G. Francio and W. Leitner, *Chem. Commun.*, 2011, **47**, 3691–3701.

7 E. Garcia-Verdugo, B. Altava, M. I. Burguete, P. Lozano and S. V. Luis, *Green Chem.*, 2015, **17**, 2693–2713.

8 J. Li, S. G. Ballmer, E. P. Gillis, S. Fujii, M. J. Schmidt, A. M. E. Palazzolo, J. W. Lehmann, G. F. Morehouse and M. D. Burke, *Science*, 2015, **347**, 1221–1226.

9 C. J. Richmond, H. N. Miras, A. R. de la Oliva, H. Y. Zang, V. Sans, L. Paramonov, C. Makatsoris, R. Inglis, E. K. Brechin, D. L. Long and L. Cronin, *Nat. Chem.*, 2012, **4**, 1038–1044.

10 A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114–1117.

11 D. L. Browne, S. Wright, B. J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner and S. V. Ley, *Rapid Commun. Mass Spectrom.*, 2012, **26**, 1999–2010.

12 J. P. McMullen, M. T. Stone, S. L. Buchwald and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2010, **49**, 7076–7080.

13 R. A. Bourne, R. A. Skilton, A. J. Parrott, D. J. Irvine and M. Poliakoff, *Org. Process Res. Dev.*, 2011, **15**, 932–938.

14 H. Lu, M. A. Schmidt and K. F. Jensen, *Lab Chip*, 2001, **1**, 22–28.

15 P. J. Kitson, M. H. Rosnes, V. Sans, V. Dragone and L. Cronin, *Lab Chip*, 2012, **12**, 3267–3271.

16 V. Sans, S. Glatzel, F. J. Douglas, D. A. Maclaren, A. Lapkin and L. Cronin, *Chem. Sci.*, 2014, **5**, 1153–1157.

17 M. Lee, J.-P. Lee, H. Rhee, J. Choo, Y. Gyu Chai and E. Kyu Lee, *J. Raman Spectrosc.*, 2003, **34**, 737–742.

18 E. Cao, M. Sankar, S. Firth, K. F. Lam, D. Bethell, D. K. Knight, G. J. Hutchings, P. F. McMillan and A. Gavriilidis, *Chem. Eng. J.*, 2011, **167**, 734–743.

19 T. A. Hamlin and N. E. Leadbeater, *Beilstein J. Org. Chem.*, 2013, **9**, 1843–1852.

20 S. Mozharov, A. Nordon, D. Littlejohn, C. Wiles, P. Watts, P. Dallin and J. M. Girkin, *J. Am. Chem. Soc.*, 2011, **133**, 3601–3608.

21 S. Schwolow, F. Braun, M. Rädle, N. Kockmann and T. Röder, *Org. Process Res. Dev.*, 2015, **19**, 1286–1292.

22 L. Guerrini and D. Graham, *Chem. Soc. Rev.*, 2012, **41**, 7085–7107.

23 M. P. Cecchini, J. Hong, C. Lim, J. Choo, T. Albrecht, A. J. deMello and J. B. Edel, *Anal. Chem.*, 2011, **83**, 3076–3081.

24 M. Jobling, S. M. Howdle and M. Poliakoff, *J. Chem. Soc., Chem. Commun.*, 1990, 1762–1764.

25 K. L. A. Chan, S. Gulati, J. B. Edel, A. J. de Mello and S. G. Kazarian, *Lab Chip*, 2009, **9**, 2909–2913.

26 C. F. Carter, H. Lange, S. V. Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode and N. L. Gaunt, *Org. Process Res. Dev.*, 2010, **14**, 393–404.

27 S. Newton, C. F. Carter, C. M. Pearson, L. D. Alves, H. Lange, P. Thansandote and S. V. Ley, *Angew. Chem., Int. Ed.*, 2014, **53**, 4915–4920.

28 C. B. Minnich, L. Greiner, C. Reimers, M. Uerdingen and M. A. Liauw, *Chem. Eng. J.*, 2011, **168**, 759–764.

29 V. Dragone, V. Sans, M. H. Rosnes, P. J. Kitson and L. Cronin, *Beilstein J. Org. Chem.*, 2013, **9**, 951–959.

30 J. S. Moore and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2014, **53**, 470–473.

31 S. Koster and E. Verpoorte, *Lab Chip*, 2007, **7**, 1394–1412.

32 J. S. Mathieson, M. H. Rosnes, V. Sans, P. J. Kitson and L. Cronin, *Beilstein J. Nanotechnol.*, 2013, **4**, 285–291.

33 B. V. Silva, F. A. Violante, A. C. Pinto and L. S. Santos, *Rapid Commun. Mass Spectrom.*, 2011, **25**, 423–428.

34 J. J. Haven, J. Vandenbergh and T. Junkers, *Chem. Commun.*, 2015, **51**, 4611–4614.

35 J. Y. Buser and A. D. McFarland, *Chem. Commun.*, 2014, **50**, 4234–4237.

36 J. Bart, A. J. Kolkman, A. J. Oosthoek-de Vries, K. Koch, P. J. Nieuwland, H. Janssen, J. van Bentum, K. A. M. Ampt, F. P. J. T. Rutjes, S. S. Wijmenga, H. Gardeniers and A. P. M. Kentgens, *J. Am. Chem. Soc.*, 2009, **131**, 5014–5015.

37 M. V. Gomez, H. H. J. Verputten, A. Diaz-Ortiz, A. Moreno, A. de la Hoz and A. H. Velders, *Chem. Commun.*, 2010, **46**, 4514–4516.

38 M. V. Gomez, A. M. Rodriguez, A. de la Hoz, F. Jimenez-Marquez, R. M. Fratila, P. A. Barneveld and A. H. Velders, *Anal. Chem.*, 2015, **87**, 10547–10555.

39 F. Dalitz, M. Cudaj, M. Maiwald and G. Guthausen, *Prog. Nucl. Magn. Reson. Spectrosc.*, 2012, **60**, 52–70.

40 A. Nordon, A. Diez-Lazaro, C. W. L. Wong, C. A. McGill, D. Littlejohn, M. Weerasinghe, D. A. Mamman, M. L. Hitchman and J. Wilkie, *Analyst*, 2008, **133**, 339–347.

41 E. Danieli, J. Perlo, B. Blümich and F. Casanova, *Angew. Chem., Int. Ed.*, 2010, **49**, 4133–4135.

42 E. Danieli, J. Perlo, A. L. L. Duchateau, G. K. M. Verzijl, V. M. Litvinov, B. Blümich and F. Casanova, *ChemPhysChem*, 2014, **15**, 3060–3066.

43 V. Sans, L. Porwol, V. Dragone and L. Cronin, *Chem. Sci.*, 2015, **6**, 1258–1264.

44 B. J. Reizman and K. F. Jensen, *Org. Process Res. Dev.*, 2012, **16**, 1770–1782.

45 K. W. Moore, A. Pechen, X.-J. Feng, J. Dominy, V. J. Beltrani and H. Rabitz, *Phys. Chem. Chem. Phys.*, 2011, **13**, 10048–10070.

46 S. Krishnadasan, R. J. C. Brown, A. J. deMello and J. C. deMello, *Lab Chip*, 2007, **7**, 1434–1441.

47 J. P. McMullen and K. F. Jensen, *Org. Process Res. Dev.*, 2010, **14**, 1169–1176.

48 A. J. Parrott, R. A. Bourne, G. R. Akien, D. J. Irvine and M. Poliakoff, *Angew. Chem., Int. Ed.*, 2011, **50**, 3788–3792.

49 R. A. Skilton, A. J. Parrott, M. W. George, M. Poliakoff and R. A. Bourne, *Appl. Spectrosc.*, 2013, **67**, 1127–1131.

50 C. Houben, N. Peremezhney, A. Zubov, J. Kosek and A. A. Lapkin, *Org. Process Res. Dev.*, 2015, **19**, 1049–1053.

51 J. M. P. Gutierrez, T. Hinkley, J. W. Taylor, K. Yanev and L. Cronin, *Nat. Commun.*, 2014, **5**, 5571.

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