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Labes, R, Bourne, RA orcid.org/0000-0001-7107-6297 and Chamberlain, TW orcid.org/0000-0001-8100-6452 (Cover date: July / August 2020) Automated reaction optimisation in continuous flow. Chemistry Today, 38 (4). ISSN 0392-839X

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Automated reaction optimisation in continuous flow

KEYWORDS: *Self-optimisation, Automation, Flow Chemistry, Machine Learning, Organic Synthesis.*

ABSTRACT: *This article highlights some of the recent advances in the area of optimising chemical synthesis. We explore how continuous flow chemistry, coupled with automation and optimisation techniques, can constitute a powerful tool that enables searches in larger chemical spaces and can assist delivering better methods faster. The combination of methods like Design of Experiment and local and global optimisation algorithms, such as SIMPLEX and Bayesian approaches, can further enhance the information gathered while optimising a method. Coupling these methods with intelligent, cloud based, automated platforms, enables a holistic approach to optimising chemical synthesis that combines chemistry, engineering and informatics.*

INTRODUCTION

Synthetic organic chemistry underpins many scientific areas and what is possible has evolved far beyond the wildest dreams of previous generations of researchers in recent years. However, in order to continue this expansion in scope, it is fundamental that it embraces new technologies in a truly multi-disciplinary way. We believe continuous flow automated optimisation platforms are a vital tool in this regard and have far reaching implications to the field moving forward.

The discovery of new reactivities and development of new synthetic methods drives a large portion of research in chemistry. As these advances often happen in narrow chemical spaces it is paramount that new technologies are employed to assist chemists in exploring new frontiers and make it is possible to conduct method optimisation in the best, safest and faster manner possible.

In this paper we share some highlights and perspectives into automated optimisation in continuous flow platforms, often referred to as self-optimising systems.

CONTINUOUS FLOW CHEMISTRY AND AUTOMATION

In the last two decades continuous flow chemistry, as applied to chemical synthesis, has established itself as an enabling tool, gathering attention from both academia and industry. Its developments have been covered in many reviews,(1–10) but it is relevant to highlight some of its benefits and challenges.

Generally, precise control over system parameters, combined with increased heat and mass transfer, has allowed many developments that would be otherwise challenging.(5, 9) For instance, the generation and reactivity of organometallic reagents has been extensively explored with great success, mostly due to better mixing and temperature control.(11) The same is valid for reactive/unstable intermediates, that can be generated and quickly consumed, often avoiding side-reactions and decomposition. In respect to both examples, the dynamic aspect of continuous flow means the formed product can be moved away from fresh reagent, in many cases improving selectivity/yield of the desired product.(12)

A considerable bottleneck for the uptake of continuous systems is the necessity to acquire, often at high cost, equipment like pumps, valves, reactors and back-pressure regulators. However, since most modern electronics are equipped with communication ports and protocols, this also creates an opportunity to explore the potentials of automation. Despite the additional equipment cost the reduction of human resource from labour intensive and repetitive tasks, as noted by Professor Steve Ley in a previous editorial, will likely lead to an overall reduction in costly experimental time and free synthetic chemists, increasing the time to focus on data analysis, challenging chemistries and creative work.(13)

The development of open source coding languages like Python and R, and software like MATLAB® and LabView®, that provide a graphical interface, greatly expand the accessibility to programming. The increased availability of online training in these areas means that not only flow chemistry, but all scientific disciplines will benefit from the next generation of students/researchers who will be more familiar with programming and automation tools.

In the era of cloud computing, Internet of Things and Industry 4.0, it is an additional advantage that equipment can be controlled remotely. Laboratory services that incorporate remote access/control are available in biology, but in chemistry there are very few reports, mostly from academia.(14–19) Remote access laboratories can not only be envisioned as a service or a tool used to improve the running of experiments, but they have the potential to become instrumental for establishing and strengthening collaborations. In the current virus pandemic, all those features become of special importance, with social distancing rules and working remotely becoming part of the norm. In addition to remote access for visualising and controlling equipment, webcams and smart electronic laboratory notebooks (ELN), that can save experimental metadata, are tools whose presence is certain to enhance this area.

SELF-OPTIMISATION

Automated continuous flow refers to a set of experiments or actions that can be ran autonomously by the equipment and the results analysed later by the operator. If that is coupled with the latest inline/online analytical tools, then the amount of information generated in a given time is greatly improved. Many have explored this type of system, but one example that deserves special mention is Pfizer's platform, that is capable of running >1500 experiments per day.(20) Some chemists might wish to screen a set of conditions which generates such a large number of experiments, but it is far more common that a chemist would want to perform a small set of experiments, then suggest a new set based on his/her analysis.

In this sense, the next step forward is to transfer this process to the computer, enabling iterative experiments to be designed and performed based on the data that the system acquires. This automated closed loop optimisation is often referred to as a self-optimisation system (Figure 1).

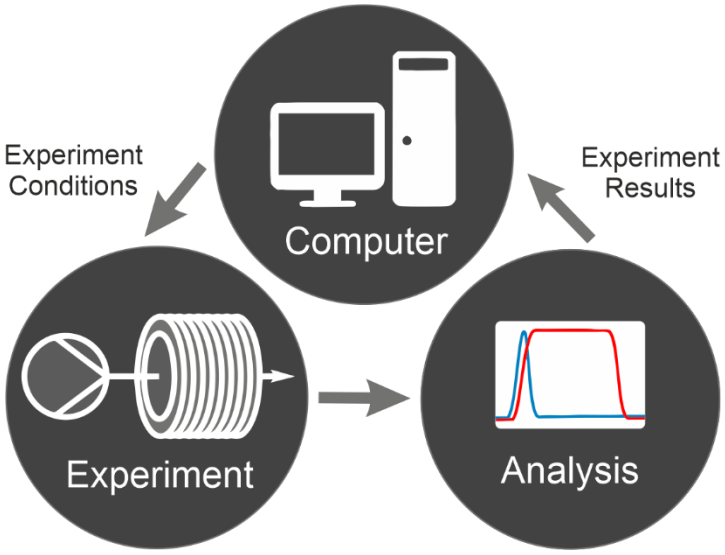

Figure 1. Diagram for a self-optimising system.

The application of self-optimisation platforms to chemical systems has led to approximately 30-40 reports, which points to the fact that despite this being an old concept,(21) it has only been adopted to any meaningful extent in recent years.(22) There is a predominance of academic groups in these reports, which highlights that this is a 'technology in development'. It is also noteworthy that most reports have focused on continuous variables (such as concentration, temperature and residence time) and the majority used local optimisers to generate sets of conditions (e.g. SIMPLEX).(23)

Consequently, there are few studies that include discrete variables, such as solvent or different reagents, and this is a key development, as most chemical methods can benefit from both continuous and discrete variables being

optimised.(22, 24, 25) Also, only a few studies have applied multi-objective optimisations.(23, 26–29) This approach is very appealing as it can give a balance between 2 diverging objectives. For example, exploring increasing reactor productivity and decreasing environmental impact; or increasing selectivity and decreasing catalyst loading.

Recent reports by Dr. K. Gilmore (multistep radial synthesis) and Prof. K. Jensen (robotic platform for flow synthesis) both demonstrate that such platforms will have increasingly modularity and be reconfigurable in nature.(30, 31) These approaches allow much greater flexibility, combining many of the benefits of both batch and flow chemistry with a single platform to accommodate different reaction requirements and multistage reactions.

OPTIMISATION OF CHEMICAL REACTIONS

Alongside optimisation using algorithms, as outlined above, there are other methods that can be used to optimise a given reaction. It is not within the scope of this paper to describe and analyse the merits of the many techniques available, but the main argument to be made is that more informed approaches are in development and will gain attention, but also combined, hybrid techniques shall be developed to increase the optimisation tools available. This will allow for faster method development as well as better understanding of the methods in question.

One variable at a time (OVAT) has been the default method by which chemists have optimised new reactions, while simpler to execute, the chances of being away from the absolute optimum are very high and increase with the number of parameters.(32) While rarely featured in undergraduate courses, design of experiments (DoE) and kinetic modelling are the more established alternatives to OVAT, especially in the industry, were there is a necessity for the development of robust processes.(32, 33) Applications of both DoE methods (e.g. MBDoE and feedback DoE) and kinetic modelling/parameter estimation continue to be developed and tools and training have and will become more accessible.(34–36)

When optimising a given reaction, minimising the number of experiments to reduce the amount of potentially limited starting materials used and waste generated is always a key consideration, and therefore, it is our view that combined approaches will gain popularity. Our group has recently published a paper in which a hybridised optimisation was performed, combining process optimisation with surface mapping, to an automated photochemical continuous flow reactor.(37) The algorithm starts the optimisation using SNOBFIT (Stable Noisy Optimization by Branch and Fit) to find the optimum and then moves to a screening stage, where it uses a surrogate Gaussian Process to map the area around this optimum. The final stage executes a DoE using a central composite face centred (CCF) design with the optimum as the centre point, to further refine the response surface model around the optimum previously defined (Figure 2). Understanding the shape of the response surface around the optimum is highly desired in a chemical process context as it informs the operator of the extent to which changes in process conditions can affect the quality of the product.

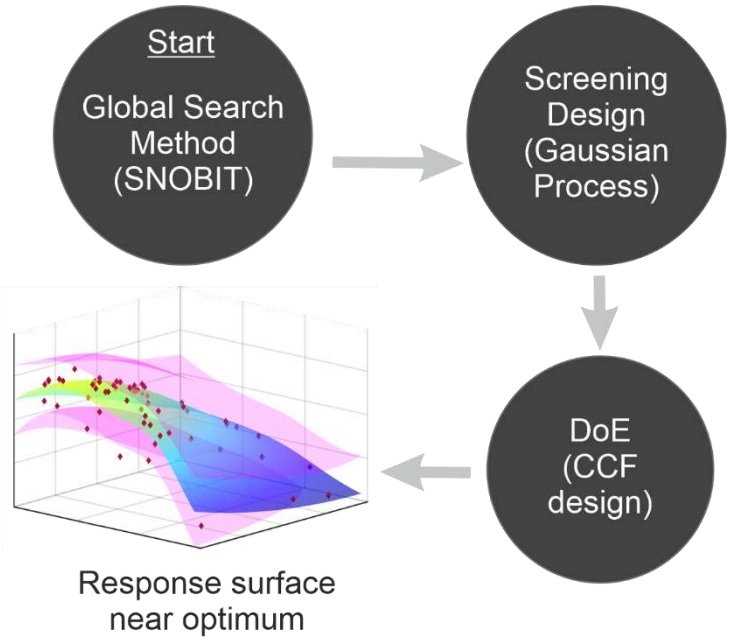

Figure 2. Simplified flow diagram for the hybridised optimisation algorithm.

OVERVIEW

It is apparent that the modern chemist requires a renewed set of skills that stretch beyond traditional training. For example, obtaining and honing the broad set of skills necessary to build and implement an automated optimisation platform, requires expertise in; flow chemistry, in/online analytics, automation and programming. Clearly, this represents a huge educational challenge. But the pronounced increase in interest and information available suggests that we are likely to see many great advances in this area in the coming years.

With so many tools available, the ability to select the correct approach to solve a given challenge also requires significant training. When choosing distinct approaches for a chemical optimisation, the best option can often be determined by the chemist/process requirements. For example, if speed and material consumption are the highest priorities, then a local optimisation algorithm (e.g. SIMPLEX) might be the best choice. In other instances, where knowledge of how specific parameter influence the system is desired, then a full DoE study will be more appropriate. These tools need to become readily available, so the chemists and engineers can make use of them to accelerate discovery and development. Using machine learning and artificial intelligence it is now possible that smart, artificial systems can make these decisions themselves and continue to improve the process as every result informs the decision-making process iteratively.

Although this text is mainly focused on continuous flow, all the optimisation tools and integration can be implemented in batch with appropriate robotic equipment. Despite that and despite the major advances in batch high throughput experimentation (HTE), to the best of our knowledge, there is no application of self-optimisation in batch chemistry. We believe it is something that will be explored soon due to the versatility of working in batch, e.g. for solid systems such as those with insoluble starting materials and products, where flow chemistry approaches are difficult to envisage.

The development and application of novel optimisation algorithms also represent a big growth area in the near future. For example, Bayesian algorithms have shown great potential optimising problems with unknown response surfaces, but there are opportunities to further tune these algorithms for bespoke chemical applications, which can reduce experimental workload and more rapidly optimise synthetic processes.

Our research group is currently investigating many of the mentioned technologies in an EPSRC funded project called Cognitive Chemical Manufacturing, where we and our partners aim to combine process development tools through a cloud-based platform.(38) That platform can control different automated continuous flow systems, in different sites, and uses data-rich technologies to accelerate the transfer from laboratory to production scale (Figure 3). This approach should also help overcome the requirement of owning expensive equipment and further enable the ability to parallelise chemical optimisations in an analogous fashion to the transformative effect that multi-core processors had to computing technologies.

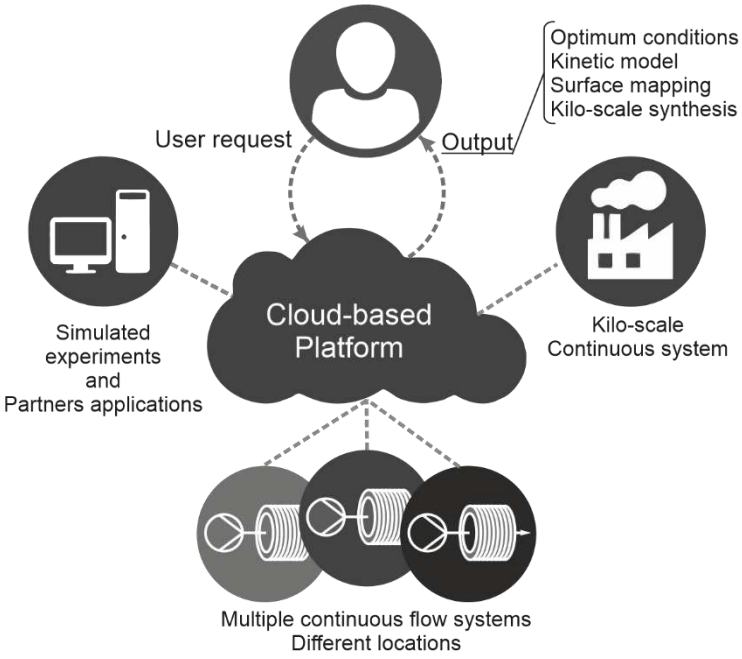

Figure 3. Conceptual diagram for the Cognitive Chemical Manufacturing project.

SUMMARY

Together with analytical techniques, continuous flow chemistry, high throughput experimentation, automation, self-optimisation platforms have come a long way from initial developments to today's state-of-the-art.

We believe that, as many different areas had to be developed to facilitate the use of automated continuous flow platforms for chemistry, many of the technologies cited here will be developed, and the holistic implementation of them, into more flexible hybrid platforms in a "lab of the future" approach to chemical synthesis that combines chemistry, engineering and informatics, will greatly improve discovery and process development.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from the EPSRC grant Cognitive Chemical Manufacturing (EP/R032807/1). RAB was supported by the Royal Academy of Engineering under the Research Chairs and Senior Research Fellowships scheme.

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