Modern Advancements in Continuous-Flow Aided Kinetic Analysis

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Abstract

Although kinetic analysis has traditionally been conducted in a batch vessel, continuous-flow aided kinetic analysis continues to swell in popularity. This can be partly attributed to the favourable characteristics of flow reactors and the growth of flow chemistry in general. However, the development of innovative techniques in recent years to obtain more kinetic information using less reaction material, has further accelerated its adoption. These advancements allow faster and more efficient routes to total process understanding, thereby allowing optimum reaction conditions to be identified in process development to maximise product outputs. This minireview documents novel methodologies reported in the recent literature, both to highlight opportunities for their exploitation and to enable further adoption of kinetic analysis in continuous-flow systems in years to come.

1. Introduction

The adoption of continuous-flow chemistry in both academic and industrial laboratories is continuing to transform the way that scientists think about chemical processes, as flow's numerous benefits become realised.[1-3] Enhanced heat and mass transfer,[4-6] safer usage of hazardous chemicals[7] and more precise reagent addition[8-10] are just a few of the attractive properties that are exploited via the use of a flow reactor platform instead of the more traditional batch vessel. However, this technology is not just viewed as a synthesis enabling tool in academia,[11] as there are several cases of its adoption in process development, scale-up and manufacture.[12-14] As building a physical model of a chemical system is often important during the transfer from chemistry research to chemical production,[15, 16] kinetic analysis utilising continuous-flow chemistry is also growing in popularity. This growth is shown quantitatively, in the number of publications containing continuous-flow kinetics studies over the past 15 years, in Figure 1.

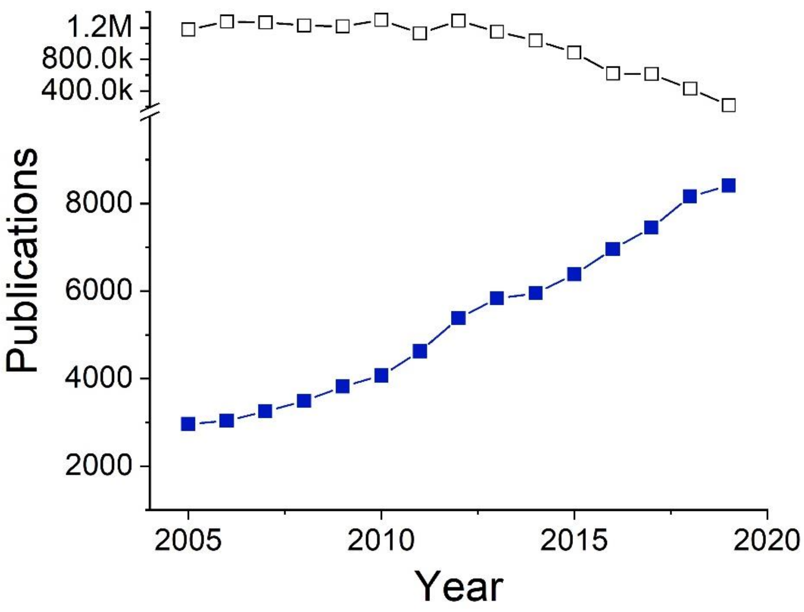


Figure 1: An analysis of Google Scholar publications per year, from 2004 - 2019, where: -■- = publications featuring both strings “continuous flow” and “kinetics”, and -□- = publications featuring the string “chemistry” as a point of reference.

Although stopped-flow techniques have been common for many years in kinetic analysis,[17] it is only continuous-flow kinetics that seem to have experienced this recent growth. This could be for a number of reasons, including: more access to equipment as custom reactor platforms are built,[18] easier experimental study due to the implementation of automated technologies and analytics,[19, 20] or simply because more researchers are engaging with the field of continuous-flow chemistry. In any case, as the number continuous-flow kinetic applications increase, as do the number of novel methodologies to efficiently conduct kinetic analysis.

In all cases, each newly reported technique succeeds in obtaining the desired kinetic information in a more efficient manner than steady-state experimentation, i.e. fewer experiments, less overall cost, faster analysis etc. This minireview will summarise these recent advancements in tubular reactors, specifically exploring new and innovative methodologies that have exploited continuous-flow properties to characterise chemical processes, rather than the individual chemical applications themselves. Kinetic analysis with respect to packed-bed reactors[21-23] and continuous-stirred tank reactors (CSTRs)[24-26] is, of course, also possible but is outside the scope of this paper.

2. Conventional methodology and reactor engineering

There is a long history of conducting and analysing chemical and enzymatic kinetics using continuous-flow, with the first reported case published around 100 years ago by Hartridge *et al.* as a means to study very fast reactions.[27] During this time, many different processes and experimental setups have been reported. A widely regarded essential requirement for kinetic experiments, however, is for the reaction system to operate in a turbulent flow regime.[28] Turbulent flow leads to fast, continuous mixing and can be predicted by calculating the Reynolds number, Re, as shown in eqn. 1, where v = average flow velocity, d = tube diameter, ρ = fluid density and η = fluid viscosity:

$$Re = \frac{vd\rho}{\eta} \qquad \text{eqn. 1}$$

Using the unitless Reynolds number, the flow regime can be predicted to be turbulent[28] when Re exceeds 4000, or laminar[29] when it is less than 2000 - a value between these bounds predicts a transitional regime. These regimes are illustrated in Figure 2a and 2b respectively. Under laminar flow conditions, there is a parabolic velocity profile - meaning that the flow velocity at the centre of the tube is double the average velocity due to friction on the walls of the tubing known as dispersion. This dispersion was originally thought to blur the time axis leading to a substantial distortion of the observed kinetics, and thus meaningful kinetic experiments under these conditions were deemed to be impossible.[30]

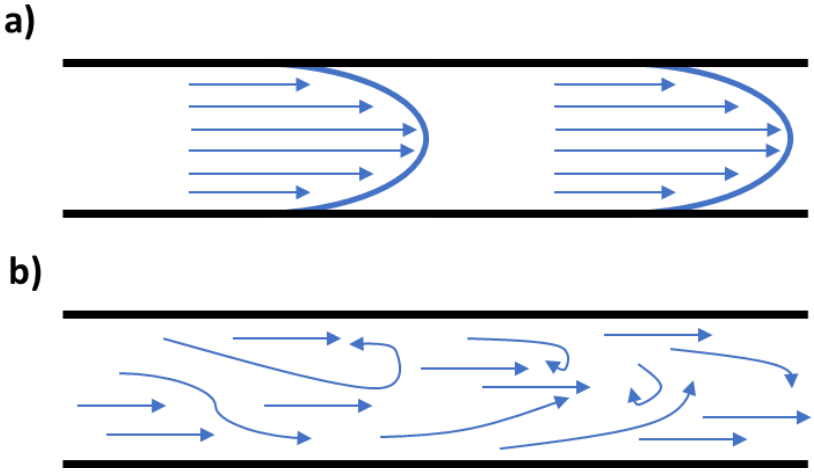


Figure 2: A diagram to show the directions of flows within a flow regime, where: **a)** represents laminar flow and **b)** represents turbulent flow.

Interestingly, these assumptions remained untested until a number of reported kinetics works from the Douglas group showed that accurate kinetic experiments could be conducted under laminar flow conditions.[31-33] The Reynolds numbers for the experiments conducted ranged between 2.8 and 8.5, implying laminar flow. However, the kinetics monitored in these systems agreed very well with results obtained conventionally by stopped-flow methods. Further work suggested that molecular diffusion has a very significant role, and under certain circumstances it can be a good approximation to neglect the effects of laminar flow i.e. for particular flow velocities with given internal diameters.[30, 34] With this approximation, the kinetics can then be analysed as if the tubular flow was homogeneous, which can lead to accurate kinetic studies even in laminar flow regimes.

This is reflected in many continuous flow settings for micro- or meso-flow volumes, as it is typically simpler to adopt an idealised plug flow reactor (PFR) model. This model states that each infinitely thin section of flow, known as a plug, travels in the axial direction of the reactor and is perfectly mixed in the radial direction only, where a uniform distribution of the reactor concentrations occurs.[35] This means that the residence time of the plug is a direct function of the length of the tubular reactor and the velocity of the fluid. This is shown in Figure 3. This model is commonly employed in the literature to simplify tubular mixing and remains an accurate approximation for kinetic measurements.[36, 37]

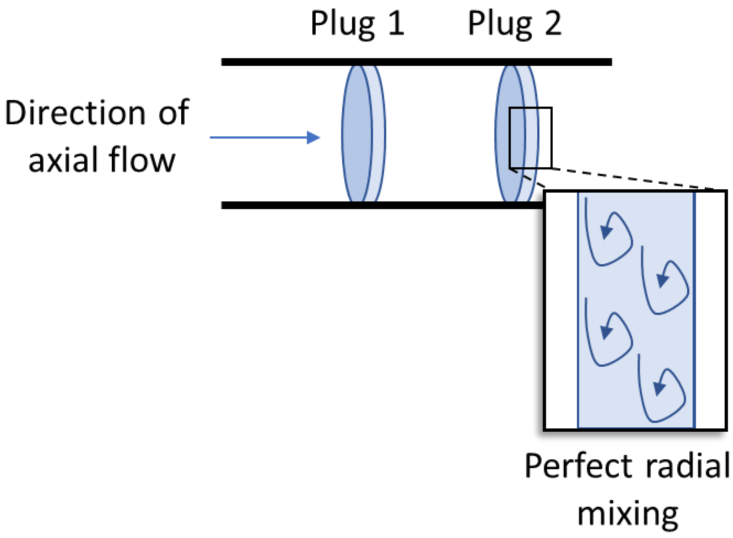


Figure 3: A plug flow reactor model, where there is perfect mixing in the radial direction but no forward or backward mixing in the axial direction. Plugs 1 and 2 are two of an endless number of infinitely short plugs existing within this reactor model.

When conducting kinetic analysis whilst utilising a plug flow model, the general axial dispersion PFR model,[35] shown in eqn. 2, may be used:

$$D_R \frac{d^2 C_i}{dz^2} - u \frac{dC_i}{dz} + r_i = 0 \qquad \text{eqn. 2}$$

Where D_R is the axial dispersion coefficient, C_i is the concentration of species i, z is the length of the reactor, u is the superficial velocity and r_i is the rate of reaction with respect to species i. If dispersion in this system is found to introduce only a small deviation from plug flow,[38, 39] eqn. 2 may be simplified to disregard the second order term, giving eqn. 3 - 5.[40] This PFR equation allows each species in a reaction to be modelled with respect to residence time, τ.

$$u \frac{dC_i}{dz} = r_i \qquad \text{eqn. 3}$$

$$\tau = \frac{z}{u} \qquad \text{eqn. 4}$$

$$\frac{dC_i}{d\tau} = r_i \qquad \text{eqn. 5}$$

With respect to the investigated chemistry, as with reactions in batch, different reactions in flow have different analytical requirements. This means that there are applications of kinetic analysis in continuous-flow utilising many different analytical techniques - including HPLC,[41] NMR,[42] IR[43] and more.[44, 45] When inline process analytical tools (PAT) are used, such as IR, typically a flow cell is placed along the flow path for non-destructive analysis of the reaction medium - this is possible because of the spectroscopic nature of these techniques, which also include UV/vis, NIR, fluorescence etc. As these tools continuously measure the reaction medium, this allows a high data density to be obtained, which can be particularly useful when utilising the flow rate manipulations discussed within this review.[46-50] However, the use of PAT alone for kinetic analysis can be challenging, as there are often multiple interfering components within the reaction medium that result in difficulties obtaining the quantitative information necessary for modelling.[51] These challenges can be overcome in some cases using multivariate modelling,[47] but the high level of expertise necessary for this task results in many researchers utilising online, discrete sampling methods instead.

Online analytical techniques, such as HPLC or GC, typically require much less expertise to gain quantitative information about the flow mixture,[52] which may be more favourable for complex kinetic analysis. As these techniques separate the individual components of the reaction medium, this simplifies the quantification of each species and further allows the researcher more easily identify unintended by-products. As this equipment often requires only simple modifications to be used in conjunction with flow, as well as the general familiarity of chemists with these more common analytical techniques, there are more reported cases of researchers utilising routine online methods for kinetic analysis. However, there are advantages to using both inline and online analysis and researchers must consider many factors including: accuracy of technique, cost, expertise level etc. Utilising both techniques, where possible, can be very beneficial - when multivariate modelling and PAT is used in conjunction with HPLC (or another discrete sampling technique), the PAT data can be normalised to the HPLC concentrations to obtain complimentary information about a process which may be difficult to detect when using discrete sampling alone.[51]

To pragmatically employ these online techniques, without an experimenter manually collecting samples, the flow path must often be diverted to allow aliquot injection into analytical equipment. This can be achieved using a 6-way valve, where a sample is initially loaded into a sample loop, then the valve position is switched to allow the delivery of this reaction medium to the analytical equipment - a schematic of this principle is shown in Figure 4.

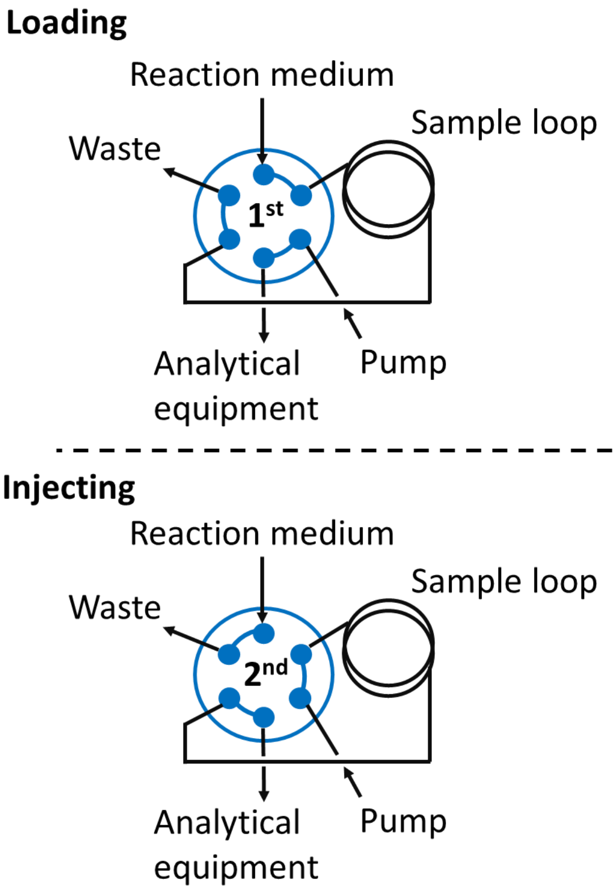


Figure 4: The principle of reagent delivery to analytical equipment, where samples are initially *loaded* into a sample loop in the 1st position, then *injected* by altering the valve to its 2nd position. Figure adapted from Plutschack *et al.*[1]

In any experiment, the frequent commonality across all of these analytical techniques (and in using continuous-flow chemistry more broadly) is that the system must reach steady state before an analytical measurement is recorded. Steady state simply refers to the current state of the reactor, whereby responses from the system are a direct consequence of the conditions applied to it.[38] This is an important distinction because as reaction parameters are changed, a resource cost (i.e. time, material) is then required for those parameters to be realised and applied to the system, thereby achieving a consistent response. This can be very inefficient, as a system typically needs approximately 1.5 - 3 reactor volumes of reagent in the acclimation to steady state, prior to each measurement.[3] This can be expensive as this wastes a relatively large amount of reaction material and time, as the time taken to reach steady state is directly proportional to the residence time required. For example, a 15-minute residence time results in up to a 45-minute wait for steady state to be achieved. In recent years, however, much attention has been devoted to more efficient sampling methodologies to either capture a reaction profile or innovatively derive kinetic information with significantly less waste.

3. Modern kinetic analysis methodologies

3.1 Data acquisition

Deviations from conventional steady state sampling for obtaining reaction profiles began in recent years with a report by Mozharov *et al.*,[53] where the authors outlined a methodology that takes advantage of the transitionary period between two steady state measurements. This is because during this period, transient reaction information is available but is otherwise lost as the reaction is not sampled during this acclimation to the next steady state. However, if the pump flow rates are manipulated to structure this transient data in a way that can be acquired and translated to regular time-series data, then an entire reaction profile can be mapped quickly and efficiently. Therefore, this negates the necessity for multiple steady state measurements and hence significantly reduces time and reaction material costs.

The transient flow method reported by Mozharov adopts an instantaneous step change in the flow rate, where the reaction initially takes place at a low flow rate, F_1, and is then increased by some magnitude to a high flow rate, F_2. This high flow rate then pushes out a transient data profile of the bulk reaction medium, whilst the liquid output is monitored by a sensitive inline analysis technique, for example Raman spectroscopy as reported by the authors. Using this technique, many measurements are taken in short time intervals to generate the reaction profile, from which kinetic information can be derived. This is possible as the residence times can be calculated from known information regarding the magnitude of F_2, the experimental times of the analytical measurements, t_n, and the dimensions of the flow path. This concept is depicted in Figure 5, with the corresponding equation shown in eqn. 6 that is used to convert species concentration in experimental time to the species concentration in residence time, where: t_0 is the time of the step change and t_2 is the experimental time taken to reach steady state:

$$\tau = t_2 \frac{F_2}{F_1} - t_n \frac{F_2 - F_1}{F_1} \qquad \text{eqn. 6}$$

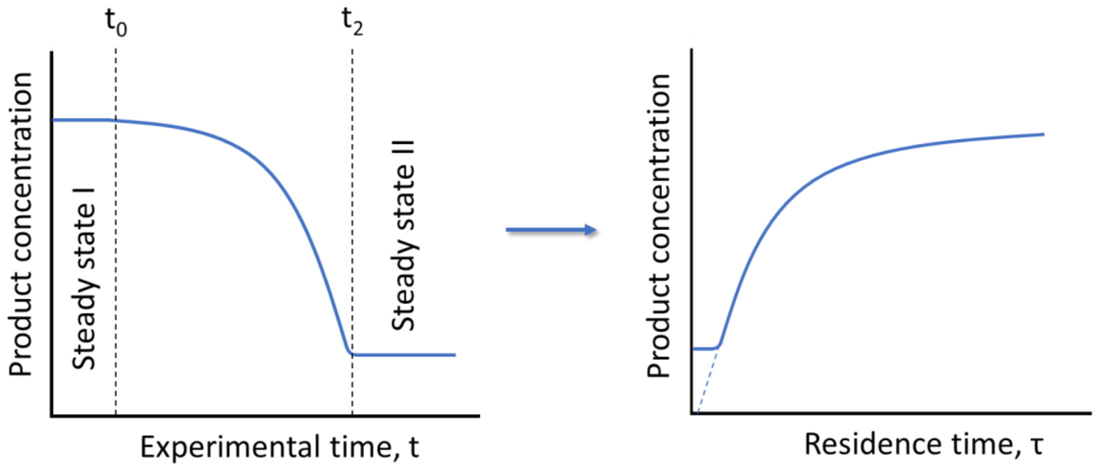
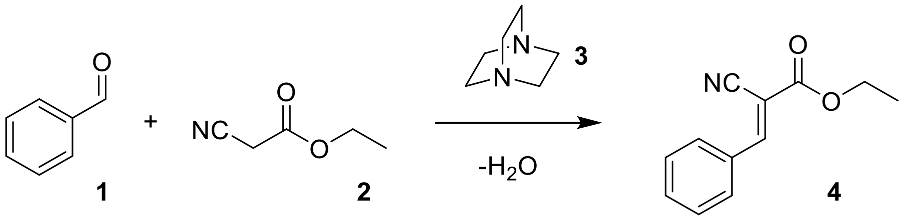


Figure 5: A depiction of how a kinetic experiment can be run utilising a step change in the flow rate between two steady states (I and II), allowing time-series data to be obtained from transient data. Figure adapted from Mozharov *et al.*[53]

This concept was used experimentally by the authors to test the accuracy of the technique in relation to conventional steady state measurements. A base-catalysed Knoevenagel condensation, as shown in Scheme 1, was studied and the corresponding reaction profiles were obtained by both steady state measurements and the described step change methodology. It was shown that the two sets of time-series data (and resulting kinetic parameters) were very comparable and although the step change profile suffered from greater experimental noise, there was a significantly reduced experimental time and reagent consumption cost. The main critique of this technique, as stated in the original publication, is that the step change in flow rate is never perfect as the system always requires time to accelerate to the higher flow rate, therefore the exact function $F(\tau)$ during this transitional period is uncertain. This non-ideality is caused by several experimental factors, such as non-rigidity of the tubing walls and the syringe, preventing an immediate change in both the flow rates and the pressure profile throughout the system.[54]



Scheme 1: The base-catalysed Knoevenagel condensation studied by Mozharov *et al.* to validate the 'step change' methodology.[53]

Moore and Jensen[54] then reported a new concept that involves a controlled ramping from one steady state to another, instead of a step change. This leads to less uncertainty in the determination of the residence times and therefore greater accuracy in the time-series data and corresponding kinetic parameters obtained from the experiment. This report introduces the concept of "pseudo-batch" reactors, referring to each fluid element passing through the flow reactor in a time that is unique, which can be viewed as many successive pseudo-batch reactions. This concept is shown in Figure 6, as pseudo-batch vessels differ in reactant composition as the flow rate decelerates from a short residence time, τ_1 to a long residence time, τ_2. An example flow ramp is also shown in Figure 7, illustrating how the residence time experienced by the reaction medium changes with respect to the declining total flow rate, Q, as the experiment progresses.

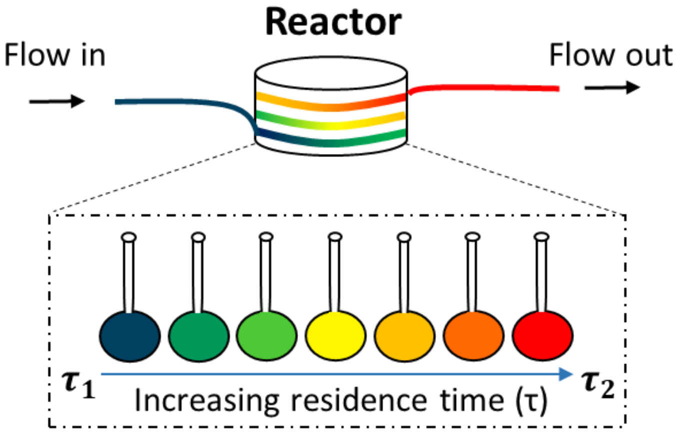


Figure 6: A depiction of how a continuous-flow reactor may be described as a series of sequential pseudo-batch reactors, where the colour represents the extent of reaction conversion from low (blue) to high (red).

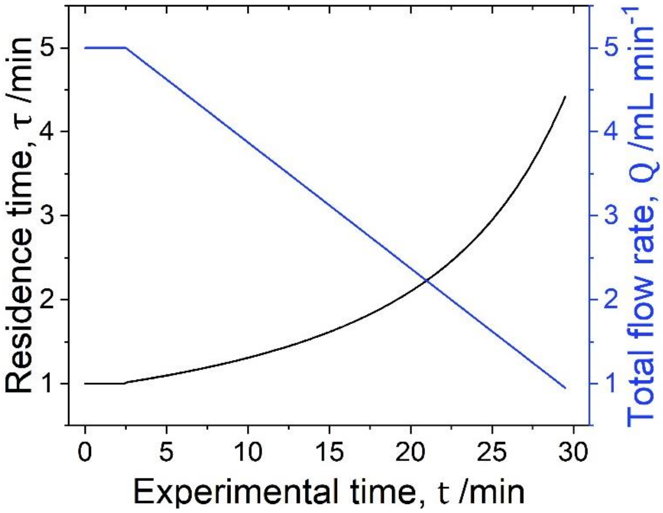
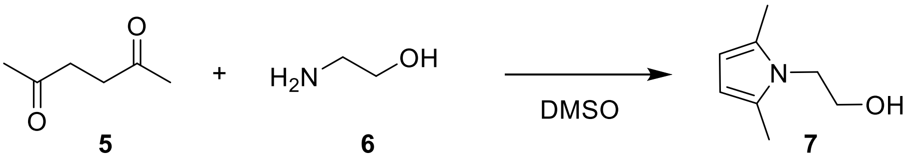


Figure 7: A graph showing the progressive residence time increase (black) as the total flow rate decreases (blue) during a controlled ramp experiment. In this example, the flow rate decreases at a constant rate of 0.15 mL min^{-1} using a 5 mL reactor volume.

The initial case study reported using this method was a Paal-Knorr synthesis (as shown in Scheme 2) monitored by an inline IR probe, where there was a strong agreement in the data sets obtained from ramped and steady state experiments.[54] This controlled ramp methodology results in a more predictable and accurate residence time profile when compared to the step change method, as well as a greater effective sampling rate with a data density 10-fold higher than previously reported. As the analytical time is also decoupled from the residence time, it was shown by Hone *et al.* that 3-minute HPLC methods could be run with only 15 seconds difference in each sampled residence time, which would otherwise not be possible in batch.[38] Since the original publication, controlled ramp experiments have been reported many times in the literature due to their experimental advantages,[50, 55-58] i.e. reduced material consumption, precise and reproducible kinetic profiling, etc.

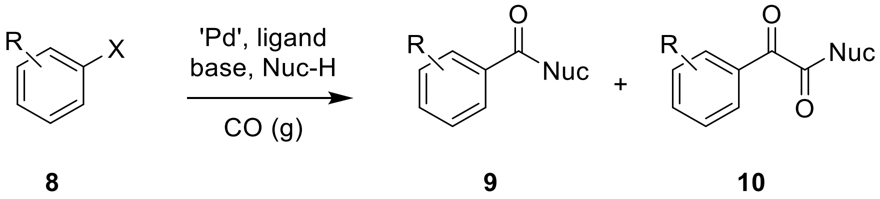


Scheme 2: The Paal-Knorr synthesis studied by Moore and Jensen to validate the controlled ramp methodology.[54]

To calculate the residence time of the fluid element at any time during the controlled ramp experiment, eqn. 7 is used, where: α is the deceleration of the flow rate, μ_0 is the initial flow rate and L is the reactor volume:

$$\tau = \frac{\alpha \cdot t_n - \mu_0 + \sqrt{(\mu_0 - \alpha \cdot t_n)^2 + 2 \cdot L \cdot \alpha}}{\alpha} \qquad \text{eqn. 7}$$

Following this publication, Moore *et al.* also reported a new methodology targeting transient temperature ramping.[59] This concept was applied to several aminocarbonylation reactions (shown in Scheme 3) where the pump flow rates were held constant and the reactor temperature was ramped from 80 °C to 120 °C. This demonstrated that activation parameters could also be obtained from transient flow experiments whilst affording the same benefits, i.e. reduction in time and reagent consumption, with comparable kinetic parameters to steady state measurements.[47]



Scheme 3: The general reaction scheme reported by Moore *et al.* for the validation of the transient temperature methodology - six reactions were conducted to identify substrate scope compatibility.[59] X = Cl or Br, R = CN, Ph or MeO.

A subsequent methodology then sought to maximise the efficiency of kinetic experiments by combining both residence time and temperature ramps in continuous-flow. Aroh and Jensen were the first to report this approach using the Paal-Knorr cyclocondensation reaction shown in Scheme 2 as a benchmark, where the residence time was ramped from 0.5 to 20 minutes and the temperature was ramped from 40 °C to 100 °C simultaneously.[60] The method was validated against multiple residence time ramps at discrete temperatures and there was found to be a very good agreement in the resulting kinetic analysis, albeit with a significant decrease in reagent consumption. The methodology has also been replicated in the literature by other groups for their own kinetic studies,[61, 62] and has recently been adapted by the use of sinusoidal-shaped controlled ramps for efficient explorations of the chemical design space.[63] As before, a PFR model is employed to enable typical residence time calculations using eqn. 7 for controlled ramps, alongside eqn. 8 to determine the temperature of each fluid element, where: $T_{j,0}$ is the initial temperature experienced by the chemical species j, b is the ramp rate, τ_j is the corresponding residence time and t_f is the time that the fluid leaves the reactor:

$$T_{j,0} = T_0 + b(t_n - \tau_j - t_f) \qquad \text{eqn. 8}$$

Another exciting advancement in reaction profiling in continuous-flow was reported recently by Sullivan and Newman, where a discrete reaction slug is continually sampled as it cycles around a reactor system.[64] A reaction slug is cycled around a figure-eight path, accomplished through the repurposing of two multi-port valves and a carrier stream (e.g. N_2), as the flow path is continuously manipulated to keep the slug within the closed-loop system. This concept is shown in Figure 8, as the valves may be in one of two alternating positions to circulate the slug within either heated reactor coil. As the slug is exiting Coil A, the valves are in the 1st position to ensure that the slug is redirected to Coil B rather than waste - the opposite is then true as the slug exits Coil B, as the valves are then in the 2nd position meaning that only the carrier it purged to waste. Figure 9 then shows how sampling of these reactor cycles represents reaction profiles. This methodology was proven in several case studies with different classes of reaction, each performed with 300 µL circulating slugs, representing a drastic improvement in efficiency over traditional kinetic experimentation in both flow and batch.

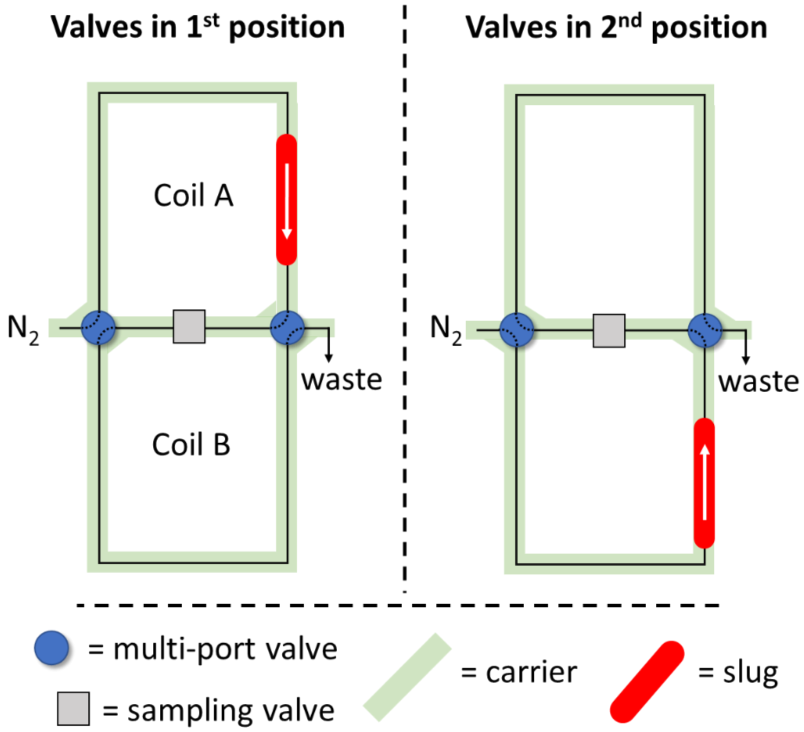


Figure 8: A schematic of the reactor coils and valves used to sample a discrete, cycling reaction slug. The valves alternate between two positions to maintain the slug within the closed-loop system. Figure adapted from Sullivan and Newman.[64]

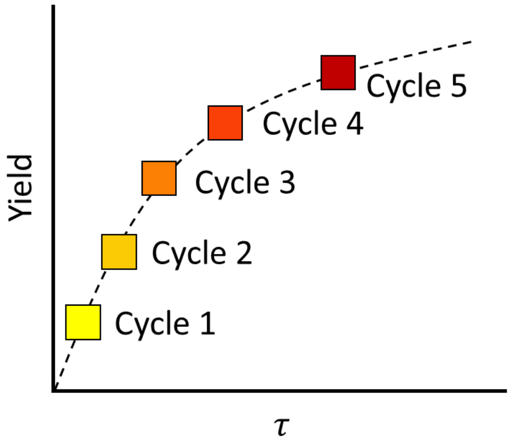


Figure 9: A schematic showing how each reactor cycle sample can be related to residence time, hence describing a reaction profile. Figure adapted from Sullivan and Newman.[64]

As each of these methodologies differ in their reactor setup (and cost), experimental accuracy and expertise necessary to conduct, careful consideration must therefore be taken when deciding on which technique to employ. The structure of the resulting data should also be a consideration for the subsequent kinetic analysis, meaning that some methods may be more favourable depending on the requirements of the experimental campaign, such as: concentration-time data, concentration-temperature data etc. Expertise barriers may also be a hinderance for researchers, as engineering/coding principles are still necessary to build these bespoke platforms even when construction information is provided in the original publications. For these reasons, there is not a singular 'best' solution as different research groups and organisations may prefer to employ different methodologies depending on their capabilities or desired experimental outcomes. For many of these common practical considerations, the continuous-flow techniques covered in this minireview are qualitatively evaluated in Table 1.

Table 1: A qualitative comparison of the continuous-flow techniques reported.

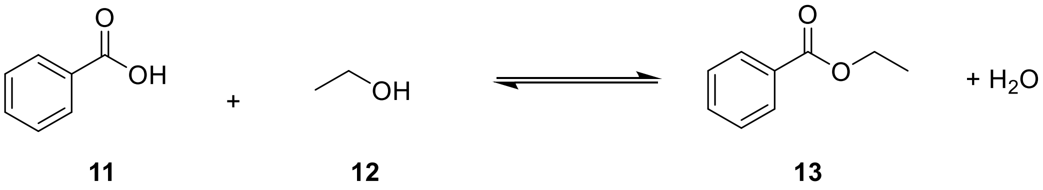
Technique	**Experimental accuracy**[a]	**Material consumption**[b]	**Equipment cost**[c]	**Expertise barrier**[d]
Steady-state kinetics	-	High	Low	Low
Step-change	Low - med	Med	Low - med	Low - med
Controlled ramps	High	Med	Low - med	Med - high
Reaction cycling	High[e]	Low	Med - high	High

a: Accuracy is relative to the high continuous-flow accuracy expected from steady-state kinetics. b: Relative chemical material consumption required. c: Relative equipment costing based on bespoke flow platforms including pumps, analytics, computation etc. d: Relative expertise barrier necessary to overcome, relating to engineering and coding difficulties. e: Based on one literature report.

3.2 Tandem experimentation and analysis

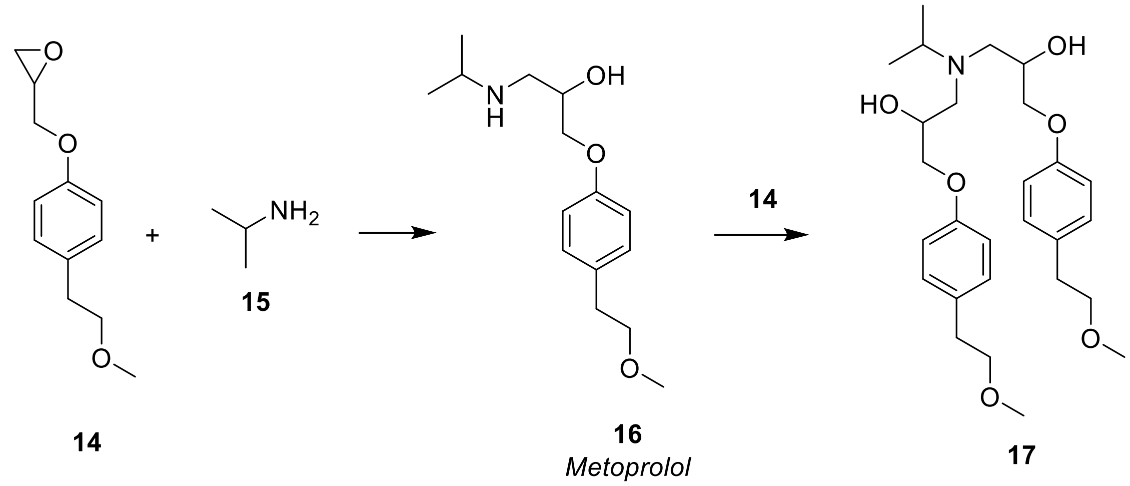
Often, kinetic analysis can be performed using reaction data obtained from continuous-flow in the same way as batch. The modelling of chemical processes using flow reactors has been reported in many ways, including the use of: reaction progress kinetic analysis (RPKA),[65, 66] variable time normalisation analysis (VTNA),[67] kinetic analysis software (such as Compunetics)[68] and other specific custom-coded solutions.[69, 70] However, alongside aforementioned experimental benefits, continuous-flow platforms also enable the unique use of automatable kinetic analysis to interpret results - this analysis may be performed sequentially or in tandem with experimentation. This reduces the time cost associated with gaining process understanding and, in some circumstances, can lead to a reduction in material consumption by utilising targeted experiments instead of obtaining full reaction profiles.

One of the most commonly reported methodologies, where targeted experiments are utilised to perform kinetic analysis, is in model-based design of experiments (MBDoE). MBDoE is a technique in which an underlying model is used to suggest candidate experiments based on a prediction of information gain for the next experiment.[71] Models are constructed using *a priori* knowledge of the chemical system often leading to a set of candidate models for which elucidation of the optimal model and associated parameters is required through iterative experimentation. The fitting routine involves the internal optimisation of an objective function to select the next optimal experiment(s). Depending upon the selected objective function, experiments are suggested for either parameter estimation or model discrimination.[72] The utilisation of this technique in flow chemistry is well established with many examples, with applications for both homogeneous and heterogeneous kinetic motif identification.[73-75] The methodology is very effective in conjunction with automated reactor platforms, with the closed loop nature of such autonomous control systems coupled with online analysis aiding in efficient experimentation. More recently, the approach has also been applied to the design of transient experiments, using a benzoic acid esterification case study shown in Scheme 4.[61] Utilising the transient regime allows access to a high information density predominantly seen in batch kinetics, alongside the mass and heat transfer benefits associated with flow experimentation. Furthermore, with the avoidance of steady state measurements, significant savings can be made in terms of material consumption and time.



Scheme 4: A benzoic acid esterification reaction explored in a recent MBDoE study by Waldron *et al.*, utilising transient experiments in their data acquisition.[61]

Novel sequential kinetic analysis techniques have also been reported in continuous-flow. Transient flow regimes have been exploited in consecutive data acquisition and modelling processes, where kinetic information from reaction profiles is autonomously interpreted after collection. Our group recently reported the integration of a chemical reaction network (CRN) identification tool[15] with a continuous-flow platform, where every feasible reaction model was constructed and evaluated based on their respective suitability to the experimental data.[40, 76] This methodology was used to determine physical model information for the formation of the cardioselective beta blocker, Metoprolol, as shown in Scheme 5. This study was found to be 24 % cheaper than steady-state kinetic experiments and 106 % cheaper than traditional design of experiments approaches to identify kinetic information, when considering material consumption alone. Fath *et al.*[77] also reported recently the coupling of flow ramp methodologies with various ‘soft-modelling’ and ‘hard-modelling’ approaches, providing a flexible framework for the screening of spectroscopic data and determination of reaction kinetics.



Scheme 5: A reaction explored in a recent sequential transient flow-CRN determination study by Taylor *et al.*, to optimise the formation of the Metoprolol product, **16**.[40]

When considering the use of these methodologies, it is also important to factor in the cost of the time of the chemists and engineers running the experiments (which would be automated) and the time cost for the interpretation of the data by scientists and statisticians (which these approaches remove). Upon consideration of these factors, alongside the much lower material consumption, this results in a significant reduction in labour, time and overall cost.

4. Conclusion

The use of continuous-flow reactor platforms to conduct kinetic analysis in recent years has yielded very exciting results. This minireview has highlighted the many innovative techniques that research groups have reported to achieve scalable process understanding in more efficient and novel ways than conventional steady-state reaction profiling. These methodologies consistently succeed in obtaining more reaction information from less reaction material, and the favourable reactor properties when compared to batch (i.e. greater heat and mass transfer, precise reagent addition, automation etc.) may continue to increase the uptake of continuous-flow aided kinetic analysis in the coming years. We envisage that the further adoption of flow reactor platforms in the age of Industry 4.0[78] will lead to more innovation in chemical manufacturing and allow a multitude of kinetic analysis techniques in process chemistry to proliferate.

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