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Enabling Technologies in Polymer Synthesis: Accessing a New Design Space for Advanced Polymer Materials

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Abstract

This review discusses how developments in laboratory technologies can push the boundaries of what is achievable using existing polymer synthesis techniques. By making advances in reactor design, online monitoring and automation it has been possible to accelerate polymer discovery while achieving enhanced precision, reproducibility, safety and sustainability. It is hoped that gaining a broad understanding of what is achievable using new technologies will encourage a step-change in the way the polymer chemistry community approaches some aspects of research. This will hopefully open a new design space for the next generation of polymeric materials.

Introduction

Since their discovery in the mid-1900s, polymers have revolutionised the way we design and manufacture products, and as a result we encounter them every day. The most obvious applications of polymers are within packaging, construction or textiles, but they are often present in many other forms such as consumer or industrial formulations (e.g. cosmetics, pharmaceuticals, detergents, lubricants, agrochemicals). In these higher value applications, there is scope for enhancing the performance or optimising for a specific target application by changing the molecular structure of the polymer chains themselves. This could include accurately tuning molecular weight, adding functional groups or making copolymers, where more than one monomer is copolymerised within the same chain. Indeed, when developing polymers designed to mimic biological macromolecules the sequence of a diverse group of monomers is crucial, and requires careful strategic assessment.[1,2] Control over the molecular weight distribution (often quantified using molar mass dispersity, *Đ*) is also extremely useful, since it can affect thermal and physical properties of the subsequent polymer, from thermal transitions and mechanical properties[3–7] to complex phase behaviour such as block copolymer self-assembly.[8,9]

In most cases, the control over polymer structure has been achieved through modification of the underlying synthetic chemistry. Perhaps the most important advance was by Szwarc in 1956, who demonstrated that by using anionic polymerisation, it was possible to synthesise polymers with defined molecular weight and extremely low molar mass dispersity.[10] This still provides unrivalled precision and the ability to achieve molar mass dispersities of as low as 1.01. It also enables production of defined polymer architectures including multiblock copolymers, star (co)polymers, bottle-brush copolymers, and cyclic polymers.[11] Unfortunately, the stringent conditions required combined with limited monomer compatibility considerably restrict its utility. Conversely, free radical polymerisation (FRP) requires much less stringent conditions, is tolerant to a wide range of functional groups, and can be carried out in water.[12] These characteristics have contributed to it being one of the most useful polymerisation processes industrially, where it is currently utilised for production of most polymeric materials used today. A significant issue with traditional FRP is that there is little control over molecular weight and molar mass dispersity, but in the last thirty years, reversible de-activation radical polymerisation (RDRP) methods have been developed which can produce well-defined (co)polymers bearing a broad range of functionalities given the tolerance to many functional groups (amines, alcohols, carboxylic acids). Most notable of these are nitroxide mediated polymerisation (NMP)[13,14], atom transfer radical polymerisation (ATRP)[15] and reversible addition fragmentation chain transfer polymerisation (RAFT).[16,17] Alongside these radical techniques, non-radical polymerisation are (re)gaining popularity, such as ring opening polymerisation (ROP).[18] Furthermore, adaptation of techniques to produce specific polymer nanomaterials such as via polymerisation-induced self-assembly are commonplace.[19] The initial generations of these methods (ATRP, NMP or RAFT) relied upon addition of some species which made them unattractive for some applications, but recent advances have eliminated or significantly reduced the reliance on such species or made them much more accessible (e.g. oxygen tolerance, photoinitiation or metal catalyst/sulphur removal).[20–22]

Despite the increasingly complex chemistry, laboratory techniques have not changed significantly; most experiments are still conducted in the flasks and glassware that have been used for decades. There is less of a focus on using non-chemical means of tailoring synthetic polymer chemistry. Herein, we present a review of how novel technologies have been utilised to expand the capability of various chain polymerisation techniques. These often follow key trends, but there needs to be strong justification for the often-significant disruption that may result from the adoption of new technologies.

Perhaps the most universal trend in the sciences and beyond is that towards sustainability and green chemistry.[23–25] Several different considerations are required and are discussed at length by Anastas and Warner in their seminal work.[23] One potential area is the energy efficiency of the chemical process – such as the driving force of the reaction (e.g. temperature, radiation) and subsequent workup. Clearly the origin of the reactants and the synthetic route selected are also important – though investigation of alternative methods can itself consume significant resources. The process of scale-up for novel processes (including any that may be considered for “greener” reasons) also warrants consideration – the initial discovery/synthetic process can influence how much work may be required to develop an effective final process.

There is also a drive to accelerate the discovery of new products and materials, which is often labour and cost intensive, but as technology develops, it is becoming clear that the traditional model for discovery may be improved by using high-throughput screening platforms.[26–29] It is rarely possible to simply take an existing reactor technology and use it in such a platform, nor is a large library of materials useful, if high-throughput analysis cannot be performed. Furthermore, by their very nature, there must be at least some aspect of automation in order to improve on the standard throughput that might be obtained by a researcher alone.

Reproducibility is also a key challenge across science – the reduction of user error and sample-to-sample variation could increase the efficiency of process optimisation and material discovery. User error might lead to the incorrect elimination of a particular experiment in a screening situation, and therefore lead to selection of sub-optimal solution. A mistake may also lead to the need to repeat a complex and/or expensive process. Even where user error is not present – the very nature of chemical processes mean that should conditions be affected by outside influences (e.g. slight leaks to atmospheric gases, temperature fluctuations), then reproducibility will be compromised. Technologies that facilitate consistency in conditions and experimental procedures, or, equally, highlight where consistency of conditions is lacking will help in improving reproducibility.

Precision in polymer synthesis is also something chemists are always striving to improve. The application of polymers in biomedical and biomimetic applications often require stringent control of polymer structure.[1,30] It can be extremely painstaking to deliver this control using wet chemistry and very work-, cost- and energy- intensive. Furthermore, this precision is even more difficult to maintain where larger scale syntheses are required.[2]

Another area where there is a constant drive for improvement is the safety of chemical processes – seen not only in a general trend, but in legislative developments also. Chemical processes may be disregarded due to health and safety considerations – particularly where large volumes are used. A particular feature of polymerisations is their often highly exothermic nature – which can disrupt isothermal conditions, adversely affecting polymerisation control.[31] Better control of these exotherms can allow us to revisit chemistries previously considered too dangerous to conduct on a useful scale.[32]

The variety of technologies available to the synthetic chemist is vast. From the range of analytical techniques to monitor chemical processes to reactor assemblies, the traditional model of “make-then-test” is becoming increasingly rare. In this review, we highlight three key areas where we anticipate new technologies will bring and indeed are bringing about new opportunities for polymer design and synthesis: (i) Novel reactor design: which may enable better delivery of reactants, better control of reaction time or improved control of conditions. (ii) On-line analysis: which gives real-time information on the process meaning conditions can be tuned 'on the fly'; and (iii) Automation: where events such as delivery of secondary payloads (e.g. a second monomer) might be triggered at a precise time-point; or where machine-learning type algorithms combined with feedback loops mean reactors can self-optimise to produce a product with defined properties without human interaction. We hope this will provide a toolkit for scientists active in polymer chemistry to develop innovative syntheses and processes.

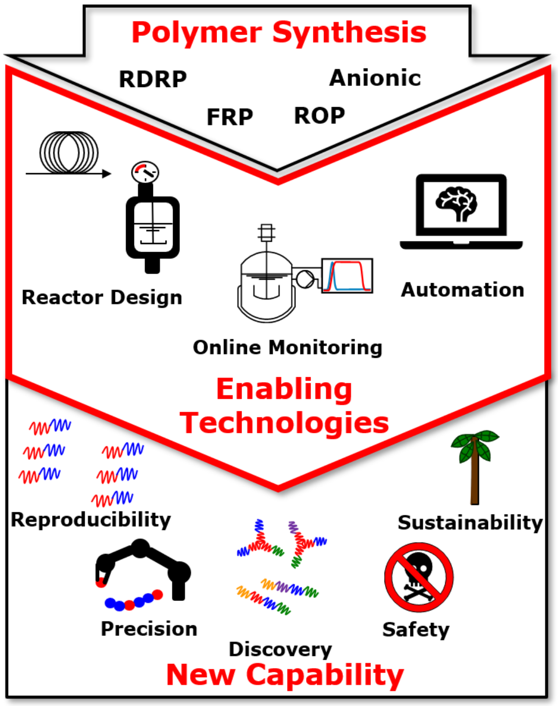

Figure 1. Diagrammatic representation of how enabling technologies represent an opportunity to develop novel polymeric materials.

Reactor design

Traditional lab scale chemistry has generally been performed using glassware such as a round-bottomed flask, which is then charged with all the required components and a stimulus for reaction applied (most often heat). Changing reactor configurations has then typically been conducted to suit scale-up, where commercial jacketed vessels equipped with overhead stirrers are used. Recently, modifying reactors to suit specific processes on the small scale has become more commonplace when aiming to access more challenging conditions.

With industrial utility for many years for many common polymers (e.g. polyethylene/polypropylene synthesis), pressurised reactors are now also widely used on a laboratory scale for more specialised polymerisations. For example, there are numerous reports of controlled and free radical polymerisations in supercritical carbon dioxide ($scCO_2$) such as the synthesis of PMMA-based microparticles (Figure 2).[33–37] One key advantage of this approach is the $scCO_2$ solvent can easily be removed by returning the vessel to standard temperature and pressure. Supercritical fluids in pressurised reactors can also be used in post-production modifications such as polymer foaming.[38] Pressurised reactors also enable the polymerisation of gaseous monomers such as vinylidene fluoride, which can be polymerised by organometallic-mediated radical polymerisation.[39] The resulting poly(vinylidene fluoride) based polymers have high value applications in aerospace and aeronautical engineering, which offsets the costly nature of the reactors under these operating conditions. Pressurised reactors also offer utility in achieving ultrahigh molecular weight polymers by controlled radical methods.[40,41]

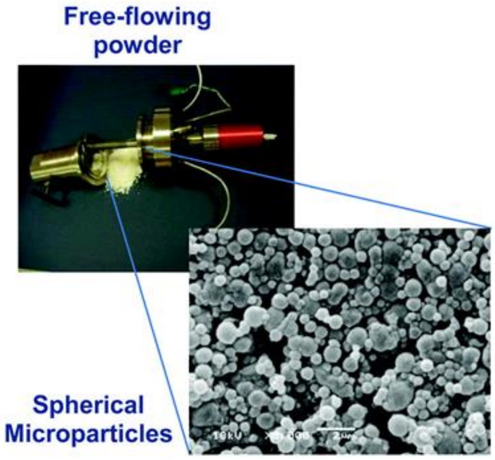

Figure 2. High pressure reactor used for synthesis of spherical polymer microparticles in scCO2. Adapted with permission from Jennings *et al*.[37] Copyright 2012 American Chemical Society.

Microwave reactors use microwave radiation to stimulate chemical reactions. Due to enhanced heating, this can result in increased reaction rates for polymerisations and have comprehensively been reviewed by Sinnwell *et al*. and Kempe *et al*.[42,43] Successful polymer syntheses have been achieved with RAFT[44], ATRP,[45,46] NMP,[47,48] and more conventional FRP[49,50]. Indeed, in many cases increased rates are observed with little or no degradation in the quality of polymer produced.[44]

Continuous reactors are a key technology in reactor design. They have been used extensively in industrial applications for decades but have been much rarer on the laboratory scale – generally only utilised when designing/optimising a process later to be used industrially.

Table 1. Comparison of benefits offered by batch and continuous methodologies, with summarised impacts upon polymer synthesis (red).

Continuous Process	**Batch Process**
Uniform conditions – More consistent conversion and molecular weight	Low barrier to entry – easy access to wide range of polymerisation techniques
Multi-scale – upscale to manufacture easier	Less susceptible to complete system shutdown – high viscosity/polymer clogging not an issue
Heterogeneous catalysis – easier integration to techniques such as ATRP	Single residence time – broader residence time distributions can lead to broadening of molecular weight distributions
Integration with online analysis/automation – Effective monitoring of conversion/molecular weight information	Efficient mixing – can handle complex heterogeneous systems requiring shear
Safer – reduced impact of exotherms	

Drawing a comparison between continuous (or flow) and batch methodologies can help to explore potential drawbacks associated with traditional methods, as well as opportunities that continuous processes may offer, and the costs associated with that (see Table 1 for a simplified treatment). Flow methods have been demonstrated for a whole host of polymerisation reactions, with the benefits of using flow reactors demonstrated for a wide range of chemistries. A key advantage of using flow in general is the reproducibility of conditions and reduced human interaction. A commonly used flow reactor is the tubular reactor which is simply a tube subjected to reaction conditions (e.g. heat/light) through which reactants are flowed – the reaction time is simply the amount of time the reactants spend in that tube; the so-called “residence time”. Early examples of flow polymerisation date back to the 1950s and 60s, including the synthesis of block copolymers via photoinitiated FRP in a photo-flow glass tubular reactor[51] and the anionic polymerisation of styrene by Szwarc and co-workers, whereby the flow method used facilitated kinetic investigation of the incredibly fast reaction (Figure 3a).[52]

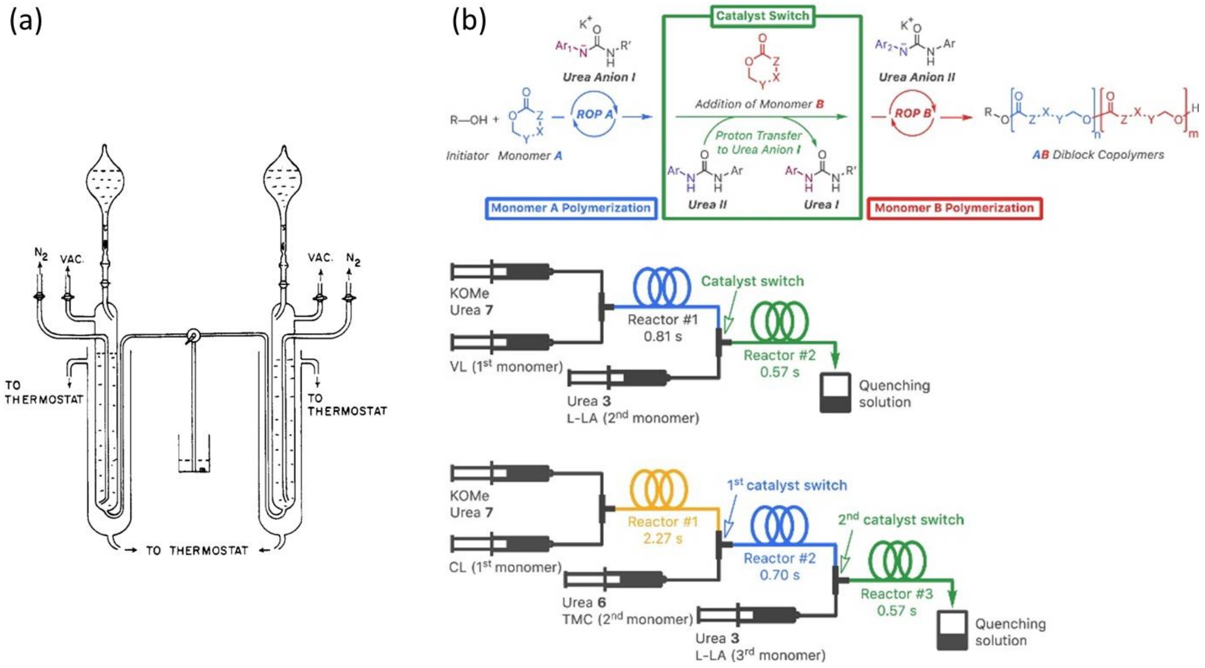

Figure 3. (a) An early report of a flow method to monitor the kinetics of the anionic polymerisation of styrene in 1962 (Adapted with permission from Geacintov *et al*.[52] Copyright 1962 American Chemical Society) (b) State-of-the-art telescoped continuous-flow block copolymer synthesis via ring-opening polymerisation (ROP) with catalyst switch. (Adapted with permission from Lin et al.[28] Copyright 2019 American Chemical Society)

The continuous stirred tank reactor (CSTR) and the tubular reactor represent the two most commonly used flow reactors, and both offer a range of advantages. With a constant flow of material in and out of both, the need for reactor downtime associated with batch methods (i.e. time between batches) is removed. Furthermore, if conditions are maintained (referred to as steady-state conditions), then the properties of polymer produced will be consistent. The key difference between CSTRs and tubular reactors lies in the so-called residence time distribution (RTD). Whereas (theoretically) all material emerging from a tubular reactor has spent the same amount of time in the reactor, there is a significantly wider distribution associated with CSTRs – since there is no set path for reactants to take. This leads to a much broader molecular weight distribution (MWD), since material can be reacting for significantly different times.[53] A full treatment (including a detailed discussion of RTDs) with examples of polymerisations performed in different reactor configurations can be found in the review of progress in reactor engineering of CRP by Zhu and co-workers.[53] While some literature exists for CSTRs, it is tubular reactors on which the bulk of research effort is focussed – perhaps due to the RTD more closely reproducing that obtained with batch.

Regardless of polymerisation type, one way in which enhanced control is afforded by continuous techniques is that the addition of different reactive components can easily be adjusted (in terms of both sequence and rate). With roots in semi-batch methodologies, where a monomer feed may be introduced to bias the sequence of a polymer chain,[54] continuous processes allow for near-unlimited combinations of feedstocks, an example of which is telescoped reactors (such as that shown in Figure 3b). Telescoping has been used to allow sequential insertion of blocks for block copolymers[55,56], or chemical modification of synthesised polymers[57], and to enable real-time analysis through dilution and sampling.[58] Furthermore, inventive injection routines, such as tube-in-tube injection for synthesis of gradient copolymers,[59] or re-cycling through the reactor to tailor MWDs[60] demonstrate that the possibilities are not only limited to what might be achieved by sequential addition to a flask. The construction of flow-reactors also offers opportunities for attempting processes which would otherwise be extremely laborious in batch, for example Lin *et al.* prepared block copolymers via ring-opening polymerisation which involved a telescoped catalyst switch to ensure optimum conditions for each monomer (Figure 3).[28]

Much of the foundation for current flow polymerisation technology is based upon thermally initiated systems. The thermal transfer is excellent for tubular reactors due to the high surface area-to-volume ratio and can result in faster reactions that are much less likely to be adversely affected by exotherms. A renaissance of work in this area began in the mid-2000s and spans a range of techniques including ATRP – described in work by Hutchinson and co-workers[61–64] – and RAFT – with the homopolymerisation of NIPAM,[65] acrylate multiblock copolymer synthesis,[66] and a series of work by Hornung and co-workers, showing variation of the monomer/initiator/RAFT agent used,[67] block copolymer synthesis,[68] and inline workup and analysis.[57,69] Ring opening polymerisation has also been used extensively in flow (it is worth noting that since the mechanism relies upon a catalyst, thermally initiated is perhaps a misnomer since reactions will often take place at room temperature).[70] Early examples include the polymerisation of N-carboxy anhydrides[71] and ring-opening multibranching polymerisation of glycidol.[72] Since then, as is the case for many polymerisation types, more complex applications have been demonstrated, such as that already discussed and shown in Figure 3b.[28] Literature for the similarly named ring opening metathesis polymerisation (ROMP) is much more sparse and recent; only a single paper showing the polymerisation of norbornene derivatives.[73] Finally, anionic polymerisation has also been demonstrated, from work in the 1960s[52] to use of more modern continuous reactors.[74–76]

Tubular and microfluidic reactors comprised of transparent material also present a particular opportunity for light-induced polymerisations since they allow for much more thorough irradiation of the reaction mixture due to reduced path lengths relative to batch reactors.[77,78] Successful photo-polymerisations have been achieved using both RAFT[79–81] and a range of ATRP-based techniques.[77,82–84] Recent developments in this field have included the successful synthesis of a range of morphologies by PISA,[80,81] and the tailoring of molecular weight distributions.[85,86] The extent of this improvement was demonstrated when the methodology was shown to increase the rate of a PET-RAFT dispersion polymerisation, where the formation of nanoparticles presented an additional barrier to the light irradiation.[80] Photopolymerisation has also been used with microfluidics for carefully controlled particle synthesis of varied shapes and sizes,[87,88] and increasingly complex particles such as Janus particles.[89] The insertion of photo-curable monomers/oligomers into a flowing immiscible liquid, followed by irradiation is the basis for achieving this control – and such particles could find use in some high-value applications such as drug delivery.[90] Further details regarding important considerations for photopolymerisation in flow can be found in related reviews.[78,91,92]

Heterogeneous catalysis is a technique that is also suited to use with flow syntheses, since the catalyst can be supported within the flow reactor.[93,94] This means that no workup is required to remove the catalyst, and the high surface area to volume ratio associated with flow reactors can be exploited to give a high catalytically active area without the need for the challenging preparations that can often be required for batch-based catalysis. A range of polymerisations have been successfully performed using supported catalysts, particularly Cu-based living radical polymerisation (LRP) systems.[95] This concept has been developed further with creative concepts such as using copper tubing as the reactor material, which also then acts as the catalyst.[63,96] Similarly, copper wire threaded down a flow reactor has been shown by Haddleton and co-workers to perform as an effective catalyst in single electron transfer (SET) LRP.[97] Copper mesh has also been used in a tubular reactor, in order to increase catalytic surface area which resulted in increased monomer conversion when compared to using copper tubing.[96] An example of further innovation in this area is immobilisation of a porphyrin based photocatalyst upon a cotton thread which enables the use of this catalyst for photopolymerisation in otherwise incompatible solvents.[98] Immobilised enzymatic catalysts have also shown improvements upon batch systems – with much improved reaction rates and end group fidelity for the ring-opening polymerisation of ε-caprolactone.[99]

The scalability of flow reactors is a much-documented benefit when contrasted to batch processes, whether by expansion of the reactor volume, or by simply running multiple reactors in parallel (often termed 'scaling out').[100–102] In contrast, scaling a batch process can be hampered by a range of issues – whether exotherms, inhomogeneities, challenges related to impurities or atmospheric gases. This enhances the green credentials of flow by eliminating several challenges associated with batch scale-up. It also allows for initial investigations and research to be performed on a smaller scale (down to milligram scales).[103,104] In terms of benefit to the user, with the reduction in material used there is an obvious reduction in cost, and ultimately less wastage of materials within screening experiments. Chip-based microreactors offer the greatest material savings, operating at the microlitre scale, and have successfully been used for ATRP[84], RAFT,[103] anionic polymerisation[76], ROP[105], click BCP synthesis.[106] Smaller scale tubular reactors also offer material savings, though the reactors are of the order of millilitres, rather than microlitres. These slightly larger reactors (which are sometimes still referred to as microreactors in the literature), have also been used for a whole range of polymerisation reactions – such as ATRP[77], RAFT[32,56,67], FRP[107] and anionic[74,75] based systems. There are methodological adjustments that can also be made to save material while working with flow systems, such as measurement of kinetics by a transient method, which drastically reduces the amount of material needed compared to traditional steady state methods.[108,109]

Clearly, for all the opportunities offered by continuous flow, there will be a range of challenges presented by adapting to a new methodology. One of the first major considerations is the RTD of material in the reactor.[110] On a laboratory scale, researchers generally strive towards ideal 'plug flow' whereby motion of material in the flow reactor is perfectly uniform in the direction of flow. This is not a realistic prospect – there will always be at least diffusive mixing and laminar flow. These both lead to a broadening of the range of residence times experienced by the material emerging from a continuous reactor. This can have a measurable influence on the properties, which can be exacerbated as reactors are scaled up. The effect can be characterised by a broadening in molar mass dispersity, as observed by Reis *et al.*[111] However, it is important to note that changes in reactor design can reduce effects. The use of microflow reactor chips with extremely narrow channels can minimise the RTD width to the extent that it has no effect; leading to near-ideal flow properties which in turn leads to narrower molar mass dispersities than equivalent batch polymers.[66] It follows that simple adjustments such as reducing tubing diameter, reducing the viscosity of the mixture or increasing the residence time can narrow the RTD, and therefore, the MWD. An alternative strategy where diffusive mixing is causing observable differences, is the use of "droplet flow", where compartmentalised slugs of liquid are segregated by either an immiscible liquid or inert gas.[86,111] This mode of flow results in recirculation of material within individual droplets, leading to improved mixing, as shown by Corrigan *et al.* achieving well defined polymers with a faster rate and lower dispersity (compared to batch) using PET-RAFT.[112] Upscaling of the process is also discussed in this work.

Other improvements in mixing (resulting in an improved polymer produced) have been achieved by adjusting the reactor geometry, from patterning of micro-reactors,[74] to re-configuring a standard tubular reactor. Simply changing the layout of the tubing from a standard coil to introducing 90° step changes in geometry at set intervals along the reactor led to a decrease in the dispersity from 1.53 to 1.39 of poly(2-(dimethylamino)ethyl methacrylate synthesised by ATRP.[113] Mixing at junctions is important, where various commercial mixers and custom mixing devices, such as packed beds have been compared.[114] Flow speed upon mixing has also been shown to influence self-assembly behaviour of block copolymers.[115]

Reactor fouling, where solid polymer accumulates within the reactor is another considerable issue often encountered in flow. Apart from the obvious risk of blockages, this can also significantly affect RTD within the reactors.[116] This is particularly problematic at higher weight percent solutions, which would be more applicable in industrial applications. Selection of appropriate reactor material is important though there can be other competing factors, as shown in work by Daniloska *et al*. exploring photopolymerisation in flow.[117–119] Using a reactor material (silicone) which was less compatible with the monomer than the solvent prevented fouling on the reactor walls; but a silicone-quartz hybrid reactor provided best results overall due to the UV-transparency of quartz enabling increased conversion.

High throughput platforms, such as automated parallel synthesisers or liquid handling robots present another opportunity in polymer synthesis. These platforms can run many polymerisations in parallel, with automated mixing of liquid components.[29] The primary applications for such platforms lie in reaction optimisation[120,121] and material discovery; such as preparing polymer libraries that can be screened for a range of properties, such as structure-activity relationships, e.g. protein binding.[122] Complex polymer architectures can be accessed, including multiblock copolymers,[123,124] and nano-objects[125,126] through a range of polymerisation mechanisms. The major advantage here is time-saving in chemical space exploration; this can be particularly beneficial when using air tolerant methods. Ng *et al*. show that deoxygenation can be “built-in” to PET-RAFT polymerisation of a wide range of monomers, enabling synthesis in well-plates using overhead light irradiation.[123] As long as the light source is uniform, conducting the synthesis in this way ensures each sample in the well plate experiences the same conditions. Parallel synthesis relies on automation, which introduces additional challenges including reactant handling and mixing. Regarding the former, liquid-handling robots are used in producing each individual reaction mixture. A recent example by Richards *et al.* demonstrated the power of combining air tolerant chemistry, a liquid handling robot and multi well-plates for discovery of new antibacterial polymers. Conducting a screen where there are so many potential monomer compositions would be unachievable using traditional reactionware but by using these enabling technologies, they synthesised and isolated 400 polymers in less than 36 hours and identified promising compositions (Figure 4).[127]

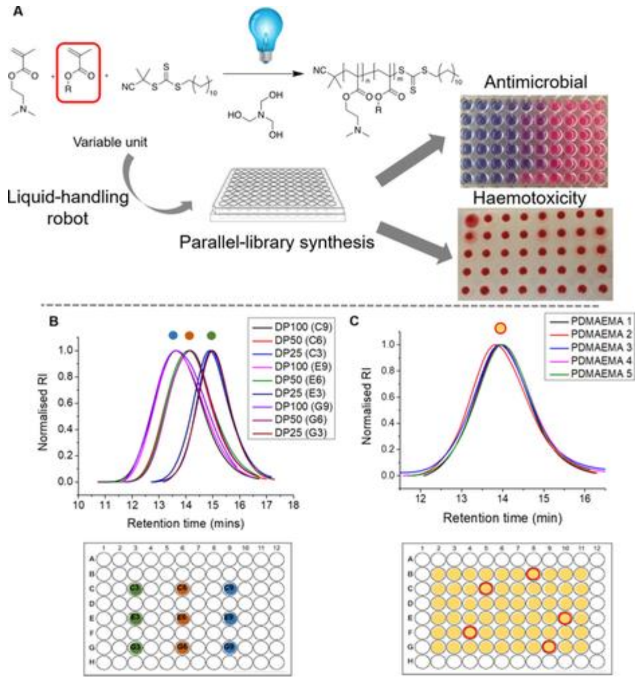

Figure 4. (A) Concept of in-air combinatorial photo-RAFT discovery. (B) SEC of 3 × 3 DP polymerizations of DMAEMA. (C) SEC of 5 randomly selected (red circles) polymers produced from 60 × DMAEMA polymerizations within a single plate. Used with permission from Richards *et al.*[128] Copyright John Wiley and Sons 2018.

As with flow chemistry, mixing needs to be considered when transferring polymerisation reactions to parallel synthesisers. In well plate examples, they often rely solely on diffusive mixing,[123] but use of global orbital[129] or mechanical[130,131] agitation has enabled access to heterogeneous polymerisations and varied polymer architectures. However, achieving this can require multiple mL of sample and hence the use of larger scale/commercial parallel synthesisers. If it is not possible to use an air-tolerant chemistry, a wide range of studies have made use of glovebox-contained synthesisers purged with inert gas to successfully achieve polymerisation using standard formulations.[130,131] High-throughput synthesisers have also been used for both and synthesis[132] and screening[133] of Ziegler-Natta catalysts used for (particularly industrially relevant) olefin polymerisations and the synthesis of appropriate support materials.[134] Adapting such platforms to perform at high pressure is required where the polymerisation itself is monitored.[133] A recent example of creative innovation in a related area is the use of a biological thermocycler (conventionally used for the polymerase chain reaction) in a similar fashion to a high throughput platform to synthesise polymers.[135] This enables access for biologists to controlled polymerisation of a range of polymer architectures without having to heavily invest in expensive chemistry equipment.

Table 2. Summary of polymerisation techniques achieved with innovations in reactor design referred to in this section (note: this is not designed to be a comprehensive library of all examples in the literature, rather a demonstration of the opportunities/possibilities with some relevant examples)

Reactor type	Advantages offered	Selected example processes
Pressurised		
- supercritical CO_2	Solvent easily removed, compatible with many monomers	Free radical,[33] NMP,[34] ATRP,[34,35] RAFT,[34,36,37] Polymer foaming.[38]
- other	polymerise gaseous monomers	Organometallic mediated[39]
	access to UHMW polymers with controlled radical methods	RAFT,[40] ATRP.[41]
Microwave	Increased reaction rates, lower energy usage	Free radical,[49,50] NMP,[47,48] ATRP,[45,46] RAFT.[44]
Continuous	*(See Table 1 for fuller summary of batch vs. continuous)*	
- Thermal initiation	Improved heat-transfer, telescoped processes	Anionic,[52,74–76] Free radical,[107] ATRP,[61–64,113] RAFT,[57,65–69,108,109,112] ROP,[71,72,111] ROMP,[73] click BCP[106]
- Light-induced	Reduced path lengths; thorough and uniform irradiation; Shape control of particles	RAFT,[79–81,85,86,114] ATRP,[77,82–84] UV-curing,[87–89] Free-radical (emulsion)[117–119]
- Heterogeneous catalysis	No work up for removal of catalyst, reduced preparation of catalyst	Cu-catalysed,[96,97] Photocatalyst-based,[98] Enzyme-catalysed[99]
Automated parallel synthesisers	Efficient construction of polymer libraries; for rapid screening of reactions/polymer properties or structure	RAFT,[122,123,125–128] NMP,[121,129] Cu-mediated,[124] ATRP[120]

Online analysis

When considering a polymerisation reaction, it is important to gain an understanding of two inter-linked main features: (a) the conversion of monomer into polymer chains and (b) information regarding the molecular weight and dispersity of the polymer product. This latter parameter is a critical feature for polymers – indeed there are a range of properties that are dependent upon the molecular weight achieved (e.g. glass transition temperature,[136] solubility,[12] mechanical properties,[12] self-assembly behaviour of block copolymers[137]).

A traditional model for analysis would at best involve sampling at time intervals, and in lots of cases simply testing the final product. While this may be sufficient for well-understood processes, it is less useful for product discovery and in gaining a detailed understanding of the reaction taking place. With improved knowledge of the progress of reaction, the user can be more time-efficient by reducing the need to use long reaction times as a guarantee of near-complete reaction. This can also improve purity, by preventing decomposition reactions which can be caused by long reaction times. Real-time knowledge of the reaction progress also enables enhanced precision, since reactants can be introduced to the system at a specific timepoint to access a desired composition or condition. From a health and safety perspective, real-time feedback can also reduce the risk of runaway reaction – most obviously by the monitoring of temperature to prevent exotherms.

The fundamentals of online analysis have been extensively reviewed by a number of authors[138–142] – a range of representative examples will be provided here, with a specific focus on the opportunities they *enable*, rather than a comprehensive treatment of online monitoring. It is also worth drawing attention to the nuances related to classifying online measurements. Another near-synonymous term used is real-time analysis, which highlights to the (advantageous) instantaneous nature of a measurement. However, a key difference to draw is between inline and at-line measurements. Where inline analysis would be performed on the reaction mixture *in-situ*, at-line measurements rely on automated sampling, and subsequent sample analysis. While inline is clearly most desirable (especially in terms of immediacy of information), there may be reasons where it may not be achievable.

Spectroscopic techniques offer a direct route to chemical observations and are usually suitable for inline applications. One such example is UV-visible spectroscopy, which has been used in real-time analysis for many years to provide kinetic information.[138,143] More recently, Hornung *et al.* have demonstrated its applicability in monitoring the second step of a telescoped process used to synthesise end-functionalised polymers by RAFT polymerisation and subsequent aminolysis.[57] In a more general application, in-line UV-visible spectroscopy also enables the characterisation of the above-discussed residence time distribution of flow reactors.[111]

Infra-red (IR) spectroscopy is another well-established technique for online analysis of polymerisation reactions – both near- and mid- IR (NIR/MIR respectively) can be applied to polymerisation monitoring.[143–145] An example of the potential of online monitoring by NIR spectroscopy is offered by Haddleton and co-workers, where real-time data for monomer conversion and temperature is correlated for the SET-LRP polymerisation of methyl acrylate – providing insights into the exotherm associated with reaction, and enabling the optimisation of catalyst amount.[31] NIR spectroscopy also allows for effective conversion monitoring of complex systems, including heterogeneous systems undergoing PISA, as shown by Boyer and co-workers.[146] This work uses NIR spectroscopy to observe the ON/OFF kinetics obtained using light mediated PET-RAFT. The use of NIR spectroscopy is well established – having been extensively demonstrated by Buback and co-workers in high-pressure monitoring of radical polymerisations over the last 30 years.[147–149] NIR has also been used in monitoring anionic polymerisation, removing the need for sampling for analysis by GPC or NMR spectroscopy.[150] This is favourable since anionic polymerisation is highly susceptible to impurities which makes such sampling more arduous and risks detrimentally affecting the polymerisation. The power of NIR monitoring is demonstrated for a range of emulsion polymerisations in work by Hua and Dubé, with high resolution kinetic plots when using an attenuated total reflectance (ATR) probe.[151]

Raman spectroscopy offers much of the same advantages as IR spectroscopy in terms of its ability to monitor polymerisations in-line. An additional feature, though, is its much-increased ability to tolerate water, which has very strong IR absorption bands and therefore aqueous reactions can be challenging to characterise. A comparison of NIR and Raman is given by Reis *et al*.[152] Raman spectroscopy has been shown by Mitsos and co-workers to successfully monitor even complex systems in water, such as the precipitation polymerisation of poly(N-vinyl-caprolactam), and provide information for both monomer conversion and particle formation, in-line.[153] Successful application of such particle syntheses rely upon tight control of particle size and other properties – this kind of analysis allows for in-process adjustments to conditions to ensure that control is maintained. In the same work, online turbidimetry is applied to monitor particle formation alongside the Raman spectroscopy – turbidimetry is shown to correlate well to polymer formation.

The key advantages with analyses like turbidimetry are cost and simplicity. Indeed, simpler analytical tools are commonly used in industrial processes, where the economy offered outweighs any reduced information. This is because while simpler analyses may not provide comprehensive information; all that is required is to provide sufficient evidence that the desired process has been achieved – and where similar process conditions are used, similar results from such an analysis can provide this evidence. On a similar theme, temperature and viscosity are two other inexpensive and easy to measure quantities in polymerisation monitoring. While generally it is assumed that the temperature of reaction is whatever is applied externally, by using a calorimetric approach, information regarding the extent of reaction can be obtained using one of either the heat-flow or heat-balance approaches.[140,154] The more sensitive heat-flow calorimetry is more common in lab settings but is complicated by calibration requirements and reactant feeds changing the mass balances.[155–159] Heat-balance calorimetry simply measures the temperature change in the heat transfer medium (input vs. output), and is more suitable for use in large, industrial-scale reactors. A direct comparison of both techniques is drawn by de Araújo and co-workers.[160] The factors that must be considered in calculating heat flows in either case are discussed in detail in reviews by Frauendorfer *et al*.[140] and Fonseca *et al*.[154] In terms of application, both methods have been used successfully in polymerisation monitoring, and applied in a range of reactor control applications.[161]

Viscometry can be used to obtain molecular weight information within a polymerisation.[138] Higher MW species have a higher viscosity, which is fundamentally related to their hydrodynamic radius. Of course, independently of this, a higher concentration of polymer (as would be generated by increased conversion) also leads to a higher viscosity, but with appropriate dilution and mathematical treatment molecular weight information can be obtained in real-time.[162,163] This information can then also be used for reactor control.[164]

When a more comprehensive picture of polymer properties is required (especially in discovery where chemistry may not be consistent) then the most appropriate tools are likely those used more conventionally offline. This is because all the techniques listed so far require some system-specific calibration. In contrast, using NMR spectroscopy to characterise conversion, and GPC to characterise the MWD allow for a more versatile platform. However, both techniques do not immediately lend themselves to use in real-time; when used offline, both rely upon sample preparation, involving dilution and potentially filtration.

The literature is richer for online GPC but true real-time GPC is not possible, since the chromatographic methodology inherently relies on a time resolved process. However, at-line GPC, which uses automated sampling has been applied successfully to both batch and flow systems. In order to achieve results within a useful timeframe, “rapid” columns are often used, from which molecular weight information can be obtained within just a few minutes. Separation of different molecular weight species, and therefore resolution, is somewhat reduced, but a general picture can be obtained. Examples include Haddleton and co-workers who show rapid GPC in conjunction with automated sampling from a batch reactor to monitor the copper mediated polymerisation of methyl acrylate[31,97,165] and Hoogenboom *et al*. who show GPC in conjunction with a high throughput platform for the polymerisation of 2-ethyl-2-oxazoline.[27] In both cases, it allows for a much more efficient characterisation, important for both online monitoring that might be used to adjust conditions and processing the volume of samples that HTP methodologies produce. Hadziioannou and co-workers have shown the utility of online GPC when used with a flow reactor – sampling from the flow at the reactor outlet.[58,166] Junkers and co-workers have also integrated GPC with a flow reactor, in an automated system which allows for programmed acquisition of GPC chromatograms at specific timepoints during a sequence of experiments.[167]

There are relatively few instances of the use of NMR spectroscopy in online monitoring of polymerisation reactions. This is because, aside from performing reactions in NMR tubes (where typical polymerisation conditions might not be easily reproduced),[168] flow-NMR has been limited to dedicated research facilities due to the expense associated with integrating flow systems to conventional NMR instruments.[169–171] Flow NMR allows for reactors to be used in their standard configurations, and sampling is either at-line (for batch syntheses) or inline for flow reactors, at the reactor outlet. The development of lower-field, "benchtop" instruments based upon permanent magnets over the last decade or so has led to a step change in spectral quality which has been used in small-molecule chemistry in a wide range of applications.[172–174] An initial example of application to polymer science monitored the emulsion polymerisation of butyl acrylate through peak-width measurements, using an older spectrometer and effective (though complex) post-processing.[175] Recently, more conventional integration of peaks for flow-NMR spectra has enabled accurate determination of monomer consumption over short reaction times allowing relatively straightforward production of detailed kinetic traces.[176,177] Furthermore, the technique is also sensitive enough to discern subtle rate enhancements such as that which occurs during RAFT dispersion polymerisation (Figure 5).[176]

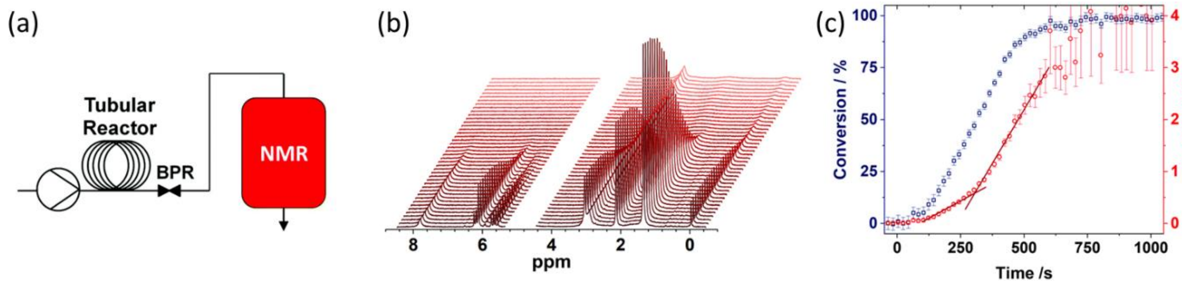

Figure 5. (a) Continuous-flow reactor equipped with benchtop flow-NMR. (b) Time-resolved ^{1}H NMR spectra obtained for the RAFT dispersion polymerisation of diacetone acrylamide in the presence of a poly(dimethylacrylamide) macromolecular chain transfer agent. (c) Conversion versus time and semi-logarithmic rate plot for the polymerisation calculated from the spectra. Adapted by permission of The Royal Society of Chemistry.[176]

Where NMR and GPC can provide information regarding the molecular mixture, self-assembly of polymers requires observation by another route. One extremely powerful technique for this is small angle x-ray scattering (SAXS). Online SAXS can provide useful in-situ measurements of self-assembly taking place in a PISA system, where reaction and self-assembly occur simultaneously. However, it requires at least a window of x-ray transparent materials to facilitate. Often this requires custom design and fabrication of reactors, which is now reasonably trivial given access to a well-equipped workshop. For some systems this may simply require a dedicated heat controlled capillary stage, [114,] but when stirring or pressure is required, more complex reactors have been fabricated. A simple example includes that demonstrated by the observation of PISA of spherical, worm-like and vesicle morphologies during RAFT emulsion polymerisation.[178,179] A similar approach for a more challenging environment was applied by Howdle and co-workers, who monitored heterogenous polymerisation in $scCO_2$ in a reactor which was able to maintain the conditions necessary and enable in-situ SAXS analysis.[180,181] SAXS has also been used in conjunction with libraries synthesised by high throughput platforms, allowing for effective characterisation of a large range of samples.[182]

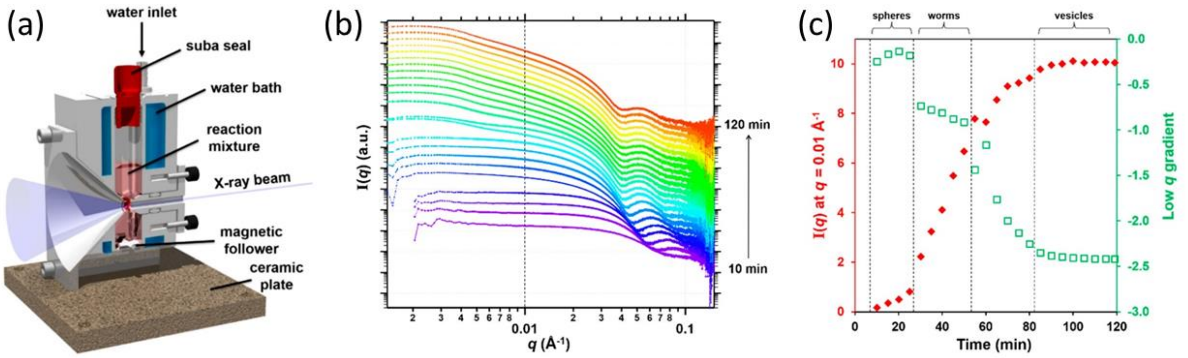

Figure 6. (a) A bespoke stirrable reaction cell used for in situ SAXS experiments (b) SAXS patterns recorded during the RAFT aqueous emulsion polymerization of methoxyethyl methacrylate at 70 °C. (c) The corresponding plot of I(q) at q = 0.01 $Å^{-1}$ and the gradient at low q ($0.005 \leq q \leq 0.015$ $Å^{-1}$) vs time which enable the morphology change during the polymerisation-induced self-assembly to be determined. Adapted with permission from Brotherton *et al*.[179]

While each of these analyses can be used in isolation to monitor a polymerisation in some fashion, a comprehensive monitoring option is offered by Reed and co-workers in the form of their automatic continuous online monitoring of polymerisations (ACOMP) technology, which is extensively documented.[138,183–186] A range of analyses are integrated into a single platform including light scattering, viscometry,[187] refractometry,[183] UV/Vis,[183,188] IR/NIR,[189] light scattering[187,190] and (more recently) NMR[191] spectroscopy which automatically samples from a reaction mixture and performs a series of measurements. Data is then processed according to the appropriate calculations, and detailed information regarding conversion and molecular weight is outputted. Unfortunately, the comprehensive platform is unlikely to be accessible the average polymer chemist due to the high cost, but it is an excellent example of what can be achieved. The opportunity presented by this impressive system is that of a fully packaged analytical tool which will enable informed process control – especially on an industrial scale.[186]

Table 3. Summary of innovations in online analysis and advantages offered by these innovations, with examples referenced in this section (note: this is not designed to be a comprehensive library of all examples in the literature, rather a demonstration of the opportunities/possibilities with some relevant examples)

Online Analysis	**Advantages offered**	**Selected example processes**
UV-Visible Spectroscopy	Non-invasive reaction monitoring, characterisation of flow reactors	End functionalisation of RAFT polymers[57] RTD characterisation[111]
IR Spectroscopy	Non-invasive reaction monitoring for wide range of monomers	Step-growth,[144] SET-LRP,[31] free radical[147–149] (and emulsion[151,152]), anionic.[150]
Raman Spectroscopy	Non-invasive reaction monitoring for wide range of monomers; tolerant to water where IR may not be suitable	Free radical: emulsion,[152] precipitation[153]
Turbidimetry	Monitor particle formation; Cheap	Free radical precipitation[153]
Calorimetry	Global reaction monitoring, including of complex systems; different approaches to facilitate greater accuracy or flexibility	Free radical: solution,[158,159] emulsion[155–160]
Viscometry	Molecular weight measurement, much reduced complexity vs. chromatography	Free radical: solution,[162] bulk[164]; polymer mixing[163]
Gel permeation chromatography	Detailed info regarding molecular weight distribution	Cu-mediated, ROP,[27] NMP,[58] ATRP,[166] RAFT[167]
NMR spectroscopy	Detailed chemical information, including conversion	Free radical: solution,[176] emulsion,[175] RAFT[176,177]
ACOMP	Comprehensive monitoring of polymerisations by extensive range of techniques	Free radical solution,[183,185,188–190]; NMP,[184] step-growth,[187] Controlled radical[191]

Automation

Automation has emerged as an important player in both material discovery and process optimisation.[192] The reduced laboratory-based workload for the researcher not only frees up thinking time, but also improves reproducibility and reliability of results. Indeed, there is often a requirement for some degree of automation when designing reactors and conducting online-analysis. For example, high throughput platforms are only made possible with automated dispensing and application of reaction stimulus, while most flow chemistry apparatus can be run remotely. Furthermore, it is often unrealistic to expect a user to process the large volumes of data which can be obtained online.

An important and established automation technology in industrial applications is computer control of reactors.[193,194] Strictly, where any temperature control is used, it is autonomous; though hotplates and oil baths perhaps do not represent the newest of innovations. Much more stringent temperature control is required for industrial applications due to the large volumes used and the subsequent potential for much more catastrophic exotherms. A range of the more advanced temperature control techniques are summarised by Hosen *et al*. in their work evaluating temperature controlling algorithms.[195] Furthermore, the automation of pumps can control reaction time and mixing ratios, allowing for simple adjustment of reaction conditions in flow. Again, much of the basis here lies in semi-batch methodology – programmed feeding has been used to modify copolymer compositions for various polymerisation types.[196,197] A particularly elegant and cutting-edge illustration of the opportunity presented by pump automation is shown in Figure 7, which shows how integration of both batch and flow techniques and careful flow control enables control of the polymer molecular geometry.[198] Similarly, Zhou *et al*. illustrate combining effective reactor design (for droplet flow) and automation can be used to generate copolymer libraries.[199] Furthermore, incorporation of automated pumps with online analysis and a CSTR has enabled control of morphology using the unconventional Belousov-Zhabotinsky driven RAFT-PISA .[200]

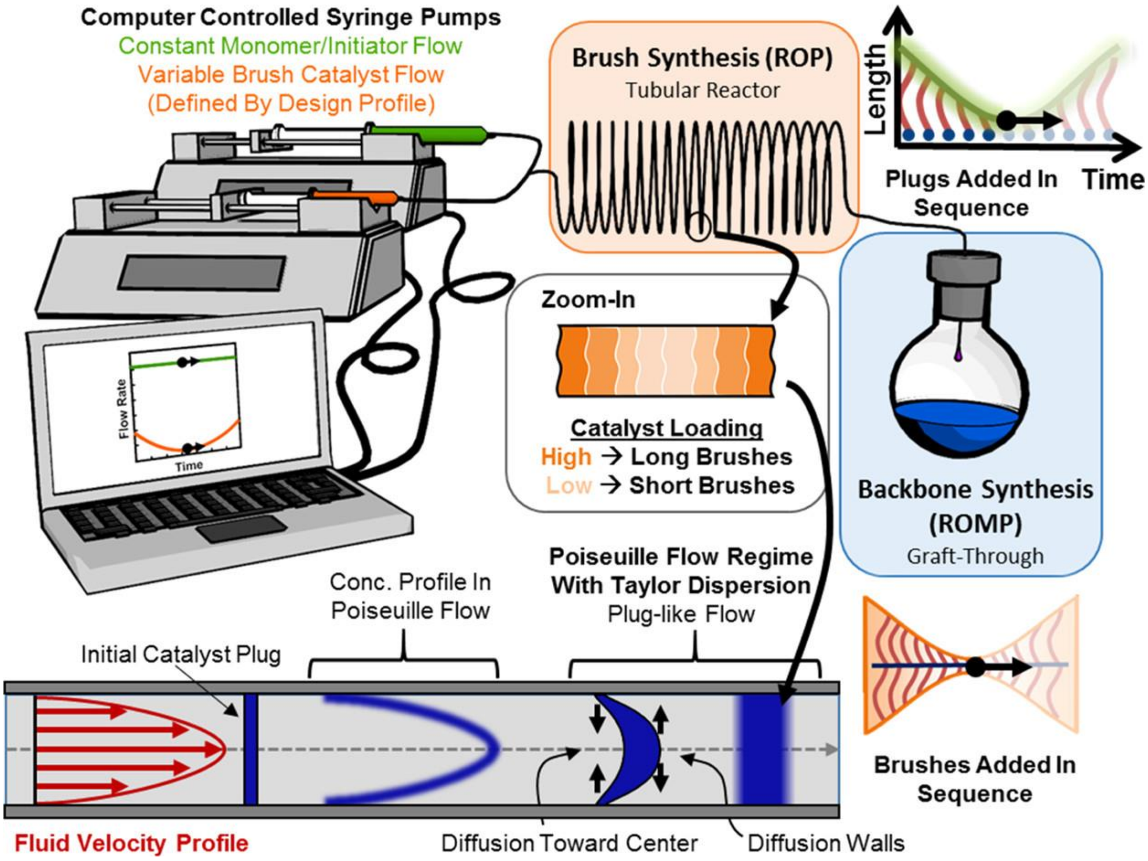

Figure 7. Automated hybrid reactor for bottlebrush synthesis with fluid mechanical elements illustrated. The setup consists of two computer-controlled syringe pumps connected to a tubular reactor feeding into a collection pot. Reprinted with permission from Walsh *et al.*[198] Copyright 2019 American Chemical Society.

Going further than simple automation of a single component of a reactor can enable more efficient and effective processes. One way in which this has been achieved is by use of optimising control systems.[161,201] Process control, relying upon mathematical models of the polymerising system, has been used in a wide range of industrial polymerisation processes for many years.[202–204] Two levels of complexity exist chiefly in developing models – simply predicting temperature, pressure and chemical concentrations as the first, and then additionally modelling polymer properties such as molecular weight as the second – following this, flow rates of inputs, temperature and pressure can all be adjusted to obtain a desired composition, as predicted by the model.[205] Key considerations for model developments include mechanism (whether chain or step), what mass balances should be included in the model and the composition of the reaction (whether homogeneous or heterogeneous). Successful integration of process control has been achieved with a range of polymerising systems, including free radical,[206] step,[207] and olefin polymerisations.[208,209] A case study for non-linear model predictive control (NMPC) of a emulsion copolymerization is offered by Kusek and co-workers.[161] They demonstrate the use of a jacketed reactor with calorimetric capabilities controlled with NMPC, which is able to reduce the reaction time required for near-complete conversion of monomers while maintaining a stable target molecular weight, and reduce temperature fluctuations in the reactor (Figure 8). Other work has also applied NMPC to similar systems with additional model features to describe molecular weight distributions[210] and with a tubular reactor.[211] The literature for this area is extensive, and only a snapshot to illustrate the opportunity is offered here. Further details can be found in a range of reviews – from older work summarising the important considerations for polymerisation process control[202–205,212] to more general process control work which discuss polymerisation processes in some detail.[213]

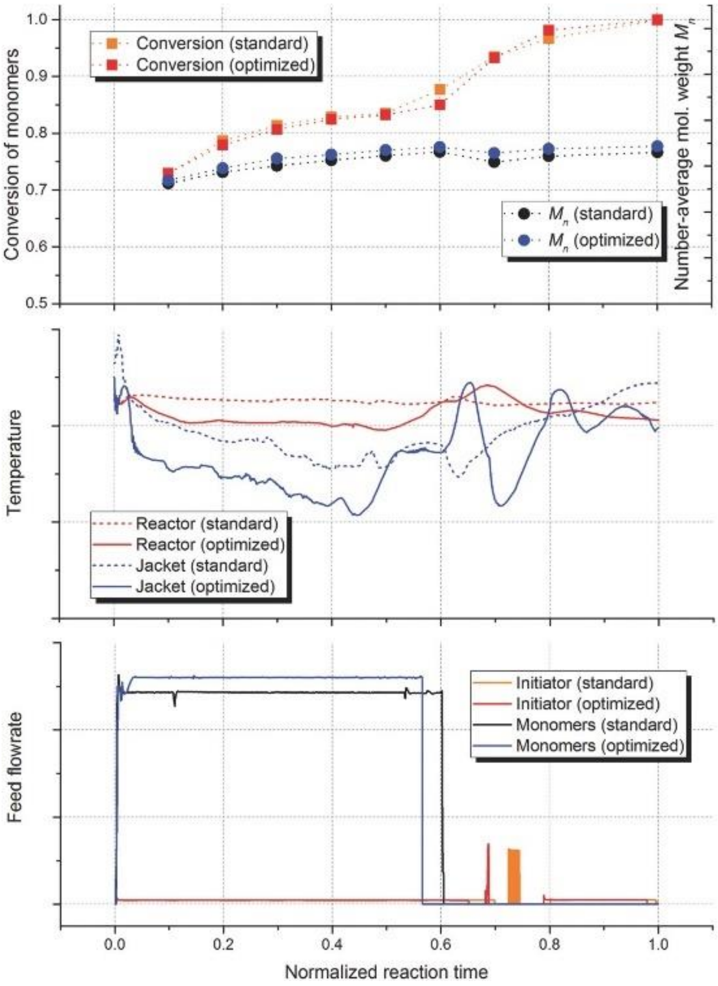

Figure 8. Comparison of standard and optimized batch reactions for a reactor controlled by non-linear model predictive control, showing evolution of conversion and product number-average molecular weight M_n (upper plot), reaction mixture temperature and reactor jacket temperature (middle plot) and monomer and initiator dosing (bottom plot). Reprinted with permission from Zubov *et al*.[161] Copyright John Wiley and Sons 2017.

The ACOMP system clearly in and of itself involves automation – and is an ideal basis for further innovation. Recent work using the platform has shown not only automated analysis, but integration of optimisation systems.[185,214–217] Targeting of molecular weight has been achieved both with simpler models[185,214] and using dynamic optimisation, with computational estimation of the state of the system from mathematical models in conjunction with the real-time analysis offered by ACOMP.[215–217] Further, the automatic tailoring of molecular weight distributions has also been achieved.[218] Predictive models have additionally been used elsewhere with online GPC to tailor MWDs.[219,220]

Where all examples mentioned so far rely upon a provided chemical model, further advances are beginning the journey towards 'artificially intelligent' reactors. Modelling based upon machine learning algorithms have been applied to a range of reactions including radical[221–224] and olefin[225,226] polymerisations. For example, Rizkin and Hartman[225] use an Artificial Neural Network for metallocene-catalysed olefin polymerisation, trained using literature values. Using this network, they were able to successfully predict polymer properties based upon kinetic constants for a range of reactor conditions and vice versa (i.e. predicting rate constants based upon obtained properties). This offers guidance for method development, thus reducing the synthetic workload. Machine learning has also been used in polymer property prediction from chemical structure, to guide future innovation in polymer design.[227–230]

In terms of synthetic application, Junkers and co-workers self-optimising continuous-flow polymer synthesis platform is perhaps the most notable advance in this area to date.[167] In this work, a continuous-flow reactor platform equipped with online GPC was programmed with an algorithm which enabled targeting of a specific degree of polymerisation by thermal or photo-initiated RAFT polymerisation (Figure 9). These researchers have also taken the next step in advancing the application of benchtop flow-NMR, whereby an algorithm was used to target a specific monomer conversion.[177]

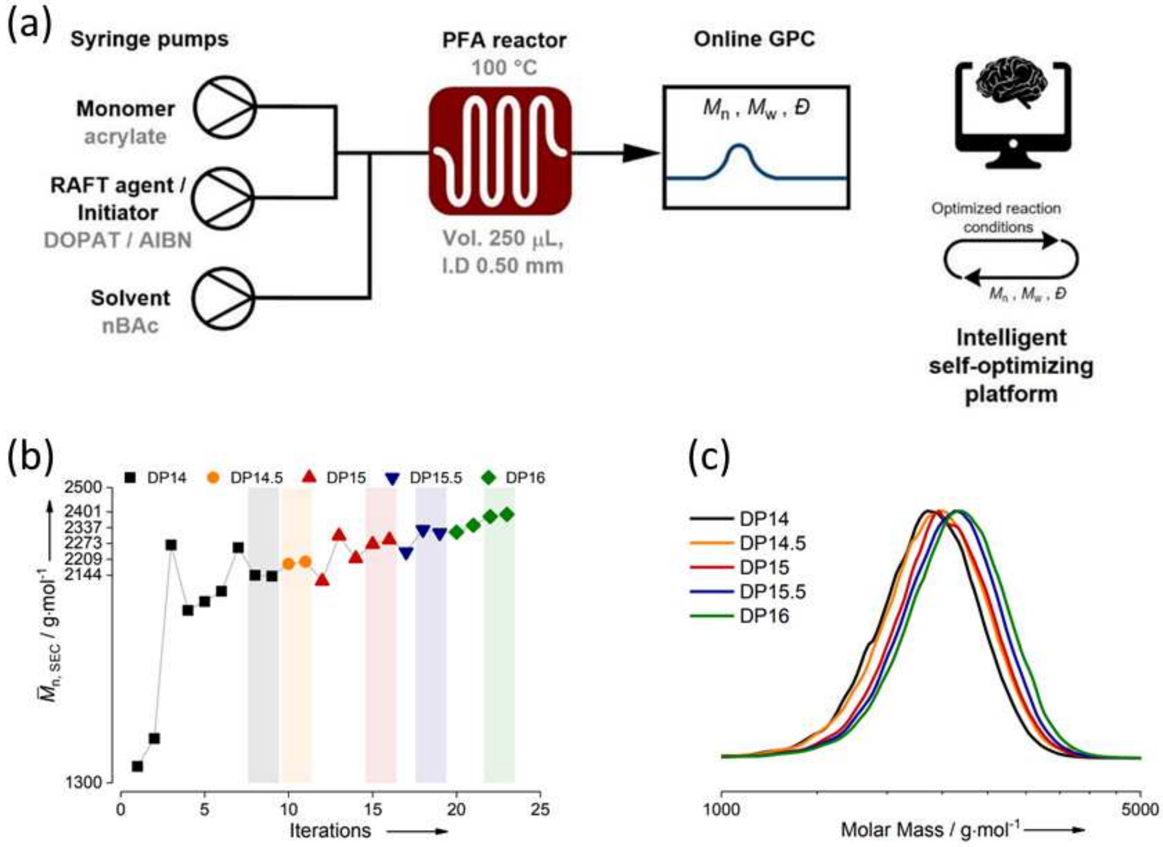

Figure 9. (a) Self-optimizing platform for the thermal RAFT homopolymerization of acrylates. (b) Optimization trajectory for the thermal RAFT polymerization of poly(n-butyl acrylate) with target degree of polymerization 14, 14.5, 15, 15.5 and 16. (c) Final molecular weight distribution of poly(n-butyl acrylate) with target degree of polymerization 14, 14.5, 15, 15.5 and 16. Adapted with permission from Rubens *et al*.[167] Copyright John Wiley and Sons 2017.

Table 4. Summary of innovations in automation (relating to polymerisations) referred to in this section with a summary of the advantages offered. (note: this is not designed to be a comprehensive library of all examples in the literature, rather a demonstration of the opportunities/possibilities with some relevant examples)

Automation	**Advantages offered**	**Selected example processes**
Computer control		
- Temperature control	Stabler temperature – better control of exotherms and more reproducible products	Free radical solution (summary of recent work also given in introduction)[195]
- Flow rate control	Dosing of monomer/other chemical components – control of final chemical structure; access to complex structures	RAFT,[196,200] ATRP,[197] ROP,[198] ROMP[198]
- Automated reactors (well-plate/flow)	High throughput for material discovery	RAFT,[199] automated synthesisers as summarised in Table 2 (Refs 120-129)
Optimising control systems	Faster targeting of products, more consistent products, optimised processes.	Free radical: solution,[193,201,206,214–217] emulsion[161,210,211]; step-growth,[207] olefin polymerisations,[208,209] RAFT[219,220]
Artificial intelligence		
- predictive/ modelling of reactions	Prediction of appropriate conditions to obtain particular polymer properties	Free radical,[221–224] olefin polymerisations[225,226]
- predictive/ modelling of properties	Guiding of chemistry required for particular properties	*Refs 224-227*
- artificially intelligent reactors	Can remove requirement for mathematical model of reaction using real-time data, ability to target output properties	RAFT[167,177]

Outlook

It is clear that new technologies are already helping polymer chemists push the boundaries of what is possible using current synthetic techniques. With respect to reactor design, batch chemistry is often still most appropriate, but there should be wider consideration of whether there can be an advantage gained by adapting the reactor. The ability for a chemist to do this is becoming more feasible with current trends in computer aided design and fabrication (e.g. 3D printing). Flow chemistry is gaining popularity in the polymer chemistry community, but there should be detailed consideration of whether it really is beneficial on a case-to-case basis. New air tolerant polymerisation techniques are beginning to enable synthetic chemists to conduct high throughput screens and advances in liquid handling are considerably reducing workload. Online monitoring techniques have evolved from basic process analytical technologies which measure temperatures and pressures, to spectroscopic techniques including NIR and NMR which allow specific quantification of the composition of the material. Chromatographic techniques, including GPC, enable rapid determination of molecular weight and dispersity while online SAXS can elucidate nanostructural properties on shorter timescales than the reactions themselves. All the aforementioned developments combined with computer control of reactors have opened up a plethora of opportunities with respect to developing 'artificially intelligent' reactors. This area is still in the early stages of development with few examples where computational intelligence is enabling self-optimisation. However, it is anticipated that high profile advances within the small molecule synthesis community will be transferrable across to polymer synthesis.[172,231–236] More widely available infrastructure combined with miniaturisation of advanced technologies mean the next generation of polymer chemists have a valuable toolbox to enable development of bespoke reactor platforms suitable for designing and synthesising a new generation of polymeric materials. The challenge that remains is the need to engage both academia and industry in adopting such 'disruptive technologies'.

Conflicts of interest

There are no conflicts of interest to declare.

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