Challenges and Recent Developments of Photoflow-Reversible Deactivation Radical Polymerization (RDRP)

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Abstract  Photo-controlled reversible-deactivation radical polymerization (photo-RDRP) has been investigated as a “green” and spatiotemporally controlling pathway for polymer synthesis. While the combination of photo-RDRP and flow chemistry has offered opportunities to increase light intensity and enable uniform light irradiation, problems associated with flow approaches still remain for photoflow-RDRP, which has hindered merging flow polymerization with other cutting-edge techniques. Herein, we summarize challenges and recent achievements in photoflow-RDRP including the development of (a) droplet/slug-flow to regulate residence time distribution, (b) mixing techniques to tailor polymer, (c) polymerization induced self-assembly, and (d) computer-aided synthesis. We hope this work will provide informative knowledge to people in related fields and stimulate novel ideas to promote polymer synthesis in both academia and industry.

Keywords  Controlled radical polymerization; RDRP; Photopolymerization; Flow chemistry; Flow polymerization

INTRODUCTION

Flow devices possess remarkably high surface-area-to-volume ratio (1.0×10^{-6}−5.0×10^{-4} m^2/m^3) compared with batch reactors (100−1000 m^2/m^3). In combination with organic and analytical chemistry as well as polymer science, flow devices have contributed to a variety of areas accredited to their superiorities in heat and mass transfer, light penetration, straightforward scalability, operation modularity and others. For example, flow techniques have served as a robust tool for parallel/long-term organic synthesis and facilitated the miniaturized kinetic studies of physicochemical processes. In recent years, by adapting flow reactors to polymer synthesis, the merits of flow chemistry have been rendered to a wide range of polymerizations, providing broadened opportunities to synthetic polymer chemistry, such as improving reaction efficiency, controlling molecular weight, diversifying polymer architecture, establishing polymer libraries, and so on, and thus making continuous-flow polymerization an increasingly emphasized research topic in recent years.

Back in early 1960s, a flow device of capillary was used for anionic polymerization of styrene by Szwarz et al. Benefit from the rapid mixing and heat/mass transfer in the tubular reactor with millimetre-scale inside diameter, they manipulated flow parameters (i.e. flow rates, residence time, reactor lengths) to investigate the kinetics of anionic polymerization. However, the concept did not attract much attention until 1990s, when a number of examples on reversible-deactivation radical polymerization (RDRP) were reported, accompanied with the potential of promoting polymer synthesis in a precise, cost-effective, automated and on-demand manner.

Thermo-initiated RDRP including reversible addition-fragmentation chain transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP), and nitroxide-mediated polymerization (NMP) have been well-documented for their high controllability. Recently, using light as an external trigger to control RDRP (photo-RDRP) has attracted many attentions. Similar to other RDRP methods, photo-RDRP holds the capability of providing polymers of well-defined molecular weights and topologies. Importantly, it furnishes exceptional advantages as follows: (1) the chain-growth process can be manipulated in a spatiotemporally controlled manner, stimulating advanced material engineering at the molecular level; (2) light of different wavelengths can serve as an environmentally benign trigger to initiate propagation under ambient conditions and enable the polymerization for biomaterials (i.e., living cells, tissues), which could be inaccessible through other protocols; (3) multiple-catalysis can be accomplished by pairing photochemical stimulus with other stimuli orthogonally. With above superiorities, photo-RDRP has been utilized to prepare complex macromolecular architectures (e.g., (multi)block, bottlebrush, hyperbranched (copolymers) and morphologies (e.g., raspberry-like nanoparticles), broaden the applic-
ations under ambient conditions (e.g. photografting on the surface of living cells,[34] converting gaseous monomer under ambient conditions,[35]), as well as advance material engineering (e.g. surface fabrication,[36,37] 3D/4D printing[38] and environmental protection[39]).

However, to meet different requirements, photo-RDRP under conventional batch conditions could be difficult. One typical example is the demand of scale-up synthesis. Due to the Beer-Lambert law, replacing a laboratory-scale batch reactor with an industrial reactor usually leads to significant degradation in light intensity, causing uneven light distribution, as well as less controllable kinetics and molecular weight distributions (MWDs). In contrast, photoflow-RDRP, which allows chain growth to be conducted in a light-transparent microchannel, has been recognized as an effective means to offer uniform light irradiation and enhanced light intensity.[40,41] Flow chemistry endows photo-RDRP with merits including not only practicable scale-up methods of scale-out (by extending collection time) and numbering-up (by assembling identical microreactors in parallel) flowlines,[1,41,42] but also precise and simultaneous regulation for multiple parameters such as flow rate, feed ratio and reactant concentration, etc.[43−47]

In recent years, given the rapid development and burgeoning interests in both microfluidic engineering and photochemistry, many polymer chemists are focusing on remaining challenges of photoflow-RDRP (e.g., how to maintain/improve controllability under concentrated/viscous conditions), and seeking pathways to integrate photoflow-RDRP with cutting-edge techniques and other research fields.

While several excellent reviews have presented photoflow-RDRP from perspectives of polymerization methods, flow reactor design, and differences between flow and batch operations,[41,48−50] this work will highlight challenges and related solutions for photoflow-RDRP reported in recent years. At the same time, the emerging innovative marriages between photoflow-RDRP and other techniques including polymerization-induced self-assembly (PISA) and computer-assisted automation will be discussed (Fig. 1). We hope this work will provide informative knowledge to people in related fields and stimulate novel ideas to further advance material engineering and industrial manufacturing.

DEVELOPING DROPLET/S LUG-FLOW TECHNIQUES TO DECREASE RESIDENCE TIME DISTRIBUTION

To provide persistent control over polymerization during the whole collection time, achieving an even distribution of all chemicals is of vital importance for photoflow-RDRP and other flow processes.[51,52] Otherwise, uneven distributed monomer, (macro)initiator and catalyst would bring different residence time distributions (RTDs), further leading to broad MWDs, deviated molecular weights (MWs) from theoretical values and undesired side reactions. These influences could be more severe when extending the reactor length, residence time, or raising the monomer concentration.[53] To overcome problems caused by broad RTDs (or high viscosity), photoflow-RDRP and other “living” polymerization methods have been normally conducted using diluted solutions. However, such solutions have increased the production costs (e.g., solvents and residence time), and could decline the production efficiency when combining with other high-tech approaches. Therefore, it is highly desirable to solve remaining problems of macromo-

Fig. 1 Overview of photoflow-RDRP: challenges and recent developments.

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In respect of fluid dynamics, Reynold’s numbers of fluids in flow polymerization are generally below 2300, proving that reagent streams are in the regime of laminar flow as explained by Taylor et al. early in 1953.[53] Under laminar flow conditions, mixing of reaction solutions is achieved by interlayer diffusion. Meanwhile, the wall shear force in flow can cause the formation of velocity dispersion profiles and variance in residence time. As a result, residence time of the reagent stream increases from the axis to the wall within the microreactor,[49] leading to the formation of RTDs (Fig. 2a). To achieve idealized plug flow, enlarging the diameter of tubing, reducing the viscosity and residence time could be helpful (Fig. 2b). However, such modifications on flow parameters could influence the polymerization by reducing the light-irradiation efficiency, limiting the production efficiency within given volume of solvent, and negatively impacting the monomer conversion.

At the beginning of flow RDRP, the monomer conversion is low, and the negative impacts of RTD are not obvious due to the efficient axial diffusion and the low viscosities. However, when the viscosity of the mixture increases with the growing monomer conversion, interlayer diffusion becomes too mild to fully minimize the RTD into a single value like the ideal plug flow shows.[51,53,56] Thus, the curve of experimental RTD usually lies between the theoretical curves of plug flow and laminar flow (Fig. 2b). When the reactor length and residence time keep extending, the mixing process introduces a RTD profile which is more similar to laminar flow.[53] The RTD could not only affect the mixing behavior, but also amplify the difference of mixture density as well as the gradient of light intensity along the wall to the center of the microchannel. As such, the formation of RTD would cause the inhomogeneity of reaction mixture and raise a series of problems such as broad MWD, deviated MW and decreased chain-end fidelity, etc.[54,57–59]

Recent years, many efforts have been devoted to solving the limitations mentioned above, and droplet flow, sometimes named as slug flow, has been introduced into application. Initially, droplet flow was developed to promote mass transfer by enhancing the interfacial and/or internal force in heterogeneous systems. For example, Whitesides and coworkers employed droplet flow to regulate the size, shape and composition of monodisperse solid particles via the photopolymerization of acrylate and divinyl crosslinkers.[62] Although the heterogeneous fluidic strategy has been previously utilized in free radical polymerizations to overcome the clogging issue,[63,64] related application in living polymerization has been rarely demonstrated until recently.

In the droplet-flow RDRP system, because the stream of reaction mixture is separated into many small droplets by immiscible mobile phase (carrier gas or liquid), the size of each droplet is small enough to enable narrowed RTD. In consequence, droplet-flow RDRP can effectively mitigate negative influences of RTD and thus contribute to precisely controlled polymerization conditions (Fig. 3). Other than photopolymerization, Leibfarth and coworkers[60] visualized the influence of conventional flow polymerization conditions on RTDs, and quantified the influence of RTDs on reaction results (Fig. 4). Using UV-absorbing small molecular tracer, they found that shorter reaction time, larger tubing diameter and higher viscosity caused a wider breadth of RTDs, and consequently led to boarder MWDs, smaller MWs and lower monomer conversions. Besides, they constructed gas/liquid segmented flow systems to minimize RTDs for the ring-opening transesterification polymerization (ROTP) of γ-valerolactone (γ-VL). In their flow setup, even using a viscous sample (η = 85 mPa-s), poly(γ-VL) was successfully generated at 60% monomer conversion (Mn = 13.6 kDa,
Laminar flow
Velocity
profile
Broad(er)
polymer Ð
Geometry
dependent
Distribution of 
residence time

Effect of tubing diameter on RTD

Effect of residence time on RTD

Effect of viscosity on RTD

Fig. 4 Relationship between RTD and (a) tubing diameter, (b) residence time, and (c) viscosity in continuous flow systems (Reproduced with permission from Ref. [59]; Copyright (2019) American Chemical Society).

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D = 1.15
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indicating the superiority of slug flow on ROTP.

The utilization of slug flow in photo-RDRP has been rarely reported until 2018, when Boyer and coworkers\[65\] designed a slug-flow process using \( \text{N}_2 \) as the separating phase in photo-induced electron transfer RAFT (PET-RAFT) polymerization of dimethylacrylamide (DMA). Influences of the tube diameter, volume, flow rate and slug size have been investigated (Fig. 5a). They found that Reynolds numbers of over 1900 were achieved by decreasing the slug size and increasing the flow rate, affording polymers without MW tails and improved control over MWD as analysed by size exclusion chromatography (SEC), when compared with the a laminar-flow system. Furthermore, a multi-pump flow setup was designed to facilitate the synthesis of copolymers mixture with tailored composition gradients and variable MWDs (including from narrow to broad MWD) via the chain-extension in a one-pass photoflow manner (Fig. 5b).

Thereafter, Corrigans et al. applied the slug-flow method to another metal-free PET-RAFT polymerization using Erythrosin B (EB) as a photocatalyst (PC).\[66\] In contrast to continuous-flow polymerization, this slug-flow metal-free PET-RAFT polymerization exhibited enhanced mixing efficiency, consistent residence time and steady-state fluidic behaviour. As indicated by the instantaneous changes of \( M_n \) and \( D \) over reaction time, slug-flow conditions constantly provided well-defined polymers even when the residence time was over 10 h (Fig. 6A). The instantaneous monomer conversions obtained in slug flow were considerably high (above 95%) and consistent over the whole flow process (Fig. 6B). Aside from the appreciable scale of high molecular-weight polymer, they also found no signs of polymer residues by washing the reactor with solvent after all slugs were forced out using air. On the
contrary, in the continuous-flow polymerization, polymers of high dispersity were observed when washing the tubing reactor with organic solvent. This difference is because laminar flow as well as the wide RTD cause the undesired formation of high-molecular-weight polymers, which could attach onto the tubing wall and fail to be blown out using an air pump.

In 2019, Chen and coworkers demonstrated the employment of a non-polar organic solvent as the carrier phase and a polar mixture of monomer/solvent/trithiocarbonate/PC as the reaction phase to establish a droplet-flow photo-RDRP platform.

In this liquid/liquid flow system, the carrier phase of $n$-hexane exhibits much lower surface tension to the tubing reactor (made of perfluoroalkoxy alkane (PFA)) comparing to the droplets of reaction mixtures (e.g., monomer=$N,N$-dimethylacrylamide (DMA), solvent=dimethyl sulfoxide (DMSO)). Therefore, the surface of tubing reactor should be easily wetted by $n$-hexane even in the presence of reaction mixtures, allowing the generation of a continuous carrier phase (Fig. 7A). Based on the design, seven homopolymers of polyacrylates and polyacrylamides ($M_w=17.4–43.1$ kDa) have been successfully generated with up to quantitative monomer conversion in less than 60 min residence time (Fig. 7B), and their molar mass distributions are maintained below 1.25.

Similar to observations reported by Boyer, broad MWDs and deviations of MWs have been observed in a continuous-flow approach. Notably, the liquid/liquid flow approach en-
in flow to produce polymers with tailored dispersities. Consequently, homo and block (co)polymers of tunable dispersity and complex structures can be facilely synthesized using photoflow techniques.

**Synthesis of Homopolymers of Narrow MWDs**

During a polymerization, the viscosity of reaction mixture increases with monomer conversion due to interactions of polymer chains, especially for a concentrated solution. For example, when the conversion of DMA (78 wt% of DMA in DMSO, Fig. 8) reaches 95% via RAFT polymerization, the final viscosity is about 1.4 × 10^5 times that of the initial value, and the viscosity undergoes a dramatic increase after 75% monomer conversion. In comparison, for a solution containing 48 wt% DMA in DMSO, the viscosity at a complete monomer conversion is only about 60 times that of the original mixture. Therefore, flow RDRPs are normally conducted at monomer concentrations of less than 40 wt%. The increased difficulties in mixing caused by viscosity in comparison to conventional batch operations could restrict the applicable scope of flow RDRPs.

![Fig. 7](https://doi.org/10.1007/s10118-021-2529-8)

**Fig. 7** (A) Graphic representation of the droplet-flow polymerization; (B) Images of (a) droplet flow and (b, c) a single droplet generated within a PFA tubing reactor wrapped around a glassware; (C) Polymerization of different monomers with the liquid/liquid flow approach (Reproduced with permission from Ref. [67]; Copyright (2019) American Chemical Society).

ables the usage of highly concentrated droplets as reaction mixtures (up to >99 wt% monomer in droplets), suggesting that RTD in photoflow-RDRP could be effectively minimized using the droplet-flow strategy. Given the ease of control of two liquid phases, this method could be further adopted to promote other living polymerizations for a broad range of monomer concentrations.

**DEVELOPING MIXING TECHNIQUES TO TAILOR POLYMERS**

Mixing techniques have also been developed in photoflow-RDRP to overcome the shortcomings including viscosity variation, uneven mixing, tube clogging, etc. On the other hand, researchers have subtly utilized the uneven mixing behavior
such technique has not been developed for living polymerization. Due to the increased complexity of a sonicated photoflow setup, combined knowledge with chemical engineering could be helpful to fertilize this technique.

**Synthesis of Homopolymers with Broad but Controlled MWDs**

The properties of polymers are dictated by the distribution of molecular weights. For example, polymers of bi- and multimodal MWDs possess interesting mechanical properties (e.g., toughness, tensile strength, creep resistance).\(^{[71,72]}\) However, the on-demand regulation of different fractions of polymers with a targeted broad MWD is quite challenging.

In 2017, Boyers and coworkers developed a photoflow PETRAFT polymerization that successfully enabled the preparation of poly(dimethylacrylamide) (PDMA) with broad MWDs but controlled shapes in SEC profiles.\(^{[22]}\) To fulfill the goal, nearly ideal plug flow was required to generate polymers of different MWs and narrow MWDs at different stages in one-pass. To limit the axial mixing and achieve ideal plug flow, authors investigated the influence of flow parameters on mixing behavior. As shown in Fig. 10, when a long tube and small reaction volumes were used, extensive mixing was afforded to generate polymers of identical MWD (single green bar in top right of Fig. 10). When a short tube and small reaction volumes were combined, moderate mixing was provided to give slightly mixed MWD in the middle part of elution time (green bar in middle right of Fig. 10). When a short tube and large reaction volumes were combined, separate MWDs were observed at different elution time, indicating the highly limited and favorable mixing behavior during photoflow-RDRP (two long bars in bottom right of Fig. 10). When using the optimized parameters, propagation at different stages was mixed in the tube to achieve controlled shapes (e.g., square, bimodal) of SEC profiles.

![Fig. 9](https://example.com/fig9.png)  
**Fig. 9** Three devices to generate droplets flow: (A) flow-focusing; (B) T-junction; (C) co-flowing stream geometries (Reproduced with permission from Ref. [61]; Copyright (2009) The Royal Society of Chemistry).

**Synthesis of Block Copolymers**

During the synthesis of a block copolymer, a stream of macroinitiator (e.g., first block of a copolymer) will mix with another stream of monomer in the flow line. However, due to the different viscosities of two streams, it would be difficult to achieve an entirely homogeneous stream using a conventional mixer, especially when a stream of macroinitiator of a high concentration was used. To produce well-defined block copolymers via photo-flow-RDRP, increasing efforts have been made in recent years.

To avoid the mixing problem, Miyake and coworkers prepared a solution of macroinitiator and monomer in a single syringe for organocatalyzed ATRP in flow.\(^{[73]}\) However, this protocol is not suitable for a continuous chain-extension starting from the synthesis of the first block of macroinitiator. Perrier\(^{[74]}\) and Chen\(^{[75]}\) groups have demonstrated that it is important to mix macroinitiators and additional monomers using mixing loops for RAFT polymerization and photo-RDRP under flow conditions, respectively, to provide block copolymers of narrow MWDs. However, the mixing time and length of the mixing loop could be different, depending on the viscosity of solutions. The demand of case-by-case optimization of mixing methods and usage of additional mixing loops has rendered the chain-extension somewhat less efficient and inconvenient. Additionally, because PFA and polytetrafluoroethylene (PTFE) tubes, which are typically used for photoflow reactors, are gas permeable, it would further cause different levels of air permeation and inconsistent polymerization results via a radical propagating mechanism.

Frey\(^{[42,76]}\) Nagaki\(^{[77]}\) and Yoshida\(^{[78,79]}\) groups have revealed that the development of fast mixing devices is critical to provide well-defined block copolymers via anionic/cationic polymerications.\(^{[42,51]}\)

Inspired by the packed-bed reactors using stainless steel beads in biphasic transition-metal catalyzed organic synthesis,\(^{[80]}\) Zhong et al. developed a packed-plug mixer using SiO\(_2\) beads and all commercially available materials.\(^{[81]}\) With the packed-plug mixer (3 cm in length), the macroinitiator stream could be efficiently mixed with the monomer stream in seconds as indicated by the color change of the combined stream (Fig. 11a). Chain-extension from two macroinitiators including poly(methyl acrylate) (PMA) and poly(N-isopropyl acrylamide) (PNIPAM) (\(M_n=4.4−8.1\) kDa, \(\bar{D}=1.2\)) has been studied using four acrylamides under white light irradiation. Using the self-made mixer, clearly improved control over MWD has been realized when comparing to control experiments using a conventional Y-mixer (ca. \(D=1.1−1.3\) versus 1.4−1.9, Fig. 11b). Notably, the authors demonstrated that the packed-plug mixer exhibited increasing importance when the concentrated macroinitiator chain was employed into flow, or the interaction between polymer chains was enhanced via hydrogen bond interaction (e.g., PNIPAM used as a macroinitiator).

In 2019, Boyer and coworkers developed a practical protocol for the synthesis of di- and triblock copolymers in tubular reactors via PET-RAFT polymerization using Eosin Y disodium salt photocatalyst (PC, exposing to green light irradiation) without macroinitiator isolation (Fig. 12).\(^{[44]}\) Within only 10 min of residence time, full monomer conversion was reached for acrylamides and acrylates, generating polymers of close to...
Polymers could be theoretically produced at a rate of 300 g/day with oxygen tolerance. Comparing to previous examples, the utilization of micromixer tee and increased flow rates are attributed to enhanced mixing of viscous streams during chain-extension. The micromixing unit has also been used by the Junkers group in the synthesis of block copolymers via photo-induced iniferter polymerization of methacrylates. In their example, block copolymers of less than 10 kDa were synthesized from poly(methacrylate) macroinitiator ($M_n=5.0$ kDa, $\bar{M}_w=1.25$).

**Fig. 11** (a) Comparison between a Y-mixer and a packed plug by mixing two streams of different colors. Red stream is eosin-Y and DMA (30 wt%) in DMF, blue stream is PMA (25 wt%) in DMF. (b) Comparison of chain extensions from a same macroinitiator (PMA) via photoflow-RDRP using two different mixers. (Reproduced with permission from Ref. [81]; Copyright (2019) The Royal Society of Chemistry).

**Fig. 12** (a) Tubular flow reactor for the synthesis of di- and triblock copolymers; (b) Normalized SEC profiles of diblock polymers; (c) normalized SEC profiles of homopolymer (DP=10), di- (DP=20) and triblock (DP=30) polymers, indicating the successful chain extension from homopolymer. (Reproduced with permission from Ref. [44]; Copyright (2019) American Chemical Society).

**PISA USING PHOTOFLOW TECHNIQUE**

Photoinitiated polymerization-induced self-assembly (photo-PISA) has facilitated the preparation of polymeric nanoparticles (PNPs) of varied and high-order morphologies under ambient conditions. Transforming photo-PISA conducted under batch conditions into flow could take advantage of the uniform and enhanced light irradiation, as well as the on-demand productivity, and could stimulate the generation of complicated architectures of PNPs.

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100 kDa and high chain-end fidelity. Polymers could be theoretically produced at a rate of 300 g/day with oxygen tolerance. Comparing to previous examples, the utilization of micromixer tee and increased flow rates are attributed to enhanced mixing of viscous streams during chain-extension. The micromixing unit has also been used by the Junkers group in the synthesis of block copolymers via photo-induced iniferter polymerization of methacrylates. In their example, block copolymers of less than 10 kDa were synthesized from poly(methacrylate) macroinitiator ($M_n=5.0$ kDa, $\bar{M}_w=1.25$).
In 2018, Junkers, Boyer, Zetterlund and coworkers reported the synthesis of PNP s via photo-PISA under continuous-flow conditions for the first time (Fig. 13). A trithiocarbonate substituted by poly(ethylene glycol) (PEG) was employed as an iniferter in the presence of hydroxypropyl methacrylate (HPMA) exposing to blue-light irradiation in water. Poly(ethylene glycol)-b-poly(hydroxypropyl methacrylate) (PEG-b- PHPMA) nanoparticles of morphologies including sphere, worm and vesicle were prepared in flow, providing improved control of morphology in comparison to conventional batch procedures, and allowing scalable synthesis of nano-objects for in situ encapsulation of bioactive compound (doxorubicin).

Later, Boyer and coworkers investigated photoflow PISA in alcoholic solvent. Due to the weaker carbon-sulfur bond in poly(methacrylate)-based macroinitiator (macro-RAFT agent), the generation of carbon radicals with photo-initiators exhibited less impact on the propagation rate than the acrylate-based macroinitiator, which was consistent to the results of photo-RDRP under batch conditions reported by the Chen group. While DMSO solvent is frequently used in photopolymerization, the photoflow approach enabled the employment of ethanol solvent to generate sphere-like PNP s of uniform sizes. Authors hypothesized that the mobility of polymers in flow could be easier than that in batch, thus promoting the morphology transition under flow conditions.

In 2019, the same research group applied photoflow PISA via PET-RAFT polymerization using a Eosin Y/triethanol amine catalytic system. Chain lengths of both solvophilic and solvophobic blocks have been investigated to expand the compositional space of worms, jellyfish and vesicles in flow (up to 20 wt% solid content). Interestingly, using the same macroinitiator and monomer, the batch and flow operations have generated PNP s of different morphologies as shown by the transmission electron microscopy (TEM) results in Fig. 14. In-depth understanding on the mechanistic difference for the particle formation is still waiting to be demonstrated. The scale-up potential of the continuous-flow synthesis could lead to the preparation of 60 g PNP s in 24 h without intermediate purification.

Very recently, Tan, Boyer and coworkers reported a photoflow PISA exposing to light irradiation of dual wavelengths (Fig. 15). This dual-wavelength photo-PISA technique efficiently provided nano-objects with different morphologies (spheres, worms and vesicles) with air tolerance, which could allow the preparation of PNP s in water and alcohol/water systems using either methacrylate or acrylate as core-forming monomers under batch and flow conditions.

**COMPUTER-AIDED PHOTOFLOW-RDRP**

Despite the advancement of living polymerization, the precise synthesis of polymers still requires batch-to-batch operation, which could be a time- and labor-consuming process. While flow chemistry has offered opportunities to integrate with high-tech tools, the combination of photoflow-RDRP with computer science has recently brought considerable improvements, enabling automated construction of polymer libraries and inline self-optimization for targeted polymers.

**Automated High-throughput Polymerization**

Chemical composition, architecture, molecular weight and its distribution all play important roles in determining polymers’ properties. Therefore, it is desirable to develop practicable, transformable and programable methods to build polymer libraries which can span broad ranges of structure-property spaces.

In 2019, Waymouth, Park and coworkers established a programmable flow polymerization technique to generate polyester and polycarbonate libraries (Fig. 16). Thanks to the high activity and selectivity of ring-opening polymerization (ROP) promoted by urea anion catalysts, the in-flow catalyst switch strategy enabled the rapid generation of 100 block copolymers in 9 min from monomers. The rapid polymerization allows the continuous-flow of a series of different samples without clear mutual interference between two adjacent samples. Alternatively, this setup can be employed to generate polymers at a rate of multiple grams per minute based on the same polymerization process.

In the same year, the Chen group reported the development of a computer-aided photo-RDRP in a continuous droplet-flow pathway (Fig. 17a). Because longer reaction time is demanded for the photo-RDRP in comparison to ROP, a continuous-flow manner will lead to chemical diffusion between nearby samples, and produce polymers of chemical compositions deviated from programmed injection. Therefore, reaction mixtures are divided into different droplets using continuous and immiscible carrier phase. In this platform, 275 droplets of samples could be generated in 11 min (2 μL for each droplet), and for a sequence of droplets, their chemical compositions and concentrations can be manipulated through a program. To prove the concept, 11 copolymers of varied compositions were synthesized in 11 min, where 25

![Fig. 13 Reactor setup for the synthesis of PEG-6-PHPMA nanoparticles which enabled monitoring of particle morphology. (Reproduced with permission from Ref. [86]; Copyright (2018) American Chemical Society).](https://doi.org/10.1007/s10118-021-2529-8)
droplets were collected for each copolymer to ensure enough samples for proton nuclear magnetic resonance (1H-NMR) (Fig. 17b), SEC and glass transition temperature characterization. Although a higher production efficiency has yet to come, the droplet-flow polymerization strategy has broadened the opportunities to establish polymer libraries based on various monomers, mechanisms, as well as concentrations.

In 2020, Guironnet and coworkers have reported a protocol to synthesize polymers with targeted MWD profiles via mathematic procedure of directly converting design to synthesis (Fig. 18). They utilized a computer-controlled flow reactor to continuously generate polymers with narrow MWDs, which then accumulated to customize different shapes of MWD profiles, like triangle (Fig. 18a) and square (Fig. 18b), using anionic polymerization of styrene. Meanwhile, ring-opening metathesis polymerization (ROMP) was also implemented to generate triangular and squared MWDs of different heights (Fig. 18c). The predicted MWD profile has shown a good match with experimental result (Fig. 18c). Although this strategy has high requirements on polymerization to further customize different shapes of MWD profiles, the versatile protocol could be highly efficient due to the automated operation.

![Fig. 14](image1.png) TEM micrographs of PDMA-b-(PDAAm-co-PDMA) PNPs via aqueous PET-RAFT PISA via batch and flow processes. Evolution of morphologies obtained by varying the target degree of polymerization at 17.5 wt% solid content. Scale bars are 0.5 μm. PDAAm=poly(diacetone acrylamide), S=sphere, BW=branched worms, HBW=highly branched worms, BO=bilayer octopi, JF=jellyfish, V=vesicles, and PV=patchy vesicles. (Reproduced with permission from Ref. [89]; Copyright (2019) American Chemical Society).

![Fig. 15](image2.png) Optical image of the reactor setup for a photoflow PISA exposed to light irradiation of dual wavelengths. (Reproduced with permission from Ref. [90]; Copyright (2020) American Chemical Society).

![Fig. 16](image3.png) Programmable flow polymerization technique used to generate polyester and polycarbonate libraries. (Reproduced with permission from Ref. [91]; Copyright (2019) American Chemical Society).

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Fig. 17 Progamed photoflow-RDRP for high-throughput and scalable polymer synthesis aided by computer: (a) picture of the computer-aided photoflow setup; (b) $^1$H-NMR spectra of copolymers with gradient changes of chemical compositions. (Reproduced with permission from Ref. [67]; Copyright (2019) American Chemical Society).

Fig. 18 Design of MWD shapes and GPC traces of synthesized polymers: graphs of (a) designed triangle MWDs, (b) designed square MWDs, (c) targeted shapes of two discrete squares and a triangle, and their resulting GPC traces and prediction. (Reproduced with permission from Ref. [93]; Copyright (2020) Nature).
Automated Self-optimization

The combination of flow chemistry and online characterization has found applications in areas such as organic synthesis and analytic chemistry. Infrared, UV-Vis, NMR, mass spectrometry, SEC, as well as other measurements have been utilized as characterizing tools when monitored by computer. With the development of algorithms, the online analysis can be readily reached and employed to achieve automated self-optimization. Because the precise synthesis of a specific polymer could require extensive efforts, the self-optimization aided by a computer could simplify this process and dramatically reduce time and labor costs.

In 2019, Junkers’ group reported the autonomous self-optimizing RDRP in flow, and applied this technique to photoiniferter polymerization and RAFT polymerization. In their work, an online SEC system was coupled to a continuous-flow reactor, followed by real-time computer analysis and optimization. In the flow setup, three reagent streams were mixed by static mixers and delivered into the tubing reactor with changeable flow rates. The online SEC system equipped with an evaporative light scattering detector (ELSD) could provide information including average MW and MWD in time. The collected results were fed back to a machine-learning algorithm for predefinition of the next targeted polymer and corresponding reaction parameters, such as concentrations of the RAFT agent and monomer, as well as residence time (Fig. 19). In this way, the results of newly obtained polymers could gradually approach the target one. This platform can also be used for high-throughput screening and enhancing process control, providing an automated pathway to reach the desired synthetic goal.

Fig. 19 Autonomous platform for self-optimized polymer synthesis. The product stream is injected into an online SEC system and subsequently analyzed and processed by the optimization algorithm. (Reproduced with permission from Ref. [98]; Copyright (2019) WILEY-VCH Verlag GmbH & CO. KGaA).

CONCLUSIONS

In the last century, the development of Schlenk line has facilitated many investigations on living ionic/radical polymerization and metal-catalyzed polymerization in both academic and industrial fields, as well as popularized polymer synthesis in areas of material science, catalysis, energy, etc. However, related operations under batch conditions could still be time/labor-consuming and difficult for non-experts. Advance-ment of flow polymerization opens an alternative pathway to access polymers by simply clicking pumps or computers, which might be able to free scientists from thinking “how to make” to “what to make” in future.

Nonetheless, photoflow polymerization remains at its beginning stage. Despite few examples aforementioned, novel polymers of more complex structures and tailored MWDS, which may hold intriguing physical properties (e.g., unique solubility, aggregation performance in different solutions) and interesting material characteristics (e.g., mechanical properties, the processability of polymer melts, rheological properties) are still urgently needed for advanced material engineering. By exploiting the potentials of photoflow techniques, synthesis of polymers with on-demand molar mass, composition and topology could be accessed with promoted efficiency, accuracy and scalability in a streamlined pathway.

Meanwhile, applications of photoflow systems also deserve more efforts. For example, for photoflow-assisted PISA, the solvent range, solid contents and morphologies could be expanded. For the computer-aided photoflow-RDRP, both program-controlled process and automated inline optimization are emerging topics and still have a long way to go before industrial application.

As highlighted with recent examples of photoflow-RDRP, researchers have moved their attentions from simply using photoflow as a technique to accelerate or scale-up photoflow-RDRP to solving intrinsic challenges (i.e., RTD, viscosity) accompanied in flow, manifesting fluidic self-assembly behaviors (i.e., photo-PISA), or exploring capabilities of automating polymer synthesis. Given the broad applications of photopolymerization, increasing interests in flow synthesis, and rapid development of computer science, we believe that the continuous growth of photoflow-RDRP will provide unprecedented tools to advance material engineering, and enable the discovery of new polymers and synthetic solutions.

BIOGRAPHY

Mao Chen obtained his B.S. and Ph.D. degrees at Wuhan University (2006, 2011) under the supervision of Prof. Aiwen Li and Prof. Xumu Zhang. From 2012 to 2014, Mao worked with Prof. Buchwald’s lab at MIT as a Postdoc. Subsequently, he joined Prof. Johnson’s lab at MIT, and was promoted to research scientist in 2016. Also in 2016, Mao started the independent research career at Fudan University (www.polymaolab.com). He received Overseas Talent Program of China (2017), Thieme Chemistry Journals Award (2019), and is currently serving as young editor board member of Journal of Functional Polymers, advisory board member of Polymer Chemistry.

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REFERENCES

1 Steinbacher, J. L.; McQuade, D. T. Polymer chemistry in flow: new polymers, beads, capsules, and fibers. J. Polym. Sci., Part A:
Zhong, Z. R. et al. / Chinese J. Polym. Sci. 2021, 39, 1069–1083

Polym. Chem. 2006, 44, 6505–6533.
1 DeMello, A. J. Control and detection of chemical reactions in microfluidic systems. Nature 2006, 442, 394–402.
2 Geyer, K.; Codee, J. D.; Seeberger, P. H. Microreactors as tools for synthetic chemists—the chemists’ round-bottomed flask of the 21st century? Chem. Eur. J. 2006, 12, 8434–8442.
3 Watts, P.; Willes, C. Recent advances in synthetic micro reaction technology. Chem. Commun. 2007, 443–467.
4 Voicu, D.; Scholl, C.; Li, W.; Jagadeesan, D.; Nasimova, I.; Greener, J.; Kumacheva, E. Kinetics of multicomponent polymerization reaction studied in a microfluidic format. Macromolecules 2012, 45, 4469–4475.
5 Knox, S. T.; Parkinson, S.; Stone, R.; Warren, N. J. Benchtop flow-NMR for rapid online monitoring of RAFT and free radical polymerization in batch and continuous reactors. Polym. Chem. 2019, 10, 4774–4778.
6 Wilms, D.; Klos, J.; Frey, H. Microstructured reactors for polymer synthesis: a renaissance of continuous flow processes for tailormade macromolecules? Macromol. Chem. Phys. 2008, 209, 343–356.
7 Geacintov, C.; Smid, J.; Szwarz, M. Kinetics of anionic polymerization of styrene in tetrahydrofuran. J. Am. Chem. Soc. 1962, 84, 2508–2514.
8 Matyjaszewski, K. Comparison and classification of controlled/living radical polymerizations. In Controlled/living radical polymerization, American Chemical Society, Washington, DC, 2000, Vol. 768, pp 2–26.
9 Braunecker, W. A.; Matyjaszewski, K. Controlled/living radical polymerization: features, developments, and perspectives. Prog. Polym. Sci. 2007, 32, 93–146.
10 Chiefarì, J.; Chong, Y. K.; Ercole, F.; Kristina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. Living free-radical polymerization by reversible addition-fragmentation chain transfer: the RAFT process. Macromolecules 1998, 31, 5559–5562.
11 Wang, J. S.; Matyjaszewski, K. Controlled living radical polymerization—atom-transfer radical polymerization in the presence of transition-metal complexes. J. Am. Chem. Soc. 1995, 117, 5614–5615.
12 Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. Polymerization of methyl-methacrylate with the carbon-tetrachloride dichlorotris(triphenylphosphine)ruthenium(ii) methylaluminum bis(2,6-di-tert-butyloxophenoxide) initiating system-possibility of living radical polymerization. Macromolecules 1995, 28, 1721–1723.
13 Hawker, C. J.; Bosman, A. W.; Harth, E. New polymer synthesis by nitroxide mediated living radical polymerizations. Chem. Rev. 2001, 101, 3661–3688.
14 Yagci, Y.; Jockusch, S.; Turro, N. J. Photoinitiated polymerization: advances, challenges, and opportunities. Macromolecules 2010, 43, 6245–6260.
15 Tehfe, M. A.; Louradour, F.; Laléeve, J.; Fouassier, J. P. Photopolymerization reactions: on the way to a green and sustainable chemistry. Appl. Sci. 2013, 3, 490–514.
16 Yamago, S.; Nakamura, Y. Recent progress in the use of photoirradiation in living radical polymerization. Polymer 2013, 54, 981–994.
17 Gong, H.; Ma, M.; Zhou, Y.; Zhao, Y.; Gu, Y.; Chen, M. Photoredox controlled living polymerization. J. Funct. Polym. 2019, 32, 271–291.
18 Shen, L. L.; Lu, Q. Z.; Zhu, A. Q.; Lv, X. Q.; An, Z. S. Photocatalyzed RAFT polymerization mediated by a supramolecular catalyst. ACS Macro Lett. 2017, 6, 625–631.
19 Yang, Y. Q.; An, Z. S. Visible light induced aqueous RAFT polymerization using a supramolecular perylene diimide/cucurbit 7 uril complex. Polym. Chem. 2019, 10, 2801–2811.
20 Li, S. Z.; Han, G.; Zhang, W. Q. Photoregulated reversible addition-fragmentation chain transfer (RAFT) polymerization. Polym. Chem. 2020, 11, 1830–1844.
21 Corrigan, N.; Almasri, A.; Taillades, W.; Xu, J.; Boyer, C. Controlling molecular weight distributions through photoinduced flow polymerization. Macromolecules 2017, 50, 8438–8448.
22 Pan, X. C.; Tasdelen, M. A.; Laun, J.; Junkers, T.; Yagci, Y.; Matyjaszewski, K. Photomediated controlled radical polymerization. Prog. Polym. Sci. 2016, 62, 73–125.
23 Cambie, D.; Bottecchia, C.; Straathof, N. J.; Hessel, V.; Noel, T. Applications of continuous-flow photochemistry in organic synthesis, material science, and water treatment. Chem. Rev. 2016, 116, 10276–10341.
24 Nie, H. J.; Li, S. Z.; Qian, S. J.; Han, Z. Q.; Zhang, W. Q. Switchable reversible addition-fragmentation chain transfer (RAFT) polymerization with the assistance of azobenzenes. Angew. Chem. Int. Ed. 2019, 58, 11449–11453.
25 Zhang, Y. X.; He, J. J.; Dai, X. C.; Yu, L. L.; Tan, J. B.; Zhang, L. Combining the power of heat and light: temperature-programmed photoinitiated RAFT dispersion polymerization to tune polymerization-induced self-assembly. Polym. Chem. 2019, 10, 3902–3911.
26 Shanmugam, S.; Xu, J. T.; Boyer, C. A logic gate for external regulation of photopolymerization. Polym. Chem. 2016, 7, 6437–6449.
27 Chen, M.; Deng, S.; Gu, Y.; Lin, J.; MacLeod, M. J.; Johnson, J. A. Logic-controlled radical polymerization with heat and light: multiple-stimuli switching of polymer chain growth via a recyclable, thermally responsive gel photoredox catalyst. J. Am. Chem. Soc. 2017, 139, 2257–2266.
28 Wu, C.; Chen, H.; Corrigan, N.; Jung, K.; Kan, X.; Li, Z.; Liu, W.; Xu, J.; Boyer, C. Computer-guided discovery of a pH-responsive organic photocatalyst and application for pH and light dual-gated polymerization. J. Am. Chem. Soc. 2019, 141, 8207–8220.
29 Anastassiou, A.; Nikolau, V.; Pappas, G. S.; Zhang, Q.; Han, C.; Wilson, P.; Davis, T. P.; Whittaker, M. R.; Haddleton, D. M. Photoinitiated sequence-control via one pot living radical polymerization of acrylates. Chem. Sci. 2014, 5, 3536–3542.
30 Tanaka, J.; Hakkinen, S.; Boece, P. T.; Cong, Y.; Perrier, S.; Sheikh, S. S.; You, W. Orthogonal cationic and radical RAFT polymerizations to prepare bottlebrush polymers. Angew. Chem. Int. Ed. 2020, 59, 7203–7208.
31 Zhao, Y.; Ma, M.; Lin, X.; Chen, M. Photoorganocatalyzed divergent reversible-deactivation radical polymerization towards linear and branched fluoropolymers. Angew. Chem. Int. Ed. 2020, 59, 21470–21474.
32 Han, S.; Gu, Y.; Ma, M.; Chen, M. Light-intensity switch enabled nonsynchronous growth of fluorinated raspberry-like nanoparticles. Chem. Sci. 2020, 11, 10431–10436.
33 Sebra, R. P.; Reddy, S. K.; Masters, K. S.; Bowman, C. N.; Anseth, K. S. Controlled polymerization chemistry to graft architectures that influence cell-material interactions. Acta Biomater. 2007, 3, 151–161.
34 Jiang, K. M.; Han, S. T.; Ma, M. Y.; Zhang, L.; Zhao, Y. C.; Chen, M. Photoorganocatalyzed reversible-deactivation alternating copolymerization of chlorotrifluoroethylene and vinyl ethers under ambient conditions: facile access to main-chain fluorinated copolymers. J. Am. Chem. Soc. 2020, 142, 7108–7115.
35 Bai, H. D.; Huang, Z. H.; Yang, W. T. Visible light-induced living surface grafting polymerization for the potential biological applications. J. Polym. Sci., Part A: Polym. Chem. 2009, 47,

https://doi.org/10.1007/s10118-021-2529-8
polydispersity in tubular RAFT miniemulsion polymerization. 

AlChE J. 2006, 52, 1566–1576.

57 Hu, X.; Zhu, N.; Fang, Z.; Guo, K. Continuous flow ring-opening polymerizations. React. Chem. Eng. 2017, 2, 20–26.

58 Danckwerts, P. V. Continuous flow systems. Continuous flow systems. Distribution of residence times. Chem. Eng. Sci. 1995, 50, 3855.

59 Reis, M. H.; Varner, T. P.; Leibfarth, F. A. The influence of residence time distribution on continuous-flow polymerization. Macromolecules 2019, 52, 3551–3557.

60 Song, Y.; Song, J.; Shang, M.; Xu, W.; Liu, S.; Wang, B.; Lu, Q.; Su, Y. Hydrodynamics and mass transfer performance during the chemical oxidative polymerization of aniline in microreactors. Chem. Eng. J. 2018, 353, 769–780.

61 Tumarkin, E.; Kumacheva, E. Microfluidic generation of micorgels from synthetic and natural polymers. Chem. Soc. Rev. 2009, 38, 2161–2168.

62 Xu, S. Q.; Nie, Z. H.; Seo, M.; Lewis, P.; Kumacheva, E.; Stone, H. A.; Garstecki, P.; Weibel, D. B.; Gitlin, I.; Whitesides, G. M. Generation of monodisperse particles by using microfluidics: control over size, shape, and composition. Angew. Chem. Int. Ed. 2005, 44, 724–728.

63 Daniloska, V.; Tomosovka, R.; Asua, J. M. Designing tubular reactors to avoid clogging in high solids miniemulsion polymerization. Chem. Eng. J. 2013, 222, 136–141.

64 Liu, Z.; Lu, Y.; Yang, B.; Luo, G. Controllable preparation of poly(butyl acrylate) by suspension polymerization in a coaxial capillary microreactor. Ind. Eng. Chem. Res. 2011, 50, 11853–11862.

65 Corrigan, N.; Manahan, R.; Lew, Z. T.; Yeow, J.; Xu, J. T.; Boyer, C. Copolymers with controlled molecular weight distributions and compositional gradients through flow polymerization. Macromolecules 2018, 51, 4533–4563.

66 Corrigan, N.; Zhermakov, L.; Hashim, M. H.; Xu, J.; Boyer, C. Flow mediated metal-free PETRAFT polymerisation for upscaled and consistent polymer production. React. Chem. Eng. 2019, 4, 1216–1228.

67 Zhou, Y.; Gu, Y.; Jiang, K. M.; Chen, M. Droplet-flow photopolimerization aided by computer: overcoming the challenges of viscosity and facilitating the generation of copolymer libraries. Macromolecules 2019, 52, 5611–5617.

68 Kohler, J. M.; Li, S. N.; Knauer, A. Why is micro segmented flow particularly promising for the synthesis of nanomaterials? Chem. Eng. Technol. 2013, 36, 887–899.

69 Noel, T.; Buchwald, S. L. Cross-coupling in flow. Chem. Soc. Rev. 2011, 40, 5010–5029.

70 Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J. Photodimerisation of maleic anhydride in a microreactor without clogging. Org. Process Res. Dev. 2010, 14, 405–410.

71 DesLauriers, P. J.; McDaniel, M. P.; Rohlffing, D. C.; Krishnaswamy, R. K.; Secora, S. J.; Benham, E. A.; Maeger, P. L.; Wolfe, A. R.; Sukhadiia, A. M.; Beaulieu, B. B. A comparative study of multimodal vs. bimodal polyethylene pipe resins for PE-100 applications. Polym. Eng. Sci. 2005, 45, 1203–1213.

72 Kukalyekar, N.; Balzano, L.; Desai, P. R.; Peters, G. W. M.; Rastogi, S.; Chaddick, J.; Marten, H. C.; Whitaker, R. W. M. Oxygen tolerant aqueous RAFT photopolymerization. Macromol. Rapid. Commun. 2017, 38, 1–19.

73 Taylor, G. Dispersion of soluble matter in solvent flowing slowly through a tube. Proc. Math. Phys. Eng. Sci. 1997, 219, 186–203.

74 Russum, J. P.; Jones, C. W.; Schork, F. J. Impact of flow regime on
Zhong, Z. R. et al. / Chinese J. Polym. Sci. 2021, 39, 1069–1083

75 Gong, H.; Zhao, Y.; Shen, X.; Lin, J.; Chen, M. Organocatalyzed photocontrolled radical polymerization of semifluorinated (meth)acrylates driven by visible light. Angew. Chem. Int. Ed. 2018, 57, 333–337.

76 Morsbach, J.; Müller, A. H. E.; Berger-Nicoletti, E.; Frey, H. Living polymer chains with predictable molecular weight and dispersity via carbanionic polymerization in continuous flow: mixing rate as a key parameter. Macromolecules 2016, 49, 5043–5050.

77 Endo, Y.; Furusawa, M.; Shimazaki, T.; Takahashi, Y.; Nakahara, Y.; Nagaki, A. Molecular weight distribution of polymers produced by anionic polymerization enables mixibility evaluation. Org. Process Res. Dev. 2019, 23, 635–640.

78 Nagaki, A.; Miyazaki, A.; Yoshida, J. I. Synthesis of polystyrenes-poly(alkyl methacrylates) block copolymers via anionic polymerization using an integrated flow microreactor system. Macromolecules 2010, 43, 8424–8429.

79 Nagaki, A.; Kawamura, K.; Suga, S.; Ando, T.; Sawamoto, M.; Yoshida, J. Cation pool-initiated controlled/living polymerization using microsystems. J. Am. Chem. Soc. 2004, 126, 14702–14703.

80 Wang, E.; Chen, M. Catalyst shuffling enabled by a thermo-responsive polymeric ligand: facilitating efficient cross-couplings with continuously recyclable ppm levels of palladium. Chem. Sci. 2019, 10, 8331–8337.

81 Zhong, F.; Zhou, Y.; Chen, M. The influence of mixing on chain extension by photo-controlled/living radical polymerization under continuous-flow conditions. Polym. Chem. 2019, 10, 4879–4886.

82 Yeow, J.; Boyer, C. Photoinitiated polymerization-induced self-assembly (photo-PISA): new insights and opportunities. Adv. Sci. 2017, 4, 1700137.

83 Warren, N. J.; Armes, S. P. Polymerization-induced self-assembly of block copolymer nano-objects via RAFT aqueous dispersion polymerization. J. Am. Chem. Soc. 2014, 136, 10174–10185.

84 Zeng, R. M.; Chen, Y.; Zhang, L.; Tan, J. B. R-RAFT or Z-RAFT? One-step photocontrolled polymerization-induced self-assembly (photo-PISA) by using in situ bromine-iodine transformation reversible-deactivation radical polymerization. Polymers 2020, 12, 150.

85 Zaquen, N.; Yeow, J.; Junkers, T.; Boyer, C.; Zetterlund, P. B. Visible light-mediated polymerization-induced self-assembly using continuous flow reactors. Macromolecules 2018, 51, 5165–5172.

86 Zaquen, N.; Azizi, W. A. A. W.; Yeow, J.; Kuchel, R. P.; Junkers, T.; Zetterlund, P. B.; Boyer, C. Alcohol-based PISA in batch and flow: exploring the role of photoinitiators. Polym. Chem. 2019, 10, 2406–2414.

87 Quan, Q.; Gong, H.; Chen, M. Preparation of semifluorinated poly(meth)acrylates by improved photo-controlled radical polymerization without the use of a fluorinated RAFT agent: facilitating surface fabrication with fluorinated materials. Polym. Chem. 2018, 9, 4161–4171.

88 Zaquen, N.; Zu, H.; Kadir, A. M. N. B. P. H. A.; Junkers, T.; Zetterlund, P. B.; Boyer, C. Scalable aqueous reversible addition-fragmentation chain transfer photopolymerization-induced self-assembly of acrylamides for direct synthesis of polymer nanoparticles for potential drug delivery applications. ACS Appl. Polym. Mater. 2019, 1, 1251–1256.

89 Liu, D.; Cai, W.; Zhang, L.; Boyer, C.; Tan, J. Efficient photoinitiated polymerization-induced self-assembly with oxygen tolerance through fuel-wavelength type I photoinitiation and photoinduced deoxygenation. Macromolecules 2020, 53, 1212–1223.

90 Lin, B.; Hedrick, J. L.; Park, N. H.; Waymouth, R. M. Programmable high-throughput platform for the rapid and scalable synthesis of polyester and polycarbonate libraries. J. Am. Chem. Soc. 2019, 141, 8921–8927.

91 van de Walle, M.; De Bruycker, K.; Junkers, T.; Blinco, J. P.; Barner-Kowollik, C. Scalable synthesis of sequence-defined oligomers via photoflow chemistry. ChemPhotoChem 2019, 3, 225–228.

92 Walsh, D. J.; Schinski, D. A.; Schneider, R. A.; Guironnet, D. General route to design polymer molecular weight distributions through flow chemistry. Nat. Commun. 2020, 11, 3094.

93 Harper, K. C.; Moschetta, E. G.; Bordawekar, S. V.; Wittenberger, S. J. A laser driven flow chemistry platform for scaling photochemical reactions with visible light. ACS Cent. Sci. 2019, 5, 109–115.

94 Laudadio, G.; Deng, Y.; van der Wal, K.; Ravelli, D.; Nuho, M.; Fagnoni, M.; Guthrie, D.; Sun, Y.; Noël, T. Cisp3-H functionalizations of light hydrocarbons using decatungstate photocatalysis in flow. Science 2020, 369, 92–96.

95 Ge, L.; Yan, J.; Song, X.; Yan, M.; Ge, S.; Yu, J. Three-dimensional paper-based electrochemiluminescence immunodevice for multiplexed measurement of biomarkers and point-of-care testing. Biomaterials 2012, 33, 1024–1031.

96 Yeo, L. Y.; Chang, H. C.; Chan, P. P.; Friend, J. R. Microfluidic devices for bioapplications. Small 2011, 7, 12–48.

97 Rubens, M.; Vrijisen, J. H.; Laun, J.; Junkers, T. Precise polymer synthesis by autonomous self-optimizing flow reactors. Angew. Chem. Int. Ed. 2019, 58, 3183–3187.

98 Gentekos, D. T.; Siﬁ, R. J.; Fors, B. P. Controlling polymer properties through the shape of the molecular-weight distribution. Nat. Rev. Mater. 2019, 4, 761–774.

99 Whitfield, R.; Truong, N. P.; Messmer, D.; Parkatzidis, K.; Rolland, M.; Anastasakil, A. Tailoring polymer dispersity and shape of molecular weight distributions: methods and applications. Chem. Sci. 2019, 10, 8724–8734.

https://doi.org/10.1007/s10118-021-2529-8