Flow Chemistry as a Platform for Experimental Multi-objective Optimization of Heterogeneous Polymer Synthesis

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Introduction

The traditional discovery of functional polymers has long been hindered by the vastness of chemical parameter space and the labor-intensive nature of Edisonian experimentation. Within the wider chemical synthesis community, automated reactors underpinned by AI-directed optimization frameworks have been shown to autonomously navigate multi-dimensional reaction spaces to achieve multi-objective goals. These so-called "self-driving laboratories" come in a variety of formats, ranging from static or mobile robots, gantry-based liquid handlers through to (micro)fluidic reactor platforms. [1-5] The latter technology typically uses automated liquid handling to control the flow of material through a temperature-controlled reactor geometry (normally a tube). The ability to easily automate these systems has resulted in a wide array of microfluidic self-driving labs for small-molecule chemistry and nanomaterials synthesis.[4, 6-8]

In polymer chemistry, flow has been used for anionic, free-radical and reversible deactivation radical polymerization.[9] Furthermore, the integration of online analytics has gradually evolved towards the ability to rapidly screen polymerisation parameter space;[10] conduct self-optimization campaigns to target molecular weights,[11] predefined monomer conversion[12] or conduct multi-objective Bayesian optimization.[13] Herein, we describe our work which has realised the ability to conduct self-optimization of heterogeneous polymerisation.

Self-driving polymerization platforms

Many industrially and academically important polymerization systems rely on the reaction occurring in a heterogeneous environment, which can be much more difficult to transfer into flow reactors. Our initial work focussed on transferring Reversible addition fragmentation chain transfer polymerization (RAFT) mediated Polymerization-Induced Self-Assembly (PISA) into flow. PISA involves the synthesis of an amphiphilic block copolymer which undergoes in-situ self-assembly to form well-defined nanoparticles. We first demonstrated this in flow for the polymerization of diacetone acrylamide in the presence of a polydimethylacrylamide precursor polymer using a rudimentary system comprising a pump and stainless-steel reactor. This was effectively used to synthesise nanoparticle dispersions but fouling of the stainless steel meant prolonged operation was not possible. [14] This was mitigated by moving to perfluoroalkane (PFA) tubing and using faster chemistry (using a more reactive initiator) which sped the reaction up to the extent full conversion could be achieved in 10 minutes (down from ~1h).[15] This "ultrafast" PISA process presented a model system for developing and evaluating a suite of online monitoring techniques suited to heterogeneous systems. Benchtop NMR was used to monitor conversion of this process in real-time, with subtle rate changes being discerned in the high-resolution data[16].

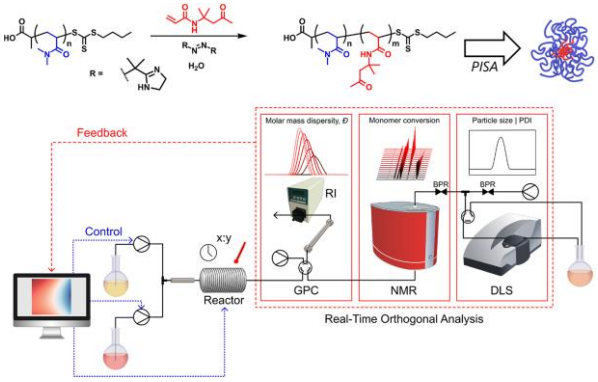

Figure 1. Overview of the RAFT-PISA for formation of nanoparticles, and the SDL integrating a flow reactor and online GPC, ^{1}H NMR spectroscopy and DLS. Reproduced from Knox et al, Polym. Chem., 2025,16, 1355-1364.[18]

Through the development of an in-line light scattering instrument in tandem with benchtop flow-NMR it was also possible to target particle size for a PISA process.[17]

Importantly, several of these established techniques, alongside our self-optimization workflow for RAFT solution polymerization[13]

provided the foundation for the evolution of a Self-driving lab for conducting PISA. The know-how developed facilitated the development of SDL for monitoring all critical parameters which determine the quality of the polymer nanomaterials produced via PISA.[18] This comprised a two-pump flow-reactor which led to a switching valve which extracted sample for online gel permeation chromatography (GPC; for molecular weight distribution determination), then directly through a benchtop NMR spectrometer (for conversion determination) and then via a second switching valve which extracted sample for dynamic light scattering (DLS; nanoparticle size and polydispersity determination).

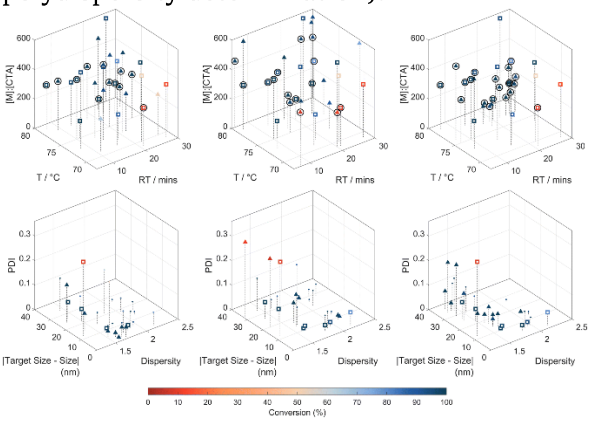

Figure 2: Comparison of the three optimization algorithms selected for this work in targeting 80 nm particles (a) TSEMO, (b) RBFNN/RVEA and (c) EA-MOPSO. Reproduced from Knox et al, Polym. Chem., 2025,16, 1355-1364.[18]

This configuration allowed for the efficient navigation of a complex, multi-dimensional parameter space. Initially, this was exemplified through a full factorial 64 experiment screen which facilitated the ability to map the reaction parameter space in order to evaluate three optimization approaches with a view to achieving a series of optimization goals targeting: (1) maximum monomer conversion (2) minimum molar mass dispersity (3) targeting 80 nm nanoparticles (4) minimising particle polydispersity.

Initially, the mapped space was used as a model to evaluate the algorithms *in silico* including Thompson sampling efficient multi-objective optimization (TSEMO), radial basis function neural network/reference vector evolutionary algorithm (RBFNN/RVEA) and multi objective particle swarm optimization, hybridised with an evolutionary algorithm (EA-MOPSO). These were then effectively evaluated directly on the platform via a cloud-based framework to elucidate a series of Pareto-optimal samples. Whilst minimal difference in performance was observed it was noted that each algorithm tended to explore different regions of the parameter space.

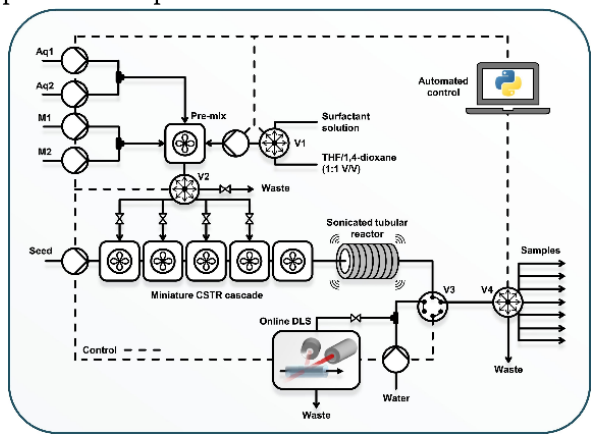

Figure 3: Outline of the autonomous flow reactor platform for conventional free-radical emulsion polymerization. Reproduced from Pittaway et al, Chem. Eng. J. 2025, 507, 160700.[19]

In our second-generation platform, a similar methodology was applied to free-radical emulsion polymerization of styrene.[19] In this case a different platform was developed to target a particle size, whilst minimising the concentration of key components (surfactant and seed-particles). Again, an *in silico* methodology was used to evaluate an adapted TSEMO optimization method which consecutively maximised and minimised particle size. This enabled a mapping of achievable particle sizes within a defined parameter space. This process was then executed on the physical platform providing a real insight into the feasible outcomes.

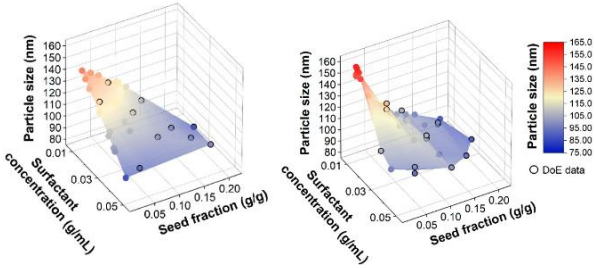

Figure 4: Fig. 9. *In silico* (left) and experimental (right) particle size mapping optimization campaigns to screen particle size. From Pittaway et al, Chem. Eng. J. 2025, 507, 160700.[19]

It is clear from this activity, that SDLs present an exciting opportunity in polymer chemistry. This is particularly relevant in a time where there is a critical need for sustainable, high-performing and affordable polymers.

Acknowledgments
The Engineering and Physical Sciences Research Council are thanked for funding this work through EPSRC grants EP/S000380/1 and EP/V0055089/2.

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