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Transforming Nanomaterial Synthesis with Flow Chemistry

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Abstract: Microfluidic methods for the synthesis of nanomaterials allow the generation of high-quality products with outstanding structural, electronic and optical properties. At a fundamental level, this is engendered by the ability to control both heat and mass transfer in a rapid and precise manner, but also by the facile integration of in-line characterization tools and machine learning algorithms. Such integrated platforms provide for exquisite control over material properties during synthesis, accelerate the optimization of electronic and optical properties and bestow new insights into the optoelectronic properties of nanomaterials. Herein, we present a brief perspective on the role that microfluidic technologies can play in nanomaterial synthesis, with a particular focus on recent studies that incorporate in-line optical characterization and machine learning. We also consider the importance and challenges associated with integrating additional functional components within experimental workflows and the upscaling of microfluidic platforms for production of industrial-scale quantities of nanomaterials.

Keywords: Flow chemistry · Microfluidics · Nanomaterials · Synthesis

1. Introduction

Colloidal nanomaterials have been the subject of enormous attention in recent decades owing to their size-dependent chemical, optical, magnetic, and electronic properties.[1] They have engendered significant advances in a variety of applications, including energy harvesting, chemical sensing, drug delivery and therapeutics.[2] Key to their utility in real-world applications is the ease with which bottom-up synthetic routes may be optimized to produce materials with user-defined properties in sufficient quantity. Traditional approaches for synthesizing colloidal nanomaterials are flask-based and, whilst simple to perform and scale-up, are typically inefficient, slow and difficult to optimize. These features present a distinct challenge to the experimentalist and obstruct efficient material discovery and optimization.[3] Fortunately, all of these issues may be avoided by the adoption of flow-based rather than batch reactors. Indeed, over the past three decades, ‘flow chemistry’ has become an invaluable technique for the synthesis of a wide variety of small molecules,[4] macromolecules,[5] and materials.[6] In flow chemistry, reactions are performed in continuously flowing streams (that can comprise a single fluid phase or multiple phases) rather than in a fixed batch reactor. Flow reactors can be formed from a single conduit (such as tubing, a capillary or channel) or combine multiple functional components (such as mixers, extractors and filters) in a more complex and integrated workflow.[7] In this perspective, we provide a brief discussion of the use of flow chemistry in the synthesis of nanomaterials, highlighting important past and current contributions to the field, and suggesting exciting new avenues for flow chemistry in the future.

2. Flow Chemistry for Nanomaterial Synthesis

Flow chemistry can be performed using a variety of platforms, instruments and techniques, which vary according to the needs of the experiment. As the name suggests, all flow chemical methods aim to perform a reactive process within a moving fluid stream. That said, almost all flow chemistry reactors can be classified as operating in either a continuous-flow or segmented-flow regime (Fig. 1a). In continuous-flow reactors, reagents are delivered and react within a single fluid phase, whilst in segmented-flows, droplets are generated by combining two immiscible phases and used to form isolated vessels in which to perform reactions. Each format offers the experimentalist different features and advantages. Briefly, continuous flow formats are simple to assemble and able to process almost all fluids, whilst segmented-flow (or droplet-based) reactors are ideally suited for high-throughput operation, allowing the optimization of reactive processes in a time- and cost-efficient manner. Interested readers are referred to some excellent articles elsewhere that provide a more detailed exploration of the background and use of these techniques in synthetic and materials chemistry.[7–10]

At a general level, flow chemical methods are advantageous since both thermal and mass transport are enhanced when compared to their macroscale analogues. This is a direct result of the increase in surface area-to-volume ratio as reaction environments are downsized, and means that both solute and temperature gradients may be created or homogenized in a rapid and precise manner.[7] In turn, this ensures exquisite control of the reaction environment and minimal experiment-to-experiment variability. For reaction optimization, the adoption of microfluidic components guarantees the efficient use of precious reagents, enabling researchers to rapidly perform reactions under several different experimental conditions, whilst limiting sample consumption. Finally, it should not be forgotten that flow chemical methods are adept at performing reactions that are problematic on larger scales; for example, when operating at high pressures[11] or when using volatile or toxic chemicals.[12]

The benefits of performing reactions in flow have been shown to be especially significant when synthesizing nanomaterials. The small reaction volumes and uniform conditions associated with such formats are highly beneficial in exerting control over nanocrystallite properties, such as size, shape and dispersity. This is crucial, since structural features commonly impact functionality. An excellent example in this regard are compound semiconductor nanomaterials (or quantum dots), where both the average particle size and population dispersity directly influence their band gap

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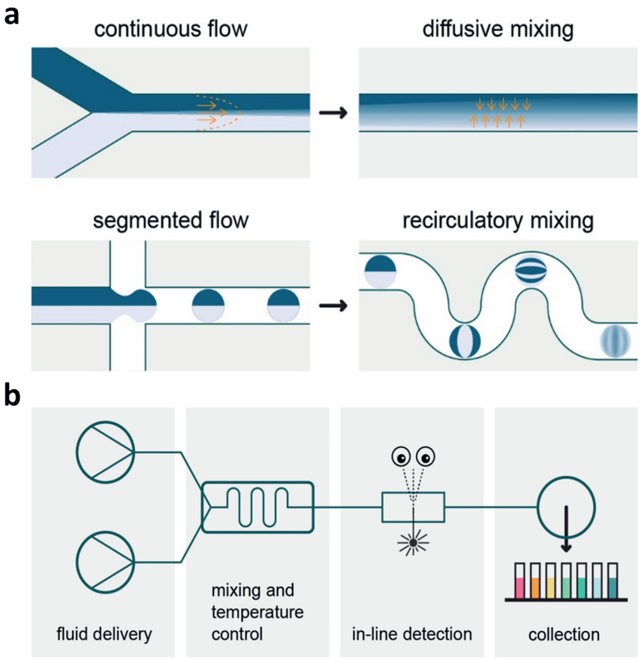

Fig. 1. (a) Typical flow regimes in a standard microfluidic flow reactor. Continuous-flow regimes are generally characterized by low Reynolds numbers, resulting in diffusive mixing and laminar flows. The use of segmented-flows enhances mixing *via* chaotic advection and minimizes residence time distributions. (b) Schematic of a basic flow reactor system for nanomaterial synthesis. The system consists of fluid delivery, a reaction zone and collection. Simple flow reactors can be made from low-cost components. Both off-the-shelf and custom-made systems have been reported in the literature.

energies, emission wavelengths and colour purity; characteristics that modulate their efficacy in optoelectronic applications (*e.g.* solar cells and LEDs).[8] Further, the ease of integration of in-line detection and analysis in flow (most notably using optical spectroscopy) allows for real-time measurement of material properties *in situ*, providing information on reaction kinetics, or as an end-point measure of final nanomaterial characteristics.[9] This feature has allowed researchers to harness the technique as a powerful tool in high-throughput experimentation (HTE).[3] Fig. 1b shows a schematic of the basic requirements for an effective nanomaterial synthesis and analysis platform.

Although the advantages of flow chemistry are well-recognized, challenges remain and affect our ability to fully harness its true potential. First, whilst reactions can be performed to generate material in a continuous fashion, the small instantaneous volumes limit production rates (space-time yields) of even well-optimized reactions. Reactions cannot be 'scaled-up' in the normal sense, since the advantages engendered by microscale operation will be lost, and thus the concepts of 'scale-out' or 'numbering-up' must be used to generate production-scale quantities. Second, whilst the adoption of small-scale channels or tubing is advantageous with respect to controlling heat and mass transport, fouling and blockage become issues that often prevent application in real-world situations. In this regard, the adoption of segmented-flow formats can be especially valuable, since droplets or plugs contained within an immiscible carrier fluid are isolated from the reactor surface.[13] Finally, many chemistries can be difficult to reliably perform using flow chemistry and require significant process optimization. This is especially true for reactions involving solid-phase chemistry or significant work-up/purification. In these situations, new technologies and methods must be developed on a case-by-case basis.

3.The Early Years

In 2002, Edel and co-workers first proposed the use of a microfluidic reactor for nanoparticle synthesis, reasoning that reductions in scale would lead to significant gains in controlling both the chemical and thermal environment of a reaction.[14] In the ensuing years, there have been a plethora of reports describing the use of microfluidics for nanomaterial synthesis.[15,16] These studies have varied widely in terms of the target material and system complexity, but all leverage to some extent the unique features of flow-based experimentation. Popular experimental innovations include the incorporation of precise temperature control,[17,18] the use of in-line detectors,[19] greatly reduced sample consumption,[20] the integration of multistage processes,[21] the integration of liquid–liquid phase separators to recover product contained in the discrete phase[22] and the use of machine learning algorithms for smart reactor operation.[23,24] We now highlight a select number of early and noteworthy studies, in which microfluidic tools added value to the nanomaterial chemist's toolbox.

As discussed, the ability to precisely regulate temperature within microfluidic system is especially useful in exerting control over both nucleation and nanoparticle growth. Excellent early examples in this regard were reported by Nightingale *et al.*[17] and Chan *et al.*,[18] who demonstrated highly controlled growth of CdSe nanocrystals at temperatures up to 300 °C (Fig. 2a). In addition, a number of research groups very quickly realised the value in integrating optical detectors to probe product quality in a rapid, in-line and efficient manner. For example, Krishnadasan and co-workers reported the use of a continuous-flow microfluidic reactor to synthesize CdSe nanocrystals, where product quality was assessed by monitoring the time-integrated photoluminescence (PL) of product exiting the reactor.[19]

Such an approach enabled the authors to rapidly assess the influence of reaction temperature, flow rates and reaction time on product characteristics. This basic method was further refined by inclusion of a low-level machine learning algorithm that assessed the 'quality' of the product and updated the synthesis parameters to ensure optimum optical performance of the produced nanoparticles.[25]

As noted, adoption of droplet- or segmented-flows, brings a number of advantages with regard to synthetic robustness and experimental throughput. Unsurprisingly, droplet-based systems have become the preferred format for flow-based syntheses of nanomaterials. Excellent early studies showcasing these features include the millisecond synthesis of CdS and CdS/CdSe core-shell nanoparticles,[13] the synthesis of gold nanorods using an oscillatory segmented-flow reactor with *in situ* UV-vis spectroscopy,[20] and the investigation of the kinetics of PbS nanoparticle nucleation and growth using in-line photoluminescence and absorbance spectroscopy.[26] The latter study highlights the importance of efficient and rapid product analysis particularly well, with similar systems being applied to the synthesis of a range of other nanomaterials, including hybrid organic–inorganic and fully inorganic lead halide perovskite nanocrystals.[27–29]

Whilst some nanomaterials may be directly generated in a single synthetic step, others require more elaborate workflows. In this regard, Jensen and co-workers presented an elegant multistage, high-temperature and high-pressure reactor platform for the synthesis of a range of III–V core/shell quantum dots.[21] Significantly, the modular nature of the platform enables processes such as reactant mixing, aging, sequential growth, shell formation and annealing to be performed in a user-defined manner, with the final stage of the system being connected to a detection unit for in-line optical characterization.

Perhaps, the most significant technical development in flow chemistry has been the integration of machine learning algorithms to stabilise system operation[30] or target bespoke reaction outputs.[24] For example, Epps *et al.*[31] demonstrated the synthesis of

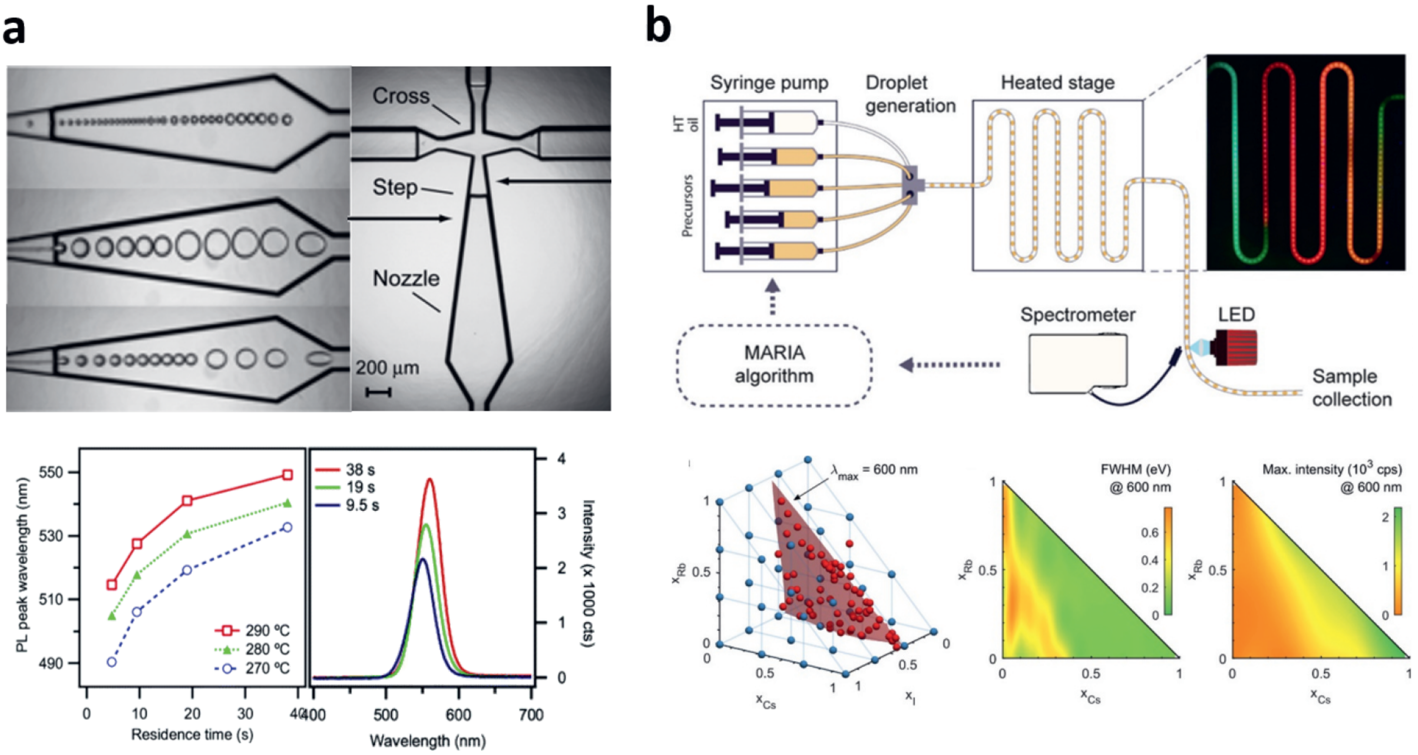

Fig. 2. (a) Top: A microfluidic reactor for CdSe nanoparticle synthesis, showing the droplet generation region, as well as droplet formation. Bottom: Growth curves of peak wavelength vs residence time at different temperatures and online emission spectra at different growing times, determined through residence time variation at 290 °C. Adapted from Chan *et al*.[18] (b) Top: Overview of the experimental setup for the synthesis of (Cs/FA) $Pb(Br/I)_3$ NCs (FA = formamidinium) using the multiparametric automated regression kriging interpolation and adaptive sampling (MARIA) algorithm. Bottom: Example of a $(Rb/Cs/FA)Pb(Br/I)_3$ NC synthesis in which the Cs doping, Rb doping and halide ratio were optimized for maximal emission intensity. Adapted from Bezinge *et al*.[24]

$CsPbBr_3$ nanoparticles in an automated, segmented-flow reactor equipped with an optical flow cell. Interestingly, the authors developed an optical velocity and length sensor (OVAL) comprising a 'slug-counting' algorithm to control liquid slug length and velocity within multiphase flows.[30] Additionally, Bezinge *et al*.[24] developed a Multiparametric Automated Regression Kriging Interpolation and Adaptive sampling algorithm (MARIA) to guide microfluidic reaction workflows and identify reaction conditions that yield tailored $(Cs/FA)Pb(Br/I)_3$ and $(Rb/Cs/FA)Pb(Br/I)_3$ nanocrystals with outstanding optical properties (Fig. 2b).

4. Contemporary Applications and Innovations

When assessing the utility and impact of 'smart' or 'intelligent' microfluidic platforms for nanomaterial synthesis, the distinctions between automation, autonomy *via* algorithmic optimization, and autonomy *via* optimization through machine learning, are important. For clarity, 'automation' describes the operation of a microfluidic reactor independent of human influence during use with a predetermined experimental protocol, as demonstrated by Knauer *et al*.[32] There is no decision making or change of the experimental parameters independent of the protocol. An 'autonomous' microfluidic reactor on the other hand distinguishes itself through direct control over reaction parameters outside of predetermined protocols, as shown by Malmstadt and co-workers.[33] In recent years, significant advances in the automation of microfluidic reactors for nanomaterial synthesis have been reported. For example, Knauer *et al*.[32] reported the use of a tube-based, segmented-flow reactor to synthesize gold nanorods. Importantly, use of an automated flow rate program and a multichannel absorbance sensor enabled rapid and comprehensive parametric scans, yielding new information regarding the electrostatic properties and morphology of non-spherical metal nanoparticles. In a similar fashion, Cai and co-workers presented an automated microfluidic reactor for the study of branched gold nanostructures in continuous flow.[34] The platform is able to robustly synthesize gold in a variety of 'nanoshapes', with in-flow isolation of reaction intermediates providing the opportunity to follow nanoparticle growth and deformation (Fig. 3). Very recently, a centrifugal microfluidic reactor, developed by Nguyen and colleagues, was used to generate and screen branched gold nanoparticles in a high-throughput manner.[35] Such a screening approach allowed the production of an array of nanoparticle morphologies without human interference and in a fully-automated fashion.

The development of self-optimized and autonomous systems has continued apace in recent years, with most optimization algorithms operating by starting with an initial guess of reaction conditions (based on user intuition or an existing database) and then finding new conditions that allow the production of a bespoke material, most often defined by its photophysical properties. For example, Malmstadt and co-workers recently used a multichannel, gas-liquid flow reactor to perform high-throughput $CsPbBr_3$ nanomaterial synthesis in a feedback-controlled manner.[33] Significantly, feedback control was used to optimize the optical properties of the product and allow scaled-up production. Similarly, Bui *et al.* used a hysteresis algorithm to track the synthesis of $MAPbBr_XI_{3-X}$ quantum dots in a tube-based microfluidic reactor with in-line PL detection,[36] with the algorithm going through an iterative feedback control process, which is terminated when the observed peak wavelength of the emission of the nanoparticles matches a predefined target emission wavelength. The implementation of algorithmic optimization in multistage platforms has also seen much progress. For example, Pinho *et al*.[37] demonstrated a sophisticated and self-optimized microfluidic platform with multiple flow cells for absorption tracking of seed-mediated particle growth. Here, optimization is based on a golden section algorithm that distinguished itself through its sim-

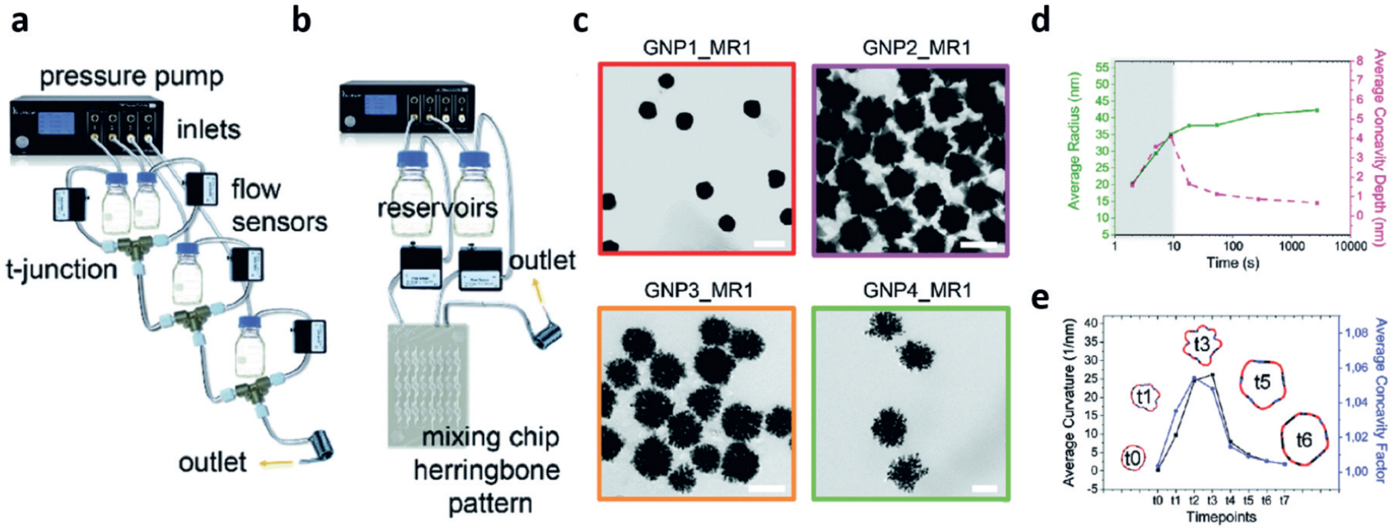

Fig. 3. An automated microfluidic flow platform for the study of branched gold nanoparticles (GNPs) (a) A schematic illustration of the microfluidic reactor 1 (MR1), comprising four asymmetrical inlets and T-junctions. (b) A schematic illustration of microfluidic reactor 2 (MR2), comprising two symmetrical inlets *via* a micromixer chip. (c) Representative TEM images of GNPs produced with MR1 under varying conditions. Growth kinetics of the GNPs can also be studied by evaluation of (d) the average of radius (green curve) and concavity depth (pink curve). (e) Average surface curvature of gold nanoparticles at various time points. Adapted from Cai *et al*.[34]

plicity and fast conversion within a small number of iterations, targeting the size of the gold and silver nanoparticles produced (Fig. 4a). Additionally, Ahrberg *et al.* recently presented an automated, multistep droplet reactor for the synthesis of iron oxide/gold core-shell nanoparticles. Integration of in-line absorbance analysis and a Simplex optimization algorithm allowed for efficient optimization of complex core/shell nanoparticles on short timescales and within ten iterations.[38]

Instead of algorithms acting as the 'brain' of a microfluidic platform, machine learning can be used to excellent effect in flow chemistry.[39] Machine learning is a subset of artificial intelligence (AI) that looks to design and build algorithms and/or models that learn 'patterns' by processing large amounts of training data. These models can then make new projections (*experiment prediction*) or explore hidden features that have yet to be investigated (*experiment planning*). For the interested reader, several excellent review articles have examined the potential of automation, algorithms, and AI in materials science.[3,40–42] Recently, Li and co-workers[43] described an innovative system for the discovery of chiral inorganic perovskite nanocrystals (Fig. 4c). Their 'Materials Acceleration Operating System in Cloud' (MAOSIC) platform is an 'intelligent cloud lab' spread over multiple physical labs, integrating automation and AI to synthesize nanomaterials with specific properties. Such an approach to materials synthesis defines an entirely new way to collaborate and integrate theoretical analysis with experimental measurements, and is likely to significantly accelerate innovation in materials discovery. In a similar vein, Abdel-Latif and colleagues presented a modular microfluidic workflow, comprising an AI-guided decision-making agent for inorganic lead halide perovskite quantum dot parameter space mapping.[44] Such a strategy enables autonomous learning, optimization, and on-demand manufacturing of user-defined nanomaterials, and can in principle be applied to a wide range of chemistries. Similar approaches can be used to good effect in the flow-based synthesis of noble metal nanoparticles. For example, Mekki-Beranda *et al*. recently described a high-throughput, two-step microfluidic platform integrating absorbance detection and combining a Gaussian process-based Bayesian optimization with a deep neural network (DNN).[45] Interestingly, the algorithmic framework goes through a first loop, in which 2–5 runs are used to sample the parametric space as a training set for the DNN. A second loop is then used to validate the DNN (Fig. 4b). Using this scheme, a detailed study of silver nanoprisms was performed, in which the most important parameters when targeting silver nanoprisms were found to be the silver nitrate and silver seeds. In testing three different ML models, Tao *et al.*[46] showed the synthesis of Au nanoparticles in an oscillatory droplet-based reactor, in which the nanoparticles properties were observed in-line through absorbance detection. The platform was guided by the Gryffin ML algorithm.[47] This platform was tested on a green synthesis of gold nanoparticles, targeting specific spectroscopic features. Further study of the correlation between optical properties and experimental conditions was performed using three machine learning models, specifically a random forest (RF), a Gaussian process (GP) and a support vector regression (SVR), all revealing similar results. This optimized synthesis was performed in 160 hours using less than 10 mL of sample, thus demonstrating an advanced, green and low consumption approach for optimizing colloidal nanoparticle synthesis.

5. The Future

Technological developments in flow chemistry will come in a number of forms, including the in-flow integration of new chemical techniques, improvements in existing technologies (*e.g.* mixers, reactors and detectors) and the continued rise of machine learning methods. An area ripe for development is flow photochemistry. Although flow-based photochemical reactors have been used for many years,[7,48,49] there are relatively few reports of photochemical syntheses of nanomaterials but some recent progress has been made. For example, Bianchi *et al.* reported a photochemical flow process for the readily scalable production of spherical gold nano-particles using a commercial photochemical flow reactor.[50]

As has been seen, the vast majority of in-line characterization methods involve photoluminescence- or absorbance-based measurements. Whilst these are ideally-suited for analysing a wide range of nanomaterials, including noble metal nanomaterials, quantum dots and perovskite nanocrystals, many nanomaterials will not absorb or fluoresce to any appreciable extent. Accordingly, a future focus should be placed on integrating other optical methods, such as vibrational and photothermal spectroscopies, with flow-chemical systems. Moreover, it should be re-

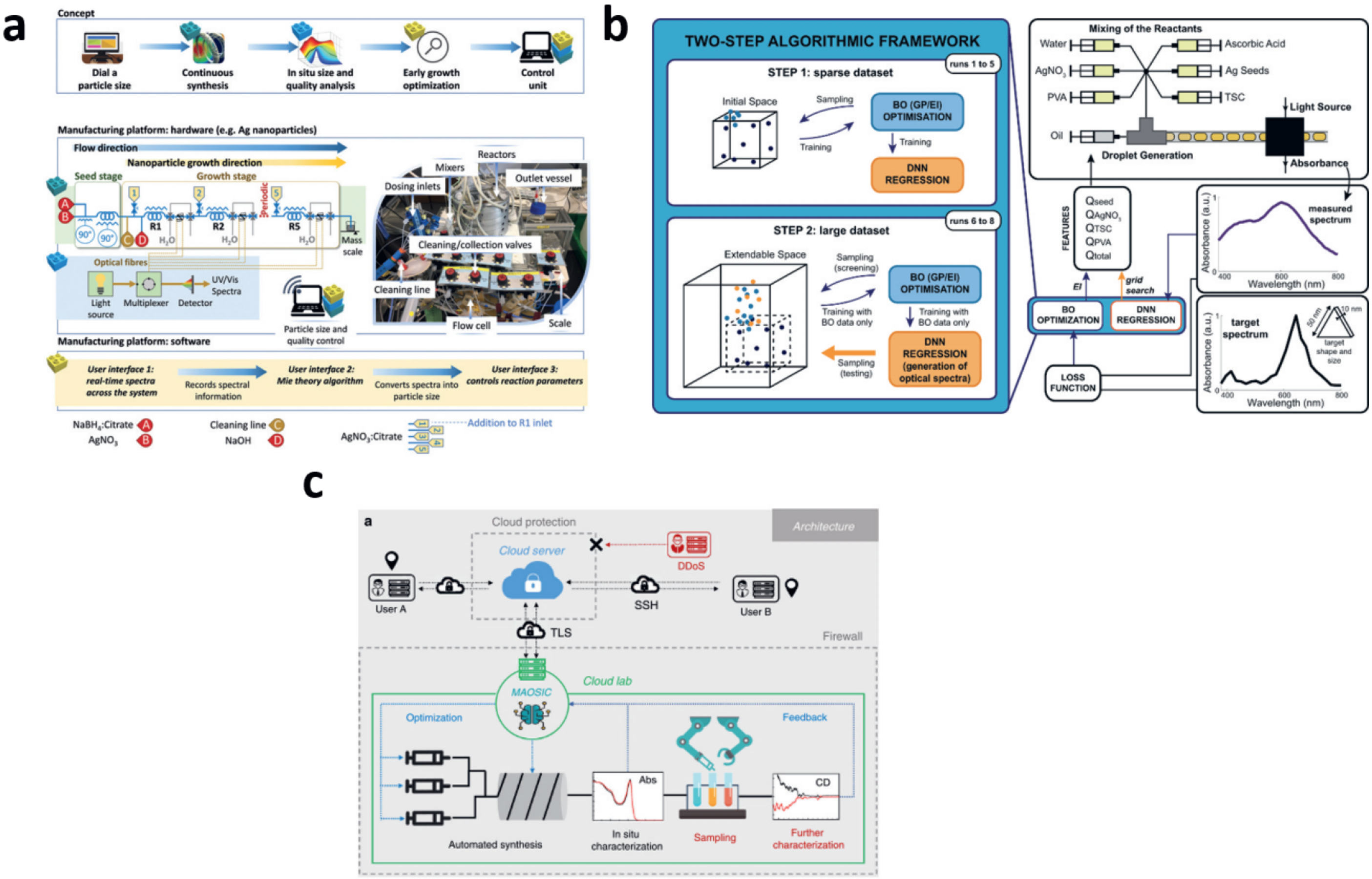

Fig. 4. (a) A conceptual overview of the microfluidic reactor, with a seed and a growth stage and an optical detection unit for UV/Vis absorption measurements, and an illustration of the integrated software interface for optical data analysis and parameter control. Adapted from Pinho *et al*.[37] (b) A schematic of a two-step algorithmic framework, and schematics of the experimental setup and output for silver nanoparticle synthesis. Adapted from Mekki-Berrada *et al*.[45] (c) A schematic of the workflow associated with a cloud lab and an illustration of the microfluidic reactor used for the automated synthesis of nanomaterials. Adapted from Li *et al*.[43]

membered that more sophisticated analyses (such as NMR and mass spectrometry) can be optimally performed off-line and will provide valuable information not accessible to optical techniques. Whilst these cannot be performed in a high-throughput manner, they are likely to be useful when characterizing the physical and chemical properties of complex nanostructures. Again, the interested reader can find a fuller discussion of nanomaterial characterization techniques,[51] and how they may be integrated with flow-based systems elsewhere.[52] That said, it is manifest that innovations in this space will open up flow-based methods to a much broader range of chemistries.

Another underexplored area is the in-line purification of nanomaterials. In this regard, researchers must consider potential changes to material properties during purification, and whether a clear correlation can be drawn between these and the characteristics of the as-synthesized products. In the future, it is likely that the purification and solvent exchange steps, plus other downstream processes will be incorporated into the general flow chemistry process. Indeed, Lüdicke and co-workers recently developed a flow reactor capable to study the performance of automated purification of quantum dots *via* in-line solid phase extraction (Fig. 5a).[53] This platform can synthesize and immediately analyse material in-line; both pre- and post-purification.

Due to the extensive parameter space that requires exploration when synthesizing new or improved nanomaterials , it is clear that the ability to process and exploit larger volumes of data will become ever more critical. While several studies in this perspective have leveraged algorithms to conduct data analysis, or to assist as part of reaction optimization, there is still much potential to expand this from simple nanomaterial synthesis platforms towards the development of more sophisticated systems that extend the scope of high-throughput experimentation from pure synthesis to fully autonomous robotic platforms. In this regard, Coley and co-workers recently described how innovations in flow chemistry, high-throughput experimentation and AI can be leveraged to produce a robotic platform for data-driven synthesis planning and the intelligent synthesis of organic compounds (Fig. 5b).[54] Lastly, it should be remembered that the use and application of sophisticated AI and machine learning algorithms is far from trivial, as their implementation typically requires niche expertise, large datasets and immense computational power to build accurate models. That said, advantage can be had when using relatively simple freely available machine learning tools, such as Google's TensorFlow platform,[55] for multidimensional regression and parameter space visualization.

Finally, alongside the development of lab-based flow-chemistry processes, there is much current interest in investigating how these platforms may be configured to generate industrially relevant amounts of product. In this case, cost will always be king. While the inherent cost of flow-based processes may be lower due to the benefits previously highlighted, the initial investment (or activation barrier) is still substantial at the industrial level and, as such, a significant risk.[56] Accordingly, it is up to researchers to address some of the technical barriers and demonstrate that any in-

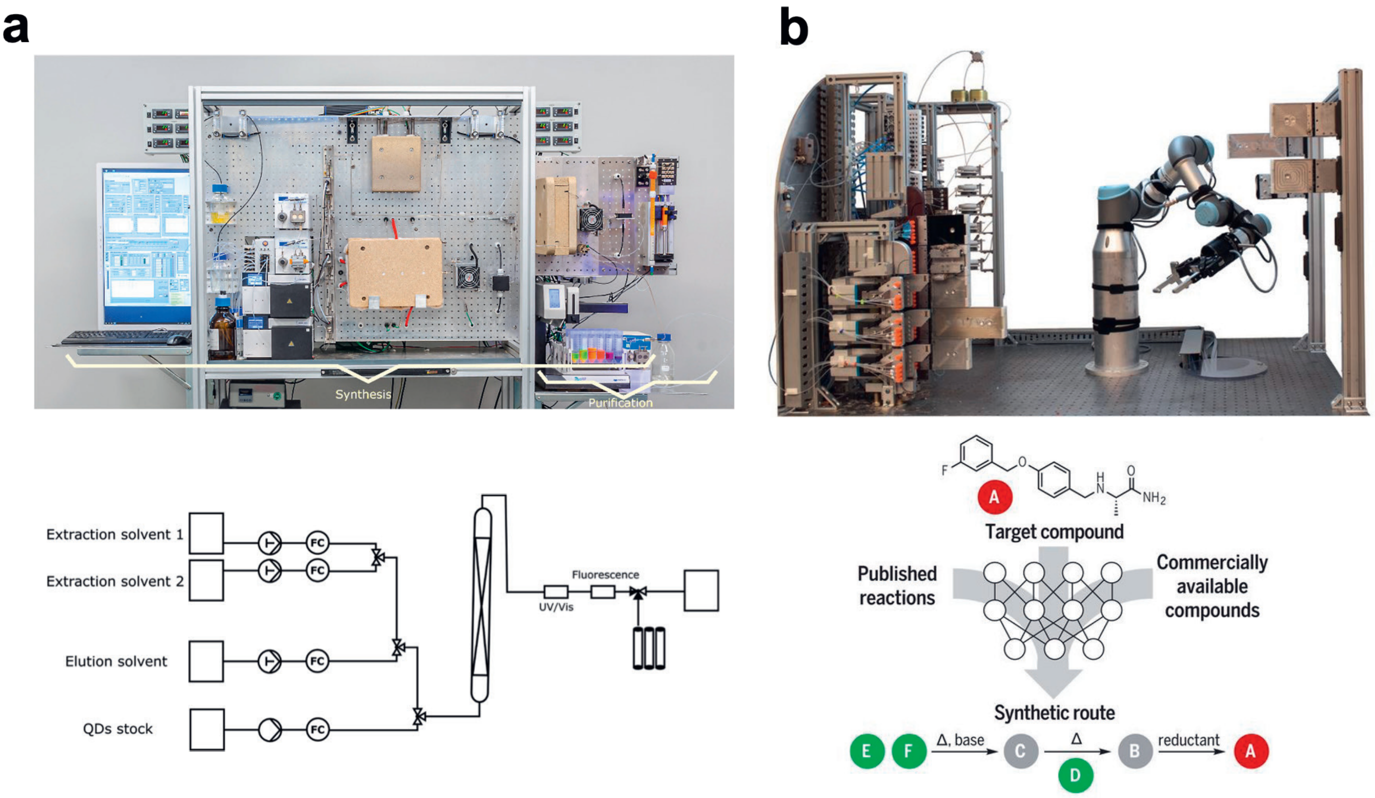

Fig. 5. Tackling some of the challenges in the field of flow chemistry. (a) Top: A flow reactor platform integrating CdSe/ZnS synthesis and purification, with fully integrated reactor control. Bottom: A flow chart for the design of the purification module of the reactor detailing the separate components alongside the optical characterization modules. Adapted from Lüdicke *et al*.[53] (b) Top: An AI-driven automated flow chemistry system using a microfluidic reactor platform embedded in a larger system that includes a robotic arm for configuring the system between each experiment. Bottom: A neural-network algorithm is used to converge onto a target compound by examining existing published data and commercially available compounds. Adapted from Coley *et al*.[54]

vestment is worth it. In terms of technical challenges, the ability to process solids and avoid blockages are examples of challenges that must be overcome before widespread adoption.[57] Low production rates can also be problematic, and thus effort must be focused on increasing throughput by adjusting reactor designs to handle larger volumes or numbering up reactors (parallelization).[58] The key here is finding a way to increase throughput without losing the benefits afforded by the microscale. Further, there is also a lack of standardization and consistency across research laboratories in terms of equipment, workflows and techniques, although an increasing number of companies now manufacture flow chemistry components and systems, offering standard options to both academic and industrial researchers.

6. To Conclude

We hope that this brief perspective has highlighted the increasingly important role of flow chemistry in the field of nanomaterial synthesis. Activities in this space have been driven by basic features such as enhanced mass and heat transfer, decreased sample consumption, improved synthetic control and the ability to integrate functional components within accessible formats. All of these are especially important in nanomaterial synthesis, where the control of particle size, shape and size-distributions is essential. It is evident that in recent years, automation has been a major advance in the field. Coupled with high-throughput experimentation, this has opened up the world of 'big-data', with advanced flow platforms offering an increased volume, velocity and variety of data. When combined with such platforms, the use of machine learning models and algorithms has resulted in self-driving platforms capable of experimental prediction or planning.

Whilst progress has been significant, there are still open questions and challenges. Reactor engineering in flow chemistry is still progressing, with new or improved technologies for reaction processes and analysis, as well as the exploration of processes that remain underdeveloped. Further to this, the application of AI and machine learning in flow chemistry is still in its infancy, with more sophisticated algorithms becoming accessible to a wider variety of researchers. Additionally, public data repositories are becoming essential, encouraging interdisciplinary collaboration and standardization, with a number of tutorials, and general practice guides already published.[59]

Finally, making flow chemistry a viable tool for commercial nanomaterial production remains an ambition, with several technical challenges such as in-line purification and increased production rates yet to be fully solved. When such challenges are resolved, the costs and barriers to integrating flow chemistry on an industrial level will be lowered, uptake will increase, and the field of nanomaterial development will thrive.

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