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Flow Chemistry: A Sustainable Voyage Through the Chemical Universe en Route to Smart Manufacturing

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Abstract

Microfluidic devices and systems have entered many areas of chemical engineering, and the rate of their adoption is only increasing. As we approach and adapt to the critical global challenges we face in the near future, it is important to consider the capabilities of flow chemistry and its applications in next-generation technologies for sustainability, energy production, and tailor-made specialty chemicals. We present the introduction of microfluidics into the fundamental unit operations of chemical engineering. We discuss the traits and advantages of microfluidic approaches to different reactive systems, both well-established and emerging, with a focus on the integration of modular microfluidic devices into high-efficiency experimental platforms for accelerated process optimization and intensified continuous manufacturing. Finally, we discuss the current state and new horizons in self-driven experimentation in flow chemistry for both intelligent exploration through the chemical universe and distributed manufacturing.

1. INTRODUCTION

Owing to pressing negative environmental impacts, raw material shortages, and vulnerabilities in chemical supply chains, it has become increasingly important to improve the adaptability as well as the energy, time, and material efficiency of each step of the chemical process life cycle. The coronavirus disease 2019 (COVID-19) pandemic has highlighted many of these issues, as the world has become acutely aware of supply-chain dependencies that are vulnerable to regional catastrophes and geopolitical instabilities. Modular, accessible, distributed manufacturing approaches have the potential to withstand these disruptions through risk diversification (1, 2). In addition, reconfigurable chemical manufacturing systems are amenable to pivoting chemical production to address changing market demands. Beyond supply chain resiliency, the COVID-19 pandemic has also emphasized the need for rapid chemical discovery and formulation optimization. Although many of these needs primarily concern the development and production of active pharmaceutical ingredients (APIs), advantages of modular and reconfigurable continuous processes extend to the synthesis of other fine chemicals and advanced materials, specifically, chemicals and materials related to renewable energy, catalysis, and even outer-space manufacturing. These advantages include reduced energy costs and materials waste and the ability to integrate with rapidly emerging artificial intelligence (AI)-guided process exploration and optimization strategies to achieve smart manufacturing. Microfluidics-based technologies can enable the realization of these new paradigms and meet the demands of the next generation of modular, accessible, and sustainable chemical and materials research, development, and manufacturing (3).

The potential of microfluidics toward sustainable chemical processes is attributed, in part, to intrinsic advantages that arise at microfluidic length scales (<1 mm). High surface-to-volume ratios of flow reactors, compared to batch analogs, result in precisely tunable and enhanced heat- and mass-transfer rates and thereby enhanced kinetics, as well as reduced spatiotemporal variability. Additionally, at microfluidic characteristic length scales, capillary forces dominate over gravitational forces (4), a trait often used for separations. These properties, combined with low reagent consumption and smaller unit operation footprints, can be leveraged toward time-, energy-, and materials-efficient innovations in chemical science and engineering through fundamental and applied studies of the chemical universe, as represented in **Figure 1**.

In studies that aim to build a foundational knowledge of reaction mechanisms or kinetics, systematic high-volume data collection is essential. Small reagent volumes and fast and uniform heating/cooling rates make microfluidic reactors well suited for such studies, as they can be used for high-throughput experimentation with minimized waste generation and downtime. Moreover, microfluidic reactors afford reproducible and precise control over reaction conditions, including mixing, reagent stoichiometry, temperature, and pressure. This precision, and the ease of microfluidics-based chemical process automation, can enable reliable big-data collection for accelerated studies of chemical reactions and materials synthesis. Additionally, coupled to online characterization techniques, the time-to-distance correlation of microfluidic reactors allows for accurate reaction kinetics studies of mass transfer–limited chemical processes. Through automated online reaction monitoring, reaction mechanisms and pathways may be elucidated with high precision.

Working in parallel with studies on molecular and material property engineering and discovery, a large body of research is dedicated to the design of microfluidic devices and techniques for enhanced chemical processing in flow (known as flow chemistry). This research is focused primarily on developing microfluidic process modules that capitalize on advantages of microscale fluidic systems to enable efficient chemical transformations and analyses. The four categories of these technologies form the basis of all unit operations in chemical engineering: (*a*) mixing

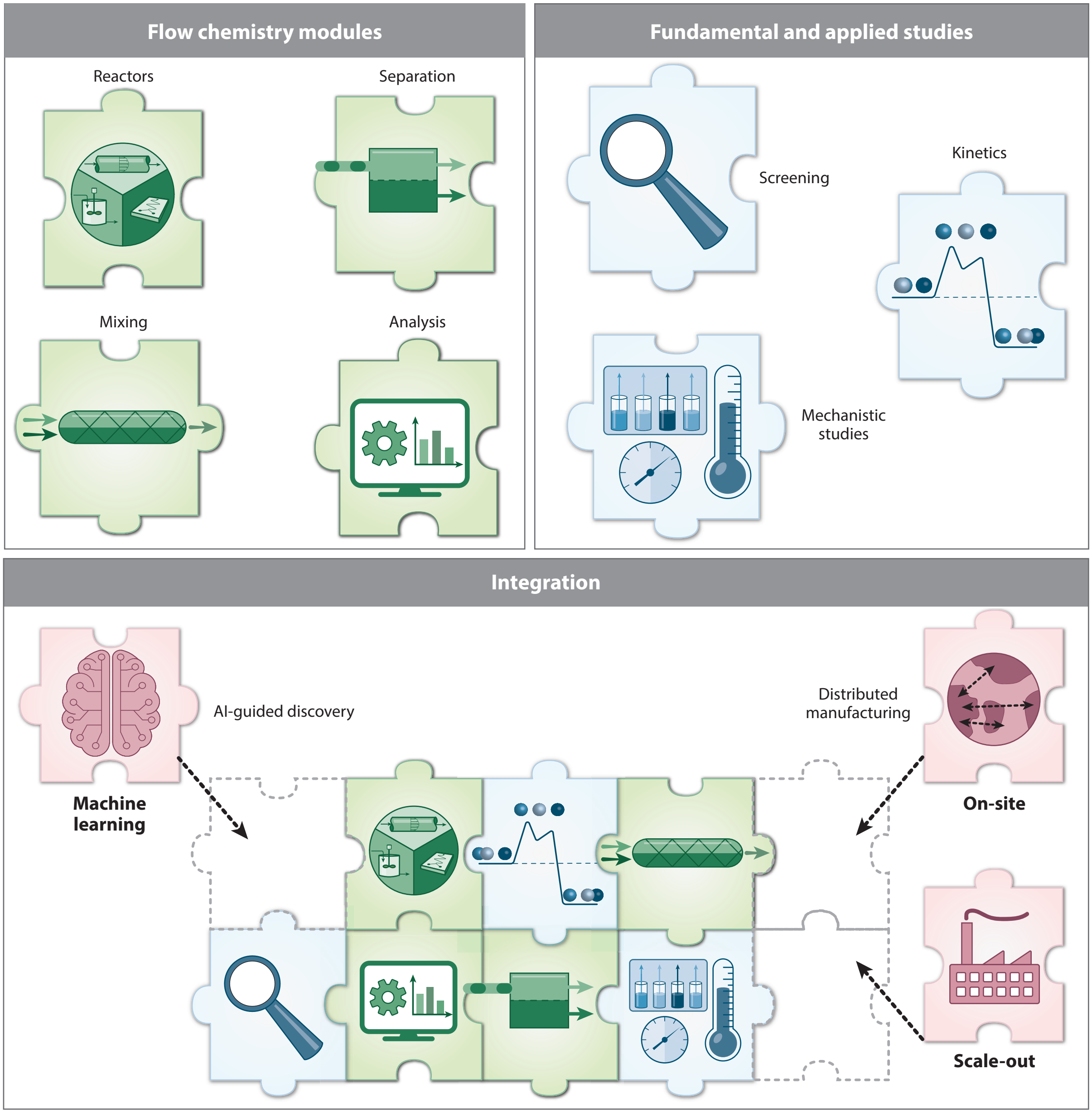


Figure 1

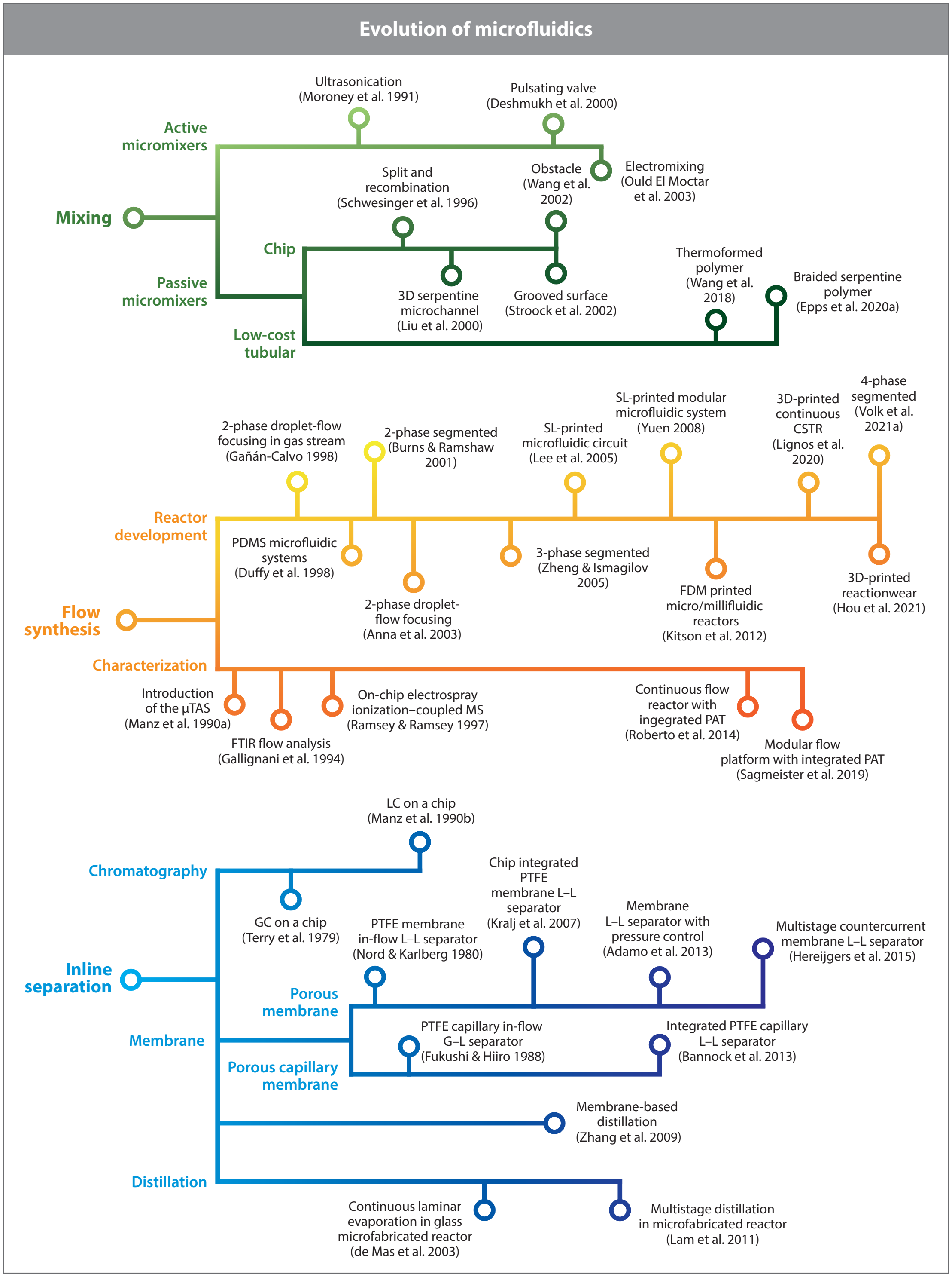
Illustration of the plug-and-play, modular nature of microfluidics-based technologies for advancements of fundamental and applied studies in chemical science and engineering. Integration of these microfluidics-based technologies with emerging concepts of artificial intelligence (AI)-guided chemical space exploration and distributed manufacturing enables modern chemical engineering research directions, including AI-guided chemical discovery and on-site manufacturing of advanced functional materials and molecules.

(precursor formulation and material handling), (*b*) flow reactors (performing chemical transformations), (*c*) separation (product purification and recycling), and (*d*) online analysis (product characterization and validation). Many of these microfluidics-based unit operations are intensified by increased surface-to-volume ratios, dominant capillary forces, and short diffusion path lengths, resulting in decreased time, energy, and material costs compared to their batch counterparts. The evolution of these microfluidic unit operations, detailed in **Figure 2**, has trended from complex, expensive, highly specialized microfabricated devices (commonly referred to as microfluidic chips) toward modular, accessible, and reconfigurable designs. This progression has been enabled by advancements in additive manufacturing as well as the availability of commercial, chemically resistant, microcapillary tubing and porous membranes. However, the primary driving force for the realization of accessible, high-performance, modular, microfluidic unit operations is the need for tailor-made flow chemistry platforms to achieve on-demand continuous manufacturing.

The large library of microfluidics-based unit operation modules developed over the past few decades can cover an expansive array of complex chemical processes. Integration of these process modules can therefore enable continuous on-site manufacturing through reduced process footprints and infrastructure demands. In addition, these microfluidic chemical processing modules could be operated in parallel to increase throughput. This scaled-out (or numbered-up) approach, unlike scaled-up processes, does not require extensive resources to adapt lab-scale synthesis protocols to industrial operations.

The capstone of combining microfluidics-based unit operations is through the integration of fundamental and applied knowledge of chemical reactions conducted in flow with AI-guided modeling and decision-making strategies to achieve intelligent and sustainable chemical universe exploration and smart, on-site manufacturing of advanced functional materials and molecules. The combination of chemical/material informatics or black-box process-optimization techniques with modular and reconfigurable bespoke reactor design produces an extremely powerful tool in both cutting-edge research (academia) and manufacturing (industry). Algorithm-guided, self-driving flow chemistry technologies enable the exploration and control of larger reaction spaces without user intervention. These technologies therefore reduce the burden of tedious manual processes and allow researchers to focus on defining search spaces, target properties, and scientific problems. In the context of chemical manufacturing, AI-guided flow chemistry platforms could be used for accelerated on-site production of specialty/fine chemicals and advanced materials through algorithm-guided formulation and synthetic route discovery followed by automated reconfiguration and operation of microfluidic process modules. The realization of these smart manufacturing techniques will offer greater control and versatility in production and distributed chemical manufacturing. Because of these attributes, microfluidic systems have been used recently in a growing number of autonomous experimentation studies, including pharmaceutical formulation discovery and materials performance optimization.

Understanding the current state of flow chemistry toward sustainable manufacturing and research requires perspective on the development of microfluidic technologies toward accessible, cost-effective, and modular components. Through this lens, we discuss advancements in microfluidics for sustainable chemical process development, with an emphasis on modular devices and technologies within each chemical engineering unit operation. We highlight the advantages and limitations of each microfluidic technique and detail their larger role in industrially relevant processes as well as research and development. We then highlight the integration of microfluidics-based unit operation modules with AI-guided experimentation toward accelerated discovery of advanced functional materials and molecules as well as resilient distributed chemical manufacturing.



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Timeline of advancements in primary microfluidics-based unit operations toward improving sustainability of chemical processes through reduced footprints, enhanced materials and energy efficiency, and accessible components (5–34, 35, 48, 104, 150). Abbreviations: μTAS, micro total analysis systems; CSTR, continuous stirred-tank reactor; FDM, fused deposition modeling; FTIR, Fourier-transform infrared spectroscopy; GC, gas chromatography; LC, liquid chromatography; L–L, liquid-liquid; MS, mass spectroscopy; PAT, process analytical technology; PDMS, polydimethylsiloxane; PTFE, polytetrafluoroethylene; SL, stereolithography.

2. MICROFLUIDICS-ENABLED CHEMICAL SYNTHESIS: FROM PRECURSOR FORMULATION TO ONLINE REACTION CHARACTERIZATION

Achieving reconfigurable, automated, reactive systems for advanced continuous on-site manufacturing and AI-guided syntheses requires microfluidic chemical engineering synthesis process modules that can effectively replace analogous batch operations. The field of flow chemistry has developed and demonstrated a wide variety of designs to fulfill this need. Although many of these technologies have been developed in isolation, with a focus on intensifying their individualized roles, a growing body of research has prioritized designing them for reconfigurable systems (35–38). This modularization can be expanded to encompass a larger number of research studies and manufacturing configurations through increased accessibility and standardization of microfluidic components. Because there are many instances where microfluidic processes are not suited to replace batch techniques, most notably solids handling, modular microfluidic components must also be designed for integration into semicontinuous processes.

This section provides an overview of microfluidic process modules and designs that have been, or have the potential to be, integrated into reconfigurable continuous or semicontinuous manufacturing strategies for the accelerated development and distributed production of fine chemicals and advanced materials. Microfluidic formulation, synthesis, and separation approaches, for sustainable research and manufacturing, are discussed. **Figure 3** provides a summary of the process modules and design strategies pertaining to these categories. In this context, sustainability is multifaceted and includes decreased environmental and economic impacts as well as intensified research and supply-chain resiliency. The specific attributes that contribute to these aims include reduced reaction times, waste generation, hazardous material volumes, and energy costs, as well as improved precision, ease of automation, and reconfigurability.

2.1. In-Flow Precursor Formulation and Delivery

Consistent precursor formulation, which entails controlling the composition and introduction of precursor feeds, is necessary to achieve steady-state unit operations and subsequently reduce waste generation. Therefore, precursor formulation strategies that can be integrated with microfluidic reactors are necessary to achieve consistent chemical transformations in flow, specifically, in scaled-out processes. In addition, precision precursor formulation is necessary for fundamental studies exploring chemical spaces and reaction kinetics/mechanisms through varying continuous (e.g., concentration) or discrete (e.g., chemical species) variables. Moreover, the ability to control reactant formulations at nanoliter scales enables material-efficient studies of complex chemical syntheses with multivariate and high-dimensional reaction parameter spaces.

One way to precisely formulate precursors using microfluidic-based technologies, especially at microliter-scale volumes, is by using liquid handlers. Liquid handlers (39) can be used to vary discrete variables (e.g., different catalysts and solvents) (40), to mix reagents (41) through oscillation of droplet mixtures (in either the liquid handler needle or microfluidic tubing), and to vary

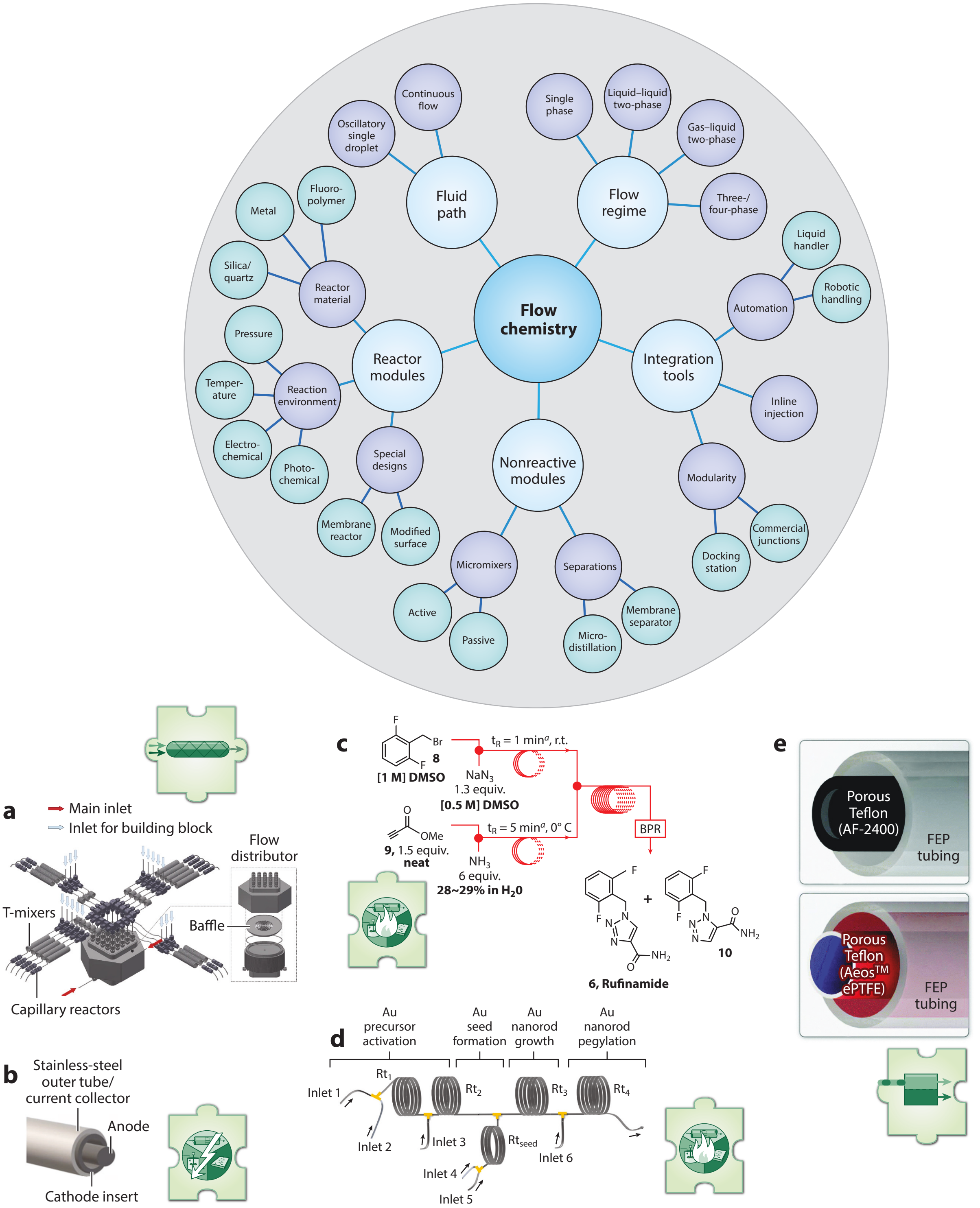


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Figure 3 (*Figure appears on preceding page*)

Diagram of modular flow chemistry design features. (*a*) A flow distribution module for scaled-out chemical manufacturing with a uniform precursor distribution across 16 parallel microreactors [adapted from Ahn et al. (54) (CC BY 4.0)]. (*b*) A continuous cylindrical electrochemical flow cell for the anodic methoxylation of *N*-formylpiperadine [adapted with permission from Jud et al. (65); copyright 2020 John Wiley and Sons]. (*c*) Copper coil flow reactor used to synthesize rufinamide through catalytic interaction with the tubing [adapted with permission from Zhang et al. (74); copyright 2014 American Chemical Society]. (*d*) A multistage microfluidic reactor to separate the seed and growth stages of Au nanorods [adapted from Uson et al. (113) (CC BY-NC-ND 4.0)]. (*e*) A tube-in-tube microfluidic reactor and liquid–liquid phase separator for the continuous liquid–liquid extraction of switchable hydrophilicity solvents triggered by CO_2 [adapted with permission from Han et al. (71); copyright 2021 Royal Society of Chemistry]. Abbreviations: BPR, back pressure regulator; DMSO, dimethyl sulfoxide; ePTFE, expanded polytetrafluoroethylene; FEP, fluorinated ethylene-propylene.

reactant droplet volumes (42). These systems can be automated and integrated with microfluidic reactors, enabling high experimental throughput, limited waste generation, AI-guided chemical space exploration, and an additional level of safety for operators (43). In one example, Perera et al. (44) demonstrated the advantages of combining liquid handlers with flow reactors for the rapid screening of Suzuki–Miyaura coupling reactions. By using a well-plate autosampler, reaction conditions could be screened at a rate of more than 1,500 reactions a day, with only nanomolar amounts of each reagent per condition.

In addition to precursor formulation using liquid handlers/robotic methods, in-flow mixing strategies can be used to form homogeneous precursor mixtures before entering a reaction zone. Many of these strategies use passive micromixers ranging in complexity from tube-based to 3D-printed geometries. Advancements in additive manufacturing have expanded these designs to include more intricate patterns and materials with superior chemical and thermal stability (e.g., stainless steel, glass, ceramics, and fluoropolymers) (45). Zhang et al. (46) reported an example of a metallic, 3D-printed showerhead micromixer fabricated using direct metal laser sintering.

Enhanced mixing before a reaction zone can also be achieved using multiphase flow formats, whereby precursors are fed into a microfluidic reactor with an immiscible carrier phase (either gas or liquid). Multiphase systems benefit from axisymmetric recirculation within formed liquid droplets (or slugs), which significantly enhances mixing compared to single-phase flow formats (47). In turn, each droplet (or slug) can function as a miniaturized reactor for kinetic studies. Additional inert phases can be added to two-phase flow systems to form three- or even four-phase flow formats (48), which can improve system stability and enable self-synchronized precursor injection into moving droplets for multistage syntheses. Nightingale et al. (49) demonstrated controlled in-line precursor injection into a train of moving reactive phase droplets by using a three-phase flow format in which reactive phase droplets [cadmium selenide (CdSe) quantum dot (QD) precursors in octadecene] were formed using perfluorinated polyether as a carrier fluid and argon gas as an inert spacer. Downstream inlets were used to inject additional precursors into the moving droplets containing in-flow synthesized CdSe QDs. Compared to two-phase flow, the three-phase format resulted in more consistent downstream injection, enabling the use of multistage, sequential precursor addition.

Despite the advantages associated with microfluidics for applications such as high-throughput reaction screening and accelerated process optimization, specific challenges in precursor formulation and mixing must be addressed to apply flow chemistry strategies to large-scale chemical manufacturing. Retaining small reactor diameters provides numerous benefits, namely, shorter diffusion length scales, well-controlled mixing, superior control over reactor temperature, rapid heat transfer to/from the reactor, and improved kinetics. Although scale up, or increasing channel diameters, is possible, a substantial increase in microfluidic reactor diameter can adversely impact the aforementioned benefits of microfluidics. The alternative option is to use a numbered-up or scaled-out strategy (50–53), in which multiple parallel microfluidic reactors with an identical geometry are used to increase the chemical manufacturing throughput. The numbering-up strategy can be complicated to implement, as any pressure difference between the parallel streams can result in substantial variations in flow rates (residence time) in each individual microreactor. To overcome pressure variations and thereby achieve uniform precursor distribution, formulation, and mixing across parallel microfluidic reactors, flow distribution modules that balance pressure across multiple feed lines have been developed (50). **Figure 3*a*** illustrates a flow distribution system developed by Ahn et al. (54), which was designed to facilitate microfluidic reactor parallelization through proper reagent flow distribution, even in the event of downstream clogging. The uniform precursor distribution was accomplished by using baffles to dampen variations, ultimately achieving a standard deviation of average mass flow rates between 16 parallel microreactors of less than 1%.

2.2. Organic Synthesis

Flow chemistry platforms, which have access to a wide range of synthesis modules for novel chemical transformation routes, are well suited to conduct challenging organic reactions and produce fine and specialty chemicals, such as APIs. Compared to bulk and commodity organic chemicals, APIs are produced at relatively smaller scales and with more stringent purity requirements. Beyond common APIs, small-scale synthesis approaches are necessary to produce orphan status drugs for which large-scale manufacturing is infeasible. In addition, an accelerating demand for new organic molecules, combined with tightening economic constraints on experimentation time, waste generation, and reactor footprints, requires organic synthesis intensification (55). Enhanced heat- and mass-transfer kinetics can significantly reduce the environmental impact of organic syntheses through lower energy and materials cost, as well as reduced pollutant production. Opportunities for improving energy efficiency also lie in using alternative energy sources, such as microwave and light irradiation.

2.2.1. Alternative energy source reactors. Light, microwaves, and electricity from sustainable energy sources can be used for unique chemical transformations and greener synthesis routes. For example, electrochemical redox reactions can be carried out with high reaction rates under more energy-efficient conditions, without the production of hazardous waste from chemical oxidants and reductants. Similarly, light and microwave irradiation can be used as traceless reagents (high- and low-energy photons) that produce faster chemical transformations compared to thermochemical alternatives. However, the ability to use these alternative energy sources in industrial batch reactors is hindered by large reactor pathlengths and interelectrode distances. Microfluidic reactors, because of their high surface area–to–volume ratios and micron-scale reactor path lengths, can enable the facile scale-out of microwave, photochemical (56–58), and electrochemical (59–62) reactions while simultaneously enhancing reaction kinetics. In addition, microfluidic reactors mitigate issues of nonuniform irradiation in photochemical reactors because each unit volume passing through a continuous flow microreactor is exposed to the same average photon flux.

Commercial availability of transparent, chemically resistant tubing has made photochemical reactors more accessible and reconfigurable than batch reactors. A wide range of light-driven organic syntheses, including transition-metal catalysis, enantioselective catalysis, and biocatalysis, have therefore been conducted using quartz or fluoropolymer tubing reactors. For example, Wei et al. (63) used a quartz tube flow reactor illuminated with simulated visible light (250–780 nm) to achieve rapid and efficient photocatalytic synthesis of pyrrolidine-2-one cycles, with reaction times reduced from 4 h in batch to 20 min in flow. Straathof et al. (64) presented another photochemical microreactor with a highly modular design composed of inexpensive, commercially available perfluoroalkoyalkane (PFA) capillary tubing and fluidic components. The PFA tubing–based flow reactor was coiled around an aluminum tape–coated syringe, and light-emitting diodes were wrapped around the reactor. Gas–liquid segmented flow (using O_2 and CF_3I gas), which benefits from high interfacial areas, was used for photocatalytic gas/liquid reactions (photocatalytic aerobic oxidation of thiols to disulfides and photocatalytic trifluoromethylation of heterocycles and thiols) with excellent yields.

Similar to emerging photochemical flow reactors, electrochemical flow reactors designed from commercially available metal tubing and standard fluidic fittings have recently been developed and used for energy-efficient chemical transformation. A recent example is Jud et al.'s (65) pipe cell flow reactor, which had an annular shape capable of withstanding higher pressures compared to flat-plate approaches, shown in **Figure 3*b***. The outer annulus of the flow reactor was composed of stainless-steel tubing (the current collector) concentric with cathode materials, and the inner annulus contained a fixed working electrode graphite rod, operated as the anode. This electrochemical flow reactor was used with a model reaction, the anodic methoxylation of *N*-formylpiperadine, and achieved excellent conversion and selectivity in both single-pass and recycled electrolyte operation. In addition, the pressure and temperature were varied systematically to demonstrate the negative effects of redissolved hydrogen on yield.

2.2.2. Membrane reactors. Gas-permeable membranes, with low mass-transfer resistances, can be integrated with tube-based microfluidic reactors in tube-in-tube reactor configurations (41, 66–72) to increase the rate of gas delivery to a reaction mixture. Similar to gas–liquid segmented flow reactors, active volumes of hazardous toxic and flammable gases in the membrane-based flow reactors are significantly smaller than batch-scale processes (50–100 times lower). Bourne et al. (73) demonstrated these benefits, using a tube-in-tube microfluidic reactor for the two-step synthesis of branched aldehydes from aryl iodides. Two tube-in-tube microreactors made with a commercially available gas-permeable membrane (Teflon AF-2400) were used in series for the ethylene Heck reaction and syngas hydroformylation step, respectively. In-flow reaction screening with small hazardous gas volumes enabled rapid and safe process optimization.

2.2.3. Heterogeneous catalytic microreactors. In addition to reactant phases, surfaces of microfluidic reactors can also participate in chemical transformations, including heterogeneous catalytic reactions. Compared to packed bed microreactors, reactors with catalytic channel surfaces are more resistant to clogging and achieve lower pressure drops, making them more amenable to scaled-out chemical manufacturing processes. Many of these catalytic microreactors are constructed from commercially available components, such as stainless-steel and copper tubing. Catalytic microfluidic reactors can be constructed readily from commercially available components (e.g., copper tubing) without the need for additional surface treatments. Using microfluidic reactors with active catalytic surfaces can also decrease the active volumes of dangerous synthesis intermediates. For example, Zhang et al. (74) used a copper coil flow reactor for the synthesis of the triazole-containing antiseizure drug rufinamide, shown in **Figure 3*c***. The reaction sequence involved the copper-catalyzed cycloaddition reaction of alkynes with hazardous and explosive organic azides. By using a multistage tube-based flow chemistry platform, the hazardous azides were synthesized in situ and then immediately reacted in the copper-coil microfluidic reactor, thereby mitigating the need for purification and storage in large quantities. Other organic syntheses that require catalyst materials not available as commercial tubing can be carried out using modified reactor surfaces (75).

2.2.4. Multistage synthesis in flow. Sequential multistage synthetic routes, also known as telescoped reactions, are often pursued to achieve a higher level of complexity in organic molecules using commercially available starting chemicals. In-flow telescoped reaction techniques have notable potential in the development of APIs and other organic molecules (e.g., specialty polymers) by limiting hazardous active volumes and increasing throughput. However, continuous flow strategies still suffer from significant limitations, which have restricted their application to complex telescoped reactions. Syntheses that require complex in-line separations (solvent switch), solids handling, and purification procedures can be more difficult to implement in a robust multistage flow chemistry platform compared to batch processes. With these limitations in mind, a range of flow chemistry studies have effectively used microfluidic reactors for multistage syntheses by adapting microreactor designs or batch chemistries to mitigate drawbacks of continuous flow operations (76). In addition, hybrid flow chemistry strategies that integrate microfluidic reactors with flask-based modules have been demonstrated as an effective approach to mitigate the aforementioned challenges of microfluidics reactors for telescoped reactions.

A prominent example of APIs that use hazardous precursors and intermediates are those made using cyanogen bromide (BrCN), including cyanamides, guanidines, cyanates, and nitriles. The handling of BrCN and its precursor, elemental bromine, imposes considerable safety hazards. However, these hazards can be mitigated through telescoped synthesis of BrCN and its subsequent precursors. In one example, Glotz et al. (77) demonstrated this process in a multistage flow chemistry platform integrated with various process modules. In this modular flow chemistry strategy, BrCN was formed in a cooled PFA tubing flow reactor by mixing cooled Br_2 and potassium cyanide. Following BrCN formation, the BrCN reaction mixture was extracted into the organic phase by mixing with dichloromethane in a glass microreactor and subsequently separated from the aqueous phase using a membrane extraction unit. The optimized BrCN was then fed into a heated PFA reactor coil for bromination reactions. The bromination product, 2-aminobenzimidazole, was made soluble to avoid microreactor clogging using a cosolvent. This work provides an excellent example of the potential of multistage microfluidic reactors, integrated with online separation and characterization modules, for distributed manufacturing, specifically for the on-site synthesis and immediate use of hazardous reagents. Further applications of this multistage flow chemistry strategy could enable lower-risk, sustainable distributed manufacturing.

2.3. Solid Handling in Flow

Despite progress made in formulating entirely solution-phase chemistries, in many reaction pathways, the use of solid reagents is unavoidable without significant reductions in quality. Over the past decade, a range of microfluidics-based techniques for solids-based chemistries have been developed to mitigate this issue. For example, in instances where small solid particles are present in a suspension, a more homogeneous flow mixture can be achieved with the introduction of baffles in the channel wall and periodic pulsating of the flow, a system also known as an oscillatory baffled reactor (78, 79). Sharma et al. (80) achieved a similar effect through a flow reactor consisting of a series of partially rounded cavities with alternating inlet and outlet positions. Various active solids dispersion strategies have also been presented, such as Mo & Jensen's (81) use of continuous stirred tank reactors in series or the Archimedes screw–driven flow channel presented by Sharma et al. (82). In instances where agglomerate crystallization can occur over time, causing microreactor wall fouling, either introduction of an ultrasound wave (83, 84) or injection of equivalent crystal seeds (85) along with the reactive mixture can mitigate precipitate formation. Although the current state of solids handling in flow systems is varied in approach and depends largely on application, the progression of these technologies could unlock an otherwise absent region of the chemical universe to flow chemistry.

2.4. Inorganic Synthesis

Inorganic reactions in microfluidic reactors have primarily involved the synthesis of colloidal inorganic nanomaterials (86). Compared to organic molecules, inorganic nanomaterials have a broad range of physiochemical and morphological characteristics that are strongly influenced by reaction conditions. Therefore, the performance of inorganic materials, often based on optical, electronic, and catalytic properties, can be controlled through tuning microfluidic process parameters such as temperature, mixing time, and residence (reaction) time. The precise control over synthesis parameters microfluidic reactors afford has led to the synthesis of high-performing inorganic nanomaterials, including noble metal and metal oxide nanoparticles (87, 88), metal–organic frameworks (89, 90), silica nanoparticles (91), and various quantum-confined nanostructures (92). In addition, microfluidic synthesis methods enable scalable production of process-sensitive materials. Microfluidic strategies contribute to sustainable inorganic syntheses through process intensification, scalable transfer of laboratory systems, and the potential to provide high-performance advanced functional materials relevant to energy and environmental applications.

2.4.1. High temperature and pressure syntheses. Solution-phase synthesis of QDs with size-, composition-, and ligand-tunable optical and optoelectronic properties has emerged as an energy-efficient alternative to epitaxial growth strategies for various device applications, including photonics. However, reliable control over colloidal QD composition, morphology, size, crystallinity, and polydispersity, at an industrially relevant throughput, has remained a challenge owing to unscalable hot-injection strategies in batch. Scalable microfluidic reactors, however, can be used for controlled production of QDs owing to rapid heat and mass transfer and spatially resolved temperature gradients (93–98). Specifically, because of their rapid mixing and reduced axial dispersion, multiphase microfluidic reactors have been widely used for the controlled synthesis of a wide range of colloidal QDs. Examples include well-studied II-VI, IV-VI, and III-V QDs (e.g., CdSe, CdTe, InP, PbS) (99–102), as well as recently developed metal halide (e.g., $CsPbX_3$; X = Cl, Br, I, Mn:$CsPbCl_3$) (103–108) and hybrid organic–inorganic (e.g., $FAPbX_3$, $MAPbX_3$) (109–111) perovskite QDs. Additionally, supercritical solvent systems, which promote fast diffusion rates while retaining reagent miscibility, have been implemented in microfluidic reactors to decrease the size polydispersity of CdSe and InP QDs. These continuous-flow microreactors, built from either silicon/Pyrex chips or stainless-steel tubing, enable the use of an otherwise hazardous strategy through their low active volumes and facile process automation and control. Further implementation of high-pressure/high-temperature microreactors can enable the use of more chemically desirable solvents in high-temperature syntheses.

2.4.2. Multistage syntheses. Further control over nucleation and growth steps of colloidal nanocrystals can be achieved using multistage microfluidic reactors. In one example, Pan et al. (112) synthesized lead sulfide (PbS) QDs using a three-stage microfluidic reactor composed of a mixing zone and independently heated nucleation and growth stages. By varying nucleation and growth temperatures and residence times, the ideal synthesis conditions for the in-flow manufacturing of PbS QDs with narrow emission linewidth and target bandgaps suited for solar cells were identified rapidly. Furthermore, the throughput of this synthesis was reported to be two times higher than those of batch alternatives. Uson et al. (113) applied a similar approach toward the synthesis of Au nanorods, as shown in **Figure 3*d***. After a precursor activation stage, Au seeds were formed by the downstream addition of a strong reducing agent, followed by the growth of nanorods through the addition of preferential surface ligands. This multistage flow chemistry strategy produced a viable manufacturing route for an otherwise unscalable synthesis.

Multistage flow reactors have found further applications beyond distinct nucleation and growth designs, and they can be applied toward the postsynthetic treatment of nanoparticles to either tune their compositions (e.g., postsynthesis anion exchange reactions of metal halide perovskite QDs) (114) or form more complex materials, including hybrid and heterostructure nanoparticles (115–117). In one example, Hassan et al. (118) reported the preparation of fluorescent SiO_2-Au-γ-Fe_2O_3 nanocomposites using two microreactors in series. The residence time and flow velocity could be modified to effectively tune the surface density of the adhered nanoparticles, thus allowing control over the self-assembly process to achieve the desired plasmonic and/or magnetic characteristics of the final product.

2.5. In-Flow Separation

Multistage chemical reactions typically require intermediate product separations between different reaction stages. In addition, modern chemical processes require energy-efficient separation and purification steps to create high-quality products and enable sustainable manufacturing. For example, in-line separation techniques can be used to continuously recover solvents and catalysts, thereby reducing waste generation. Separation techniques can also be used for the analysis of in-flow synthesized materials and molecules both on- and offline. Microfluidic separation techniques were originally pioneered for this purpose through use in micro total analysis systems and lab-on-a-chip devices (119). Since then, in-flow separation techniques have expanded to encompass a range of conventional chemical engineering operations for gas–liquid and liquid–liquid separations, including distillation (120), chromatography (121), and membrane separations. In addition to more conventional separation unit operations, a wide array of more specialized active and passive microfluidics-based separation strategies have been developed, specifically for the continuous separation of nanomaterials in flow. These include centrifugal force– and inertial force–driven separations, optoelectronic tweezers, capillary electrophoresis, and magnetophoresis (122).

2.5.1. Microdistillation. Because surface forces dominate over gravitational forces at micron length scales, controlled boiling is difficult to achieve without gravity-assisted dampening of fluid motion. In addition, because of a lack of nucleation sites, solutions can become superheated (123). Given these limitations, unlike conventional distillation techniques, many microdistillation devices operate below boiling point conditions. Instead, a carrier gas can be used to aid volatile vapor transport. Many microdistillation approaches use commercially available porous membranes or microfabricated nanopillars as a contact interface between gas and liquid streams (119, 124). Forced convection of a room-temperature or heated gas over the contact interface aids evaporation and removal of volatile components. Alternatively, gas–liquid slug and slug-annular flow formats can be used to achieve direct contact between gas and liquid phases. Downstream condensation modules and gas–liquid membrane-based separators can then be used to retrieve the distillate. These microdistillation devices benefit from improved mass transfer from thin liquid films and high surface-to-volume ratios. Because of these factors, many microstripping and microdistillation devices can achieve efficient separations at moderate temperatures.

Although the use of a gas phase can aid evaporation, direct vapor streams, and in some instances enable controlled boiling (125), it necessitates further downstream gas–liquid separation to recover condensates. Alternative carrier gas–free microfluidic distillation strategies have been designed that direct vapor–liquid flow using capillary forces (126, 127). In one example, Lam et al.

(128) fabricated a microfluidic distillation device, consisting of micropillar-lined channels to partition vapor and liquid streams. A pressure gradient between heated and cooled zones of the microfluidic device, combined with negative pressure from the bottoms removal syringe, as well as capillary driving forces, resulted in the co-current flow of liquid and vapor. Through the flow of liquid back to an effective reboiler zone, multistage distillation was achieved. Using capillary forces in this way is analogous to zero-gravity heated-pipe distillation columns that employ wicking materials to redirect condensates to an evaporation zone (129). Within these microcontact systems, thin liquid films can result in dramatically improved mass transfer over conventional packed distillation columns. To achieve similar multistage distillation in a continuous format, many of the outlined distillation strategies can be used in series.

2.5.2. Liquid–liquid extraction and separation. Microfluidic distillation techniques have advanced significantly, but their application is still limited to volatile and thermally stable components. In addition, many devices that require thermal separation of rectifying and stripping sections require complex microfabricated designs. Microscale continuous liquid–liquid extraction (LLE) and phase separation are an alternative process for effective separation of substances that are nonvolatile, close in vapor pressure, or sensitive to heat. Many microfluidics-based LLE strategies have been designed using affordable and accessible components, making them excellent time- and materials-efficient separation strategies for reconfigurable flow chemistry systems.

Similar to some microdistillation devices, microfluidic LLE extraction can be achieved by leveraging dominant surface forces and using disparities in surface tension for selective liquid–liquid phase separation. Although the surface energy of microfabricated capillary channels can be changed through functionalization, these processes are time consuming and prone to degradation. Alternatively, continuous LLE can be achieved using commercially available porous membranes, such as polytetrafluoroethylene (PTFE) membranes (130), which are selectively wet by the more hydrophobic liquid phase, as discussed in several synthesis examples. In one example, Sahoo et al. (131) used a PTFE membrane sandwiched between two microchannels for the multistage synthesis of carbamates by the Curtius rearrangement of isocyanates. In the continuous liquid–liquid phase-separation stage, the organic solvent containing an azide intermediate preferentially wet and permeated through the PTFE membrane. Using this in-line liquid–liquid separation module, complete separation of organic and aqueous phases was achieved while limiting the active volume of the hazardous azide intermediate. Complete separation and robust continuous operation were achieved in this format because the organic phase did not contain suspended solids that could potentially clog micropores. To circumvent clogging, liquid–liquid separation of organic phases containing micrometer-sized particle suspensions can be achieved by using hydrophobic ducts rather than microporous membranes. Alternatively, modified and inherently hydrophilic microporous membranes can be used for separations in which the aqueous phase is the permeate. However, commercially available, chemically resistant, hydrophilic microporous membranes are still needed to meet the demands of most chemical processes.

2.5.3. Switchable solvents. More recently LLE strategies, employing switchable solvents, have been developed that can be used for energy-efficient solvent recovery, a normally vital but expensive and energy-intensive process in organic/inorganic synthesis. Switchable solvents, when exposed to a stimulus (e.g., chemical or thermal), can rapidly and reversibly change a variety of their physiochemical characteristics (e.g., hydrophilicity, volatility, or ionic strength) (132). The practical use of switchable solvents thus requires limited mass- and heat-transfer resistances, which can be achieved readily in microfluidic reactors (72, 133). Using this strategy, Han et al. (71) developed a continuous microfluidic LLE process utilizing switchable hydrophilicity solvents (SHSs) that change their hydrophilicity upon exposure to CO_2, illustrated in **Figure 3*e***. The SHSs were exposed to CO_2 through a pressurized, home-built tube-in-tube microfluidic reactor, using commercially available fluidic components. The low mass transfer resistance and high gas–liquid interfacial area of the gas-permeable tubular membrane (Teflon AF 2400) in the tube-in-tube microfluidic reactor configuration enhanced gas–liquid mass transfer rates, resulting in SHS extraction times two orders of magnitude faster than those of batch processes.

2.5.4. Chromatography. A more conventional separation technique that has been demonstrated at the microscale is chromatography. Micro-chromatography separations have been developed both to limit solvent analyte volumes needed for analysis and to perform on-line characterizations. Micro-chromatography separation strategies have typically used microfabricated channels as filter elements. In one example, using microfabricated solids-separation sections coupled with open-channel electrochromatography, Broyles et al. (134) created an efficient on-chip sample concentrator and separator equivalent to high-performance liquid chromatography (HPLC). Other, more novel chromatographic processes achieved only in microfluidic devices have also been demonstrated. As a recent example, Prodromou et al. (135) developed a transparent microfluidic chip loaded with azobenzene-cyclized peptide-coated beads to trap target proteins with a high level of selectivity. The azobenzene confirmation could be changed by illumination with specific light wavelengths to achieve rapid and reversible switching of binding affinities, but only in microfluidic channels, because of their small pathlengths.

2.6. Toward Accessibility of Flow Chemistry Modules

The recent trend of the field of flow chemistry toward tube-based microreactors has resulted in more accessible and reconfigurable system designs. Whereas microfabricated chip reactors can be built for specialized applications, narrower channels, and smaller reactor footprints (117), tube-based systems are faster to design, build, and modify at a fraction of the expense. Accessible development and reconfiguration reduce the barrier of entry to flow chemistry by offering intuitive systems from standardized and commercially available fluidic components. Recent developments in tubular systems have expanded their accessible parameter space to cover a wide range of temperatures, pressures, and residence times. Beyond basic microfluidic design and assembly, a variety of more advanced microfluidic unit operation modules may be assembled from the same commercial components, including 3D serpentine and thermoformed vortex mixers and tube-in-tube membrane phase separators. Step-by-step protocols for assembling many of these components, as well as tubular reactors, have been made available to the larger scientific community to facilitate entry into modular flow chemistry systems.

2.7. Online Characterization

Characterization within microreactors is a powerful tool to understand and control chemical processes. In a traditional experimental approach, aliquots must be collected from a batch reaction vessel and characterized manually by the user. This process is slow and material intensive and often results in imprecise sampling of desired reactive conditions. Flow chemistry platforms, however, are conducive to high-efficiency, automated measurement techniques, which enable the generation of large, high-precision data libraries in real time with minimal reagent consumption and waste generation for both organic and inorganic materials and molecules (136, 137). Furthermore, in situ monitoring of microreactors enables analysis of otherwise unobservable reaction conditions. Exploitation of the spatiotemporal relationship between microreactor length and reaction time enables precise, reproducible measurements at reaction times on the order of milliseconds.

Nondestructive analytical tools are particularly suited to capitalize on spatiotemporal relationships unique to microfluidic reactors. For example, in situ monitoring of photoluminescence (PL) and absorption spectra of inorganic nanomaterials synthesized in-flow has been demonstrated with a dynamic sampling point system. Epps et al. (103) combined an in situ PL and absorption monitoring module with a translating platform to achieve automated mobile monitoring of multiple sampling locations corresponding to different reaction times within a single equilibrated system. This modular microfluidic platform could perform spectroscopic measurements on residence times as low as 100 ms and up to 17 min by tuning the sampling position and flow velocity (**Figure 4*c***). Furthermore, the mobile sampling strategy, coupled with noninvasive monitoring methods, presented the added advantage of decoupling fluid velocity from residence time. By measuring PL and absorption spectra at multiple locations along the microfluidic reactor within a single set of flow rates, the work demonstrated advection tunable reaction pathways and optical properties for cesium lead bromide ($CsPbBr_3$) nanocrystals. The emission peak wavelength at equal reaction times could be tuned by as much as 25 nm by strictly altering the flow velocity, and therefore the precursor mixing rates. The observations and sampling rate achieved in this study would be unattainable using conventional flask-based methods.

Inverse to translational-stage sampling, oscillatory single-droplet microreactors operate by repeatedly passing a single reactive droplet through a stationary in situ sampling point. This design allows for near-indefinite sampling of a microliter-sized reactive droplet, resulting in extremely material-efficient kinetic and mechanistic studies. Abolhasani et al. (95) implemented this technique in the heat-up synthesis of CdSe, CdTe, and InP QDs with in situ sampling of UV-Vis absorption spectra at the reaction temperature. In this study, 7,500 spectra with a time resolution of 3 s were collected across a range of temperature and composition screening experiments using a total of 1.7 mL of QD precursors (**Figure 4*d***). With the 15-min reaction times explored in this study, a sampling efficiency of 33 nL/spectra was achieved, surpassing equivalent flask-based techniques.

Beyond the translational flowcell and the single-droplet reaction monitoring techniques, other nondestructive online reaction characterization methods have been demonstrated as powerful characterization tools when used in a stationary sampling point attached to the outlet of a continuous microfluidic reactor (138). Real-time measurements and automated sample processing can result in the generation of significant amounts of experimental data. Such high sampling rates in microfluidic reactors can enable rapid exploration and mapping of large, experimentally accessible reaction spaces for both organic and inorganic syntheses. For example, Lignos et al. (139) developed an online fluorescence lifetime spectroscopy (FLS) device for the analysis of radiative lifetime in mixed halide $CsPbX_3$ (X = Cl, Br, I) perovskite QDs under varying environmental conditions. This online FLS technique could conduct and automatically analyze 1,000 FLS measurements in only 5 h of continuous operation, a feat that if conducted through manual experimentation would take months of continuous work. This unique capability enabled researchers to systematically investigate the influence of anion and cation loading rates on fluorescence lifetimes of $CsPbX_3$ QDs. Similar examples have been demonstrated for an array of other online characterization tools, including infrared spectroscopy/Fourier transform infrared spectroscopy (140), Raman spectroscopy (141), X-ray absorption spectroscopy (142), X-ray diffraction (143), small-/wide-angle X-ray scattering (144, 145), nuclear magnetic resonance spectroscopy (146), susceptometry (147), and dynamic light scattering (148). Application of these online characterization modules will significantly enhance the sustainability and efficiency of screening, optimization, and manufacturing of emerging advanced materials and molecules using flow chemistry.

When operating multistage organic synthesis in flow, destructive analytical techniques (e.g., gas chromatography mass spectrometry and HPLC) (69, 149) may be positioned downstream

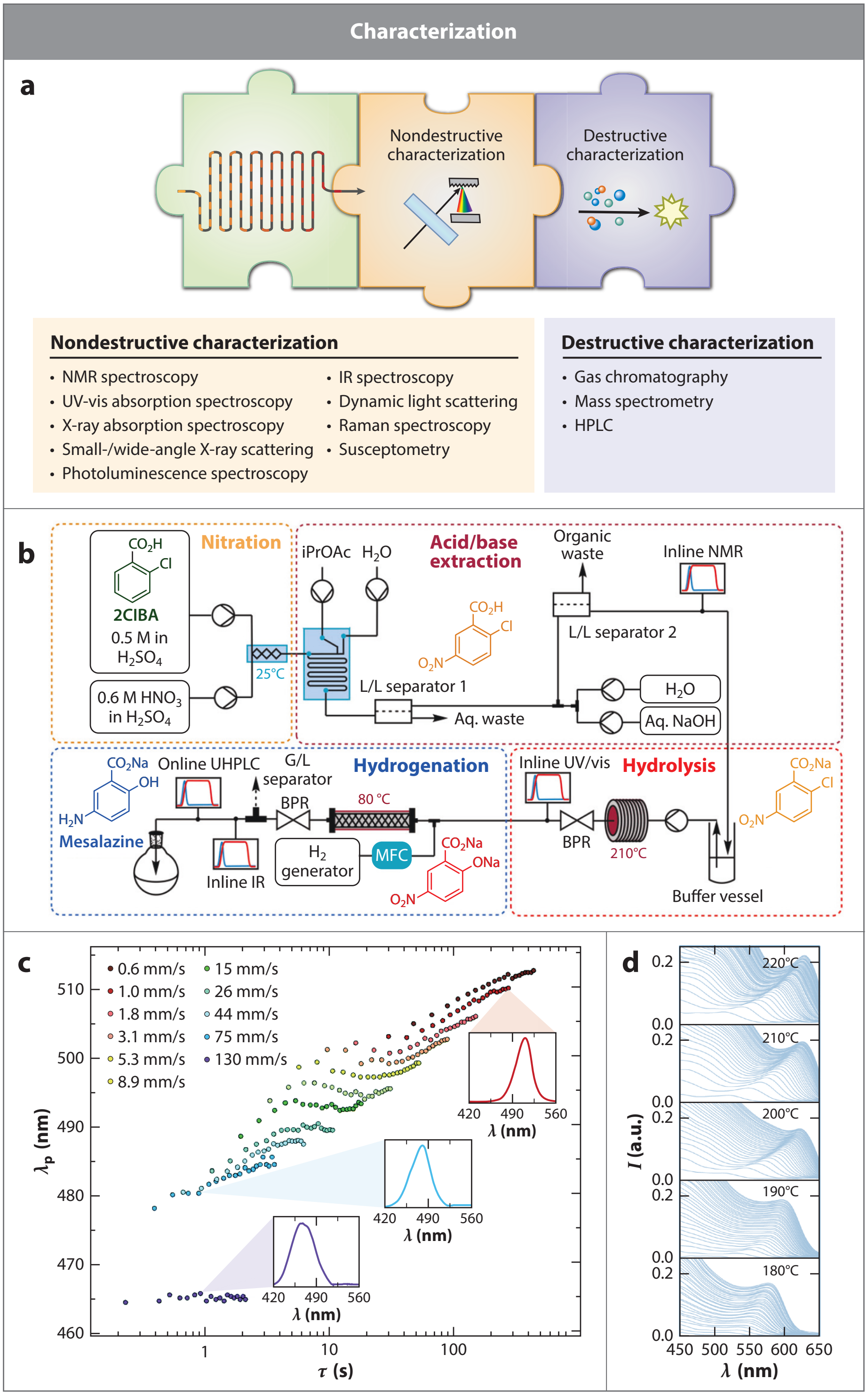


Figure 4

(*a*) Summary of nondestructive and destructive online characterization techniques that have been integrated with microfluidic reactors. (*b*) Schematic of an advanced multistage flow chemistry platform using multiple online characterization tools for active pharmaceutical ingredient synthesis [adapted with permission from Sagmeister et al. (151); copyright 2021 John Wiley and Sons]. (*c*) Peak emission wavelength as a function of reaction time for 11 different flow velocities from the synthesis of $CsPbBr_3$ QDs using a mobile optical sampling [adapted with permission from Epps et al. (103); copyright 2017 Royal Society of Chemistry]. (*d*) In situ time evolution of CdSe QDs as a function of growth temperature [adapted with permission from Abolhasani et al. (95); copyright 2015 American Chemical Society]. Abbreviations: IR, infrared; LLE, liquid–liquid extraction; NMR, nuclear magnetic resonance; QD, quantum dot; UHPLC, ultra-high-performance liquid chromatography; UV, ultraviolet.

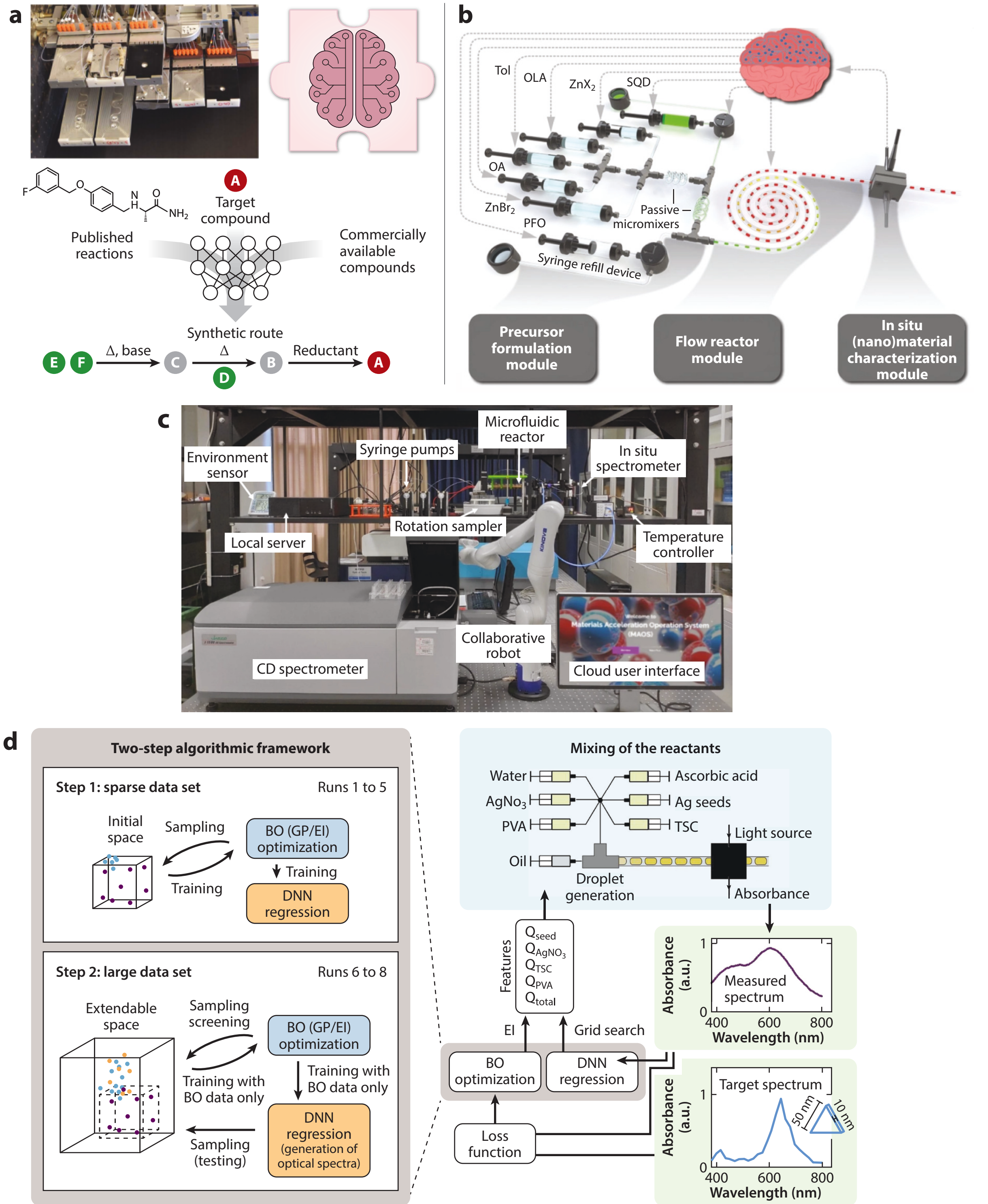
of nondestructive methods, producing a more comprehensive understanding of the process (**Figure 4*a***). Recently, Sagmeister et al. (150) demonstrated this multi-analytical technique strategy with both destructive and nondestructive techniques for multistage synthesis of APIs, resulting in a powerful and versatile process optimization strategy. A later iteration of this work simultaneously implemented four different analytical techniques—nuclear magnetic resonance, UV-Vis absorption spectroscopy, IR spectroscopy, and ultra-HPLC—toward the data-driven optimization of mesalazine synthesis in flow (151) (**Figure 4*b***). A dynamic reaction monitoring strategy was implemented by applying controlled condition ramps at various sections of the three-stage chemical synthesis. Continuous monitoring through each of the analytical tools allowed for the collection of more than 45,000 data points. Analysis of this large data set was augmented through neural network–guided feature prediction, which allowed for comprehensive profiling of reaction parameters. The same platform was then operated under the continuous mode to achieve a throughput of 1.6 g/h of mesalazine. This study is an exemplary case for the application of online reaction monitoring techniques integrated with microfluidic reactors to enable data-driven process optimization toward the control and ultimate production of APIs and other solution-processed materials and molecules.

3. MOVING FORWARD: AI-GUIDED DISCOVERY AND MANUFACTURING OF MATERIALS AND MOLECULES ENABLED BY MODULAR FLOW CHEMISTRY PLATFORMS

Although the ever-expanding toolbox of microfluidics-based unit operations for precursor formulation, reaction, and online analysis is powerful by itself, its true potential can be unlocked when integrated with advanced data science and AI techniques (152–156). AI-guided modeling and experiment selection algorithms coupled with rapidly generated and abundant real-time online experimental data allow for the creation of self-optimizing flow chemistry platforms (known as self-driving laboratories) for accelerated discovery, process development, and optimization of novel materials and molecules. These autonomous experimental systems enable researchers to both explore and optimize larger reaction spaces with elevated speed and efficiency without user intervention, thereby unlocking a larger portion of the chemical universe. Beyond optimization and global learning of high-dimensional reaction spaces, the AI-guided modular flow chemistry platforms can enable rapid on-site and on-demand manufacturing of advanced functional materials and molecules with desired physicochemical properties.

AI-guided experimentation algorithms have been implemented in microfluidic reactors using both prior knowledge–informed and uninformed strategies. Informed AI algorithms, coinciding with the field of cheminformatics, use existing knowledge of the target class of reactions extracted from literature data to predict and navigate through unexplored outcomes. This strategy was applied recently to the retrosynthesis of APIs and other organic molecules in flow using reconfigurable microfluidic platforms. Uninformed experimental algorithms attempt to build an understanding of the target reaction without any prior knowledge by selecting both optimal and high-uncertainty experiments. These techniques are applied in systems where high sensitivity to the reaction environment limits batch-to-batch and lab-to-lab reproducibility, e.g., colloidal nanocrystals.

Coley et al. (157) presented one of the most effective applications of AI-guided retrosynthesis of APIs in an autonomous flow chemistry platform. This work used millions of organic reactions reported in the Reaxys database and filings in the US Patent and Trademark Office to develop and train a retrosynthetic planning software package for organic molecules. The user could then select an organic molecule, and the software package would identify a favorable multistage reaction



(Caption appears on following page)

Figure 5 (*Figure appears on preceding page*)

Examples of artificial intelligence (AI)-guided synthesis in flow using (*a*) literature data mining for retrosynthesis of target active pharmaceutical ingredients using a reconfigurable flow chemistry platform integrated with a robotic arm [adapted with permission from Coley et al. (157); copyright 2019 American Association for the Advancement of Science]; (*b*) stable noisy optimization and a robotic sample collection arm for chiral perovskite nanostructures [adapted with permission from Li et al. (161); copyright 2020 Nature Communications]; (*c*) Bayesian optimization methods with a modular microfluidic platform to tune peal emission energy, emission linewidth, and quantum yield of $CsPbX_3$ (X = Cl, Br, I) quantum dots [adapted with permission from Epps et al. (162), copyright 2020 John Wiley and Sons]; and (*d*) Bayesian optimization methods for autonomous metal nanoparticle synthesis [adapted with permission from Mekki-Berrada et al. (164); copyright 2021 Springer Nature]. Abbreviations: BO, Bayesian optimization; CD, circular dichroism; DNN, deep neural network; EI, expected improvement; GP, Gaussian process; PVA, polyvinyl alcohol; TSC, trisodium citrate.

pathway to achieve a favorable reaction yield. A multistage microfluidic unit operation system around the design specifications of the AI-selected synthetic pathway of the target organic molecule would then be formed automatically by a robotic arm that positioned a set of reconfigurable microreactor blocks, consisting of temperature-controlled tubing lengths, packed bed reactors, additional reagent injection, and a membrane separator (**Figure 5*a***). With this autonomous flow chemistry platform, end-to-end continuous manufacturing of 15 APIs was demonstrated successfully without any user intervention or added labor. This autonomous flow chemistry platform was a capstone system in the self-driven synthetic path discovery and retrosynthesis of organic molecules, and future iterations of this work will likely attain even greater mastery of the chemical universe.

Despite the recent success of cheminformatics in self-driving laboratories, many scientific fields cannot exert the same degree of universal control attained in organic synthesis and APIs. For example, in many areas of nanoparticle synthesis, materials are synthesized in multistage protocols with precise temperature gradients and high sensitivities to ambient exposure. Reproduction of many nanoparticle synthesis reactions is often not viable from system to system, which makes the development of a database for nanoparticles equivalent to Reaxys, for example, more difficult. These systems instead implement uninformed experiment selection algorithms, which can be used to efficiently navigate a reaction space in isolation and without prior information (110, 158). A notable example of an uninformed method is Huyer & Neumaier's (159) Stable Noisy Optimization by Branch and Fit. Krishnadasan et al. (160) first implemented this algorithm in flow, applying it toward the black-box optimization of CdSe QD syntheses. More recent work has demonstrated the functionality of this algorithm toward the search for chiral perovskite nanostructures (**Figure 5*b***). Li et al. (161) integrated a microfluidic reactor with a robotic arm for automated offline circular dichroism spectroscopy of in-flow synthesized nanocrystal samples. With this design, autonomous optimization of circular dichroism in $CsPbBr_3$ nanocrystals was achieved.

Similarly, Bayesian optimization methods use the prediction of a given model combined with that model's uncertainty to efficiently navigate an experimental space and improve the overall understanding of the system in an iterative manner. The nature of Bayesian methods allows for the same architecture to optimize for a desired target and achieve an acceptable global model. Although Bayesian methods may be used with prior knowledge, these techniques are more commonly implemented into uninformed self-driving laboratories using flow chemistry techniques. For example, Epps et al. (162, 163) applied Bayesian optimization methods toward the autonomous, in-flow tuning of peak emission energy, emission linewidth, and quantum yield in the anion exchange of $CsPbBr_3$ perovskite nanocrystals (**Figure 5*c***). This study used an ensemble of neural networks combined with Bayesian algorithms to achieve tunability and optimization of three target parameters simultaneously. Similarly, Mekki-Berrada et al. (164) used Bayesian optimization methods for the optimization of various metal nanoparticle syntheses (**Figure 5*d***). The key development of this work was in the use of deep neural networks to predict the absorption spectra output of each experiment. This approach circumvented the need for multi-objective handling by predicting the spectra themselves from which those properties would be derived. The AI algorithms applied in autonomous closed-loop platforms have been discussed in greater detail in prior reviews.

4. CONCLUDING REMARKS

Modular microfluidic unit operations present an opportunity to achieve a safer, more efficient, and more resilient manufacturing framework for specialty chemicals and advanced functional materials. In addition, they could significantly accelerate formulation discovery and process optimization, while minimizing labor, energy, and materials resources. However, the realization of microfluidics-based sustainable manufacturing requires scalable strategies suitable for complex reaction pathways. The practicality and performance of scale-out microfluidic processes must be compared, beyond conventional batch processes, to emerging continuous reactors that intensify heat and mass transfer rates through alternative approaches, such as vortex and spinning disk reactors (165, 166). Furthermore, despite an extensive library of developed microfluidic process modules, a standardized approach to selecting and building the appropriate modular configuration for a specific reactive system has yet to be established. Advanced microfluidic systems with focused applications will most likely continue to play a role in optimized system design, but greater effort toward the design and sharing of accessible, plug-and-play unit operation modules would significantly reduce the barrier of entry for flow chemistry and further propagate modern chemical science and engineering. The same can be said for microfluidics-based self-driving laboratories. The broader release of user-friendly process automation tools and AI-guided modeling and experiment selection algorithms suitable to flow chemistry would enable significant improvements in the rate of materials and molecular discovery and optimization, further driving the development of autonomous laboratories and sustainable distributed manufacturing. Over the past few decades, microfluidic systems have spread into many facets of chemical engineering, and in the coming years, we expect to see continued leaps in the development and application of these technologies.

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Errata

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