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Role of continuous flow processes in green manufacturing of pharmaceuticals and specialty chemicals

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Recently, focus has turned towards increasing chemical process safety and sustainability for fundamental and applied research as well as manufacturing of pharmaceuticals and specialty chemicals. Flow chemistry techniques have attracted significant interest as a way to implement and improve chemical processes in order to satisfy the growing demand for chemical sustainability. In this article, we discuss emerging flow chemistry technologies with applications in green manufacturing of high-value chemicals and efficient screening of chemical reaction space. Continuous manufacturing techniques are increasingly being utilized to reduce the amount of material and energy utilized in a process while incorporating real-time analysis, control, and enhanced process safety. Beyond continuous production, flow screening techniques can rapidly search a multi-dimensional reaction space to improve process design, performance, and efficiency. Furthermore, time-efficient and material-efficient (*green*) flow screening platforms can be utilized to develop the next generation of process development technologies including predictive reaction models and process scale-up strategies.

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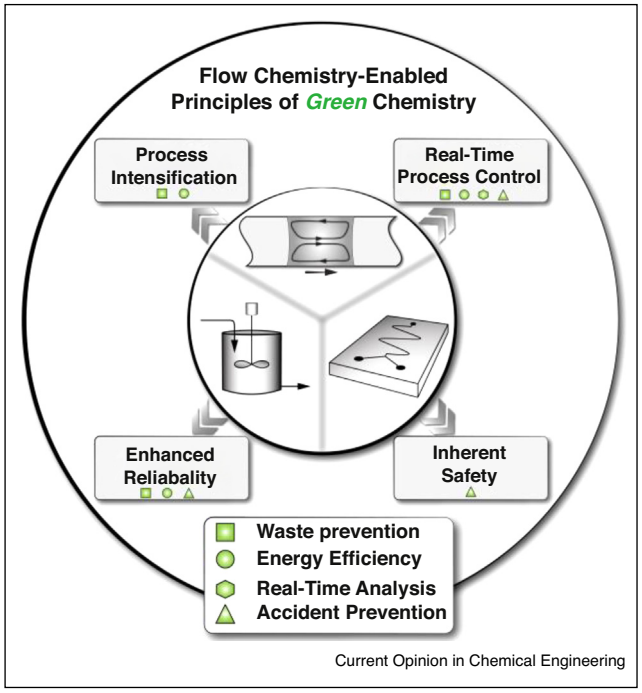
Introduction

The introduction of the concept of green chemistry in 1998 by Paul Anastas and John Warner [1] resulted in a monumental shift in chemical discovery and manufacturing, particularly for high-value materials such as active pharmaceutical ingredients (APIs) and fine chemicals. Developing 12 tenets, including waste prevention, process safety, hazard minimization, and energy efficiency, they outlined a vision for the future in industrial chemical syntheses. Building on this grand vision, in order to achieve greater sustainability, a variety of new processing routes and technologies are continuously being developed to further improve process sustainability. Although continuous flow strategies have been prevalent in the large-scale production of commodity chemicals [2] over the last century, only recently implementation is beginning to spread throughout the specialty chemical and pharmaceutical industries. Continuous flow synthesis techniques are increasingly being adopted in pharmaceutical and chemical industries for high-throughput reaction screening [3••] as well as bench-scale and industrial-scale production [4]. This trend is fueled by the numerous benefits offered by continuous flow processes compared to their batch counterparts, namely, inherent process intensification (improved heat and mass transfer rates), decreased process downtime, *in-situ* process monitoring, real-time process control, enhanced process safety, and ease of scale up. From a sustainability perspective, continuous flow reactors and high-throughput screening setups can be implemented to address various green chemistry principles, including waste minimization, energy efficiency, and process safety (Figure 1). Waste minimization is achieved through several techniques, namely recycling, coupling unit operations, increased yield, and improved process control. Energy efficiency of a process is improved by the nature of steady-state operation and the ability to transfer energy between unit operations in a process to minimize the overall energy requirement. Process safety can also be enhanced through the inherent intensification of continuous manufacturing and reduced reactor volume, alongside real-time monitoring and control techniques.

In continuous flow syntheses, reactants are fed through reactors of varying shapes and sizes with the product mixture removed at the same rate from the exit end of the reactor. Flow reactors can be constructed out of a variety of chemical-resistant materials (e.g. silicon, glass, thermoplastics, ceramics, and metals) and can be fabricated using different methods, including (micro)fabrication [5–7], additive manufacturing [8•,9], and tubing/extrusion [10–13] (Figure 2).

Depending on the production scale, the channel (or tube) diameters found in continuous flow reactors can vary drastically from O(0.1)–O(10) mm [14••]. On the basis of production scale, continuous flow reactors can be

Figure 1



Benefits of flow chemistry with relevant green chemistry principles.

divided into three distinct classifications: (i) micro-scale, (ii) milli-scale, and (iii) macro-scale reactors. Micro-scale reactors possess microchannel length scales on the order of hundreds of microns, benefiting from short diffusion lengths and excellent heat and mass transfer rates. Microreactors, typically only capable of producing products on the scale of kg/yr, are mostly suited for very high-value materials, such as APIs [15], or for material-efficient reaction screening and optimization purposes [16]. Milli-fluidic reactors, usually with channel length scales on the order of 1–2 mm, can achieve higher chemical production throughputs (up to hundreds of kg/yr) than microreactors, and are suitable for synthesizing fine or specialty chemicals [8•]. Macro-scale reactors, possessing either large diameters (greater than 5 mm) [14••], or large numbers of parallel channels or reactor plates [6,17,18] (numbered-up strategy), are capable of synthesizing products at industrially relevant scales (tons/yr).

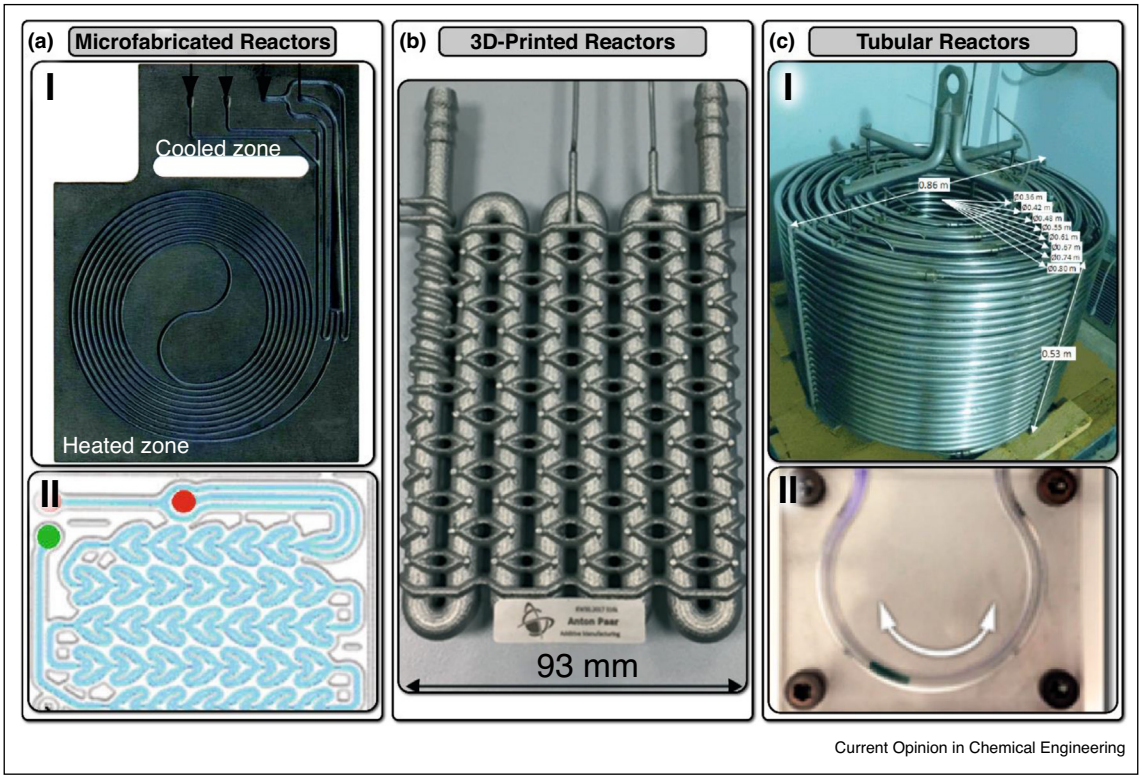
An emerging area, in which flow chemistry techniques are being adopted more widely, is material-efficient high-throughput reaction screening and optimization. Currently, most molecular discovery and chemical reaction optimizations in the pharmaceutical and chemical industries are conducted using individual reactions in batch. Considering the flask-based molecular discovery and optimization, large-scale production of APIs and specialty chemicals are commonly performed in batch, albeit trending towards continuous manufacturing. However, chemists and chemical engineers are increasingly realizing that converting chemical syntheses from small batch experiments to large continuous flow processes is not a trivial task, whereas 'scaling out' a continuous small-scale process is a more facile strategy [18–20]. Scale-up from a small batch reactor (flask) to a large-scale continuous flow reactor or from a lab-scale continuous flow reactor to a large-scale batch reactor is challenging, as maintaining multiple relevant process parameters while increasing the characteristic length scale of the reactor is problematic.

Introduction to modern flow chemistry

With the rapid progress of continuous flow processes, it is vital to understand the process dynamics and limitations to be able to identify areas for improvement as well as being able to preserve consistent operation across a range of reaction scales and potential reactor configurations. Dimensionless numbers are key parameters in evaluating the performance of chemical processes as they usually arise from non-dimensionalizing fundamental conservation and rate equations. A nondimensionalized system can be expressed through a smaller number of dimensionless quantities than number of process variables, reducing the dimension of the parameter space required to fully specify a process. Maintaining the performance of a reaction across multiple reactor scales and configurations requires relatively consistent dimensionless quantities for heat transfer (Nusselt, Prandtl, and Biot numbers), mass transfer (Sherwood, Schmidt, Peclet, and Biot numbers), as well as mixing and reaction rates (Reynolds, Damköhler, and Thiele numbers). A detailed discussion of the importance of dimensionless numbers in flow chemistry processes can be found elsewhere [21].

When changing reactor size, knowing which parameters to vary in order to increase process throughput and which modifications would result in undesirable system behaviors, allows the engineer to navigate the challenges of increasing process scales. Common detrimental shifts in regimes of operation would be moving from a well-mixed reactor (reaction-limited regime) to one that has transport limitations (mass transfer-limited regime) resulting in significant temperature or concentration gradients as well as undesirable side products. These phenomena can be described using the Damköhler (Da) number, the dimensionless ratio of the reaction rate to the rate of mass transfer. The desirable reaction-limited regime occurs when $Da << 1$ and the undesirable mass transfer-limited regime occurs where $Da >> 1$, when the mass transport in the reactor is not fast enough to supply reagents to keep up with the comparatively fast reaction kinetics. Varying the reactor size dramatically influences the mass transfer rate resulting in a dramatic shift in reactor performance if the system changes Damköhler regime. Minimizing the reactor variability simplifies modeling and control of the process as well as improving the consistency of the products [22].

Figure 2



Examples of various flow reactors. **(a)** Microfabricated reactors including (I) silicon carbide-based microreactor, Newman *et al.* [7], and (II) glass-based microreactor, Nieves Ramacha *et al.* [5]. **(b)** 3-D printed stainless-steel flow reactor with coupled cooling channel, Gutmann *et al.* [8•]. **(c)** Tube-based microreactors including (I) jacketed stainless-steel tubular reactor, Johnson *et al.* [10] and (II) single-droplet Teflon tube reactor, Hwang *et al.* [52•]. Images reproduced with permission from: Royal Society of Chemistry, 2013 (Ai), Springer Nature, 2015 (Aii), Royal Society of Chemistry, 2017 (B), American Chemical Society, 2012 (Ci), and Royal Society of Chemistry, 2017 (Cii).

Flow chemistry-enabled *green* synthesis, discovery, and manufacturing

In this article, we aim to highlight some of the key benefits of the emerging flow chemistry technologies as they apply to making progress towards meeting the applicable tenets of green chemistry as well as highlighting recent groundbreaking work in the field, illustrating such benefits. From an application point of view, flow chemistry strategies can be classified into processes designed for (1) continuous manufacturing and (2) rapid reaction screening and optimization. Both fields of flow chemistry benefit from general advantages of continuous flow reactors with a few minor differences in the specific applied green chemistry principles with specifics discussed below.

Green continuous manufacturing

Flow chemistry has been an important tool in the manufacturing of fine and commodity chemicals as well as having a rising influence in the pharmaceutical industry [23] in recent years. One of the main green aspects of flow chemistry techniques is the waste minimization through various process intensification routes. The primary mode of waste prevention in large-scale manufacturing in flow is being able to improve the efficiency of the unit operations (e.g. mixing, reaction, separation, and purification modules) over normal batch operations. One major technique for increasing efficiency is through the implementation of recycling streams [24].

Continuous recycling of unreacted starting materials, catalysts, and/or extraction solvents whenever possible has a profound impact on the overall mass efficiency (E Factor) of a given process. Recycling unused reagents increases the effective residence time in the reactor and overall conversion of the process and reduces the amount of wasted precursors, which is especially important when dealing with valuable API feedstocks or process intermediates. Recycling the solvent streams used in extraction and purification steps minimizes the wasted solvent for a given separation to the amount lost due to non-ideal partitioning of two-phase mixtures [25].

Inherent process intensification characteristics of continuous manufacturing technologies allows for unit

operations with increased efficiency as compared to their batch counterparts. For example, a given liquid–liquid extraction can be enhanced with flow by providing additional extraction equilibria beyond the single equilibrium provided by batch liquid–liquid extraction. This can be achieved through running the extraction solvent countercurrent to the process stream through several extraction stages, effectively scrubbing more extractant from the process stream per amount of solvent than a single pass in batch [14••] (Figure 3a). Extractions can also be further intensified by the application of phase separation membranes in order to minimize the volumetric footprint of the equilibration stages and separatory apparatus [26•] (Figure 3ci). Additionally, in-line liquid–liquid phase separators have been developed using a simple porous capillary and block housing to further reduce the separation footprint while minimizing waste in multi-phase reaction systems [27]. Membranes can also remove the additional post-reactor separation steps necessary in many multi-phase (gas–liquid or liquid–liquid) reaction systems [28] (Figure 3cii). Furthermore, membranes can limit the formation of explosive or combustible mixtures of vapors inside the reactor [17].

Recent advances in cost-effective fabrication of high-pressure silicon/glass and stainless steel flow reactors [29] are opening the way to use more volatile green and bio-derived solvents such as 2-methyl tetrahydrofuran (2-MeTHF) [30–32], γ-Valerolactone (GVL) [33,34], and ethanol [35–37] to reduce the reliance of a process on oil derivatives. 2-MeTHF and GVL come from the same initial source of pentose sugars in biomass with the 2-MeTHF having GVL as a process intermediate. The high volatilities of many of these solvents can be mitigated by utilizing high-pressure flow reactors that allow for maintaining the reaction in the liquid phase, while accessing the increased reactivity of higher temperatures.

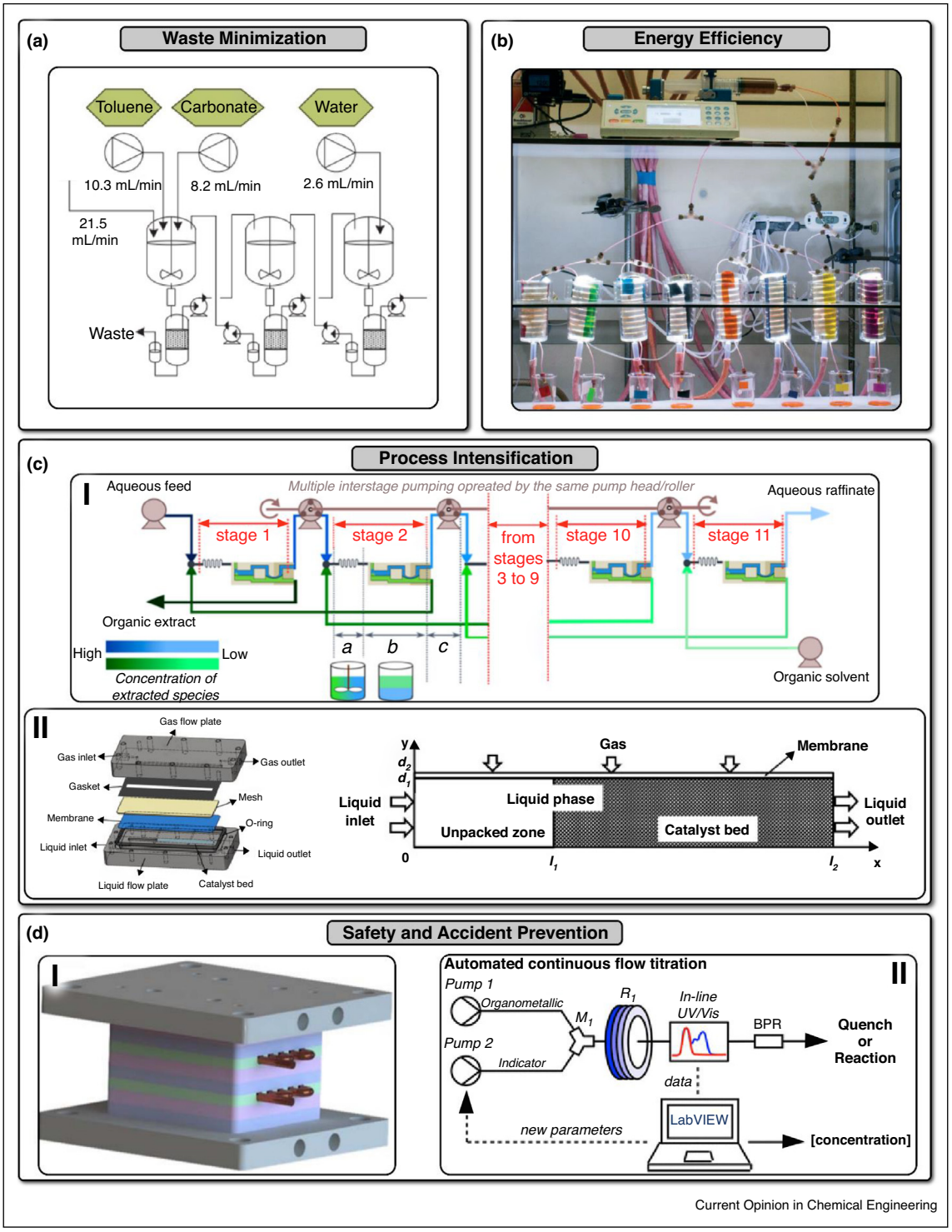
Analogous to the improvements possible in increasing mass efficiency of a process, flow chemistry and continuous manufacturing can allow for a significant improvement in the energy efficiency of a process through (1) operating under steady-state regime and (2) thermally coupling process steps that would be separated in time in a conventional batch process. Steady-state operation is ideal for minimizing energy costs as all the peripheral equipment can be maintained at a desired temperature and the only heat requirement would be the process stream itself, whereas in batch operations all the equipment must be cycled to the correct temperature as well. Unit operation coupling in continuous processing allows for operations with complementary heat requirements to be coupled through a heat exchanger, allowing the stream that is cooling to provide the heat for another stream [14••,38]. Process energy efficiency of chemical reactions conducted in flow can be further improved through coupling the flow reactor with light [18,39,40–42] (e.g. photo-chemical reactions) or electrons [43•,44] (e.g. electrochemical reactions). Photo-chemical reactions benefit from flow chemistry, primarily due to the shorter reactor characteristic length scale compared to batch (flask) reactors, resulting in increased photon flux per unit volume of the reaction mixture [18] (Figure 3b). Moreover, micro/milli-fluidic channels result in higher voltage gradients and lower power losses in electro-flow chemistry applications compared to relatively large batch reactors.

Alongside the improvements afforded to process efficiency, another major benefit of flow processing is the increased safety compared to batch synthesis [45]. Although large-scale continuous processes can involve large volumes of potentially hazardous materials at elevated temperatures and pressures, for a given production scale the continuous process will have a smaller instantaneous volume at a given time, minimizing the amount of risk if a part of the process were to fail. Because of the increased operational safety of smaller instantaneous reaction volumes, the flow process can generally be operated at further elevated temperatures and pressures required to increase the reaction performance and yield. Additionally, safety controls such as cooling systems and relief valves benefit from a smaller volume of material and improved surface area to volume ratios for highly exothermic reactions [17] (Figure 3di). One safety feature possible for continuous processing is that reactions can be performed in a telescopic manner with hazardous intermediates being produced in one operation and then immediately consumed in another [23,46,47] (Figure 3dii), eliminating the need for separation and stockpiling of large quantities of hazardous materials.

Green reaction screening, process development, and optimization

Flow chemistry strategies are not only increasingly being adopted by industry and academia for production of pharmaceuticals, APIs, fine chemicals, and bulk chemicals; they are now commonly being implemented as material-efficient and time-efficient strategies to rapidly screen the massive parameter space of chemical reactions and optimize process conditions. This article is not meant to be an exhaustive review of high-throughput flow screening technologies, as more comprehensive reviews already exist [48]. We seek to only discuss the green chemistry advancements and advantages of high-throughput *in-flow* reaction screening techniques. Microscale flow chemistry platforms utilized for high-throughput reaction screening excel at two primary green chemistry principles: (1) waste prevention and (2) minimizing risk of accidents. Both benefits are largely attributable to the quantities of material required for evaluating each reaction condition (1–100 μL). High-throughput reaction screening is usually conducted in microreactors with reactant and reactor volumes at the microliter scale,

Figure 3



Examples of green chemistry principles addressed by continuous manufacturing techniques. **(a)** Waste minimization: Continuous counter-current liquid-liquid extraction for kg-scale API synthesis, Cole *et al.* [14••]. **(b)** Energy efficiency: Continuous numbered-up gas-liquid photoredox microreactor platform, Su *et al.* [18]. **(c)** Process intensification: (I) Continuous multi-stage liquid–liquid extraction intensified using membrane flow-separators, Weeranoppanant *et al.* [26•]; (II) Continuous flow membrane reactor for aerobic oxidation, Wu *et al.* [28]. **(d)** Safety and accident prevention: (I) Stacked membrane microreactor array with coupled heat exchanger plates, Mo *et al.* [17]; (II) Continuous titration and control of organometallic reagent delivery, Bedermann *et al.* [64]. Images reproduced with permission from: the American Association for the Advancement of Science, 2017 (a), Royal Society of Chemistry, 2015 (b), American Chemical Society, 2017 (Ci), Elsevier, 2019 (Cii), Royal Society of Chemistry, 2018 (Di), and American Chemical Society, 2019 (Dii).

thereby minimizing waste production while significantly reducing accident probability and severity (Figure 4a).

Utilizing microreactors, a broad spectrum of continuous (e.g. temperature, time, concentration, and pressure) and discrete (e.g. reagents, catalysts, and solvents) reaction conditions can be efficiently screened, both in terms of time and material. The greatest strength of utilizing microreactors for high-throughput reaction screening lies in the required reagent volumes, which can range from nanoliters [49] to 15+ μL droplets [50], thereby minimizing waste and the use of toxic and/or expensive reagents. Compared to batch syntheses, which are most often conducted at the milliliter scale (1–20 mL or higher), in-flow reaction screening techniques can test anywhere from hundreds up to as many as 10 000 [51] reactions or reaction conditions with greater repeatability and precision while consuming the same volume of material as is required in a single standard batch reaction.

The flow-based reaction screening platforms can be implemented to test a broad variety of single/multi-phase reactions including cross-coupling [3••,52•], photo-redox catalysis [11,53,54], amination [39,52•], sulfonylation [43•], and hydroformylation [55•] reactions through integration of microreactors with automated sample handling and in-line characterization techniques [56]. For example, it was recently demonstrated that an automated flow chemistry platform can screen up to 1500+ pharmaceutically relevant chemical reactions per day while consuming nanomoles of material per reaction (Figure 4b) [3••]. Screening of discrete reaction parameters, including solvents, catalysts, and ligands, has been conducted using both continuous [3••,54,55•,57•,58••] and single-droplet [50,55•,59,60] flow processes. Furthermore, flow strategies can be used to evaluate a broad spectrum of continuous process conditions, including residence time [15], temperature, and pressure (Figure 4c). Flow screening platforms can also be extended to more exotic reactions and materials such as polymers [61•] (Figure 4d) and inorganics [62]. Rapid screening of continuous and discrete reaction parameters is typically accomplished using process automation and in-line/*in-situ* process characterization [3••,63], enabling rapid on-the-fly tuning of reaction parameters with data collection to efficiently explore massive reaction parameter spaces while consuming minimal amounts of materials.

Flow screening techniques can also be utilized to help minimize human, financial, and environmental risks associated with chemical synthesis. There are two primary hazard classifications that can be addressed using flow screening and optimization platforms: hazardous reagents [64] (e.g. pyrophorics, highly energetic compounds, highly toxic compounds, etc.) and hazardous reaction conditions (e.g. high temperature, pressure, reaction exothermicity/runaway reaction risk, etc.).

Unfortunately, hazardous chemicals are often an unavoidable part of chemical synthesis. Flow screening and optimization techniques can prevent or mitigate such risks as explosions, fires, and exposures to hazardous chemicals by significantly reducing the reaction volume from milliliter to microliter scale. Furthermore, microreactors enable the inclusion of additional engineering controls (e.g. temperature and pressure relief systems, inert atmospheres, and blast shields) or process automation (e.g. reagent injection, sample handling, and control systems) [3••,12,23] which serve to mitigate inherent hazards and are more difficult to implement with traditional flask-based batch techniques.

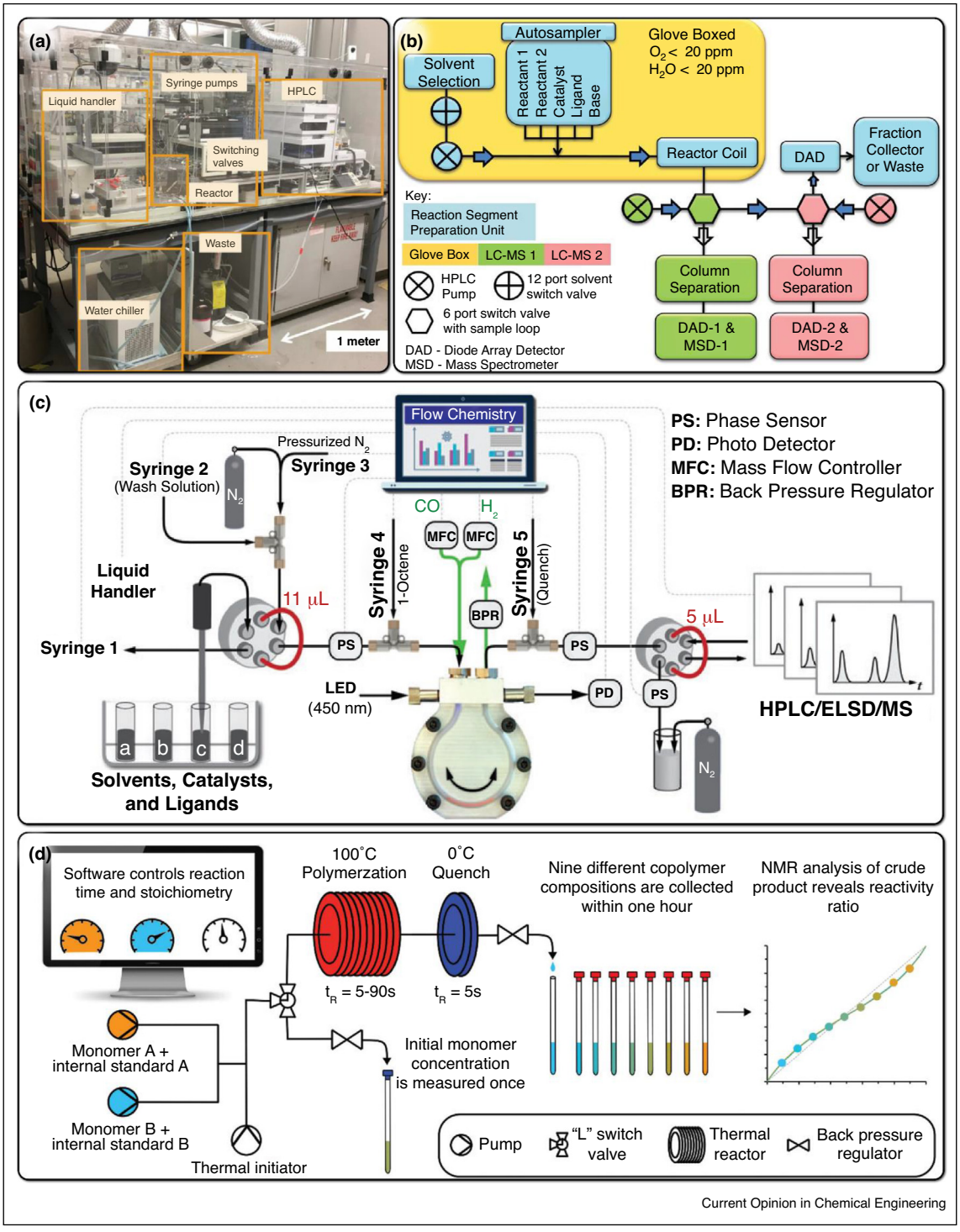
While it is ideal to conduct reactions at ambient temperature and pressure, many prevalent reactions necessitate the use of potentially hazardous reaction conditions (i.e. high temperature, high pressure, or high exothermicity/runaway reaction risk). Small reaction volumes are beneficial for mitigating inherent hazards, as the risks associated with undesirable conditions, particularly high pressure and reaction exothermicity are minimized in smaller reactors. High pressures (ranging from 5 to 300 bar) [53,55•] can be safely achieved in flow with substantially lower risk due to the significantly reduced reactor volume and the ratio of microchannel surface area to wall thickness, as well as automation and engineering controls. Additionally, reaction exothermicity can be addressed by the excellent heat transfer in microreactors and the in-line monitoring and controls that can be implemented to provide sufficient heat removal from the reactor system.

Outlook: future *green* directions including predictive algorithms, machine learning, and automation

A promising recent development in green chemistry is the introduction of switchable solvents [65,66] allowing chemical engineers to develop processes to be more energy and material efficient during their separations. These switchable solvents allow for dramatic energy saving when replacing conventional separations like distillation with liquid-liquid extractions as well as enhanced recyclability due to their easy recoverability provided by the switchable properties.

Among the most promising research in flow synthesis is the integration of flow reactors with predictive algorithms to facilitate organic synthesis reactions. These autonomous material discovery and reaction optimization technologies [67••,68,69,70••,71] constitute one of the most exciting developments in flow chemistry technology in the 21st century and present an extremely intriguing route through which numerous green chemistry principles might be applied. When combined with automation and flow reactors, predictive material synthesis and reaction optimization methods will ideally be applied to

Figure 4



Examples of high-throughput, material-efficient screening processes utilizing flow chemistry techniques. **(a)** Single-droplet flow screening platform for photoredox catalysis screening, Hsieh *et al.* [11]. **(b)** Ultra-high-throughput nanomole-scale flow screening platform developed by Pfizer, Perera *et al.* [3••]. **(c)** Tube-in-tube single-droplet flow screening platform for material-efficient studies of hydroformylation reactions, Zhu *et al.* [55•]. **(d)** Material-efficient continuous flow evaluation of comonomer reactivity ratios, Reis *et al.* [61•]. Images reproduced with permission from: American Chemical Society, 2018 (a), American Association for the Advancement of Science, 2018 (b), Royal Society of Chemistry, 2018 (c), and Royal Society of Chemistry, 2018 (d).

repeatably, rapidly, and safely produce the chemical process and products with minimal time and material investment (waste minimization). Currently, when target compounds are identified as candidates for certain pharmacological purposes (through *ad-hoc* manual search), it is necessary for research chemists and engineers to test a broad range of synthetic routes (often in batch) to find a suitable synthetic route to produce the desired chemical. Manual molecule discovery, reaction optimization, and manufacturing scale-up all require substantial investment of resources, including time and materials, and can result in massive amounts of chemical waste. By employing machine learning and predictive models to identify the most promising synthetic routes, it is possible to *intelligently* survey the massive chemical reaction parameter space and focus on a few *green* synthetic processes, thereby dramatically reducing chemical waste generated during the API discovery and chemical reaction optimization process. One of the requirements for strategies involving machine learning to work is the availability of large, accurate reaction datasets. As such, flow chemistry strategies, particularly those used for screening, are ideally suited for integration with these techniques, primarily to produce the high-quality datasets necessary to train and test accurate machine learning algorithms. Furthermore, green chemistry principles (e.g. atom economy, hazards in chemical synthesis, solvent safety, energy efficiency, renewable feedstocks, derivatization, and catalysis) can be programmed into the algorithm used to develop the synthetic techniques or can be considered by the chemists and engineers responsible for selecting the syntheses that will ultimately be used for production. In this way, machine learning combined with flow chemistry can be used to address many of the green chemistry principles first proposed by Anastas and Warner. Once suitable synthetic routes are identified utilizing machine learning methods, it is possible to interface such technologies with reconfigurable telescoped reaction platforms [58••,72,73,74••]. These reconfigurable flow reactors will enable end-to-end continuous manufacturing of desired APIs or specialty chemicals by automatic selection of the most efficient (*green*) synthetic pathway utilizing sustainable feedstocks and (*green*) solvents, followed by autonomous modification/reconfiguration of the multi-step reaction platform resulting in safe process operation with minimal waste production.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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