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Perspective

From Batch to Continuous Flow Processing in Chemicals Manufacturing

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Introduction

Many simple synthetic organic chemicals produced in large volumes, such as ethylene dichloride and methanol, are manufactured by highly efficient continuous or semicontinuous flow processes.[1] However, continuous processing is still a very limited part of the toolbox of laboratory chemists synthesizing new molecules for drugs, biocides, herbicides, pesticides, inks, chemical additives, and many other specialty chemical applications. Not surprisingly, continuous processing for the industrial manufacturing of such molecules is rare.

Things have started to change. Laboratory-scale flow reactors, which are commonly referred to as microreactors[2–4] due to their very small-size flow channels, have brought continuous processing to the synthesis laboratory. Academic labs are publishing continuous synthetic routes for drugs such as Ibuprofen,[6] and major corporations have announced production and or processes for production of drugs and drug intermediates by continuous processing.[7,8] In addition to providing a new way to run reactions and synthesize a very broad variety of specialty chemicals, the technology of microreactors is well-suited for combinatorial, high throughput, rapid screening of catalysts.[5] A recent review of the patent literature has also revealed an increasing number of patents and published applications, demonstrating the intensity of activities in process engineering for the continuous manufacturing of fine chemicals.[9]

Benefits, often declared in work that has been published, include: better product yields and quality; use of lower amounts of catalyst, solvent and other materials; less extreme operating conditions; improved safety; improved impurity profiles; and ease of scaling up. While this appears promising for the long-term future of flow reactors, there continues to be much debate[10–12] over when and how to use this technology at the laboratory and manufacturing scales. Much of this debate is well-founded because deploying such a new technology requires careful analysis of a complex series of technical and economic assumptions. In order to move beyond debate and achieve an actionable point of view on flow reactors, we discuss in this Perspective a simple analytical framework, which can serve as a guide for in-depth technical evaluations and ultimately full process development for manufacturing. Not covered here is the use of flow reactors (microreactors) for research purposes, as good discussions of deciding when to use flow reactors vs. batch flasks in laboratories can be found elsewhere.[11]

The ultimate goal of a preliminary analysis, subsequent testing and final manufacturing process optimization is to answer the basic question, "will the product cost less to manufacture?" Safety, product and process quality, environmental impact, ease of scaling-up and throughput control are also important factors, and introduce constraints that may render some processes technically infeasible. A further part of a full economic analysis is to determine if the product's profit margins allow acceptable return on the required capital investment. This of course depends heavily on the characteristics of the product's market,[12] which must be carefully analyzed in conjunction with the process development and engineering.

It is not the intention of this Perspective to answer any of these questions directly, but rather to provide a semi-analytical framework that may or may not justify the actual undertaking of continuous flow chemistry and the optimization of process parameters; two activities which would enable the answers to be obtained with high precision.

Working Definition of Flow Reactors

The term "continuous flow reactor" is an old one and continuous flow reactors, e.g., continuous flow stirred

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Table 1. Initial Assessment of Flow Reactor Applicability

Pressures exceeding the reactor capability? Temperatures exceeding the reactor capability? Chemistry not compatible with reactor materials? Equilibrium reactions?	Zone 1: *Likely no benefits and/or not doable*	*Increasing applicability*
Solid precipitates formed? Very slow kinetics? Solid reactants or catalysts? Gas reactants? Homogeneous catalysts? Gas evolution?	Zone 2: *Possible benefits, but technical challenges*	
Reaction benefits from pressures > 120 N/m^2 Unstable intermediates? Fast kinetics? Highly toxic reactants or byproducts? Reaction requires or benefits from $t < -10$ °C Rapid mixing required to optimize the reaction? Highly exothermic? Over-reaction possible? Requires precise stoichiometric control?	Zone 3: *Advantages likely*	

reactors, tubular reactors, have been in use by the chemical industry for many years. For the purposes of this article, the term continuous flow reactors (or simply, ''flow reactors'') is confined to reactors which are part of continuous processes for the production of nonpolymer chemicals in the range of 1–50,000 metric tons per year (as total mass throughput which assumes as many as 30 reactors in parallel which is a reasonable practical limit). With this constraint, we will use the term continuous flow reactor to mean those reactors with chemical flow channels on the order of 0.5–3 mm in width, and flow rates through each reactor in the range of 0.5–80 L/h. This eliminates discussion of laboratory-scale equipment or manufacturing equipment that is used to produce commodity chemicals at hundreds of thousands of tons per year.

Primary Screening Criteria

One of the initial arguments regarding the applicability potential of flow reactors relates to their versatility. Specifically, the breadth of types of chemical reactions they can handle is very wide and includes the capability to accommodate multiphase systems, which comprise several liquid phases and solids. Most of the reports of successful use of flow reactors have been based on homogeneous reactions,[10] but there has been an increasing number of reports about successful application in multiphase systems including slurries.[8,13] It is commonly accepted that 20%–30% of commercially important homogeneous nonpolymer reactions could be run more efficiently in continuous flow reactors.[2,10]

In addition, while much of the focus on continuous reactors is improving yield and selectivity, recent analysis[14] indicates that economic benefits can be obtained by reducing or eliminating equipment for mixing and thermal control.

If in addition we consider multiphase systems, other work[15] suggests that as much as 60% of commercially important nonpolymer reactions could be run more efficiently in continuous flow reactors, excluding high-volume commodities such as methanol. In this Perspective, we build on this analysis and add a secondary economic dimension, which provides a useful platform of assumptions to guide further work.

The starting point of the framework, employed in this study, uses simple questions in three separate groupings as a screening method, to determine if there could be advantages with flow reactors, as shown in Table 1. Reactions which have characteristics closest to the bottom of the table would enjoy most of the benefits when run in continuous flow reactors, as opposed to batch reactors. The three ''zones'' in this analysis can be characterized as follows.

Zone 1: Likely no benefits and/or not feasible

Reactions which have one or more of these characteristics are at high risk of not working well and/or of achieving no economic benefit when run in flow reactors. This is because reaction parameters exceed known flow reactor limits due to materials or design. Also, the chemistry itself may be corrosive to the reactor components. If the answer to one of these questions is ''yes'' further work is probably not useful, but should not be completely ruled out because the reaction may work well at reduced pressures or temperatures in a flow environment.

Zone 2: Possible, but with technical challenges

Reactions which have these characteristics will present technical challenges, but still may work and have advantages when run in a continuous flow reactor. One example is a hydrogenation reaction employing a solid-phase catalyst.[8] In this case, two Zone 2 items were identified, yet the reaction was quite feasible in flow and advantages were demonstrated. Furthermore, with respect to solids formation, the use of ultrasound[16] technologies has also demonstrated capability to remove and/or prevent solid formation in flow reactor channels.

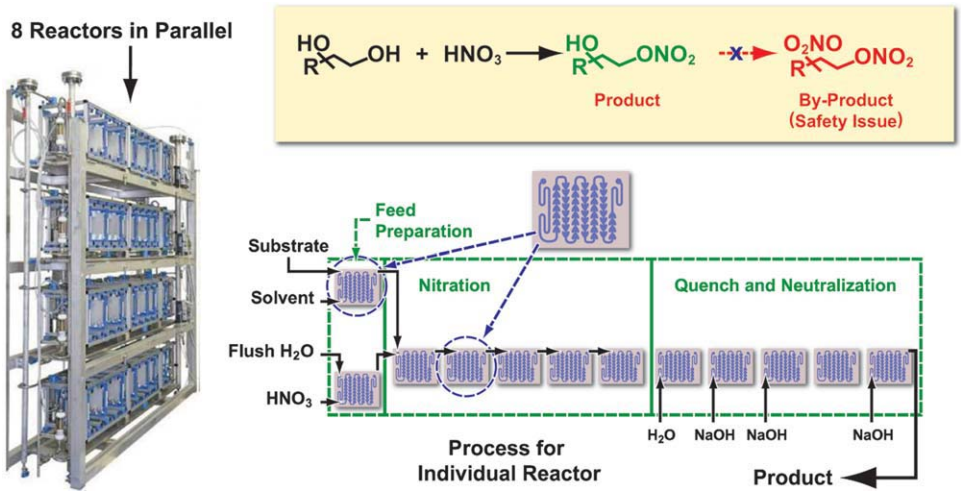

Figure 1. Selective nitration in a flow reactor.

Zone 3: Advantages likely

Reactions which possess characteristics listed in the Zone 3 are expected to gain significant advantages when run in continuous flow reactors. Benefits include lower costs, better product quality, improved safety and ease of scale-up.

Qualitative Economic Analysis

Assuming that there are positive indications from the primary screening questions in Table 1 (no Zone 1 and limited Zone 2 entries) a deeper evaluation should follow that prioritizes the potential economic benefits. This second analysis does not provide high-precision conclusions, but is very important because it serves to focus the technical work that is needed to produce the anticipated top potential economic benefits. Such an evaluation takes a holistic approach that includes impact on downstream and upstream unit operations so that benefits to total cost of ownership (full operating cost) can be better understood.

The backbone of this qualitative economic analysis should consider the following five "benefit areas" which are applicable to any manufacturing operation:[17]

1. Energy, water and raw material costs (including solvents for running the reaction and cleaning the equipment).
2. Labor costs.
3. Capital depreciation costs.
4. Product yield and quality.
5. Product throughput.

In addition, there are a number of indirect benefits which are harder to quantify, but which should also be considered:

- Plant safety.
- Speed of scaling up.
- Ease of switching products (i.e., multipurpose).
- Flexibility to turn throughput up or down with ease.

In order to prioritize these benefit areas, the following potential changes must be evaluated. The list is not meant to be exhaustive, but only a guide to the most probable areas of change that need to be analyzed:

(a) process flow (number and complexity of processing steps),

(b) upstream and downstream processing equipment,

(c) in-process and final product tests,

(d) generation of off-specification product that must be reworked or scrapped,

(e) practical scale-up limits for the flow reactor, and

(f) change in product (e.g., product impurity distribution).

While carrying out this analysis, it is important to look at all of these areas at the same time to ensure that a cost reduction in one area is not offset with a cost increase in another.

To illustrate the aforementioned points, let us consider an example using a reaction that has been reported previously.[7] This reaction is part of a process that carries out a hazardous nitration of an organic substrate, and seeks to minimize by products, while providing the highest degree of throughput and plant safety. Figure 1 shows the process flow of materials for this reaction through an individual reactor which is comprised of a series of 12 connected plates which contain the fluidic channels for the chemistry. A dye has been used in the channels to illustrate the path, as well as to show the nonlinear heart shaped structures which serve to keep the heterogeneous reaction mixture from separating. Not obvious in the figure are two additional fluidic channels in each plate for continuous flow of a cooling liquid. Also shown in the figure is a rack which contains eight of these 12-plate reactors in parallel.

When we apply the analysis in Table 1 to this reaction example, we conclude that advantages are likely to arise because the reaction is highly exothermic with unstable intermediates. Also, since there is no Zone 1 or 2 characteristics, there is enough merit to proceed to a deeper level of analysis that may be used as the basis of a testing plan.

To illustrate the next level of analysis, in Table 2 we have rated the attractiveness of the major factors that affect the economics, as well as the factors affecting safety, speed of process scale-up, capability of the process configuration for multipurpose production, and ease of adjusting process output. Elements I to V in Table 2 can be considered as the "direct" economic benefits, because they translate directly into product costs. The last four elements in Table 2, at the righthand side of the table, represent indirect economic benefits which are important but harder to quantify. Safety is worthy of special mention. A safer manufacturing operation produces indirect

Table 2. Example of Predicted Economic Impact of Changes for Nitration Reaction Shown in Figure 1

	Direct Economic Impact					Indirect Economic Impact			
Potential Changes When Using Flow Reactors ↓	I. Energy, Water & Raw Materials	II. Labor	III. Depr.	IV. Yield and Quality	V. Through-put	Safety	Speed of Scale-up	Multi-Purp.	Easy to Change Output
Process Flow	→	↑	↑	↑	↑	↑	↑	→	↑
Other Equipment	↑	↑	↑	→	↑	↑	↑	→	↑
Testing	→	↑	→	→	↑	↑	↑	↑	↑
Scrap & Rework	↑	↑	↑	↑	↑	↑	↑	→	→
Scale-up limits	↑	↑	↑	↑	↑	↑	↑	→	↑
Change in product	↑	↑	↑	↑	↑	↑	↑	↓	↑

→ = neutral benefit or does not apply; ↑ = positive; ↓ = negative

economic benefits due to factors such as fewer injuries, but safety can also be captured as a direct benefit in the "other equipment" category. A good example would be the reduction or complete elimination of expensive equipment or building infrastructure to minimize the impact of explosions.

Where estimates are possible, virtually all the entries in Table 2 suggest either neutral or positive economic benefits, indicating that this reaction is suitable for further technical investigation, which would begin with testing in a bench-scale flow reactor. Such tests need to be made using equipment that will give results that will be relevant to commercial flow reactors used for manufacturing. This implies that flow rates, channel sizes and heat management parameters must be comparable. Improper choice of bench-scale testing equipment can lead to erroneous conclusions.

Other Considerations for Cost, Quality and Business Impact

Beyond the analysis presented earlier, there are a number of other considerations that can have an indirect impact on cost and quality.

The quality by design (QbD) approach, which is used extensively in pharmaceutical manufacturing, is facilitated by the use of continuous flow reactors. This is due to the fact that these reactors operate at steady state, allowing continuous measurement and control of critical operating parameters such as temperature, pressure and flow rates. Such parameters can be also controlled in batch operations, but large temperature and concentration variations, that can occur in a batch reactor due to low surface-to-volume ratios, lower the effectiveness of feedback control, and in some cases control is not possible at all on a time scale that matters. For example, in order to eliminate unwanted side reactions, the continuous precise dosing of a reactant may be necessary. In batch this may be impossible because the time of mixing can far exceed the reaction time leading to great inhomogeneity across the reaction zone. A further example is represented by a common synthesis pathway where a very fast step is comprised of two consecutive steps with a very unstable intermediate. In a batch environment limitations in control permits only the outcome of the two consecutive steps, while in a continuous process it is often possible to control each step independently which can lead to improvements in selectivity and fewer byproducts.

Pharmaceutical manufacturing also employs a contamination review question (CRQ) methodology,[18] which is designed to improve product quality by eliminating operational errors and also minimize operator exposure to chemical hazards. Since many operations are eliminated in continuous flow reactors (examples include improved selectivity allowing elimination of a distillation step and or fewer washing steps after crystallization), when compared to the set of operations required for batch reactors, the risk is greatly reduced. Many of the contamination review questions simply disappear, since they are irrelevant for continuous flow reactors.

Because flow reactors operate very efficiently due to improvements in yield, selectivity, lower solvent and catalyst use, and reduction in size of downstream work-up equipment, a lower capacity plant can have similar cost per unit of chemical output, when compared with a much larger traditional batch plant. This can have a profound impact on the distribution of costs and allow for much more efficient overall supply chain efficiency, when considering the final product made from the output of the flow reactor. For example, high-performance chemicals, used for semiconductor manufacture, could be produced very close to the point of use with the benefit of continuous supply and no distribution costs.

Another important consideration is the cost and risk of scale-up from the laboratory to production scale. In scaling traditional batch reactions expensive and time consuming trials must be accomplished in order to assure final product quality at commercial scale, while minimizing operating costs. In the case of flow reactors, the scale-up risk can be substantially reduced, because the manufacturing process development can be accomplished in a small-scale apparatus that has the same critical reactor parameters (surface-to-volume ratio, flow rate, heat-transfer properties, mixing properties, etc.), as a full-scale production unit. This reduces the time to market and lowers overall business risk.

Semiquantitative Analysis: Case Examples

Use of the approach, described earlier, allows a semiquantitative determination of the economics of flow technology deployment in the case of a new plant, as well as integration of the technology into an existing plant. This analysis has been used recently to guide significant technical evaluation in three cases presented later. In all examples, the economic benefits suggested from the qualitative economic analysis were validated by the details of the ensuing technical work. We have chosen these examples because they span a variety of different sources of economic benefits, thus, illustrating the breadth of the technology. We have also performed a more

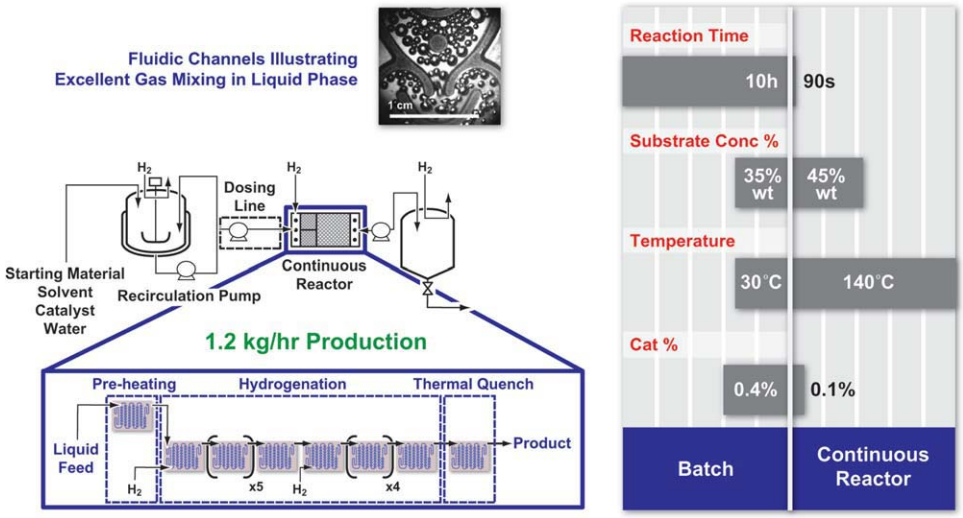

Figure 2. Slurry hydrogenation in a continuous flow reactor.

detailed economic analysis for two of the three presented cases in order to illustrate specifically how operating and plant costs can be reduced through the use of flow reactors.

Case 1 was described in Figure 1, and shows the benefits arising from the application of flow reactor technology in the case of a selective nitration.[7] Benefits were obtained from the ability to operate at higher concentrations, thereby reducing solvent use, while at the same time improving yield and selectivity. These factors lead to significant reduction in the size of the downstream equipment, overall plant footprint, and energy consumption per unit of product, while enhancing process safety due to low-liquid holdup in the plant and lower materials inventory. Additionally, a short development cycle was demonstrated by moving the process from laboratory to pilot to commercial scale plant designs in less than 16 months.

Case 2 is a selective highly exothermic hydrogenation reaction, which uses a noble metal catalyst in slurry form in combination with hydrogen gas. The schematic for a continuous process is shown in Figure 2. This case presents a different set of economic advantages, since the optimized batch reaction already had achieved high yield and selectivity ($\sim$100%).[8] However, when the reaction was run in batch mode it required a long period of time (>10 h) to achieve the desired conversion, thus, leading to low-throughput per unit time. When run in continuous flow, there is a drastic reduction in the required reaction time (<2 min), but more importantly a full plant of comparable output per unit time would cost significantly less to build and operate because of the following improvements: (a) reduction in the amount of catalyst used, (b) smaller equipment footprint, and (c) significantly cheaper facilities costs, due to eased safety requirements (low volumes of hazardous in-process materials eliminates need for a bunker).

Case 3 presents a different set of economic benefits.[19] The process is the conversion of glycerin to the fuel additive 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane-t-butyl ether-(STBE), and is usually performed in catalytic distillation equipment in the presence of a large amount of solvent. A new synthesis route has been proposed to maximize atom usage efficiency, limit the side product (water), and allow catalyst (H_2SO_4) recycling. This simplified process is very difficult to carry out in a batch process for three reasons: isobutylene is a very difficult material to handle with the necessary levels of safety; a large amount of solvent is required to maintain effective control of reaction temperature; the separation of distinct phases is difficult and expensive. However, the use of flow reactors reduced the volume of needed solvent, reduced the reaction time, thus, leading to higher process throughputs, and provided a safer handling of the hazardous isobutylene.

In Figure 3, a detailed economic analysis is shown for two of the aforementioned three cases. Standard plant engineering design methodology was employed in each case for both batch and flow reactors. For the analysis of costs for a plant based on a flow reactor, published operational parameters for the commercially available Corning® AdvancedFlow™ Reactor were used. In each case there is a reduction in the cost to build and operate a flow reactor plant. Reduction in plant capital cost is most dramatic for the hydrogenation reaction, and in all cases there is reduction in labor costs and the use of raw materials. Operating costs were reduced between 15 and 40%. In addition to these dramatic cost savings, safety considerations enable larger throughput operations with flow reactors, because of limitations in operating large batch reactors, when highly exothermic conditions exist. In such cases, the flow reactor may be a business enabler, since production of chemicals with batch reactors at the required scale may be cost prohibitive.

The "Green" Factor

Economic improvement and reduction in carbon footprint are often simultaneously achieved when continuous flow reactors technology is applied, due to lower raw material, water and energy usage.[12,20] Lower solvent usage is also a general benefit and comes from the following two factors: flow reactors can usually operate at higher concentrations; the amount of solvent used for cleaning is dramatically

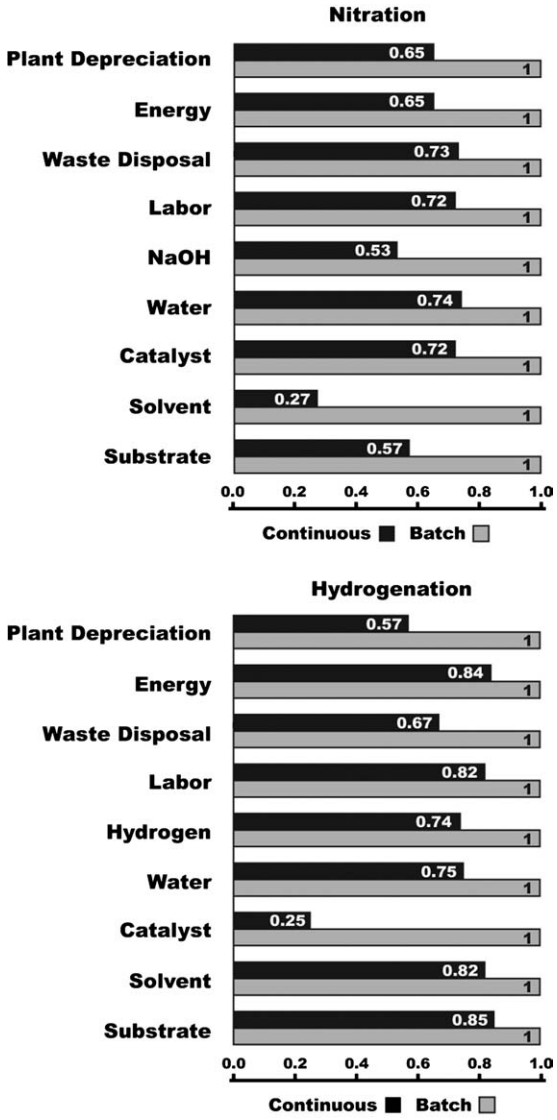

Figure 3. Fractional costs by category of operating continuous flow vs. batch reactor plants for two commercial reactions.

reduced as a result of the low-internal volume of flow reactors compared to batch reactors. Meaningful carbon footprint analysis is complex and not covered with any rigor here, but it is clear that this benefit is an important attribute of flow reactor technology, and will be increasingly important with the move to climate change regulations around the world.

The Future

We believe the future for continuous flow reactors is bright, but as with any emerging technology there are risks. This Perspective has focused on a series of questions, which must be asked in order to assess technical and economic risks as well as opportunities in deploying this technology. It is important though to note that the full array of processing, monitoring and control equipment for the flow reactors discussed in this Perspective is not yet fully developed. For example, availability of certain specialized equipment such as pumps, controllers and online analyzers to fit a specific application cannot be assumed to be available and/or of adequate capabilities and effectiveness. New equipment is coming into the market rapidly, but significant investment in time is required for testing and proper selection.

In addition, new technology adoption is always difficult. This means that the best teamwork between chemists, engineers, financial analysts and manufacturing staff must be brought to bear to carefully identify all the risks and opportunities. Unless this is done early and consistently throughout the deployment of the new technology, the overall risk increases significantly. This cautionary note is especially true in the present case, because of the radically different nature of continuous flow and batch reactors. Many of the traditional engineering heuristics, used in designing and deploying batch reactors-based processes simply do not apply in the case of continuous flow reactor processes.

Concluding Remarks

Continuous flow reactors represent an emerging manufacturing technology that promises to have significant benefits of cost, quality and safety for large areas of chemical manufacturing. Study of these reactors as well as commercial deployment is increasing rapidly, but the radically different nature of the technology, when compared to that of batch reactors has made evaluation and deployment difficult. Using a simple framework of questions, it is possible to quickly determine where such technology makes sense, and then develop top areas to study in order to optimize the benefits. Benefits include lower plant and production costs, improved quality and safety, faster and cheaper scale-up, and lower carbon footprint.

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