PERSPECTIVE

Frontiers in Reactor Engineering

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The key challenge for reactor engineering is to establish the scientifically based sustainable technologies necessary for meeting the future energy, environmental, and materials needs of the world. This goal requires advancing our scientific understanding of multiscale kinetic transport interactions to enable better reactor choice and to ensure higher reactor and process efficiencies.

Reactor technology is involved in all chemical transformations by which raw materials—renewable, nonrenewable, and intermediates derived therefrom—are converted to products such as fuels, basic and specialty chemicals, materials for construction and communications, fibers for clothing, fertilizers, pharmaceuticals, and a variety of consumer products (Fig. 1). The selection of a particular process chemistry and an associated reactor technology determines the energy and mass efficiency of the process, as well as its environmental impact.

Chemical reaction engineering emerged early in the last century, when it became apparent that economical large-scale continuous production of chemicals and fuels required more than the knowledge of chemistry. To enable the reactant molecules in a large-scale reactor to undergo chemical transformations at conditions mimicking those achieved in the laboratory, it was necessary to engineer the flow of reactants and their mixing and to provide for adequate addition or removal of heat. In heterogeneous systems, which are prevalent in industrial use, it was necessary to understand the contact between the phases involved and to describe the transport of reactants, intermediates, and products within a phase and between phases. Thus, reaction engineering developed as a discipline by introducing the scientific principles that quantify the interactions between chemical kinetics and the transport of momentum, heat, and mass (1–3). The resulting multiscale methodology (Fig. 2) provides the means for comparison of different reactor types by the quantitative assessment of various measures of performance, such as productivity, yield, selectivity, energy efficiency, and environmental im-
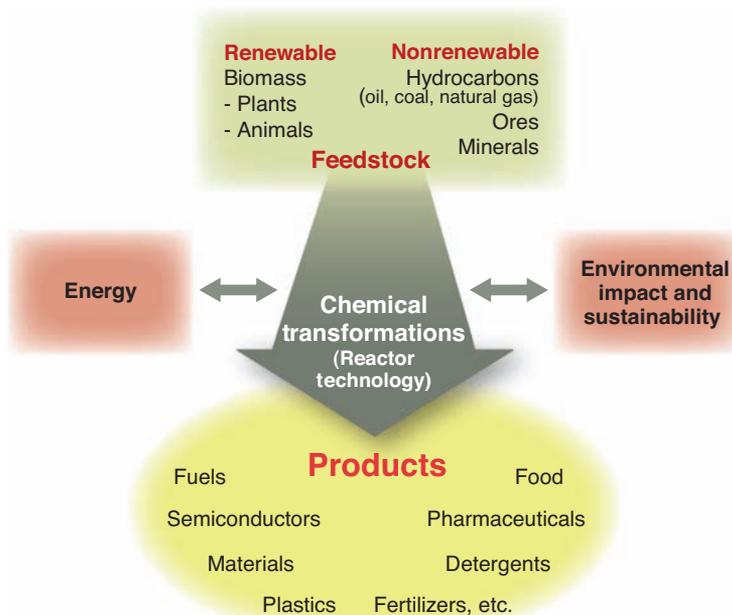

Fig. 1. Inputs and outputs of chemical reactor processes.

pact, as a function of operating and feed variables. This approach is applicable to all chemical transformations (4). The quantitative description on each scale (Fig. 2) can be obtained at different levels of knowledge, and hence provides different levels of certainty. As we increase the level of scientific understanding at each scale, we move farther to the right on the bars indicated in Fig. 2.

After the Second World War, reaction engineering played a pivotal role in the successful development of various reactor technologies in the petrochemical industry, and then spread to the manufacture of polymers, composites, semiconductors, and optical fibers; to biotechnology and the production of antibiotics; and to the synthesis of specialty chemicals. The scientific knowledge used at each scale (Fig. 2) in all of these applications was often rudimentary. It did not go much beyond empirical rate forms at the molecular scale, basic quantification of the effect of catalyst pellet size on catalytic performance at the particle (meso) scale, and assumptions of ideal flow patterns (plug flow or perfect mixing) at the reactor scale. Reaction engineering was practiced as a combination of science and empiricism using what might

be called the "principle of optimum sloppiness." This meant that reactor designers did not search for an ideal reactor to best meet the chemistry requirements, nor did they design commercial units a priori. Instead, the reactor type with which a company was most familiar was generally applied, either through repurposing of existing plant infrastructure or through the use of established empirical scale-up procedures to reproduce performance achieved at the bench scale. Scale-up in parallel (i.e., replication of multiple units identical to the small-scale prototype) was favored as less risky than vertical scale-up, the latter requiring a change in reactor dimensions. As a consequence, currently available "best reactor technologies" may not be optimal.

Notably, even the rudimentary application of reaction engineering concepts in the petrochemical industry led to much smaller amounts of unwanted products produced per unit of desired product (lower E-factors) than were encountered in industries that did not make use of such concepts. Nonetheless, the global negative environmental impact of commodity-scale processes is too large to ignore. We are greatly in need of a new generation of reactor technology, even though many of the old technologies are kept profitable by moving them to the developing world. This will require increased levels of scientific understanding of the mesoscale and large-scale kinetic transport interactions. The use of basic reaction engineering concepts is currently spreading to emerging areas such as biomaterials, drug delivery, bionanotechnology, biomass conversion in supercritical water, chemical looping combustion, carbon dioxide sequestration, methane activation, biodiesel synthesis, and hydrogen production (5). Many claim that the emphasis on diverse applications testifies to the maturity of the discipline, which in turn implies incorrectly that all the important scientific developments have already been accomplished. That view does not reflect reality well.

Our current increased awareness of the finiteness of our resources raises the bar for future reactor technology. Instead of continuing the application of principles at the rudimentary level, the main task now is to provide an improved scientific basis for conducting chemical transformations in an environmentally acceptable, energy-efficient, and sustainable manner. This means that products that minimize damage to the environment should be identified first (via life-cycle analysis) (6). Then, reaction pathways to create these products—preferably from renewable

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resources—should be synthesized on the basis of green chemistry principles. The effectiveness of the multiscale approach in developing green technologies for such pathways has been illustrated by the Center for Environmentally Beneficial Catalysis at the University of Kansas.

To reduce the risk of scale-up failure for new technologies, increased levels of scientific understanding will be required at each scale (Fig. 2). On a molecular scale, quantum and molecular dynamics calculations coupled with microkinetic concepts will yield a more detailed understanding of surface chemistry and catalysis, leading to improved mechanisms and better kinetic rate description. On the micro- to mesoscale, further advances are needed to describe the interactions of turbulent mixing with the kinetics, mass transfer, and heat transfer of multicomponent, multiphase systems (7, 8). On the reactor scale, developments in computational fluid dynamics (CFD) codes are making inroads (9, 10), replacing ideal-flow models. Simulations in multiphase systems are vastly aided by imaging tools for the assessment of phase distributions and flows, which provide needed validations for the codes. Quantification of the mesodomains on the basis of first prin-

ciples is resulting in better design of reactor internals through assessment of the role of films in trickle beds or reactors with structured packing. All of this is done with the aim of obtaining higher rates per unit reactor volume and better selectivity at higher mass and energy efficiency (11).

Currently there is a good scientific basis for a number of such process intensification schemes (12), such as combining reaction and separation in one unit to overcome equilibrium limitations, adopting a dynamic mode of reactor operation to increase productivity and selectivity, miniaturizing the reactor in order to enhance all transport rates by reducing distances for transport, and conducting the reaction at supercritical conditions with more rapid diffusion. All of these approaches reduce waste and positively affect the environment. For example, in equilibrium limited reactions it is highly advantageous to remove the product in situ or adopt a dynamic mode of operation. The former can be effectively accomplished by reactive distillation (e.g., Eastman Chemicals commercial methyl-acetate synthesis) (13), by catalytic distillation (14) as used in a number of refinery processes [e.g., (15)], or by selective product removal

via membranes (16). Using in situ adsorption, 100% conversion of syngas to methanol has been demonstrated in an adiabatic reactor (17). The reverse-flow dynamic operation of adiabatic packed beds, in which the feed direction is periodically reversed for an exothermic reaction, results in an exit conversion far exceeding that achievable in steady-state operation (18). This idea of periodic operation of packed bed reactors, with feed switching from end to end, can be extended by coupling an exothermic reaction (e.g., methane combustion) with an endothermic one (e.g., methane steam reforming), leading to high thermal efficiency and productivity (19, 20). This reactor-regenerator concept has potential uses in solar energy storage and clean coal combustion. Successful periodic operation has been commercially demonstrated for a number of systems that use UOP's pressure swing adsorption-desorption process (21).

Additionally, because microreactors have high surface-to-volume ratios, they offer enhanced mass and heat transfer coefficients by up to two orders of magnitude at laminar flow conditions and low pressure drop. They offer high volumetric productivity, low manufacturing and operating costs, and increased safety because of the small amount of chemical compounds they contain at any given time (22, 23). Successful bench-scale direct fluorinations, chlorinations, sulfonations, and hydrogenations have been demonstrated. Each of these applications relies on the advantage of scale-up by multiplication of individual reactors (scale-up by numbering up). It has been shown (23) that multichannel integrated design enables scale-up to large production rates even for highly exothermic reactions such as the direct fluorination of aromatics. Siemens-Axiva, Clariant, Evonik (formerly Degussa), Velocys, and others are in hot pursuit of commercialization of microreactor technology. Despite all the advantages of the microreactors (and the availability of technologies to mass-produce them in silicon, glass, and steel or other metals), they are not widely used even after two decades of intense research. In part this is because they require very fast reactions and active, stable catalysts—an uncommon combination. More important, microreactors are more prone to clogging and to leaks between channels because of their small dimensions, and their reliability and life onstream are unknown. All of these are potentially solvable problems on a case-by-case basis. However, the perceived risk factor is too large for them to replace existing large-scale installations. Most likely, acceptance of microdevices will occur first in highly energetic fast reactions and in situ production of hazardous chemicals, followed by applications in consumer products and distributed power systems.

Most reactors used in commercial applications with the largest environmental footprints are multiphase in character and are large. To reduce their footprint, there is a need for advancing the sci-
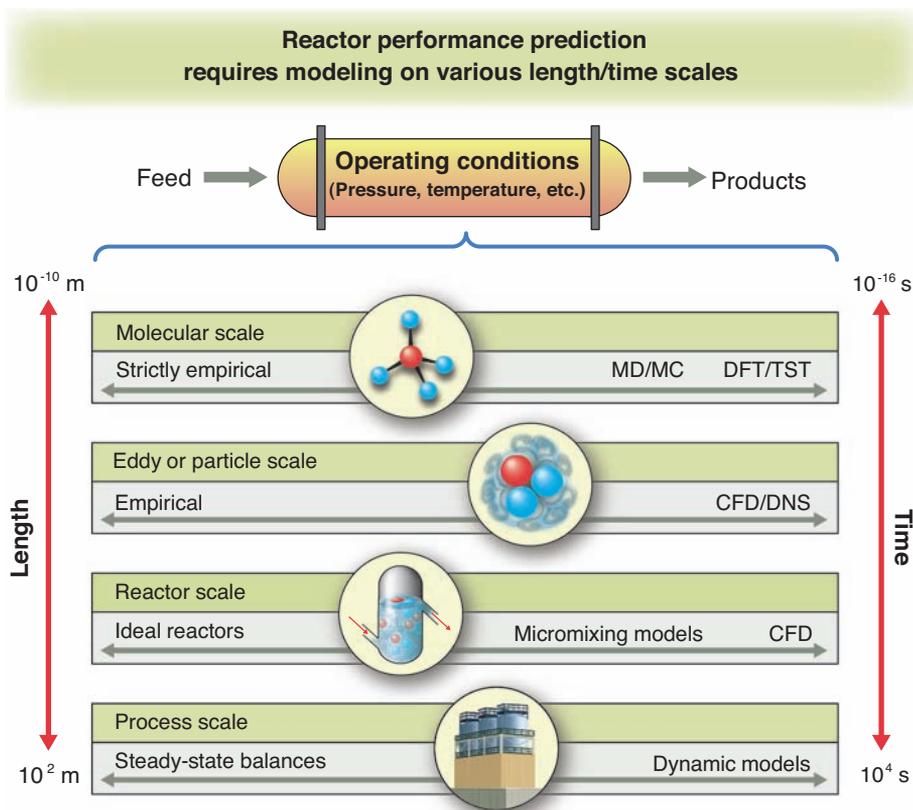
Fig. 2. The time and length scales involved in different facets of a reactor process, from individual molecular interactions to flow dynamics at a catalyst surface, interactive flows of reactant and product streams in the reactor, and ultimately, integrated considerations in the full plant. Modeling techniques developed for rigorous analysis at each scale are noted at the right [molecular dynamics and Monte Carlo (MD/MC) simulations, density functional theory and transition state theory (DFT/TST), and computational fluid dynamics and direct numerical simulation (CFD/DNS)].
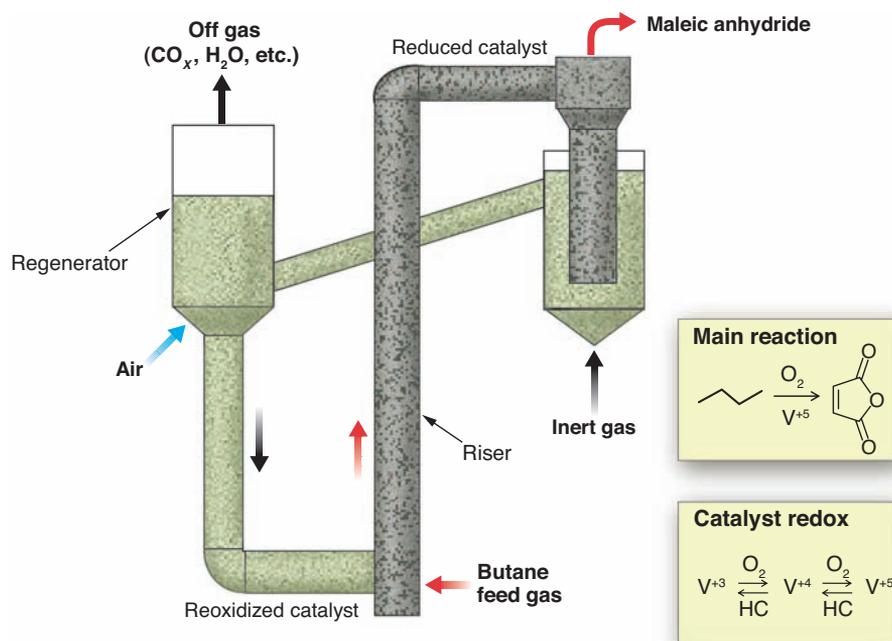
Fig. 3. Schematic of a circulating fluidized bed reactor for maleic anhydride synthesis.

entific basis for scale-up of such units (i.e., packed beds, trickle beds, fluidized beds, mixed slurry systems, bubble columns) (*24*, *25*). In particular, the currently assumed ideal flow pattern (i.e., perfect mixing or plug flow) must be replaced by more realistic descriptions. Although CFD programs for multiphase systems are available, their predictions must be validated. Noninvasive techniques that can provide data in such opaque systems have been developed (*26*). The suggested procedure for the development of scientifically based reactor models for scale-up and design is as follows: The physics and statistics of flow are captured experimentally over a range of conditions; the CFD model is tuned to represent a set of data and then tested for predictability on a new set of conditions; upon validation, the CFD model is used to generate information needed for the development of an appropriate flow model to be coupled with kinetics. The success of this approach has been demonstrated for stirred tanks, bubble columns, and fluidized beds and risers (*24*).

The need for such an advanced approach in describing the solid-flow field in the riser of the circulating fluidized bed (CFB) is illustrated by an example from the fuel-processing field. Currently, worldwide licensed alkylation processes for the production of high-octane fuels make use of strong mineral acids (HF and H_2SO_4) as catalysts, which present environmental hazards. A liquid-solid riser for solid acid–catalyzed alkylation offers an environmentally friendlier alternative. The alkylation reaction takes place in the riser, and the solid acid catalyst is regenerated in a fluidized bed of the CFB system. The flow pattern in the riser affects catalyst activity and selec-

tivity. The prevailing knowledge base (heuristics) suggests that both liquid and solids can be assumed in plug flow. A fully validated CFD model predicts close to plug flow of liquid but indicates a backflow of solids (documented by radioactive particle tracking) (*27*). Thus, riser design based on existing heuristics would lead to the wrong conclusion regarding the state of the catalyst in the riser, and a more detailed description of the flow is needed for proper design and scale-up.

Another example to consider in this light is production of maleic anhydride by partial oxidation of butane, which is often described as a green process because it results in much higher theoretical mass and atom efficiencies (100% for carbon) (*28*). Ultimately, a green process can be achieved here only if the developed vanadium-phosphorus-oxide (VPO) catalyst stays highly selective and active. However, this VPO catalyst does not stay highly selective and active in wall-cooled, packed tubular reactors operating at steady state—the traditional setup used because of its ease of scale-up in parallel. Catalyst selectivity is much improved in transient operation, arguing for a CFB arrangement (Fig. 3) (*29*). The oxidized catalyst meets butane in the riser, where partial oxidation takes place; upon separation of the products, the catalyst is reoxidized in the fluid bed of the CFB. Excellent conversion and selectivity are obtained at laboratory and pilot plant scales, so the key issues in scale-up to a commercial unit are maintenance of the same contact time and variance of the solids residence times. Mean contact time depends in turn on the solids fraction in the riser and its circulation rate through the system. Unfortunately, neither parameter was

readily available for a CFB (*30*). In the absence of that information, scale-up was risky and could not be based on scientific prediction. Hence, green chemistry did not result in a green commercial process.

This experience raised doubts about the viability of CFB technology. Data are now available for the true solids residence time distributions and the statistics for solids velocities in the riser (*30*) and await suitable CFD codes that can provide adequate predictions. Such development in turn requires a better scientific description of dense gas-particle flows. Only then can the risk of CFB scale-up be reduced, thereby allowing reliable implementation of this promising technology in partial oxidations, coal and biomass gasification, chemical looping combustion, and redox catalysis.

The creation of new reactor technology thus requires not only an improved understanding of molecular interactions, but also a further advance in the theories of turbulent flows, encompassing reaction, mass, and heat transfer on all scales in complex multiphase systems; the currently used models are more than 50 years old. Reaction engineering is a versatile discipline that will without question be used to solve a number of pressing problems in energy, clean fuels, and materials processing. The question remains whether the economic, political, and regulatory environment will provide the impetus needed for the development of increased levels of scientific understanding in our multiscale methodology in order to use reaction engineering to its fullest potential for the betterment of human society.

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PERSPECTIVE

Looking Forward in Pharmaceutical Process Chemistry

Ian W. Davies and Christopher J. Welch

Core activities of process chemistry involve the synthesis of drug candidates at a scale that supports clinical evaluations and the creation of a manufacturing process that is safe, robust, and cost effective. Innovative problem solving has always been a key element in process chemistry and will be increasingly important for addressing emerging challenges in science, globalization, and commoditization. The acquisition and creation of platform chemical technologies that enable rapid problem solving through the use of high-throughput experimentation will continue to be an important focus going forward. Linking and deploying platforms throughout the discovery-development continuum is expected to enable drug discovery. Increasing collaboration with academia will also become more important for accessing technical solutions and providing the next generation of innovative problem solvers.

Pharmaceutical process chemistry involves the creation of an efficient and cost-effective synthetic route that can be used for the commercial production of a molecule designed for function by medicinal chemists (*1*). This inherent focus on efficiency and economic viability requires a deep understanding of innovative chemical problem solving at the molecular level and places process chemistry at the center of the determination of whether a preclinical candidate will remain a laboratory phenomenon or advance to the marketplace and realize its potential to profoundly affect human health.

Process chemistry embraces three core activities, each critically important in the development of a new drug. First, the drug candidate, which was previously available in only very small quantities from medicinal chemistry, must be synthesized in kilogram-level quantities so as to provide material for Good Laboratory Practices (GLP) safety studies and to enable early clinical investigations. Second, increased quantities of the candidate, which are typically several hundred kilograms but sometimes much more depending on dose and study size, are prepared in collaboration with chemical engineers. This material supports the ongoing clinical program and other activities such as the development of a commer-

cially viable formulation. Third, process chemistry must create a synthetic route for manufacture of the commercial drug that is appropriately safe, robust, and cost effective. The synthetic routes used for preparing the initial lead, the first kilogram, the material for clinical trials, and the commercial product are often substantially different from one another, reflecting the different drivers at the various stages of development. Speed and expediency are most important in discovery and early development, and production cost, safety, environmental impact, and robustness constitute the key drivers for manufacture and commercialization.

Successful innovation in process chemistry has historically involved the thoughtful application of synthetic, separation, and analysis technologies in order to quickly converge on an optimal synthesis. In the most impressive cases, completely new chemistries have been invented to solve the most challenging problems. In addition, process chemists have always been quick to identify and appropriate promising solutions from any quarter, be it internal or external, vendor or academic.

As large pharma organizations emerged in the mid-20th century, they assembled into vertically integrated enterprises capable of carrying out all aspects of chemical discovery, development, and manufacturing. Recent years have brought about alternatives to this model, with contract companies emerging to service practically all stages of drug discovery and development, from design and synthesis of discovery libraries all the way

through conducting the pivotal trials that support registration. Speed and operational efficiency are differentiators for some activities, cost and unique scientific capabilities for others. This disaggregation of chemistry activities parallels the globalization in other industries that leverage cost, but also recognizes that innovation and talent are no longer confined to any one country or geography.

A range of business models are emerging that span the spectrum from the internal execution of all activities to the virtual research and development approach, in which all chemistry activities are outsourced. In between these extremes, models will leverage off-shoring to lower-cost geographies, where in addition to cost considerations capability arbitrage can now be used to access the imagination of the expanding global pool of talent.

Open-source innovation models are also becoming increasingly important and allow traditionally internal activities such as brainstorming, troubleshooting, or problem solving to be sourced. It is clear that in the next few years, global competition will drive the industry toward Darwinian outcomes. The successful companies will adopt an innovation model that evolves internal sources of competitive advantage faster than can occurr externally while developing business processes that are capable of accessing and leveraging external sources of innovation.

As the business environment changes at the macro level, a remarkable change in the practice of chemistry can also be anticipated. Innovation in the external environment is currently growing at a rapid pace, with an increasing number of academics now working on the fundamental discovery of reactions or on the development of greener, more efficient processing technologies (*2*). In addition to new approaches coming from academia, a number of new supplier companies that cater to the specialized needs of the pharmaceutical process chemist enter the marketplace each year. The result is a sometimes bewildering array of potential solutions, highlighting the increasing need for intelligent triage.

In addition to reagents and reactions, the importance of analytical, automation, and purification tools and technologies cannot be overstated. Although the image of a robot scientist toiling away in front of a chemistry fume hood has not yet been realized, the use of high-throughput experimentation, with which reactions are first discovered then optimized by use of multiparallel-reaction screening tools, is already a practical re-

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