PERGAMON

Chemical Engineering Science 56 (2001) 293–303

Chemical
Engineering Science

www.elsevier.nl/locate/ces

Microreaction engineering — is small better?

Klavs F. Jensen[a,b,*]

[a]*Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139-4307, USA*
[b]*Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139-4307, USA*

Abstract

Microfabrication techniques are increasingly used in different fields of chemistry to realize structures with capabilities exceeding those of conventional macroscopic systems. In addition to already demonstrated chemical and biological analysis applications, microfabricated chemical systems are expected to have a number of advantages for chemical synthesis, chemical kinetics studies, and process development. Chemical processing advantages from increased heat and mass transfer in small dimensions are demonstrated with model gas, liquid, and multiphase reaction systems. These case studies also serve to illustrate benefits of integrating sensors for flow, temperature, and chemical composition with microfluidic reaction and control components. The role of reaction engineering in the development of microreaction technology is described along with new approaches to scale up based upon replication of microchemical devices. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Microreactor; Microfabrication; Sensors; Multiphase reactors; Simulation

1. Introduction

Microfabrication techniques and scale-up by replication have fueled spectacular advances in the electronics industry and more recently in microanalysis chips for chemical and biological applications. Microfabrication also raises new opportunities for applications of the reaction engineering toolbox. For a reaction engineer, the term “microreactor” traditionally has meant a small tubular reactor for testing catalyst performance, but with the widening use of microfabrication technologies, the “micro” prefix generally designates chemical systems fabricated with techniques originally developed for electronic circuits. Such systems have feature sizes in the submillimeter range and reaction components are usually integrated with sensors and actuators. The reduction in size and integration of multiple functions has the potential to produce structures with capabilities that exceed those of the conventional macroscopic systems and to add new functionality while potentially making low cost, mass production possible. Miniaturization of chemical analytic devices in “micro-total-analysis-systems” (μTAS) (Berg, Olthuis & Bergveld, 2000) represents a natural extension of microfabrication technology to chemistry and biology with obvious applications in combinatorial chemistry, high throughput screening, and portable analytical measurement devices. The merging of μTAS techniques with microreaction technology promises to yield a wide range of novel devices for high throughput screening, reaction kinetic and mechanism studies, and on-line monitoring of production systems.

Microreaction technology is expected to have a number of advantages for chemical production (Ehrfeld, Hessel & Löwe, 2000; Lerou et al., 1996). The high heat and mass transfer rates possible in microfluidic systems allow reactions to be performed under more aggressive conditions with higher yields than can be achieved with conventional reactors. More importantly, new reaction pathways deemed too difficult in conventional microscopic equipment, e.g., direct fluorination of aromatic compounds (Chambers & Spink, 1999), could be pursued. Even if a microreactor fails, the small quantity of chemicals released accidentally could be easily contained. Moreover, the presence of integrated sensor and control units could allow the failed reactor to be isolated and replaced while other parallel units continued production. These inherent safety characteristics suggest that production scale systems of multiple microreactors should

---

[*] Correspondence address: Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139-4307, USA. Tel.: + 1-617-253 4589; fax: + 1-617-258 8224.
E-mail address: kfjensen@mit.edu (K.F. Jensen).

PII: S0009-2509(00)00230-X

enable distributed point-of-use synthesis of chemicals with storage and shipping limitations, such as highly reactive and toxic intermediates (e.g., cyanides, peroxides, azides). As a demonstration of these concepts, DuPont has synthesized a number of potentially hazardous chemicals, including isocyanates, in a microreactor formed by bonding silicon wafers patterned to form channels, preheaters, and catalytic reactor sections (Lerou et al., 1996).

Microchemical systems for combinatorial synthesis and screening of small molecules and systems for nucleic acid synthesis and detection have already revolutionized drug discovery in pharmaceutical companies (Borman, 2000). Rapid screening of catalysts and product synthesis pathways could lead to analogous productivity increases in chemical industry laboratories. Experimentation at the conventional bench scale is limited by high costs of reagents and safety concerns that the small volumes and inherent safety characteristics of microreactors could effectively eliminate. The introduction of new chemicals is also limited by the risk and high capital costs of scaling from laboratory to production plant. Scale-up to production by replication of microreactor units used in the laboratory would eliminate costly redesign and pilot plant experiments, thereby shortening the development time from laboratory to commercial production. This approach would be particularly advantageous for the fine chemical and pharmaceutical industries, where production amounts are often small — less than a few metric tons per year. The strategy would also allow for scheduled, gradual investment in new chemical production facilities without committing to a large production facility from the outset.

Small reactors are already used in testing process chemistries; for example, catalyst testing often employs small tubular reactors formed by filling powdered catalysts into glass tubes. However, the overall procedure is faced with bench top analytical equipment, large panels of complex fluid handling manifolds, and containment vessels. Chemical detection is the rate-limiting step in most methods since detailed product information must be obtained using sequential screening. With the continual advances in μTAS and microfabrication techniques, these macroscopic test systems could eventually be replaced by PC-card-sized microchemical systems consisting of integrated microfluidic, sensor, control, and reaction components. Such systems would clearly require less space, utilities, and produce less waste. They would enable high-throughput screening of process chemistries under controlled conditions, which is often difficult in conventional macroscopic systems. Moreover, the small dimensions imply laminar flow, making it feasible to fully characterize heat and mass transfer and extract chemical kinetic parameters from sensor data. The high heat and mass transfer rates possible in microfluidic systems also allow reactions to be performed under more uniform temperature conditions. By using the control of fluid contacting patterns afforded by microfabrication techniques, reaction engineering has the opportunity to design reactors that achieve specific research and development objectives.

2. Microreactor fabrication

Microfabrication methods for chemical systems build, in part, on advances in microelectromechanical systems (MEMS)[1] (Wise, 1998), a field that started by using fabrication techniques developed for microelectronics to construct sensors and actuators but now encompasses a wide range of materials and microfabrication methods. MEMS-based devices are based on classical bulk machining and deep reactive ion etching (DRIE) + bonding approaches (Kovacs, 1998). Recent work at MIT serves as examples of these approaches in the following sections.

Forschnungszentrum Karlsruhe and the Institute for Microtechnology Mainz (IMM) have been the primary drivers of multichannel microreactors, micromixers, and micro-heat-exchangers fabricated in metal by use of lithography, electroplating, and molding [Lithographie, Galvanoformung, Abformtechnik (LIGA) technology] (Ehrfeld et al., 2000). Coating the interior surface of these channels with a catalytic active material turns mixers and heat exchangers into reactors. The devices have been demonstrated for a number of model gas-surface catalytic reactions, liquid phase, and gas–liquid reactions, as well as selected commercial demonstrations. The latter includes a partial oxidation reaction of a vitamin intermediate, an addition reaction for fine chemicals production, and polymer synthesis technology (Ehrfeld et al., 2000). Similar devices have been fabricated using microelectrodischarge machining (μEDM) techniques. Reactors have also been fabricated in polymers by microinjection molding, and embossing techniques. Pacific Northwest National Laboratories (PNNL) has demonstrated microfabrication by lamination of multichannel sheets. Each sheet of metal, ceramic, or plastic is patterned by a variety of techniques including photolithography, μEDM, etching (ion or chemical), and laser ablation. The sheets are then laminated to form the final microchannel reactor. Devices have been demonstrated for energy related applications, specifically fuel evaporation and reforming (Tonkovich, Zilka, LaMont, Wang & Wegeng, 1999; Ameel, Warrington, Wegeng & Drost, 1997). Lamination of patterned ceramic tapes can also be used to create microreactor components. Laminating multiple layers machined with desired patterns again makes three-dimensional device structures possible

---

[1] MEMCAD. Microcosm Technologies, Inc., 5511 Capital Center Dr., Suite 104, Raleigh, NC 27606.

(Henry, Zhong, Lunte, Kim, Bay & Santiago, 1999). In the "green state", ceramic tapes are soft, pliable, and easily patterned.

"Soft lithography" refers to a collection of techniques pioneered by Whitesides and his coworkers (Xia & Whitesides, 1998a, b). The common feature in these methods is the use of a pattern transfer element that is a transparent elastomer, usually poly(dimethylsiloxane) PDMS, having a pattern embossed on its surface. PDMS is suitable for aqueous systems, but it swells in many organic solvents and has limited temperature stability. Therefore, PDMS-based microreaction components have been used primarily in biological applications, including fluid mixers and electrophoresis. Nevertheless, when combined with other polymers, electroplating of metals and molding of ceramics, the rapid prototyping advantages of soft lithography have considerable applications in microreaction technology (Jackman, Floyd, Schmidt & Jensen, 2000).

3. Thin-wall reactors for heterogeneous gas-phase reactions

A common microreactor design used for gas-phase heterogeneous reactions is a microchannel device that can be integrated with a heat exchange layer for highly exothermic reactions (Richter et al., 1998; Wießmeier & Hönicke, 1996; Wegeng, Call & Drost, 1996). These devices have the advantage of high productivity per unit volume, but they suffer from lack of sensing and active control within the microchannel assembly — similar to conventional ceramic monolith reactors. Thin-walled microreactors realized by MEMS offer the opportunity for the integration of heaters, as well as flow and temperature sensors on the external side of the reaction region (see Fig. 1) (Srinivasan et al., 1997; Hsing, Srinivasan, Harold, Jenson & Schmidt, 2000; Quiram, Hsing, Franz, Jensen & Schmidt, 2000a). The micron-thick wall provides good thermal contact with the catalyst in the interior, and the low thermal mass of the thin wall has the further advantage of fast (~ 10 ms) thermal response times.

The catalyst can be deposited on the interior wall by a variety of techniques including thin-film deposition by physical or chemical vapor deposition and liquid preparation techniques. Thin-film deposition techniques of the catalyst are typically limited to metals and simple oxides. Moreover, the resulting film has a low surface area and must be roughened by thermal activation. Wet preparation techniques allow the creation of catalyst systems similar to those used in conventional reactors, but surface tension effects cause the catalyst solution to collect in channel corners (Franz, Ajmera, Firebaugh, Jensen & Schmidt, 2000b). Aerosol sprays or ink jet printing allows placement of the catalyst on a desired region of the membrane.

Oxidation and partial oxidation reactions of a number of compounds, including hydrogen, ammonia, and ethane, have been successfully carried out in the flammable regime (Srinivasan et al., 1997). The ability to control the catalyst temperature, and therefore the selectivity, of partial oxidation reactions is a critical factor determining reactor performance. During an exothermic reaction, the heat is supplied to the catalyst wall by both the heaters and the reaction. The primary heat loss mechanism is through conduction in the thin top wall to the reactor bulk silicon side walls. Therefore, by varying the thickness and thermal conductivity of the top wall (through microfabrication), the ability of the reactor to dissipate the heat of the reaction can be controlled. This feature provides access to a wider temperature window of operating conditions and milder oxidation conditions than can be achieved in conventional systems. As a model system, the platinum catalyzed partial oxidation

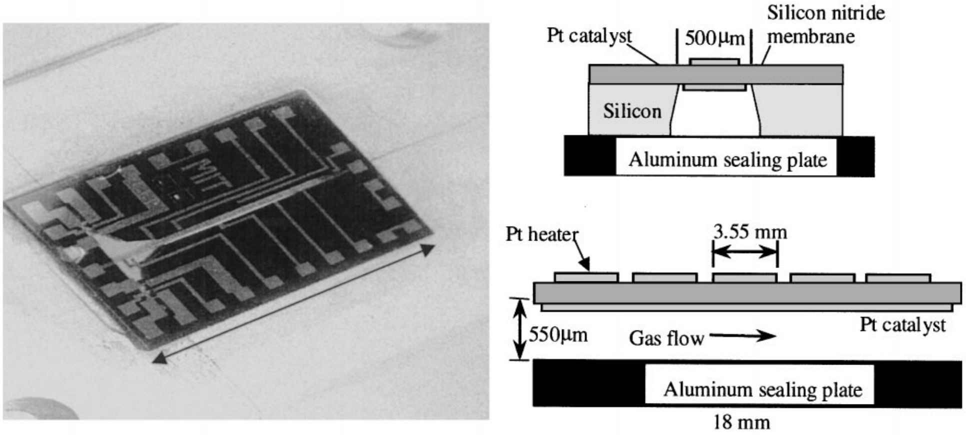

Fig. 1. Gas-phase microreactor. Photograph of device. Front view and side schematics (Srinivasan et al., 1997; Quiram et al., 2000a) (Photo: Felice Frankel).

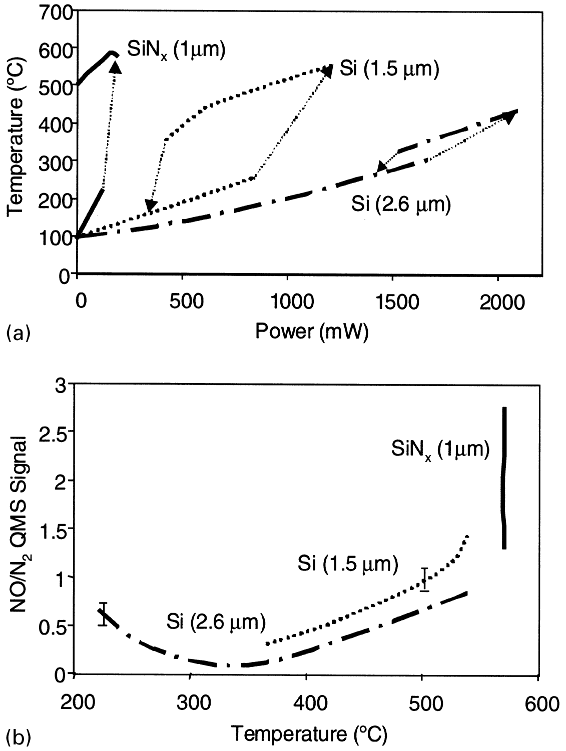

Fig. 2. (a) Ignition/extinction behavior with varying input power for ammonia oxidation over platinum in microreactors with different wall materials and thickness. (b) Corresponding variation in selectivity towards nitrogen and nitrogen monoxide (Franz et al., 2000b).

of ammonia to nitrogen and nitrogen monoxide illustrates this effect (see Figs. 2a and b) (Franz et al., 2000b).

In microreactors with a silicon-rich silicon nitride (SiN_x) top wall (1 µm thick), the catalyst is sufficiently thermally isolated so that the catalyst can be operated in an autothermal mode, that is, no power needs to be supplied following ignition. This high sensitivity to the heat of reaction is useful when the reactor is used as a fuel conversion device or as a calorimeter to extract reaction data. However, this operation is not ideal from the standpoint of catalyst temperature control, since milder oxidation conditions at intermediate temperatures between ignition and the upper steady state cannot be reached. Furthermore, the selectivity cannot be controlled. Replacing the top wall by silicon, which has a higher thermal conductivity than SiN_x removes the autothermal behavior, shrinks the distance between upper and lower steady states, and allows access to intermediate temperature regimes (see Fig. 2a). Consequently, control of the selectivity of the reaction becomes feasible over a wide range of conditions (see Fig. 2b). Moreover, the reactor can be operated under kinetically controlled conditions and it can then be used with a model to extract kinetic parameters from experiments.

4. Membrane reactors

The use of a permeable membrane allows the integration of separation with chemical reaction, as in macroscopic membrane reactors (Clausen & Nielsen, 2000). For example, the integration of a submicron-thick palladium membrane makes a highly efficient hydrogen purification device and provides the potential for conducting hydrogenation and dehydrogenation reactions (Franz, Jensen & Schmidt, 2000a). The lower right-hand corner of Fig. 3 shows front and side views of a palladium membrane microreactor. The channel in the device is 12 mm long, and the membrane width is slightly less than 700 µm. A symmetric heater design allows heating of a large area of the membrane (Quiram et al., 2000a) so as to maximize the area in the center available for hydrogen flux. A thin temperature sensor is patterned inside the heater loop to provide a measurement of the average temperature for each heater segment. The second channel in the device can either be realized by silicon microfabrication techniques (as in the example), or be fabricated in polymers by using a molding process (Qin, Xia, Rogers, Jackman, Zhao & Whitesides, 1998) depending upon process conditions in the top channel. During operation, the membrane itself is thermally isolated from the surrounding silicon, as demonstrated by reaction engineering simulation (Hsing et al., 2000). This thermal isolation enables use of low-temperature bonding materials in attaching the top device. Polymers offer low cost and ease of manufacture, although their use may be limited by their gas permeability characteristics.

The fabrication sequence for the palladium membrane microreactor (Fig. 3) serves as an excellent example of MEMS bulk micromachining techniques. A double-sided polished silicon wafer is coated with 0.2 µm of thermal oxidation silicon dioxide, and 0.3 µm of low-pressure chemical vapor deposition (LPCVD) silicon nitride. The backside of the wafer is patterned using standard photolithography, followed by a dry SF_6 nitride etch and removal of the oxide layer, using wet buffered oxide etch (BOE). The patterned nitride film will serve as an etch mask to form the membrane and one of the channels of the device. The nitride layer on the frontside of the wafer is patterned to define the perforations in the membrane, using photolithography with infrared (IR) front to back alignment, followed by a dry nitride etch. An e-beam deposited platinum/titanium film and a standard lift-off process are subsequently used to pattern temperature sensing resistors (TSRs) and heaters on the wafer frontside. The membrane is defined and the channel in the silicon is formed simultaneously, using a potassium hydroxide etch, with the oxide layer serving as an etch stop. A special fitting is used to protect the frontside of the wafer during the potassium hydroxide etch. Next, a blanket of palladium is deposited on the

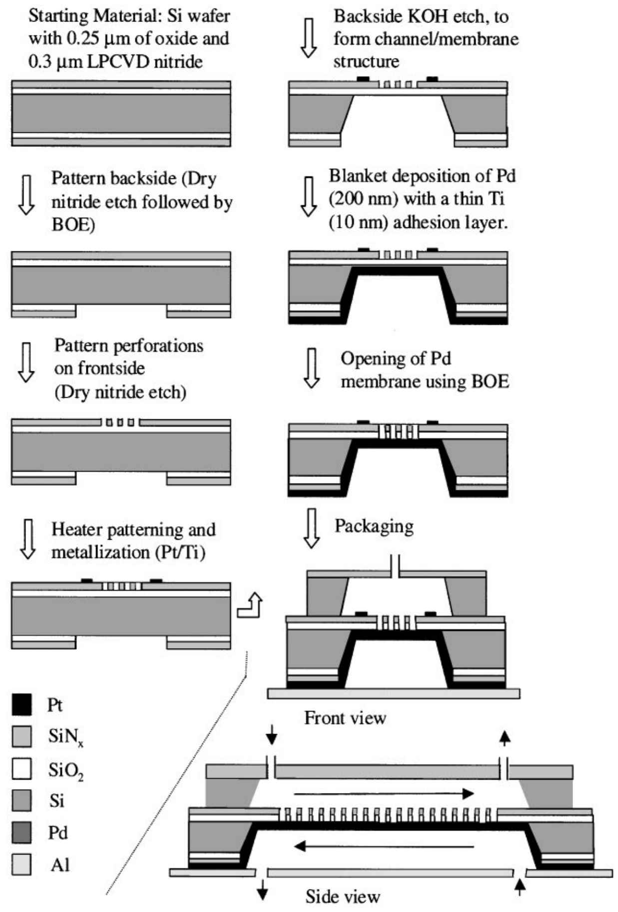

Fig. 3. Microfabrication sequence for palladium membrane microreactor (Franz et al., 2000a).

wafer backside, with a thin Ti film serving as an adhesion layer. The final step in fabricating this half of the device is to release the palladium film by removing the oxide layer in the perforations with BOE. This microfabrication process has the advantage of allowing the use of very thin palladium films (200 nm) as a membrane, since the support is made porous after the deposition of the palladium film.

Hydrogen flux across the membrane was quantified by measuring the hydrogen concentration change in the device for a known hydrogen/nitrogen mixture flow rate, with argon sweeping the hydrogen on the permeate side. At an average membrane temperature of 500°C, hydrogen flow rates of ~ 0.5–$1\ \mathrm{cm}^3/\mathrm{min}$ at standard conditions (sccm) were observed for a single active heater segment. The maximum hydrogen driving pressure gradient to achieve this flow rate was 0.1 atm. Using the total area of palladium exposed in the membrane perforations, this flow rate corresponds to a flux of about $600\ \mathrm{sccm/cm^2}$. These results suggest that the microfabricated palladium membranes are potentially much more efficient than large-scale devices. Extremely low thermal mass and high thermal isolation of the membranes result in open-loop thermal response time of the membranes of about 10 ms. The membrane thermal response time is not rate limiting in achieving hydrogen flux. The devices can also be used to carry out hydrogenation or dehydrogenation reactions. The fabrication scheme is sufficiently general to allow for incorporation of other membrane materials with selective transport properties for gases. Alternatively, the holes in the support structure could serve to disperse gas into a liquid stream or act as a particle filter.

5. Packed-bed reactors

Microreactors are natural platforms for combinatorial approaches, as well as statistically planned experimentation, but the number of catalysts that can be synthesized in thin film form is limited. Moreover, it may be difficult to translate results from thin catalyst to porous catalyst support used in applications. Therefore, it is important to develop microchemical systems that use catalyst on porous support from conventional synthesis procedures; have reproducible, spatially distributed temperature measurements and controlled temperature conditions. The high surface-to-volume ratios attainable in microfabricated structures result in improved thermal management and fast mass transfer and suggest that microfabricated multiphase systems could have performance advantages relative to conventional macroscopic systems for at least small-scale production.

Fig. 4a illustrates an example of such a reactor designed for gas–liquid–solid reactions (Losey, Schmidt & Jensen, 2000a). The design contains two main parts: the inlet manifold for each reaction channel and the filter unit at the exit of the device. Gas and liquid inlet flows are split among several channels (25 μm wide) that meet at the main reaction chamber (625 μm wide). Perpendicular to these inlet channels is a 400 μm wide channel used to deliver the catalyst slurry to the reaction chamber. At the outlet of the 20 mm long reaction chamber, a series of posts etched in the silicon retain the catalyst material.

The fabrication process for this reactor serves as a second example of typical MEMS approaches for microfabrication of chemical systems, in particular it illustrates the use of deep reactive ion etching (DRIE) (Ayon, Braff, Lin, Sawin & Schmidt, 1999) to create large aspect ratio channels. The microfabrication of the microreactor involves multiple photolithographic and etch steps, a silicon fusion bond, and an anodic bond. Examples of major steps are shown schematically in Fig. 5. The fluid channels were formed in the silicon substrate by using a timed DRIE process to approximately 300 μm. The wafer is then turned over and patterned on the backside to create ports to access the various channels. A second silicon wafer containing the fluidic manifolds is processed in a similar manner. Optionally, protective films (silicon dioxide, silicon nitride) can be grown on the silicon

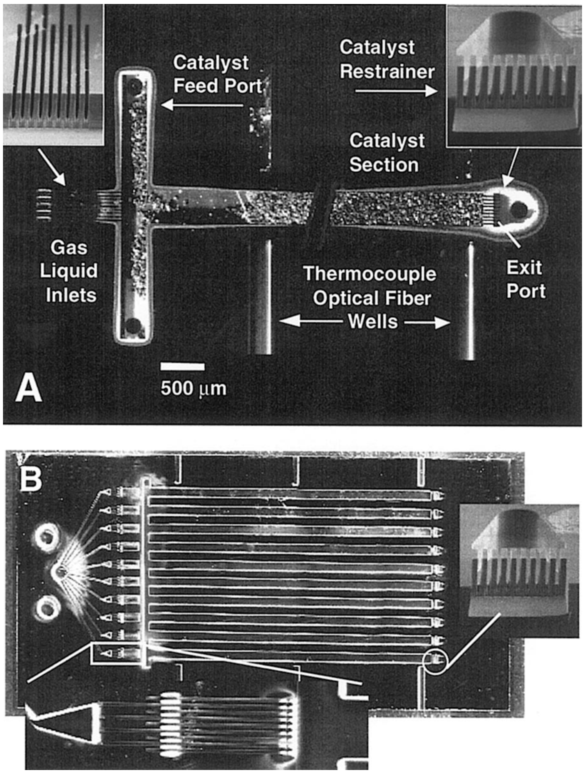

Fig. 4. (A) Photomigrograph of packed bed reactor with active carbon catalyst. Gas–liquid inlet sections on the left, catalyst support grid and exit on the right. Catalyst is introduced through the large wing sections. The vertical lines are wells for optical fibers for species monitoring. The hash marks indicate where two images have been spliced in order to view the entire device. (Photographs by Felice Frankel.) Right- and left-hand micrograph inserts show inlet and exit sections, respectively. The openings are 30 μm wide and 300 μm deep. (B) Photomigrograph of multichannel reactor (Losey et al., 2000a,b).

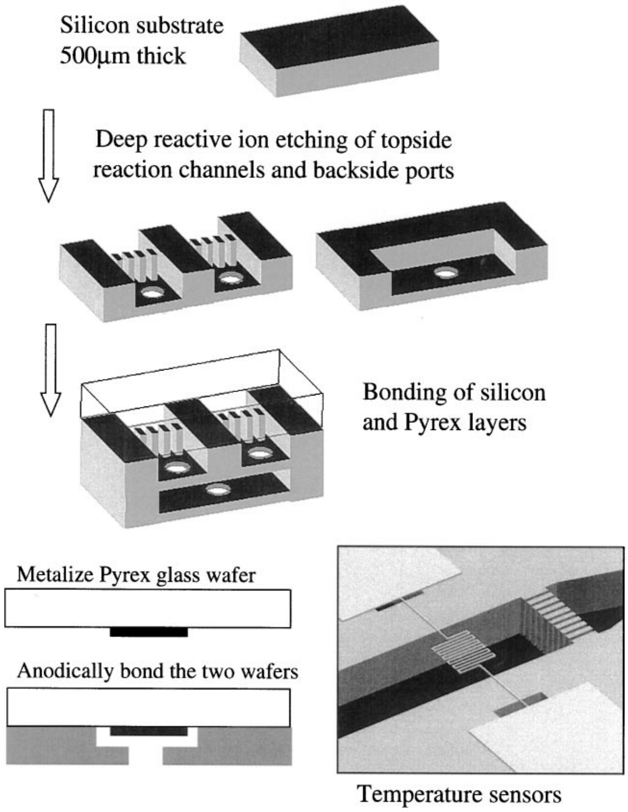

Fig. 5. Examples of major steps realized in creating packed bed reactors for multiphase reactors — deep reactive ion etching — bonding — metalization — anodic bonding.

wafers in order to protect against aggressive reagents that would react with silicon. The two silicon wafers are aligned and fusion bonded (Schmidt, 1998). The final step in the process is to cap the channels on the first layer with a Pyrex glass wafer using an anodic bond (Schmidt, 1998).

For microreaction systems in general, the engineering design challenge is to balance the gains made in heat and mass transfer by going to smaller dimensions against the increases in pressure drop. For a given volume of catalyst with constant residence time, a short, large diameter reaction channel would minimize the pressure drop. However, obtaining an even distribution of reactants over the inlet diameter and controlling the temperature profile becomes difficult, if not impossible. Splitting the flow into multiple channels, so that the effective cross-sectional area is large, reduces the pressure drop while maintaining the reactor throughput and high surface-to-volume ratio. Microfabrication methods have the potential to realize reactor designs that combine increased mass transfer rates, excellent thermal uniformity and low pressure drop. Fig. 4b shows an example of such a multichannel packed bed reactor fabricated by the same techniques as the single-channel reactor. The width of each inlet distribution channel is adjusted so that the pressure drop is the same over each channel even though the lengths of the distribution channels differ.

The production of phosgene over activated carbon in this reactor exemplifies the use of the packed-bed microreactor as an on-demand source of an important, but toxic, intermediate compound. The reaction is highly exothermic and reactants and products are difficult to handle. Complete conversion of chlorine (for a 1 : 2 chlorine to carbon monoxide feed at 4.5 sccm total flow rate) is observed at 20–30°C over a packed bed of activated charcoal.

Model reaction studies over catalyst particles have been used to characterize the mass transfer and reaction behavior of the multiphase microreactor. As in the case of macroscopic reactors, a bubble flow regime is observed at low gas flow rates; pulsing flow occurs at high gas flow rates, and a steady co-current flow is found at intermediate conditions (Losey, Schmidt & Jensen, 2000b). These results demonstrate that basic multiphase flow concepts extend to microfluidic systems. Oxidation reactions, exemplified by the oxidation of benzaldehyde, have shown the inherent safety of a small reaction volume

(4 μl) allows the reaction of pure oxygen and organic solvents at elevated temperatures. The hydrogenation of cyclohexene has served to characterize the mass transfer coefficient of the multiple-channel reactor using standard reaction engineering analysis. Values of the mass transfer coefficient for the multiple-channel microreactor have been determined to be $(K_L a)_{\text{micro}} \sim 5\text{–}15\ \text{s}^{-1}$ (Losey, 2000b), which is two orders of magnitude larger than those reported for typical macroscopic reactors, $(K_L a)_{\text{standard}} \sim 0.01\text{–}0.08\ \text{s}^{-1}$ (AlDahhan, Larachi, Dudukovic, Laurent, 1997). Therefore, for reactions that operate in a mass transfer-limited regime, microreaction devices could be considerably smaller in volume and still maintain high productivity. The greatly improved mass transfer in the microreactor over its macroscale counterpart is due, in part, to the high gas–liquid interfacial area generated by the microreactor. The two phases are forced to mix over the catalyst in a constrained volume relative to the standard pellet-size length scale in trickle bed reactors. Compared with the dimensions of laboratory trickle bed reactor catalyst pellets (4–8 mm), the 50 μm catalyst particles used in the microreactor represent a 100-fold increase in the surface-to-volume ratio. A similar improvement in performance would be expected if small particles could be used in a standard laboratory reactor. However, the use of such small particles would lead to nonuniform flow distribution and very large pressure drops.

Microfabrication also provides unique opportunities for creating catalyst support systems that avoid packing variations associated with distribution of catalyst particle sizes. For example, posts can be formed by DRIE (see Fig. 6) and rendered catalytic by wash coats and surface chemistry treatments (Losey, Schmidt & Jensen, 2000c). Similar structures have been developed for chromatography and concentration of DNA (Christel, Petersen, Mcmillan & Nortrup, 1998).

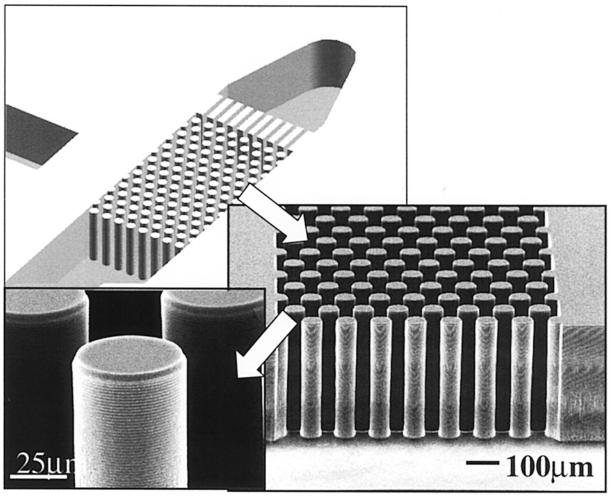

Fig. 6. Example of microfabricated catalyst packing formed by DRIE. The posts can be made porous and modified to have different organic groups (Losey et al., 2000c).

6. Liquid-phase reactors

Mixing is a critical issue in the design of liquid-phase microreactors. The small dimensions in microfluidic devices imply small Reynolds numbers and laminar flow so that mixing occurs by diffusion. This characteristic becomes both a challenge and an advantage for liquid-phase reaction systems. The slow mixing of co-flowing streams offers additional opportunities for phase transfer reactions and separation devices (Brody, Yager, Goldstein & Austin, 1996; Burns & Ramshaw, 1999), and it can be exploited in novel fabrication schemes (Kenis, Ismagilov & Whitesides, 1999).

Mixing is generally accomplished by repeated lamination of the two streams to be mixed, in order to increase the contact area and reduce diffusion lengths (Jensen, 1998; Erbacher, Bessoth, Busch, Verpoorte & Manz, 1999). One approach is to have the side flows squeeze (or “hydrodynamically focus”) the inlet flow into a thin stream, with a resulting rapid diffusive mixing (Knight, Vishwanath, Brody & Austin, 1998). In a “static mixer” scheme, the two fluids are brought into contact and the combined stream is separated into two flows along a line perpendicular to the mixing interface. These two streams are then recombined with a resultant doubling of the fluid interface and halving of the diffusion length. By repeating the process several times, very short diffusion distances are obtained, thereby producing rapid mixing (Krog, Branebjerg, Nielsen & Gravesen, 1996; Ehrfeld, Golbig, Hessel, Lowe & Richter, 1999). Ultimately, the design of a micromixing unit is a tradeoff between mixing speed, pressure drop, volume flow, feasibility of microfabrication, and integration with chemical detection devices.

Fig. 7 shows an example of a microfabricated liquid-phase reactor that integrates laminar mixing, hydrodynamic focusing, rapid heat transfer, and temperature sensing. The integrated reactor was fabricated in silicon using standard photolithography techniques and a DREIE (Ayon et al., 1999) yielding channels 50–400 μm wide and ~ 500 μm deep. An anodically bonded Pyrex wafer capped the etched channel. Temperature sensors were microfabricated on the backside of the Si wafer underneath the liquid channel. Studies with acid–base reactions show that the reactor achieves complete mixing in ~ 10 ms, depending on the fluid properties. The microfabricated heat exchanger overall heat transfer coefficient is 1500 W/m^2 K, which becomes important in controlling temperature rises in highly exothermic reactions. For example, hydrolysis of propionyl acid chloride leads to a ~ 40°C temperature rise with no heat

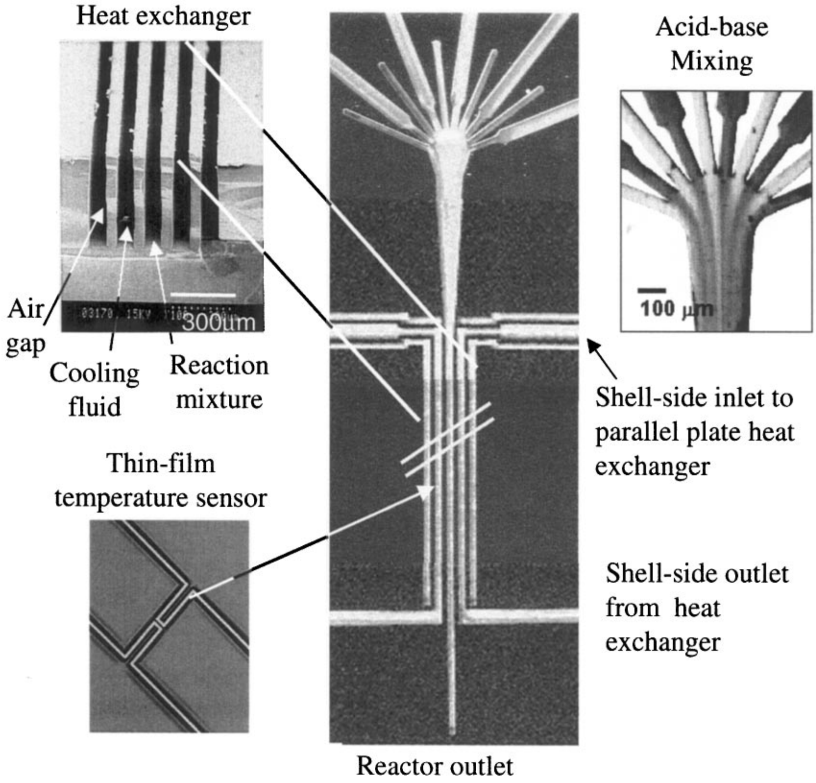

Fig. 7. Liquid-phase reactor with lamination of fluid streams, hydrodynamic focusing, and integrated with heat exchangers and temperature sensors in downstream reaction zone. Upper right-hand insert shows mixing of acid–base mixture in gray tone image of indicator color (Floyd et al., 2000b).

exchange, whereas the temperature rise is suppressed below detection when a cooling fluid is applied. When reactions can be followed by monitoring a change in color, the channel can be interfaced to an optical fiber light source and detector to enable on-line monitoring (Floyd et al., 2000b).

7. Integration of chemical sensors

The determination of chemical products and their amounts is often a time-consuming challenge in chemical research and development. In order for microreaction technology to be successful, it must include chemical sensors. Having a small reactor interfaced to large bench top analytical equipment often implies that external fluid chamber volume is much larger than the volume of the microreactor. This discrepancy raises the potential that the observed reactor volume is the reactor–analytical system interface — instead of the microreactor. The problem is avoided only if (i) the reaction reaches full conversion in the microreactor, (ii) the reactants and products are separated in the microreactor, or (iii) the reaction is quenched in the microreactor.

In the case of liquid-phase reactions that can be monitored by color changes or variations in the UV spectrum, the reactor can readily be interfaced to an optical fiber light source and detector to enable on-line monitoring (Jackman et al., 2000). However, UV–visible spectroscopy has limited chemical resolution — features are broad and common for many compounds. Infrared (IR) detection is a broadly applicable detection method that can be integrated with liquid-phase microreactors by using the IR transparency of silicon. Thickness, doping of the wafer, as well as reflections from the substrate surface, adversely affects transmission. Although the 40% transmission obtained using uncoated samples is sufficient for most applications, one can apply an anti-reflective (AR) coating to increase silicon transmission (Floyd et al., 2000a).

The short path lengths and optical densities usually imply that IR absorption spectroscopy is not practicable in gas-phase microreactors. As an alternative optical method for gas-phase detection, photoacoustic spectroscopy (PAS) offers several advantages. In photoacoustic spectroscopy, incident light is modulated at an acoustic frequency. If the optical wavelength couples to an energy transition in the gas, the gas absorbs the light resulting in a periodic gas expansion. PAS applies to many chemical compounds and its sensitivity scales inversely with dimensions. The recent detection of propane in a microfabricated photoacoustic cell illustrates the potential of the spectroscopy technique in microscale chemical analysis (Firebaugh et al., 2000).

8. Simulation of microreactor systems

Reaction engineering analysis is necessary to provide in-depth understanding of the operating characteristics of microreactors, as well as to evaluate the benefits and disadvantages associated with new microreactor designs. Several commercial software tools are available to quantify different aspects of microfabricated devices, but they are not universally applicable. Simulations serve not only as a design tool, but also as a means to interpret experimental data (Hsing et al., 2000; Quiram et al., 2000a). Models have been used to evaluate design changes such as changing the top wall material and thickness, heater design, and flow meter design (Quiram et al., 2000a) in the gas-phase reactor. Computational fluid dynamic simulations also provide insight into liquid-phase mixing. In particular, the use of simulation allows inclusion of three-dimensional wall effects often neglected in liquid-layer mixers. If all physical parameters are known, simulations should accurately reflect experimental observations, since the basic transport equations for laminar flow are well established. Thus, a reaction engineering approach to new designs can avoid costly, iterative experimental design processes where components are fabricated, tested, and then redesigned to improve performance.

9. Scale-up

In the past, the microreaction community has focused on the design of individual microreactors. No significant efforts have been made to build parallel arrays of reactors as originally envisioned by early papers in the field. The concept of scale-up by replication of many units (scale-out) at first glance may appear to be simple, but the strategy presents new challenges that have not been addressed in previous chemical system scale-up. Particularly, the areas of reactor monitoring and control become increasingly complex as the parallel array size grows to a large number of reactors.

To address issues in microreactor scale-up, DuPont and MIT have begun construction of a multiple reactor test station for gas phase systems (Quiram et al., 2000b). The fabrication of this system serves as a test case for the development of more complex microreactor-based systems. The approach addresses the difficulties in developing electrical and fluidic interfaces to microreactors that must be interchanged frequently, have heated outlet lines, and require millisecond real-time control algorithms. The multiple microreactor test station (Fig. 8) not only includes microfabricated reactors, but also integrates other MEMS components for fluidic control. This system contains all the components of a conventional catalyst test station (feed gas manifold, reactor feed manifold, reactors, and control circuitry), but with a dramatically smaller footprint. It represents the first demonstration of a parallel microreactor array that integrates reactors with fluidic distribution and control components in a scalable fashion.

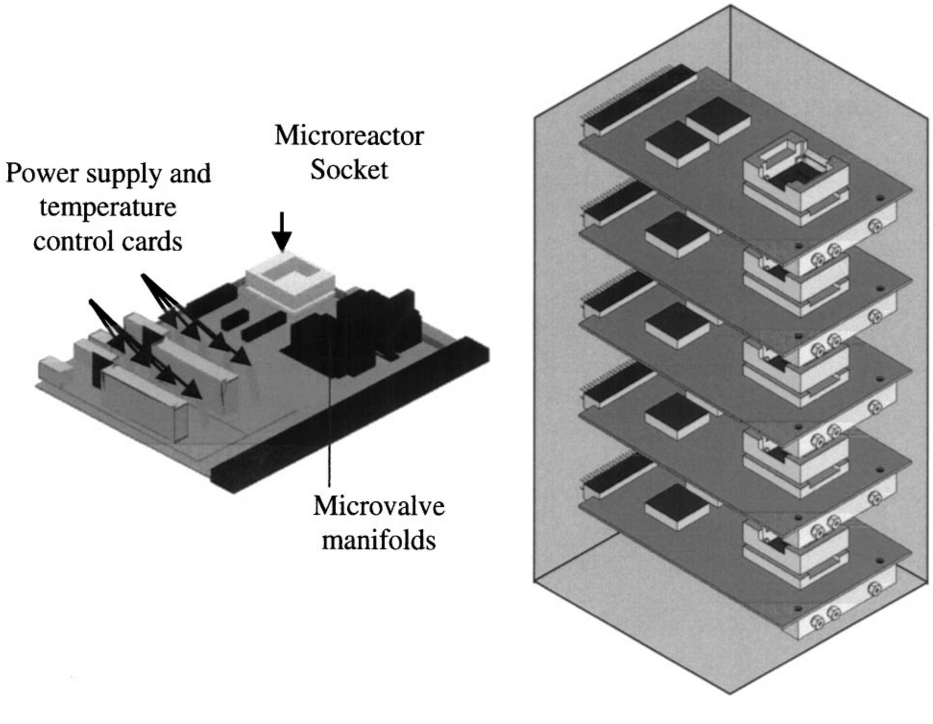

Fig. 8. Schematic of microreactor PC board and multiple microreactor system (Quiram et al., 2000c).

10. Conclusions

The examples shown here represent a small fraction of the many designs for microreactors being pursued or envisioned by different research groups. The ability of microfabrication to reproduce complex designs in a parallel fashion should invigorate the innovative nature of reactor design. In developing microreaction technology, it will be essential to focus on systems where microfabrication can provide unique process advantages. Such advantages could be derived from increased mass and heat transfer, leading to improved yield and safety for an existing process. The real value of the miniaturization effort, however, would be in exploring new reaction pathways and finding economical and environmentally benign solutions to chemical manufacturing. It will be important to exploit characteristics resulting from the small dimensions beyond the high transport rates, specifically forces associated with high surface area-to-volume ratios. The need to develop novel structures with controlled surface characteristics suggests that microreactor fabrication must go beyond classical micromachining and silicon MEMS techniques. Microfabrication in glass already forms the foundation for many biological devices, and fabrication in plastics using embossing and injection molding techniques is rapidly expanding. Ceramic reactors would be useful for high-temperature and high-corrosive environments. The family of chemical self-assembly and microfabrication techniques, "soft lithography", developed by Whitesides and coworkers (Xia & Whitesides, 1998a,b) further provide unique opportunities for microfabrication and chemical tailoring of surfaces to particular applications. Its strengths include the ability to transfer patterns onto nonplanar surfaces, formation of microstructures, and compatibility with a wide range of materials: polymers, metals, and ceramics.

In order for microreactors to move beyond the laboratory into chemical production, they must also be integrated with sensors and actuators, either on the same chip, or through hybrid integration schemes. Recall that it was the integrated circuit that created the microelectronics revolution, not the transistor itself. The integration of chemical systems with sensors in μTAS is already rapidly expanding the field, and combinations with microreactors for chemical synthesis will ultimately result in integrated chemical processors. The integration of multiple reactors presents significant challenges in fluid handling, local reactor monitoring, and control. Thus, the realization of microreaction technology will require multi-disciplinary research efforts and continued advances in reaction engineering.

Acknowledgements

The author thanks Martin A. Schmidt, the MIT microreactor group (in particular, S. Ajmeer, T. Floyd, A. Franz, S. Isogai, R. Jackman, M. Losey, and D. Quiram), and collaborators at DuPont for stimulating research interactions. The DARPA MicroFlumes Program (F30602-97-2-0100) provided financial support.

References

AlDahhan, M. H., Larachi, F., Dudukovic, M. P., & Laurent, A. (1997). High-pressure trickle-bed reactors: A review. *Industrial and Engineering Chemistry Research*, *36*, 3292–3314.

Ameel, T. A., Warrington, R. O., Wegeng, R. S., & Drost, M. K. (1997). Miniaturization technologies applied to energy systems. *Energy Conversion and Management*, *38*, 969–982.

Ayon, A. A., Braff, R., Lin, C. C., Sawin, H. H., & Schmidt, M. A. (1999). Characterization of a time multiplexed inductively coupled plasma etcher. *Journal of Electrochemical Society*, *146*, 339–349.

Berg, A. van den, Olthuis, W., & Bergveld, P. (2000). *Micro total analysis systems 2000*. Dordrecht: Kluwer Academic.

Borman, S. (2000). Combinatorial chemistry: Redefining the scientific method. *Chemical & Engineering News*, *78*, 53–65.

Brody, J. P., Yager, P., Goldstein, R. E., & Austin, R. H. (1996). Biotechnology at low Reynolds numbers. *Biophysical Journal*, *71*, 3430–3441.

Burns, J. R., & Ramshaw, C. (1999). Development of a microreactor for chemical production. *Transactions of the Institution of Chemical Engineers*, *77*, 206–211.

Chambers, R. D., & Spink, R. C. H. (1999). Microreactors for elemental fluorine. *Chemical Communications*, *10*, 883–884.

Christel, L. A., Petersen, K., Mcmillan, W., & Nortrup, M. A. (1998). Nucleic acid concentration and PCR for diagnostic applications. In D. J. Harrison, A. van den Berg (Eds.), *Micro total analysis systems 2000* (pp. 277–280). Dordrecht: Kluwer Academic Publishers.

Clausen, B.S., & Nielsen, P.E.H. (2000). Catalysis in membrane reactors. Proceedings of the Third International Conference on Catalysis in Membrane Reactors, Copenhagen, September 8–10, 1998 *Catalysis Today*, *56*, 1-1.

Ehrfeld, W., Golbig, K., Hessel, V., Lowe, H., & Richter, T. (1999). Characterization of mixing in micromixers by a test reaction: Single mixing units and mixer arrays. *Industrial and Engineering Chemistry Research*, *38*, 1075–1082.

Ehrfeld, W., Hessel, V., & Lowe, H. (2000). *Microreactors: New technology for modern chemistry*. Weinheim: Wiley-VCH.

Erbacher, C., Bessoth, F. G., Busch, M., Verpoorte, E., & Manz, A. (1999). Towards integrated continuous-flow chemical reactors. *Mikrochimica Acta*, *131*, 19–24.

Firebaugh, S. L., Jensen, K. F., & Schmidt, M. A. (2000). Miniaturization and integration of photoacoustic detection with a microfabricated chemical reactor system. In A. van den Berg, W. Olthuis, P. Berveld (Eds.), *Micro total analysis systems 2000* (pp. 49–52). Dordrecht: Kluwer Academic Publishers.

Floyd, T., Schmidt, M. A., & Jensen, K. F. (2000a). Towards integration of chemical detection for liquid phase microchannel reactors. In I. Rinard (Ed.), *Fourth International Conference on Microreaction Technology* (pp. 416–422). Atlanta, GA: AICHE.

Floyd, T. M., Losey, M. W., Firebaugh, S. L., Jensen, K. F., & Schmidt, M. A. (2000b). Novel liquid phase microreactors for safe production of hazardous specialty chemicals. In W. Ehrfeld (Ed.), *Microreaction technology: Industrial prospects* (pp. 171–180). Berlin: Springer.

Franz, A., Jensen, K. F., & Schmidt, M. A. (2000a). Palladium based micromembranes for hydrogen separation and hydrogenation/dehydrogenation reactions. In W. Ehrfeld (Ed.), *Microreaction technology: Industrial prospects* (pp. 267–276). Berlin: Springer.

Franz, A. J., Ajmera, S. K., Firebaugh, S. L., Jensen, K. F., & Schmidt, M. A. (2000b). Expansion of microreactor capabilities through improved thermal management and catalyst deposition. In W. Ehrfeld (Ed.), *Microreaction technology: Industrial prospects* (pp. 197–206). Berlin: Springer.

Henry, C. S., Zhong, M., Lunte, S. M., Kim, M., Bau, H., & Santiago, J. J. (1999). Ceramic microchips for capillary electrophoresis-electrochemistry. *Analytical Communications*, *36*, 305–307.

Hsing, I. M., Srinivasan, R., Harold, M. P., Jensen, K. F., & Schmidt, M. A. (2000). Simulation of micromachined chemical reactors for heterogeneous partial oxidation reactions. *Chemical Engineering Science*, *55*, 3–13.

Jackman, R. J., Floyd, T., Schmidt, M. A., & Jensen, K. F. (2000). Development of methods for on-line chemical detection with liquid-phase microchemical reactors using conventional and unconventional techniques. In A. van den Berg, W. Olthuis, & P. Bergveld (Eds.), *Micro total analysis systems 2000* (pp. 155–159). Dordrecht: Kluwer Academic Publishers.

Jensen, K. F. (1998). Smaller faster chemistry. *Nature*, *393*, 735–737.

Kenis, P. J. A., Ismagilov, R. F., & Whitesides, G. M. (1999). Microfabrication inside capillaries using multiphase laminar flow patterning. *Science*, *285*, 83–85.

Knight, J. B., Vishwanath, A., Brody, J. P., & Austin, R. H. (1998). Hydrodynamic focusing on a silicon chip: Mixing nanoliters in microseconds. *Physical Review Letters*, *80*, 3863–3866.

Kovacs, G. (1998). *Micromachined transducers sourcebook*. Boston: WCB/McGraw-Hill.

Krog, J. P., Branebjerg J., Nielsen, C. R., & Gravesen, P. (1996). Experiments and simulations on a micro-mixer fabricated using a planar silicon/glass technology. *Micro-electro-mechanical systems (MEMS). 1996 International mechanical engineering congress and exposition* (pp. 177–182). New York, NY, USA: ASME.

Lerou, J. J., Harold, M. P., Ryley, J., Ashmead, J., O'Brien, T. C., Johnson, M., Perrotto, J., Blaisdell, C. T., Rensi, T. A., & Nyquist, J. (1996). Microfabricated minichemical systems: Technical feasibility. In *Microsystem technology for chemical and biological microreactors*: *Papers of the workshop on microsystem technology*, *Mainz*, *20–21 February*, *1995*, vol. 132 (pp. 51–69). Frankfurt: DECHEMA.

Losey, M. W., Schmidt, M. A., & Jensen, K. F. (2000a). A micro packed-bed reactor for chemical synthesis. In W. Ehrfeld (Ed.), *Microreaction technology: Industrial prospects* (pp. 277–286). Berlin: Springer.

Losey, M. W., Schmidt, M. A., & Jensen, K. F. (2000b). Microfabricated multiphase packed-bed reactors: Characterization of mass transfer and reactions, submitted for publication.

Losey, M. W., Schmidt, M. A., & Jensen, K. F. (2000c). Gas-liquid contacting and reaction in microstructured microchemical systems, submitted for publication.

Qin, D., Xia, Y. N., Rogers, J. A., Jackman, R. J., Zhao, X. M., & Whitesides, G. M. (1998). Microfabrication, microstructures and microsystems. *Microsystem technology in chemistry and life science*, vol. 194 (pp. 1–20). Berlin: Springer Verlag.

Quiram, D. J., Hsing, I. M., Franz, A. J., Jensen, K. F., & Schmidt, M. A. (2000a). Design issues for membrane-based gas phase microchemical systems. *Chemical Engineering Science*, *55*, 3065–3075.

Quiram, D. J., Patrick L. Mills , J. F. R., Wetzel, M. D., Ashmead, J. M., Delaney, T. M., Kraus, D. J., McCracken, J. S., Jensen, K. F., & Schmidt, M. A. (2000b). Package level integration of silicon microfabricated reactors to form a miniature reactor test system. In *Technical digest of the 2000 solid-state sensor and actuator workshop* (pp. 166–169). Hilton Head Island, SC: Transducer Research Foundation.

Richter, T., Ehrfeld, W., Gebauer, K., Golbig, K., Hessel, V., Löwe, H., & Wolf, A. (1998). Metallic microreactors: Components and integrated systems. In *Process miniaturization*: *Second international conference on microreaction technology* (pp. 146–151). New Orleans, LA: AIChE.

Schmidt, M. A. (1998). Wafer-to-wafer bonding for microstructure formation. *Proceedings of the IEEE*, *86*, 1575–1585.

Srinivasan, R., Hsing, I. -M., Berger, P. E., Jensen, K. F., Firebaugh, S. L., Schmidt, M. A., Harold, M. P., Lerou, J. J., & Ryley, J. F. (1997). Micromachined reactors for catalytic partial oxidation reactions. *A.I.Ch.E. Journal*, *43*, 3059–3069.

Tonkovich, A. Y., Zilka, J. L., LaMont, M. J., Wang, Y., & Wegeng, R. S. (1999). Microchannel reactors for fuel processing applications. I. Water gas shift reactor. *Chemical Engineering Science*, *54*, 2947–2951.

Wegeng, R. S., Call, C. J., & Drost, M. K. (1996). Chemical system miniaturization. *A.I.Ch.E. 1996 Spring National Meeting*, New Orleans, LA.

Wießmeier, G., & Hönicke, D. (1996). Microfabricated components for heterogeneously catalysed reactions. *Journal of Micromechanics and Microengineering*, *6*, 285–289.

Wise, K. D. (1998). Special issue on integrated sensors, microactuators, and microsystems (MEMS). *Proceedings of the IEEE*, *86*, 1531–1533.

Xia, Y. N., & Whitesides, G. M. (1998a). Soft lithography. *Angenandte Chemie (International Edition)*, *37*, 551–575.

Xia, Y. N., & Whitesides, G. M. (1998b). Soft lithography. *Annual Review of Materials Science*, *28*, 153–184.