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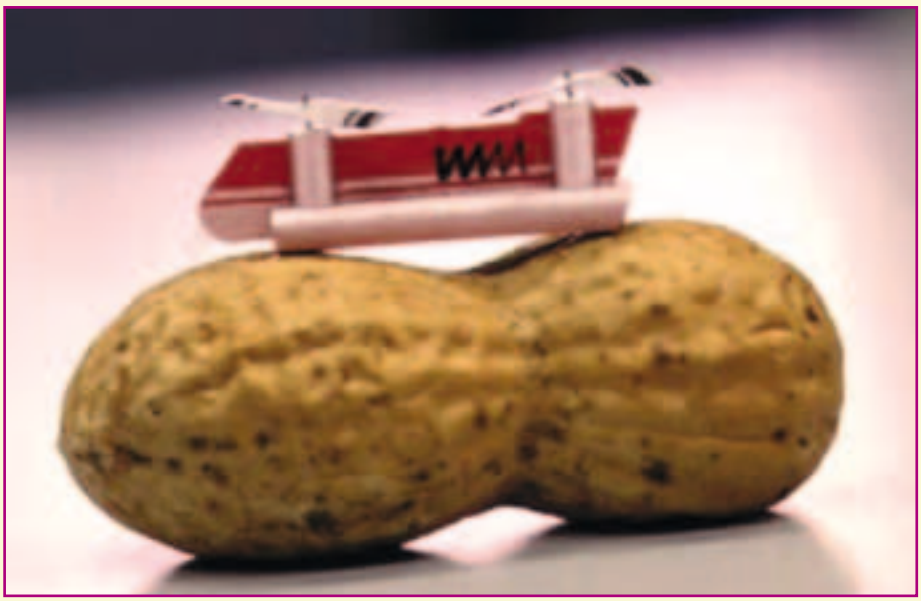

Figure 1: The flying helicopter manufactured by the Institute for Microtechnology at Mainz. This, one of the most striking examples of micro engineering, is 24 mm long, 8 mm high and weighs 400 mg. It uses two 1.9 mm diameter motors capable of nearly 500,000 rpm and torques of 7.5 μNm. It provides a spectacular showcase for the very real potential of its motors which, in fact, are aimed at applications in fast-rotating systems, e.g. scanners, drive units in heart catheters or high-tech display systems. (Photograph courtesy of the Institute for Microtechnology, Mainz.)

Microchannel reactors

Chemical engineering in another dimension?

Chemistry has caught the microtechnology bug. Increasingly it is becoming possible to carry out reactions in vessels whose dimensions are measured in micrometres, in controlled volumes down to picolitres. This article examines why this is a sensible thing to do and how the current trends in lab-on-a-chip and high-throughput experimentation are pointing chemical engineering in the direction of engineering more precise chemistry. Will we soon be able to manufacture only and exactly what we want, when and where we want it?

Introduction

Ever since the classic pictures of micron-sized gear wheels began to appear some 15 years ago, microtechnology has engendered intense excitement in the scientific community. Initially, the grounds for such excitement were thin, often amounting to an article of faith that it had to be useful for something! In recent years, however, it has become apparent that the initial faith was justified. For example, microtechnology underlies the thinking about much post-genome work on pharmaceutical discovery and testing, has led to a range of micromanipulation devices and, perhaps more spectacularly, the tiny flying helicopter made by the Institute for Microtechnology at Mainz (Figure 1).

Because of the high surface areas involved, devices involving miniature gear races inevitably have to cope with enhanced friction. To chemical engineers, however, such high surface areas represent an opportunity. Increasingly, this is being realised with the advent of systems to perform complete chemical procedures involving fluid pumping, valves, chemical reactions, separations and analysis all on one 'chip' in channels of hydraulic diameters between tens and hundreds of microns.

the technology is already much more than a laboratory curiosity

So why does size matter?

Small channels give:

- *Small length scales*, which means that the flow of the fluid, its heating and its cooling all take place under laminar conditions (i.e. no turbulence). The movement of material relative to the fluid occurs in a predictable way by classical diffusion. Thus all the processes relevant to reaction are calculable, potentially at the molecular level, so that it becomes possible (in principle) to know exactly the temperature/time and concentration/time history of reacting mixtures in a way which is not possible with turbulent flow reactors where flows are highly random. This opens the way to a far greater precision in the engineering of reactions.
- *High surface-area-to-volume ratios*, and thus vastly improved heat transfer/catalysis and so, again, precise control over reaction conditions.
- *Small volumes*, which means that there is less material contained in the reactor at any given instant; there is thus less potential for toxic reagent loss in the event of an accident. This means a lower environmental impact and a lowered risk of a severe runaway reaction of any sort.
- *Reactors on a 'chip'* broadly similar to an electronic chip, which means that instrumentation can (in principle) be integrated with the reaction channels and so provide extremely fast response control and analysis systems.
- The possibility of *extremely cheap replication and 'scale-out'* by use of parallel channels or units. The cheapness means that any microreactor system can incorporate high levels of redundancy, so that in the event of one part of the system malfunctioning, some other part can take over its role.

In short, small channels allow construction of an inherently safe, extremely well-defined chemical reactor so that it becomes possible to think about routine engineering of precise chemistry where all atoms are used efficiently and by-product wastes are avoided. On the downside, in the systems which have so far been studied, the throughputs are extremely small and in a traditional chemical engineering context this must be a major problem. However the technology is already much more than a laboratory curiosity.

The three phases of exploitation

The immediate commercial driving force for these microminiaturised systems is their exploitation for chemical and biological analysis – the so-called 'lab on a chip'. Here the emphasis is on injecting a fluid on to the chip and extracting information about it, such as its composition, structure, the presence of antibodies and so on. From its early beginning at Stanford in the late 1970s this technology has grown rapidly. It has now reached the point where household-name companies such as Corning, Agilent (a spin-off from Hewlett Packard) and Hitachi are offering a range of products for applications in the genomics field, including PCR and DNA analysis, immunoassays, sensors and so on. Figure 2 shows one commercial chip marketed by Agilent Technologies.

As this first-phase commercialisation begins to happen in earnest, the second wave of impact of these devices is emerging. This technology has teamed up with a modern approach to chemistry in which very large numbers of different molecules are produced by reactions (between, for example, whole homologous series of precursor reagents – the so-called combinatorial approach) and then screened for particular effects by a fast-response analyser. This has produced high-throughput testing techniques that are radically changing our ability to discover new molecules and materials.

Initial applications, currently attracting a great deal of research attention,

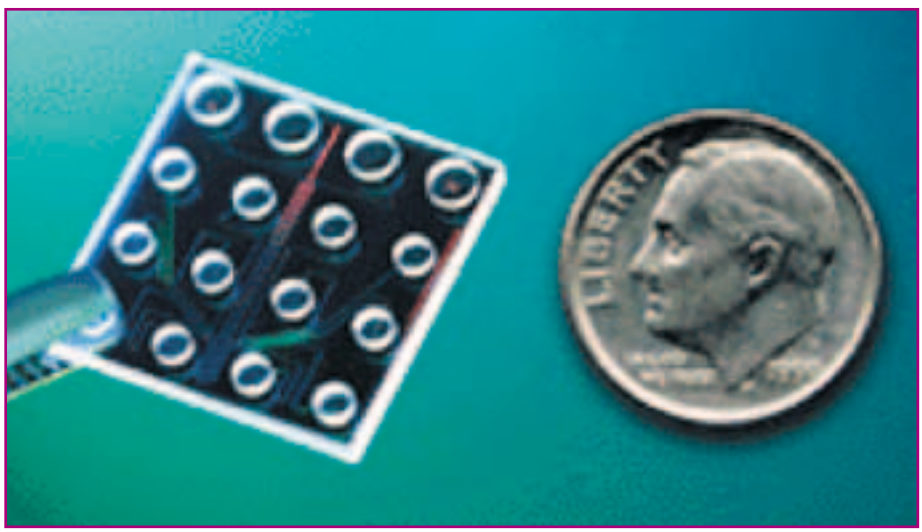

Figure 2: A LabChip® microarray marketed by Agilent Technologies: interconnected channels are etched into glass. The resulting chips can duplicate operations performed at the conventional laboratory bench in volumes ranging from nanolitres to picolitres. (Photograph courtesy of Agilent Technologies.)

include drug discovery, advanced solvent selection, materials discovery and catalyst development. The small amounts of material used, the ease of integration with automatic analysis systems together with the rapid response, make chip-based systems ideally suited for such applications and the two technologies are merging rapidly. When linked with databases and suitable searching techniques such as genetic algorithms, then a powerful platform can be created on which the rate of discovery can be enhanced by many orders of magnitude.

In terms of commercialisation, the most distant but also the most far reaching in its potential impact on chemical engineering is the idea of a 'plant on a chip', which involves putting one set of materials on to a chip and taking different materials off. The Chemical Process Industries (CPI) in the UK, as elsewhere in Europe, are forced to compete through enhanced, value-adding technology. The trend is, therefore, towards greater differentiation of products (based on the effects that can be achieved) and away from bulk chemicals sold on as a commodity on the basis solely of their molecular structure.

Increasingly the effect that will be sold will be achieved through some precise formulation involving an exact supra-molecular structure produced, for example, by a self-assembling gel. Differentiation, particularly in terms of reliability, will drive the chemical engineering of the future so that mass commercialisation, agile manufacturing and dispersed, point-of-sale manufacture are thought to be key trends.

In addition societal forces are demanding more and more that the CPI look to the sustainability of their processes. Given a demand for a particular product, this will require a 'green chemistry' approach in which solvents are not used (or at least not consumed) and where whole processes, including the reaction step, are atom efficient. A radical new approach is, therefore, required to engineering chemistry and the excitement surrounding the early work on microchannel reactors is based on the fact that it is pointing the way to achieving some of these benefits.

Microfluidics

At the small channel sizes we are considering, the flow is laminar such that packets of fluid follow smooth streamlines. Historically chemical engineers, whose primary interests centre on mixing reagents and stimulating heat and mass transfer at a large scale, have ignored the potential of laminar flow regimes and opted instead to harness the randomness inherent in turbulent flow structures to achieve their ends. In molecular terms, however, the mixing structures thus created are of a very large scale and this inevitably has an impact on the precision with which a reaction can be controlled. In microchannels, by contrast, the flows are predictable in a deterministic way. This has stimulated a renewed interest in this flow regime for fluid flow and reactor design – a field now commonly referred to as 'microfluidics'.

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Whilst there have been many suggestions made for 'on-chip' fluid pumps, the majority of research attention is being paid to just two techniques for creating flows through microchannels:

- *pressure differences*, which can move both gases and liquids;
- *electro-osmotic flows*, which are the result of an applied voltage along the length of the channel.

The latter approach is potentially the most exciting since it provides instantaneous electrical control and a velocity profile across the channel that is precise and flat. However, it can only be used in channels with appropriate surface properties.

In either case, we need to obtain flow conditions which allow reagents to mix in such a way that the temperature and composition variations with time are known and controlled as precisely as possible. For gases, the molecules mix very rapidly by diffusion at the length scales being considered. Most interest, however, centres on liquid systems and here the situation is more complex. Diffusion is generally smaller than for gases, so that mixing *across* the channel is weak. The extent of mixing along the length of the channel depends upon how the flow is induced. In pressure-driven flows, the variation of velocity across the channel follows a profile resembling a parabola. Thus fluid at the walls of the channel is flowing much slower than fluid in the centre of the channel and this causes substantial mixing in the axial direction.

For this reason, electro-osmotic systems tend to be favoured for precise control. Outside of the very thin (of nanometre order) electrical double layer at the wall, the velocity profile is uniform. If this is considered in conjunction with the extremely high levels of heat transfer that can in principle occur in microchannel systems, then it creates a very exciting opportunity completely to control the concentration/temperature/time history of a reacting system. Properly engineered, this can provide a more direct link between reactions at the molecular level and bulk flow systems than has previously been realisable.

Reactions in microchannels

Some reactions are so fast that the system is mass-transfer limited; in other

words it is the movement of the reagents that controls the rate at which the product is made, rather than the speed of the actual reaction itself. Conversely, some reactions are slower and are limited by the kinetics. For reactions between gases, microchannels show the greatest promise for mass-transfer controlled reactions. Assuming that the high surface areas allow the energy associated with reactions to be transferred appropriately, then a halving of channel diameter will quadruple the reactor intensity in terms of the reaction that can be accomplished within a given volume of reactor. This has significant implications for advanced energy-generation systems, including fuel cells.

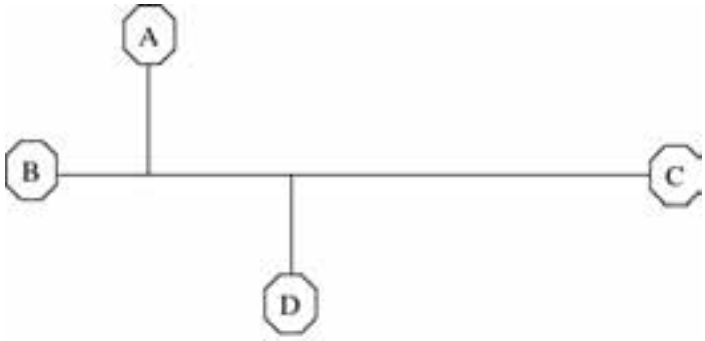
Prototype 'palm sized' compact heating, cooling and power-generation systems have been constructed that are capable of delivering as much as a kilowatt of thermal power. Because of the large surface area created by the microchannels, heat flows per unit area greater than 25 W/cm^2 have been obtained. Because of the small size of these units, they heat up quickly and can be carried easily so that they can be used for distributed and man-portable applications including room-by-room home heating, air conditioning for a soldier, or power generation for a backpacker.

In the liquid phase, it is possible to use microfluidic techniques to provide even greater opportunities for control. As well as subdividing the flow streams in parallel, it has been suggested that the flow should be 'compartmentalised' into very small (nanolitre and smaller) reacting volumes down the channel. The idea is to create, at the beginning of the channel, a continuous flow of reactant A containing discrete 'slugs' of reactant B. The reaction can then proceed at the boundary of the slugs under precisely known conditions. The situation is summarised in Figure 3.

Figure 3: Further subdivision of a reaction by means of a 'Z chip'.

Consider a reaction: A + B ⇒ C

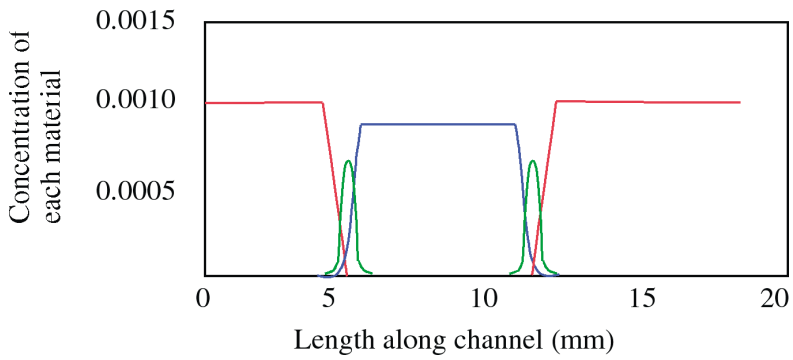
where the reactants A and B are in the reservoirs and the fluids are moved electro-osmotically.



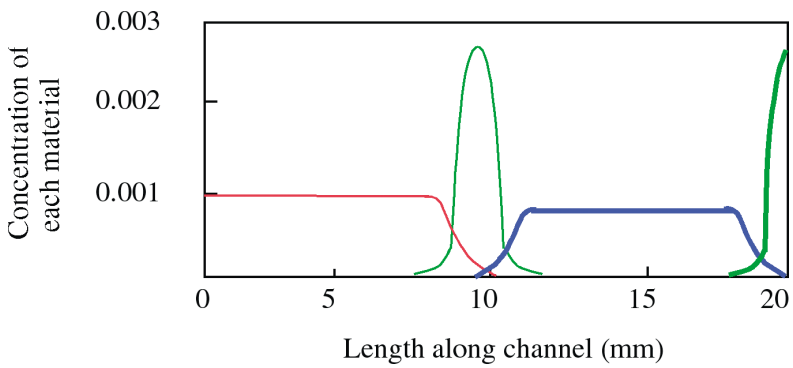
The geometry of the Z chip

By alternately pulsing the voltages at points A and B we can get slugs of B (coloured blue) in A. These can be in the nanolitre to picolitre range. The distribution of material along the length of the channel would look like this:

The reaction to C will occur at the edges of the slugs under precisely calculable conditions. Graphically, the distribution of material along the length of the channel looks likes this as the reaction begins:



After a certain length of time, there will be substantial quantities of C formed. However, A, B, and C all have different electrophoretic velocities and respond at different rates to the applied voltage gradient. Separation thus occurs as the mixture flows along the channel:



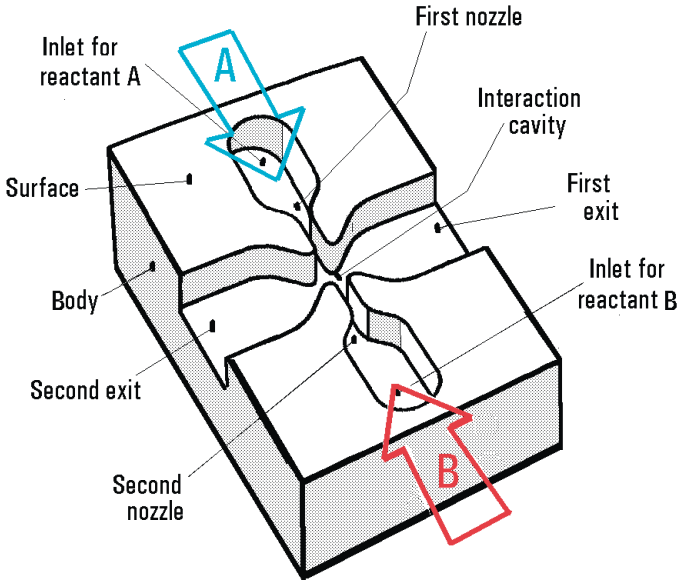
Correct design means that reaction and separation can occur in a single channel.

It has been suggested that a 'Z chip', of the geometry shown, could be used to subdivide the reactants into the slugs in series. The idea is attractive because as the product C is formed, it will also respond to the voltage gradient. In real systems, A, B and C will all respond differently so that separation will occur as the fluid moves along the channel. If the device is designed correctly, precise reaction and separation can be made to occur in a single chip.

In fact the flows are more complex than this simple picture suggests. The fluid's inertia causes its flow path to distort close to changes of curvature, such as the junctions in the channel. As a result, clean interfaces are more difficult to achieve than expected and new designs of chip are being evolved to allow the required degree of precision.

A microfluidic approach allows convention to be defied in other ways. Figure 4, for example, shows an etched oscillator–mixer that uses two opposing fluid streams. At a small scale the oscillation frequency, and hence the thickness of the layers in which the two materials are interleaved, depends upon feedback from the interaction of the streams with the wall of the cavity. By miniaturising the device, it becomes possible to generate oscillatory flows more easily and create very small length scales over which diffusion has to take place.

Figure 4: A microfluidic oscillator used for mixing two fluid streams.



Schematic of oscillator geometry

The oscillator–mixer made from through-etched stainless steel and sandwiched between two transparent plates. In operation, a stream of colourless liquid is being interleaved with a stream of blue liquid. The oscillation frequency depends upon feedback from the interaction of the jet with the cavity wall. By miniaturising the device, controlled oscillations have been achieved more easily than previously thought possible. The resulting interleaving of the two fluid streams allows mixing by diffusion to occur more quickly. (Courtesy of the Institute of Applied Catalysis.)

Engineering challenges

The first work on microchannel reactors sprang from silicon chip manufacturing techniques. As a result, early work tended to be performed on silicon substrates and in a two-dimensional geometry. Manufacturing techniques involved photochemical etching, reactive ion etching, LIGA and so on.

In the last few years, it has been demonstrated that suitable channels can be made from a very broad range of materials including stainless steel, glass and several polymers via techniques including laser cutting, moulding and electrochemical deposition. Geometries tend still to be two-dimensional with overall units being constructed from layers of material bonded together to form a single layer of channels. In fact the vast majority of the reported research still concentrates on single channels. Very few centres are attempting to create many parallel reaction streams to allow scale-up to useful throughputs. Thus two main challenges to the widespread exploitation of microchannel reactors may be identified as:

- the interface between the micro and macro environments;
- scaleout or parallelisation to achieve significant throughputs.

The term 'scaleout' is used since one of the strongly perceived advantages of microchannel reactors is that, because replicate manufacturing costs of the chips are low, higher throughputs will be achieved by placing many duplicate chips in parallel. This will create the advantage of allowing systems with high levels of built-in redundancy to make failure-tolerant plant as well as the very real prospect of disposable

chemical plant. Although these possibilities were identified many years ago, the engineering challenges underlying them have only recently begun to be tackled.

Reactors can simply be built with multiple channels in parallel on a single layer and also with layers in parallel in a stack. Reactions involve energy changes and this requires control over the heat transfer in every layer. As a result, the stacks that have been proposed tend to be of alternating layers, either by using a heat-transfer fluid to provide the necessary control over the temperature profile in the reacting layers or by matching energy-releasing and energy-consuming reactions on either side of a thermally conductive plate. Either way, extra challenges associated with sealing between internal channels arise.

It is probable that, for the commercial application of this type of technology, highly flexible modules will be necessary which can easily be connected and disconnected to achieve particular aims and a required throughput. This building-block approach to the constructing of chemical plant will require radical developments in packaging technology. This must involve standardisation of connectors and seals. It will also involve common standards for electrical connections, heat-transfer fluids, reagents, control signals and so on. Some work is already well advanced in the production of such modules.

Microchannel devices have the capacity radically to change the way that major companies do business and to change the landscape in terms of human health and happiness. This was a conclusion from a recent DTI seminar ('Microsystems – The Big Future', London, 4 April 2001) at which top-level technical managers from both Unilever and Glaxo SmithKline gave an insight into how the technology is seen as core enabler in their forward business planning. Both speakers (Dr Peter Goodfellow and Dr Kurt Schilling) agreed that it is not a matter of *whether* this technology will change their business but *when* it will. Examples of what they thought would be done using this technology included:

Microchannel devices have the capacity radically to change the way that major companies do business

- massively high-throughput experimentation for drug discovery;
- enabling highly personal diagnosis of illness at the proteomic level;
- high-throughput studies of gene expression to develop optimal plants and healthier foods;
- understanding an individual's skin care requirements at the cellular level;
- self-assessment and health monitoring.

Conclusions

The challenge for chemical reaction engineering is to develop ever more detailed understanding to give fault-free products from zero-emission processes. In short, to manufacture *only* and *exactly*:

- what we want,
- when we want it,
- where we want it.

This will require a different approach to reactor design that involves radical changes to the way we control, *inter alia*,

- mixing and
- heat transfer.

It is these features of microchannel reactors that suggest that they do have the potential to take chemical engineering into another dimension. They provide the means to use a reactor configuration, in conjunction with clever microfluidics, more directly to influence the reaction and formulation processes. Accordingly, the driving force for their use will not be miniaturisation for it own sake, nor yet distributed manufacture. It almost certainly will be the opportunity to exploit completely novel chemistry. In fact, if microchemical engineering were to turn out to be just miniaturisation for its own sake, it probably wouldn't be worth the bother. ■

Web sites

MEMS Precision Instruments site (micromanipulation devices): http://www.memspi.com

The Institute for Microtechnology, Mainz: http://www.immmainz.de/english/developm/products

Agilent Technologies: http://www.chem.agilent.com

Micro-Cats (Micro Chemical and Thermal Systems): http://www.pnl.gov/microcats/fullmenu/microchannel.html

Ray Allen was the inaugural Head of the new Chemical Engineering Department at the University of Sheffield from 1995–2000. He continues there as a research professor with a specialist interest in the modelling and visualisation of reacting flows to enable the engineering of reactors to give precise chemistry. Prior to joining the University of Sheffield, Ray worked for AEA Technology at the Harwell Laboratory where, amongst other things, he managed SPS and then became Business Development Director.

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