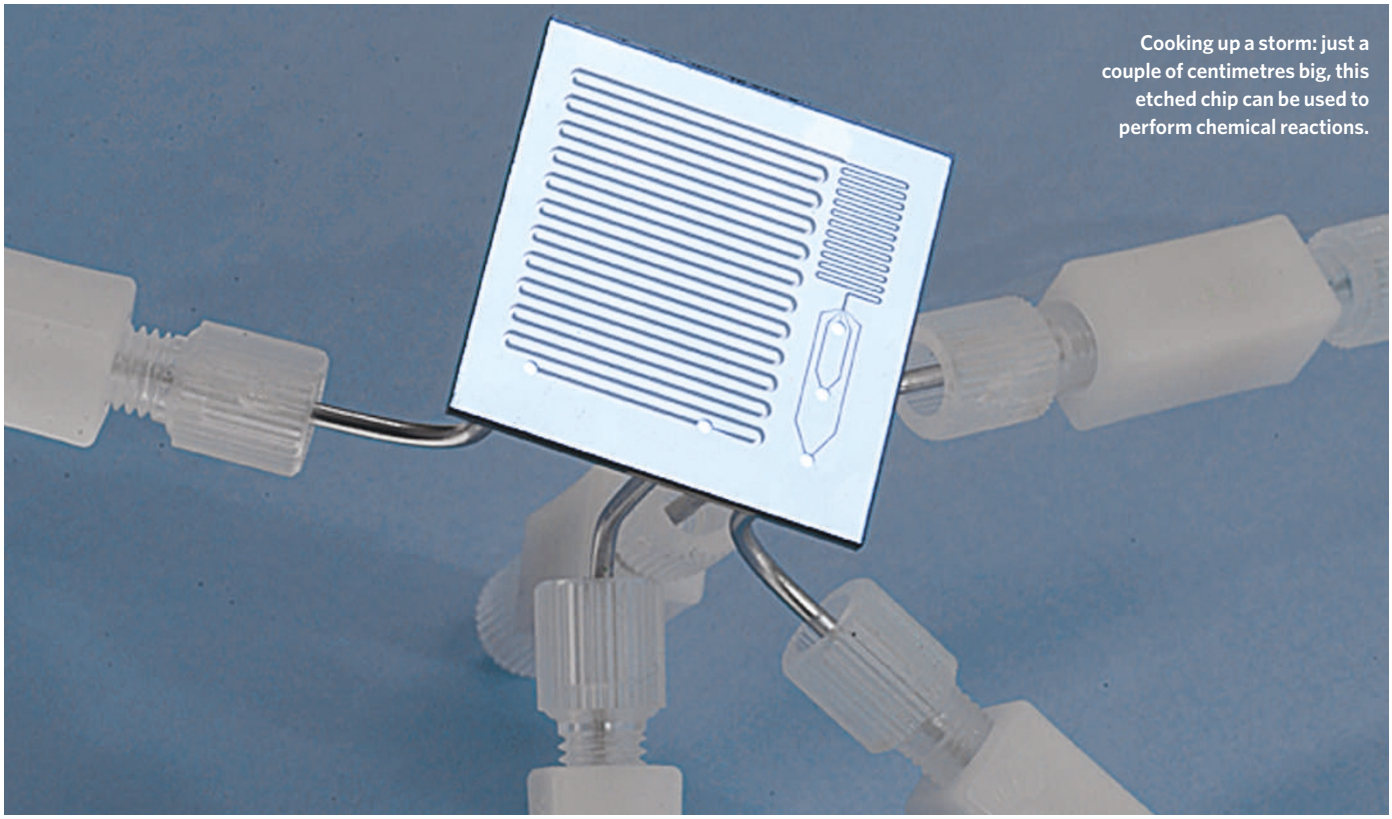


Cooking up a storm: just a couple of centimetres big, this etched chip can be used to perform chemical reactions.

F. FRANKEL/REF. 1

A little goes a long way

Faster, safer and easier to control — chemical reactions in microreactors are taking off in the lab. Now industry is being seduced by the charms of the lab on a chip. **Jenny Hogan** investigates.

A few years ago, a productive PhD student in Peter Seeberger's chemistry lab would run three or four experiments a day. Each would be a painstaking step towards optimized conditions for a new reaction — be it making a peptide or producing a sugar molecule for use in a possible vaccine.

Since then, Seeberger's expectations have soared. Now his students have to work ten times as hard. The 120 reactions that formed the basis for one recent publication[1] were completed in three afternoons.

It's not that Seeberger, at the Swiss Federal Institute of Technology in Zurich, has become a slave-driver. Rather, he has updated his lab equipment. He is working with a collection of microreactors — each one a miniature lab on a chip. The reagents are stirred up again, and again, in channels less than a millimetre in diameter, until the students get the results they need.

"People in my lab are very excited about this. It gives you time to do more chemistry," says Seeberger. "I always say that microreactors will be chemists' round-bottomed flasks for the twenty-first century."

The humble glass flask is a chemistry icon, used since alchemists tried to turn base metals into gold. But microreactors promise to make chemistry faster, cleaner and yield purer products. They might also open the door to syntheses not previously feasible on a large scale, and make dangerous — even explosive — reactions safer.

The technology has grown over the past two decades — a convergence of the miniaturization of chemical and biological analysis techniques and the engineering of computer chips. Seeberger's chips (pictured above) are typical of what is possible. Just a couple of centimetres big, they feature tiny channels etched into silicon. Chemicals are injected into the device and they react where they merge. The bends in the channels help force the reagents to mix, and the length of the channels and the flow rate determine the reaction time. With reaction volumes measuring just microlitres, conditions such as pressure and temperature can be precisely controlled and quickly changed.

End of an era: could lab-on-a-chip technology spell the end for the round-bottomed flask?

"You only have to run the system until you have one drop of product coming out of the end. You'd spend the longest time walking downstairs to the spectrometer to analyse it," says Graham Sandford, a chemist at Durham University, UK, who has used microreactors in his lab[2].

Now the technology is also making the leap into industry. Microreactors performing cleaner and safer reactions could push the batch vessels used in the synthesis of some compounds — including drugs — into retirement. Ultimately, the devices could end up integrated into drug discovery[3].

"For me, the important message is that the

technology can be applied on an industrial scale," says Volker Hessel, vice-director for research and development at the Institute of Microtechnology Mainz (IMM), which has collaborated with hundreds of chemical companies on microreactor projects.

In industry, high-value products that are typically produced in small batches, such as pharmaceuticals and fine chemicals, have much to gain from the extra flexibility offered by microreactors. Scaling up a lab procedure to batch production can sometimes require redesigning a chemical reaction from scratch. "In flow world, you just run a reaction longer," says Tony Wood, head of discovery chemistry for Pfizer in Sandwich, UK.

Wood says that Pfizer is only just beginning to explore the possibilities that the technology offers, but he hopes microreactors will change the rules for his chemists. Reactions that they now have to avoid because they are difficult to run in large volumes might become accessible. "What's interesting to me is the opportunity to pursue fields such as electrochemistry or photochemistry," says Wood. "That would enable us to functionalize molecules in a quite different way from mainstream transformations."

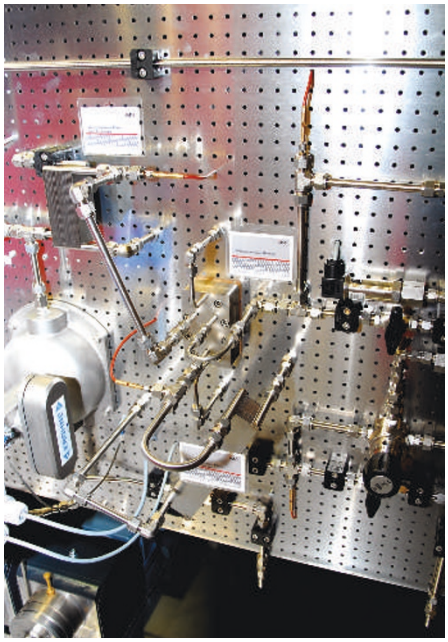
Compound interest

But there are still some engineering troubles to be overcome. Precipitates are a problem in any reaction process, but in the tiny channels and chambers of a microreactor, clogging is an ever-present danger. "Solids are problematic and if you can avoid them you will try," says Hessel. Researchers in the field cite the growing literature on systems that can handle solids as evidence that the problem of clogging will, with time, be conquered. The challenges of performing reactions in which different steps in a synthesis require different solvents are also being dealt with, say industry insiders.

As a result, industrial interest in microreactors is spreading fast, says Hessel. "It's nearly all the big names in chemistry," he notes. One idea that industry has been quick to latch on to is safety. For example, reactions that release a lot of energy may be controlled in a small flask, but risk exploding in a larger batch vessel where excess heat is harder to dissipate. With a microreactor, scaling up the reaction safely simply requires running more devices in parallel.

This encouraged Xi'an Huian Chemical in China to approach Hessel's team at the IMM to set up a microreactor plant to synthesize nitroglycerine. It took only five months for the team to get the plant running and, since September 2005, it has been producing nitroglycerine for use as a treatment for heart disease.

Switching from batch to flow chemistry is not just about refitting a plant or lab, it often requires a change of mindset. "You are in a small, innovative team in an established company that has more than 100 years' experience in chemical production and you want to change things — there are some barriers beyond the technical," says Dominique Roberge, head of a project to evaluate microreactors at Lonza, a Swiss company that manufactures intermediates for the drug industry.



V. HESSEL

Scaled down: this fine-chemical process plant features micro mixers and heat exchangers.

Even Seeberger was not an immediate convert. After learning about microreactors in 2001, he decided to investigate further in his lab at the Massachusetts Institute of Technology (MIT), where he was then based. He was fortunate that Klavs Jensen in MIT's chemical-engineering department was already making microreactors. But Seeberger wasn't impressed at first. "When Klavs showed me his devices, they looked like toys. I thought they would be useless, that you wouldn't be able to make enough material." But when he came to try it, he found that running a microreactor for a day produced 100 grams of material — far more than his students are ever likely to need for biological tests.

> **"The question of whether microreactors are going to be used in the future, I think this is already answered 'yes'." — Dominique Roberge**

Steven Ley, a chemist at the University of Cambridge, UK, is another who threw out many of his round-bottomed flasks after building a flow-chemistry lab. He welcomes the opportunity to do chemistry differently. For example, he says, some flask reactions have to be carried out at −195 °C, the temperature of liquid nitrogen, to prevent 'overcooking' the reactants, but they can be performed at room temperature in microreactors. This would make them economical for industry.

Even for existing batch reactions, microreactors can offer an attractive alternative. The flow inside their small channels is better behaved than in a large vessel, and so is more reproducible. In the drug industry, if a batch doesn't match the specifications approved by regulators, it has to be thrown away. "Many batches are lost and very often it's the culmination of several months' work," says Brian Warrington, former vice-president of technology development for GlaxoSmithKline, UK. "It's a big commercial problem."

That was one reason why Warrington pushed the idea of microreactors at GlaxoSmithKline in the late 1990s. The other was the idea of 'closing the loop'. Warrington says the ultimate goal is to have a microreactor pumping its product straight into a cell-based assay, which is hooked up to provide feedback to a computer controlling the synthesis of the next product to be tested.

Recipe for success

In his Cambridge lab, Ley is experiencing the drug industry's growing interest in flow chemistry directly. Companies are clamouring to send people to the lab for training, he says. One of his PhD students collaborates with Chris Selway, one of the drug-discovery chemists at Pfizer charged with evaluating the technology's potential for the firm.

So far, Selway remains cautious about microreactors. "We are seeing lots of claims in the literature about how good flow chemistry is and, as a company, we want to be involved in that," says Selway, "but by no means is it a tool that's going to radically take over from batch chemistry."

Industry still has to work out the economics of microreactors. Lonza began operating a pilot plant using microreactors in March and Roberge has analysed 83 reactions performed by the company[4]. He found that half could benefit from being carried out in microreactors, although solids in many of these reactions reduced that number to 16. His preliminary economic analysis suggests that the cost of building and commissioning the microreactor plant will be comparable to a batch system of similar throughput — around €250,000 (US$316,000). The main hope for future cost savings, he says, is if microreactors can deliver improved yields and so use lower amounts of raw material.

"The question of whether microreactors are going to be used in the future, I think this is already answered 'yes'," says Roberge. "The open question is what per cent of the market in fine chemicals they will take." ■

Jenny Hogan is a reporter based in *Nature*'s London office.

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For more on lab-on-a-chip technology see the Insight on pages 367–418 of this issue.