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CHEMICAL TECHNOLOGY

All together now

Stephen J. Haswell

A method that combines techniques for performing chemical synthesis, separation and measurement on a single device illustrates the considerable potential of integrated lab-on-a-chip technology.

The traditional icons of chemistry, the test-tube and conical flask, are in many situations giving way to lab-on-a-chip methodology. This route to miniaturization offers high-throughput control of reactions that range in context from chemical synthesis and measurement, through biological processing, to medical diagnostics.

The prospect of realizing the full potential of lab-on-a-chip methodology comes a little closer with work reported by Detlev Belder and colleagues in *Angewandte Chemie*[1]. The authors' strategy exploits the various benefits of performing reactions within a microfluidic environment, and interfaces this process to an efficient separation and detection system. They test their procedures by analysing the efficiency with which different mutant enzymes, created by directed evolution, select for different chiral or enantiomeric reaction products.

The potential advantages of lab-on-a-chip miniaturization include low operating volumes, faster reaction or sample-processing times, safer procedures, and the more efficient selective generation of products[2]. For processes carried out in solution, many of these advantages arise from the control of samples and reagents that can be achieved within a network of micrometre-sized fluidic channels. The temperature and concentration gradients created in such systems can be used to control reaction conditions; and the high ratios between surface area and volume can be especially effective in exploiting processes that occur at interfaces.

Microfluidic reactors do, however, have their drawbacks. For example, the price of trading the slow thermal and mass-transfer processes of a conventional reactor for the speed of a microreactor is much smaller amounts of product. But high flow rates or scaled-up procedures[3] can compensate. For instance, microreactors with channel cross-sections of only 250 μm have been used to carry out a common class of reaction, known as Mizoroki–Heck-type reactions, at a flow rate of 500 μl per minute to produce 12 g of pure product per hour[4]. So, in principle, 1,000 such reactors should be able to produce 288 kg of product per day. Another potential drawback is blockage of the channel network by particulate matter. But this problem can be minimized by careful selection of channel geometries and other parameters.

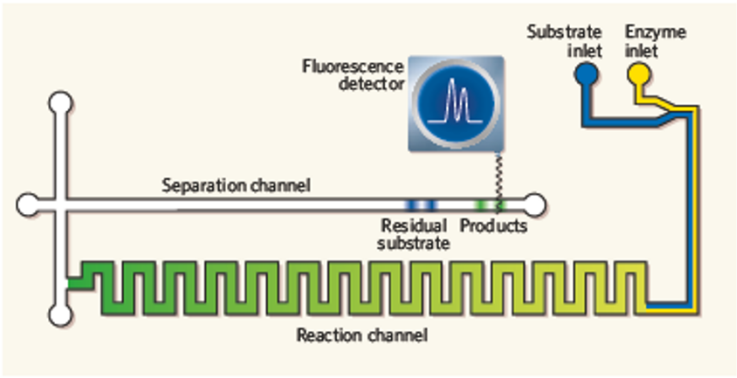

Figure 1 | Design and use of Belder and colleagues' microfluidic chip[1] for integrated chemical reaction and analysis. The system was tested on the enantioselectivity of fungal enzyme mutants. The substrate (glycidyl phenyl ether) and catalyst (epoxide hydrolase) mix in the meandering reaction channels. The reaction products and remaining substrate are separated electrophoretically in the separation channel, and the proportions of the product enantiomers are then measured with an external fluorescence detector. The chip is made of fused silica. It is about the size of a conventional microscope slide (7.5 × 2.5 cm) and a couple of millimetres thick. (Redrawn from ref. 1.)

Belder and colleagues' chip for integrated catalysis and product analysis is shown in Figure 1. In their paper[1] they describe the reaction of 10 μl of glycidyl phenyl ether with a similar volume of various mutant epoxide hydrolases derived from the fungus *Aspergillus niger*. Enzyme and substrate were allowed to mix and react for 10 minutes, before an electrophoretic separation step (which took less than 90 seconds); fluorescence detection was used to monitor the proportions of different enantiomeric forms of product. To further illustrate the value of integrating the reaction and separation–detection processes, the authors also used the chip to establish the reaction kinetics; this involved sequential injections of substrate and enzyme variants, followed by repeated analysis of the enantiomeric products as a function of time.

So far so good. But Belder and co-workers' chip[1] is also equipped with additional ports for introducing reactants, allowing up to three catalysts to be screened against one substrate in a single set of experiments. In principle, the current fabrication technology should allow this to be scaled up to tens or even hundreds of parallel streams. In terms of throughput, the authors also suggest that the 10-minute mixing and reaction time could be reduced through the introduction of a more efficient micromixer design. Finally, greater integration could be achieved by packaging the fluorescence-detection system, which at present requires an external laser source and detector to be aligned with the chip, into a single, more robust unit.

The contents of journals such as *Lab on a Chip* and *Microfluidics and Nanofluidics* attest to what has already been achieved with miniaturized chemistry. Building microreactors with full integration of chemical, biological, analytical and communication systems — for, say, remote operation — will require compromises, but it is an advantage that the fabrication of such systems has a common basis[5]. Uses of the technology will include drug discovery, where drug candidates could be synthesized and screened for toxicity and activity in minutes, with an iterative procedure allowing swifter and surer identification of the best molecules[6]. There will be other applications in personalized medicine, drug delivery, environmental and security monitoring, and forensics and space exploration.

Finally, integrated miniaturized systems should eventually be relatively cheap. They will be much more affordable than full lab facilities — not least in developing countries. ■

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