

The origins and the future of microfluidics

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The manipulation of fluids in channels with dimensions of tens of micrometres — microfluidics — has emerged as a distinct new field. Microfluidics has the potential to influence subject areas from chemical synthesis and biological analysis to optics and information technology. But the field is still at an early stage of development. Even as the basic science and technological demonstrations develop, other problems must be addressed: choosing and focusing on initial applications, and developing strategies to complete the cycle of development, including commercialization. The solutions to these problems will require imagination and ingenuity.

What is microfluidics? It is the science and technology of systems that process or manipulate small (10^{-9} to 10^{-18} litres) amounts of fluids, using channels with dimensions of tens to hundreds of micrometres. The first applications of microfluidic technologies have been in analysis, for which they offer a number of useful capabilities: the ability to use very small quantities of samples and reagents, and to carry out separations and detections with high resolution and sensitivity; low cost; short times for analysis; and small footprints for the analytical devices¹. Microfluidics exploits both its most obvious characteristic — small size — and less obvious characteristics of fluids in microchannels, such as laminar flow. It offers fundamentally new capabilities in the control of concentrations of molecules in space and time.

As a technology, microfluidics seems almost too good to be true: it offers so many advantages and so few disadvantages (at least in its major applications in analysis). But it has not yet become widely used. Why not? Why is every biochemistry laboratory not littered with 'labs on chips'? Why does every patient not monitor his or her condition using microfluidic home-test systems? The answers are not yet clear. I am convinced that microfluidic technology will become a major theme in the analysis, and perhaps synthesis, of molecules: the advantages it offers are too compelling to let pass. Having said that, the answers to questions concerning the time and circumstances required for microfluidics to develop into a major new technology are important not just for this field, but also for other new technologies struggling to make it into the big time.

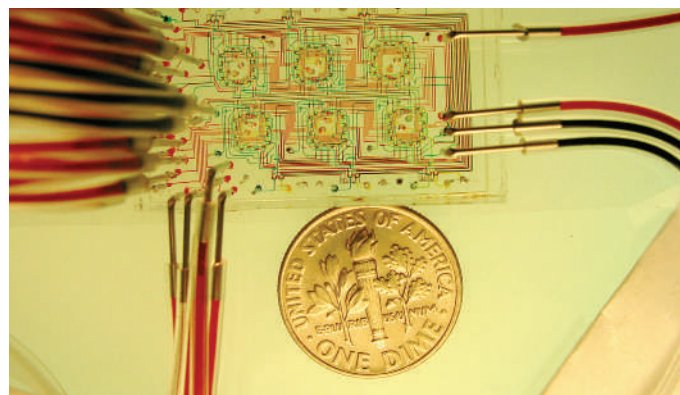


Figure 1 | A microfluidic chemostat. Microfluidic devices — here, a microfluidic chemostat used to study the growth of microbial populations — now routinely incorporate intricate plumbing. This device includes a high density of pneumatic valves. The colours are dyes introduced to trace the channels. (Image reproduced, with permission, from ref. 65.)

The field of microfluidics has four parents: molecular analysis, biodefence, molecular biology and microelectronics. First came analysis. The distant origins of microfluidics lie in microanalytical methods — gas-phase chromatography (GPC), high-pressure liquid chromatography (HPLC) and capillary electrophoresis (CE) — which, in capillary format, revolutionized chemical analysis. These methods (combined with the power of the laser in optical detection) made it possible to simultaneously achieve high sensitivity and high resolution using very small amounts of sample. With the successes of these microanalytical methods, it seemed obvious to develop new, more compact and more versatile formats for them, and to look for other applications of microscale methods in chemistry and biochemistry.

A second, different, motivation for the development of microfluidic systems came with the realization — after the end of the cold war — that chemical and biological weapons posed major military and terrorist threats. To counter these threats, the Defense Advanced Research Projects Agency (DARPA) of the US Department of Defense supported a series of programmes in the 1990s aimed at developing field-deployable microfluidic systems designed to serve as detectors for chemical and biological threats. These programmes were the main stimulus for the rapid growth of academic microfluidic technology.

The third motivational force came from the field of molecular biology. The explosion of genomics in the 1980s, followed by the advent of other areas of microanalysis related to molecular biology, such as high-throughput DNA sequencing, required analytical methods with much greater throughput, and higher sensitivity and resolution than had previously been contemplated in biology. Microfluidics offered approaches to overcome these problems.

The fourth contribution was from microelectronics. The original hope of microfluidics was that photolithography and associated technologies that had been so successful in silicon microelectronics, and in microelectromechanical systems (MEMS), would be directly applicable to microfluidics. Some of the earliest work in fluidic microsystems did, in fact, use silicon and glass, but these materials have largely been displaced by plastics. For analyses of biological samples in water, devices fabricated in glass and silicon are usually unnecessary or inappropriate. Silicon, in particular, is expensive, and opaque to visible and ultraviolet light, so cannot be used with conventional optical methods of detection. It is easier to fabricate the components required for microanalytical systems — especially pumps and valves — in elastomers than in rigid materials. Neither glass nor silicon has all the properties (especially permeability to gases) required for work with living mammalian cells.

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Thus, microfluidic devices have not developed as clones of silicon microelectronic devices. Much of the exploratory research in microfluidic systems has been carried out in a polymer — poly(dimethylsiloxane), or PDMS — the properties of which are entirely distinct from those of silicon^{2,3}. PDMS is an optically transparent, soft elastomer. Whether the microfluidic devices that ultimately become widely used will use PDMS or one of the engineering polymers (such as polycarbonate or polyolefin) remains to be seen. The ease with which new concepts can be tested in PDMS, however, and its ability to support certain very useful components (such as pneumatic valves), have made it the key material for exploratory research and research engineering at the early stages of development. Microelectronic technologies have, however, been indispensable for the development of microfluidics, and as the field has developed, glass, steel and silicon have again emerged as materials with which to build specialized systems that require chemical and thermal stability. The mechanical stability of silicon and glass are also useful in the nascent field of nanofluidics (the study of fluids in channels with nanometre-scale — ideally less than 50 nm — dimensions), in which channels with rigid walls can be useful^{4,5}.

Microfluidics has seen the rapid development of new methods of fabrication, and of the components — the microchannels that serve as pipes, and other structures that form valves^{6,7}, mixers^{8–10} and pumps¹¹ — that are essential elements of microchemical ‘factories’ on a chip. However, its impact on science has not yet been revolutionary. Revolutions in technology require both a broad range of different types of component and subsystem, and their integration into complete, functional systems. The field of microfluidics is in early adolescence, and still lacks both these essential requirements, in addition to the integration of components into systems that can be used by non-experts. As a field, it is a combination of unlimited promise, pimples and incomplete commitment. This is a very exciting time for the field, but we still do not know exactly what it will be when it grows up.

The present

A microfluidic system must have a series of generic components: a method of introducing reagents and samples (probably as fluids, although ideally with the option to use powders); methods for moving these fluids around on the chip, and for combining and mixing them; and various other devices (such as detectors for most microanalytical work, and components for purification of products for systems used in synthesis). The field has, so far, centred on demonstrating concepts for these components. Two particularly important contributions have been the development of soft lithography in PDMS as a method for fabricating prototype devices¹²; and the development of a simple method of fabricating pneumatically activated valves, mixers and pumps on the basis of soft-lithographic procedures¹³. These methods have made it possible to fabricate prototype devices that test new ideas in a time period much shorter (typically less than 2 days from design to working device) than that which could be achieved using silicon technology (typically, for non-specialists, a month or more). Quake’s pneumatic valves are particularly important as components that have enabled the design and examination of complicated devices, and these have opened up a number of areas of application (Fig. 1). ‘Quake valves’ use the restriction of a fluidic channel by an adjacent channel under pressure; their operation depends on the fact that PDMS is an elastomer, and no corresponding devices exist (or can exist) in rigid materials such as silicon and glass (or rigid engineering polymers such as polycarbonate).

Together with new methods of fabrication, microfluidics has been able to exploit certain fundamental differences between the physical properties of fluids moving in large channels and those travelling through micrometre-scale channels^{14–16}. Janasek *et al.* describe scaling relations that relate (or differentiate) macroscopic and microfluidic systems, with special emphasis on lab-on-a-chip devices (see page 374). Of these differences, the most important is turbulence (or its absence: laminar flow). On large scales, fluids mix convectively: for example, the mixing of milk when it is swirled into coffee, or smoke, leaving a chimney, with air. This type of mixing reflects the fact that in macroscopic fluids, inertia is often

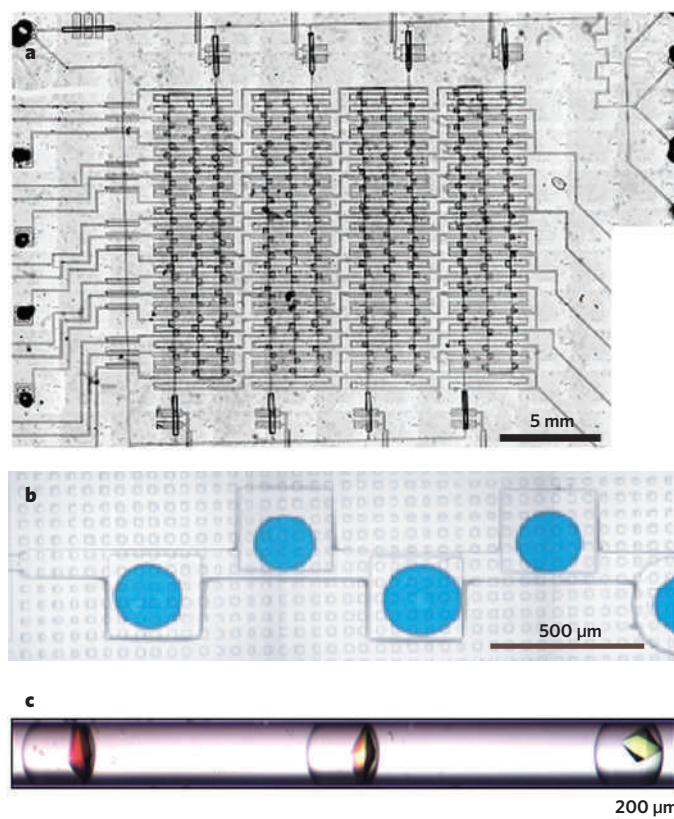


Figure 2 | Efficient screening for optimal protein crystallization conditions.

Microfluidic devices are well suited for screening conditions under which proteins crystallize, as demonstrated initially by Quake²⁰. **a**, A device in which droplets containing proteins are trapped in wells in the microchannels²¹. The droplets are then subjected to many different conditions for crystallization. **b**, An optical micrograph of dyed droplets in the wells of the device. (Images courtesy of S. Fraden and J.-u. Shim, Brandeis University, USA.) **c**, Droplets containing crystallized proteins. The droplets are produced in a microfluidic device, then collected in a glass capillary. (Image adapted, with permission, from ref. 22.)

more important than viscosity. In microsystems, with water as a fluid, the opposite is true: fluids do not mix convectively — when two fluid streams come together in a microchannel, they flow in parallel, without eddies or turbulence, and the only mixing that occurs is the result of diffusion of molecules across the interface between the fluids. Although this type of flow — known as laminar flow — requires the development of specific devices or components to accomplish mixing (when mixing is required), it has proved an advantage (and one that is characteristic of microfluidic systems) in many circumstances. The ratio of inertial to viscous forces on fluids is characterized by the Reynolds number (Re) — one of the many dimensionless parameters used in studying fluids¹⁵.

Fluids flowing in microsystems have many other interesting and useful characteristics, only some of which have been exploited. One particularly useful characteristic is electro-osmotic flow (EOF)¹⁷. When an ion-containing fluid (for example, water) is placed in a microchannel that has fixed charges on its surface (such as silicon dioxide or surface-oxidized PDMS) and an electrical potential is applied along the channel, the fluid moves as a plug, rather than with the parabolic-flow profile observed when pumping is accomplished by applying pressure to the fluid. EOF minimizes the broadening of plugs of sample that occurs with many pressure-driven systems, and allows very high resolution separations of ionic species. It is a key contributor to electrophoretic separations of DNA in microchannels¹⁸. A second potentially useful characteristic is the ability of nanofluidics to manipulate water in channels whose dimensions are similar to those of the Debye layer¹⁹: we do not, in fact, understand the characteristics of fluids at those scales, and nanofluidic systems offer windows into new phenomena in fluid physics.

Current applications

There are now enough methods of fabrication, and a sufficient range of components, to make it possible to begin to apply microfluidic systems to the resolution of problems (rather than simply to the demonstration of principles). The most highly developed of their applications is probably their use to screen conditions (such as pH, ionic strength and composition, cosolvents, and concentration) for protein crystallization^{20–22} (Fig. 2); these procedures offer the potential to screen large numbers of conditions, to separate nucleation and growth of crystals, and to minimize the damage to crystals by handling once they have formed. Some of this technology is now commercially available. Other applications for which there are laboratory demonstrations include separations coupled to mass spectroscopy²³, high-throughput screening in drug development^{24,25}, bioanalyses²⁶, examination and manipulation of samples consisting of a single cell^{27,28} or a single molecule^{29,30}, and synthesis of ¹⁸F-labelled organic compounds for positron emission tomography (PET)³¹. The area of single-molecule studies is discussed in this issue by Craighead (see page 387).

The manipulation of multiphase flows is another strength of microfluidic systems. They enable the generation and manipulation of monodisperse bubbles^{32,33} (Fig. 3) or droplets^{34–37} of a dispersed gas or liquid phase in a continuous liquid stream; these dispersions suggest new routes to the

production of polymer particles, emulsions and foams³⁸. Droplets can also serve as compartments in which to study fast organic reactions. Fluids in microchannels form the basis of new optical systems: a range of systems — from waveguides comprising a liquid with a high index of refraction flowing laminarily between two streams of low-index ‘cladding’, to applications of fluids in lenses and Bragg mirrors — are based on microfluidics^{39–44}. Psaltis, Yang and Quake paint a detailed picture of this new field, and of some of its potentials, in this issue (see page 381).

Cell biology is an area of research into which microfluidic systems bring a new capability. Jensen *et al.* (see page 403) describe types of system that seem certain to become useful new tools for cell biologists, as well as capabilities that are still needed. Eukaryotic cells, when attached and spread, have linear dimensions of 10–100 µm; these dimensions are well suited for current microfluidic devices, and PDMS — with its excellent optical transparency, low toxicity and high permeability to dioxygen and carbon dioxide — is a material that is probably uniquely suitable as a medium for the fabrication of microchambers in which to grow and observe cells^{45–48} (Fig. 4). PDMS microfluidic systems have applications in the extensive study of many areas of cell biology, including the cytoskeleton⁴⁹, the forces exerted by cells on the substrate to which they are attached⁵⁰, the contents of cells (down to the single-cell level)^{27,51}, separations of motile and non-motile cells (for example, sperm)⁵², and embryos^{53–55}.

Chemical synthesis (especially in organic and medicinal chemistry) — an area in which microfluidic systems would seem to fit naturally — has been slow to adopt microfluidic structures as a strategy for the development of new capabilities. (Some of the characteristics of chemical reactions in microsystems are discussed in this issue by deMello, page 394.) Two factors contribute to this slow adoption. First, the flexibility of conventional apparatus has, so far, not been equalled in microfluidic systems. Second, PDMS — the material most commonly used in academic studies of microfluidics — dissolves in, or is swelled by, many common organic solvents⁵⁶. The use of silicon, glass or steel^{57–59}, or perhaps polymers other than PDMS⁶⁰, may both solve this problem and allow reactions at high temperatures and pressures, but the fabrication of devices with any of these materials is more difficult than with PDMS. Pumping and valving in rigid materials such as steel must be accomplished using entirely different strategies from those used in PDMS.

The development of practical microanalytical systems^{61–64} — especially those for bioanalysis — continues rapidly, although, given its early focus, this area has been slower than expected to reach widespread routine use. Part of the problem is that there is limited technology in two parts of the cycle of analysis: sample preparation and detection. Biological samples — particularly clinical samples (such as blood or faeces), or those obtained by environmental sampling (such as soil) — are often dilute or complicated. Before these samples can be analysed by microfluidic devices, they must be converted to a form that is compatible with the intended analysis, and then introduced into the analytical device. The procedures required to complete these tasks are surprisingly sample-dependent, and not necessarily ‘micro’ in scale. After a sample has been prepared, introduced into the analytical device and processed, it must then be detected. This detection is still commonly accomplished by a microscope located off-chip. Having the microfluidic chip as just a small part of a system in which sample introduction and detection are much more complicated than the chip’s operation may be appropriate in some circumstances, but does detract from the potential advantages of microfluidic devices. Other standard problems, such as pumping, valving and on-chip reagent storage, also require better solutions than those available so far.

The future

What requirements must be fulfilled for microfluidics to become a major new technology? Will it live up to the hopes experienced at its conception? As a field, the problems it faces are those faced by most fields as they develop. The fact that microfluidics has not yet lived up to its early advertising is not a surprise, and the reasons for the rate at which it has developed are both characteristic of new technologies, and suggestive of areas in which to focus work in the future.

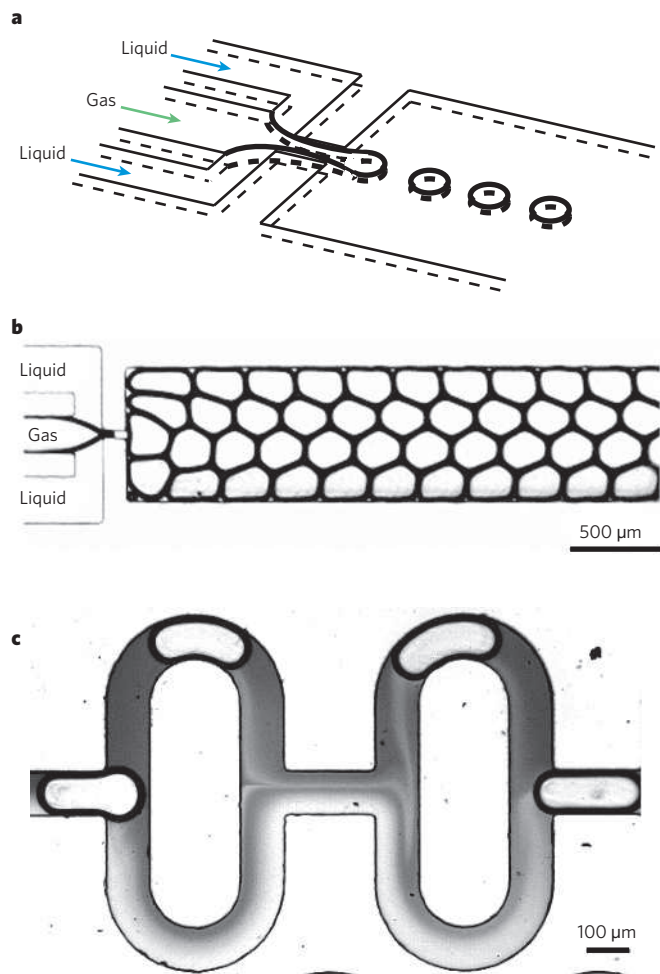


Figure 3 | Creating and using bubbles in microfluidic devices. In a microfluidic ‘flow-focusing’ device, streams of liquid pinch off a gaseous thread to produce bubbles that are remarkably monodisperse³³. The flow rate of the liquid and the pressure applied to the gas control the size of the bubbles, and the frequency with which they form. **a**, A schematic diagram of a flow-focusing system. **b**, An optical micrograph of the production of a foam comprising monodisperse bubbles. **c**, An optical micrograph of bubbles enhancing the mixing of an aqueous solution of ink (black) and an aqueous stream containing a surfactant (white).

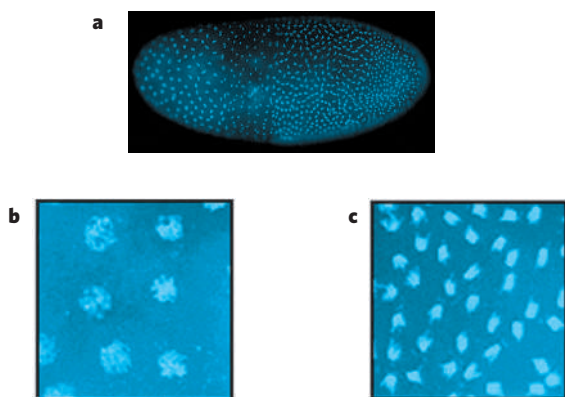


Figure 4 | A new platform for cellular and developmental biology. Laminar flow in microchannels, together with the biocompatibility of PDMS, enable new methods of studying cellular and developmental biology. One system examines the effect of temperature on the development of a fruitfly embryo⁵⁵. The embryo (the large oval in **a**) is immobilized in the middle of a microchannel. Aqueous streams of two different temperatures flow over the halves of the embryo (**b** shows the cold half, **c** the warm half); the differences in the embryo are reflected in the density of cells (marked by the light-blue nuclei). The embryo is ~500 μm wide.

General issues in introducing new technologies

The original hope for microfluidics, and that which still motivates many of us working in the field, is that it will be a practical technology — one widely used in a number of different types of application. I am confident that, ultimately, it will be, but there are several problems that it — in common with other new technologies — must first solve. Above all, it must become successful commercially, rather than remain a field based on proof-of-concept demonstrations and academic papers. The impact of microfluidic systems — as with other tools such as lasers, NMR (nuclear magnetic resonance) spectroscopy and scanning probe microscopes — will only become apparent when everyone is using them. Microfluidics must be able to solve problems for users who are not experts in fluid physics or nanolithography, such as clinicians, cell biologists, police officers or public health officials. For these applications, corporations must take on the task of making appropriate systems widely and inexpensively available.

As with all technology in transition from university laboratories to industry, the question of ‘Who owns what?’ — the problem of intellectual property — is one that must be resolved. For technology with very high value, such as biopharmaceuticals and information-processing systems, issues of intellectual property can usually be resolved by compromising on royalties, up-front payments or equity. However, some of the most interesting applications of microfluidics are those that would demand large volumes but low prices — for example, in public health monitoring, environmental monitoring, and for use in the medical systems of developing economies. In these areas, the historical differences in the valuations placed by universities and industry on university-based technology can become a serious issue: if the university places the value of an invention too high, it is simply not worthwhile to develop a commercial technology from it.

There is also the issue of the so-called ‘first-user premium’. In the introduction of a new technology, the first commercial user of that technology pays a disproportionate share of the costs of its development, and accepts a disproportionate share of the risk for that development. If the application of such a development is a very appealing — if it is of potentially high value (the ‘killer application’, or ‘killer app’) — these costs and risks are more acceptable. The high-value killer app for microfluidics has not yet emerged, although markets in research biology are certainly developing.

High-value applications

There are, in principle, high-value applications for microfluidic systems, although developing these applications requires innovations in both

microfluidics and in biomedicine; doing two things at once is always difficult. The development of new types of bioassay for monitoring patient response to therapy is one such application; development of assays for home testing, or for use in doctors’ offices at early stages of disease (early detection of ‘biomarkers’), is a second. Both are plausible developments in biomedicine, but will require both an understanding of biomarkers of disease and microfluidic systems that are highly developed. In the future, it is certainly possible that healthcare will move from treating to anticipating disease. Widespread, sensitive, frequent screening or testing will be a necessity for such anticipatory healthcare, and microfluidic systems are the most plausible technology for such testing.

Tools for the pharmaceutical industry

The pharmaceutical industry is technically sophisticated, and capable, in principle, of adopting sophisticated new technologies. The industry is also suffering from a crisis in productivity, and desperately needs new tools to guide the development of new drugs — especially to help predict the behaviour of potential new drugs in humans from performance in animals and cells. Some analytical applications of microfluidic systems in the production and use of biopharmaceuticals seem straightforward (for example, analytical systems to monitor and optimize the production of protein drugs such as therapeutic antibodies); others (such as assays based on primary human cells that could predict performance in human clinical trials) are technically more complicated, but also feasible, at least in some instances. In either case, the assays must package microsystems (almost certainly microfluidic systems) in a highly reproducible and easily manipulated format that could be used routinely by technicians.

Research

The introduction and development of new technologies is often facilitated by large, relatively cost-insensitive uses in research: equipment for processing and analysing DNA and RNA are recent examples. The development of new microfluidic tools for genomics, proteomics and metabolomics is proceeding rapidly in research laboratories, and will provide a stimulus for large-scale production.

Large-volume microanalytical tools

Among the most interesting and important of the potential applications of microfluidic systems are those toward which it was originally targeted: biomedical and related applications requiring small amounts of sample, routine operation by untrained personnel, and low cost (Fig. 5).

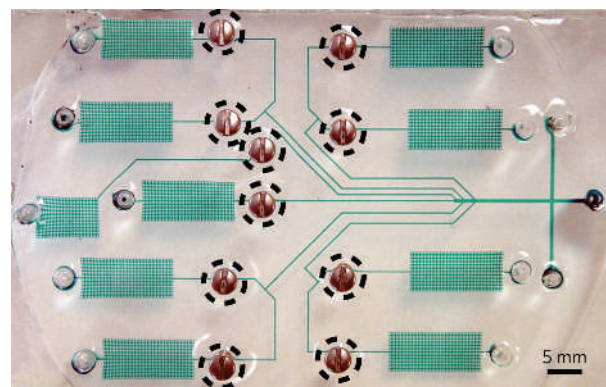


Figure 5 | A simple, inexpensive microfluidic diagnostic device.

Components of microfluidic devices can be designed to be inexpensive and easy to operate. This device⁷ performs sandwich immunoassays — tests that are used widely in medicine and biological research. The screws in this system (marked with dashed circles) act as simple, manually operated valves. Green-dyed water marks the channels. Low-cost, portable, easy-to-operate microfluidic devices such as this one may find applications in resource-poor environments. (Image adapted, with permission, from ref. 7.)

There is an appealing commonality in a number of these applications, and the volumes of appropriate analyses could, in principle, be very large (hundreds of millions of tests per year). This group of applications would include healthcare delivery and monitoring in developing economies, home healthcare and use in doctors' offices in developed economies, uses in homeland security and counterterrorism, use by first responders (police, paramedics and fire departments), applications in veterinary medicine, and incorporation into environmental and food-safety monitoring. Diagnostic systems for developing economies will require low-cost, adaptable microfluidic technology for its success; this rapidly developing field is described in this issue by Yager *et al.* (see page 412).

These applications suffer from the problem of chicken and egg: the volume of use will only be large if the cost of the analysis is low and the state of development of the assay is high; and the cost will only be low if the volume is large.

New science and technology

The development of microfluidics has just begun. A number of factors suggest that there are many early-stage applications of microsystems containing fluids, including the exploration of fluidic optics and cells, the development of new types of organic synthesis in small-channel systems, the continuing development of technologies based on large arrays of detectors and on high-throughput screening, the fabrication of microrobotic systems using hydraulic systems based on microfluidics, other fluidic versions of MEMS, and work on biomimetic systems with microfluidic components. The extension of microfluidic systems into nanofluidics — in which the dimensions of the channels and the thickness of the layer of structured fluid at the walls of the device become comparable — will make possible the exploration of the properties of near-surface water, and of ion and electrolyte transport at this interface. The biocompatibility of PDMS suggests that it might ultimately be possible to embed microfluidic devices *in vivo* for certain types of biomedically relevant analysis. Single-cell and single-molecule analysis require technologies that can work with small volumes of sample, which might allow the testing of fundamental assumptions of cell biology and molecular chemistry and biology.

Design and manufacturing systems for microfluidic devices

An important aspect of the commercial development of microfluidics — crucial to many of these applications — is the development of the technology for manufacturing microfluidic devices. Ultimately, there will probably be several such technologies, but in the early stages the definition of a single set of materials and processes needed to convert laboratory demonstrations into working commercial devices is an important step. Should devices be developed in Mylar, or PDMS, or polycarbonate? What will be the specifications for user interfaces? How important will very-large-volume technologies, such as roll-to-roll processing, be? And what about technologies for sealing and packaging?

Conclusion

So, what next for microfluidics? It is both a science and a technology. It offers great — perhaps even revolutionary — new capabilities for the future. It is also in its infancy, and a great deal of work needs to be done before it can be claimed to be more than an active field of academic research. However, the fundamentals of the field are very strong: much of the world's technology requires the manipulation of fluids, and extending those manipulations to small volumes, with precise dynamic control over concentrations, while discovering and exploiting new phenomena occurring in fluids at the microscale level, must, ultimately, be very important. ■

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