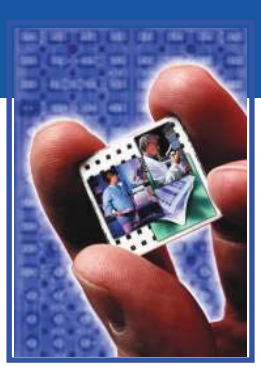

Lab-on-a-Chip: A Revolution in Biological and Medical Sciences

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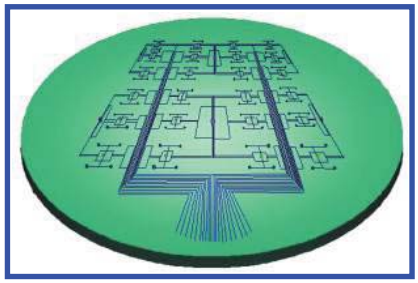


A look at some of the basic concepts and novel components used to construct prototype devices.

Over the past decade, miniaturization of analytical techniques has become a dominant trend in research. This trend encompasses various fields, from laboratories interested in creating novel microfabricated structures to application laboratories focused on specific uses. The early involvement of industry, anticipating the creation of a new industrial sector based on miniaturized analytical systems, reinforced this trend. This synergy of academia and industry spawned a rapid expansion toward practical applications.

Research into miniaturization is primarily driven by the need to reduce costs by reducing the consumption of expensive reagents and by increasing throughput and automation. For example, most are aware of the increasing cost of health care, driven in part by the cost of implementing the latest diagnostic assays. These assays, which are usually performed in microtiter plates that consume hundreds of microliters of reagents, would benefit from the use of microfabricated arrays of nanoliter volume vials. By reducing reagent consumption by a factor of 10^3–10^4, these devices could provide dramatic savings for the repetitive assays often performed in diagnostic laboratories.

Good idea, but how?

Although the idea of miniaturizing analytical systems has been around for years, the technology to do so was not available until the development of photolithography for producing integrated circuits—if photolithography could create paths and control elements for electrons, it could also produce components for the control and mobilization of fluids (*1–6*). This realization spurred a flood of applications. In the same way that integrated circuits allowed for the miniaturization of computers from the size of a room to the size of a notebook, miniaturization has the potential to shrink a room full of instruments into a compact lab-on-a-chip (*7*).

Many researchers greeted the revolutionary idea of a lab-on-a-chip with skepticism, primarily because of the unavailability of microfabricated components. At that time, only channels and reservoirs could be prepared by photolithography, and the devices relied solely on electroosmotic pumping to move liquids. Over the years, new microfluidic components such as valves, pressure systems, metering systems, reaction chambers, and detection systems have allowed the evolution from simple systems to prototypes of the lab-on-a-chip (*1, 3, 8, 9*).

This report presents basic concepts of microfluidics, novel components used to construct prototype lab-on-a-chip devices, and applications in genomics. Reviews of the use of high-throughput array devices in genomics are available (*4, 8, 10*); therefore, we will focus on microfluidic devices that perform multiple steps such as DNA amplification, clean up, separation, and detection. On a broader scale, some examples will be taken from techniques that not only make analysis faster and less expensive but also

create entirely new types of experiments that are impossible with large-scale instruments.

Fundamentals and novel building blocks

The first microfluidic devices were fabricated with photolithography on glass or silicon wafers and then used for electroosmotic pumping and electrophoretic separations. The simplicity of electrophoretic separations and the possibility of performing massively parallel separations attracted considerable attention. Applying a potential across the electrolyte-filled channel generates electroosmotic pumping, as long as the channel walls possess a fixed charge. The electroosmotic flow velocity (ν_{eo}) is given by

$$\nu_{eo} = \frac{\varepsilon\zeta}{4\pi\eta} E \qquad (1)$$

in which ε is the solution's dielectric constant, ζ is the potential arising from the charge on the channel wall, η is the solution viscosity, and *E* is the electric field in V/cm (*11*). Electroosmotic pumping is unique in that its direction can be controlled by simply applying the potential between specific points (Figure 1a), as opposed to pressure-driven flow, which requires valves to control the flow direction. Changing the applied potential, or the pH of the solution that affects the ζ near the channel wall, controls the flow velocity. Furthermore, for charged analytes, electroosmotic pumping is accompanied by electrophoretic separation, the separation of analytes based on the ratio of their charge to hydrated radius

$$\nu_{ep} = \frac{\frac{5}{3}q}{\pi r\eta} \qquad (2)$$

in which ν_{ep} is the electrophoretic velocity of the analyte, *q* is its charge, *r* is its hydrated radius, and η is the solution viscosity. The net velocity of an analyte is the sum of its electrophoretic velocity and the velocity due to electroosmosis, $\nu_{ep} + \nu_{eo}$. Given the lack of reliable microfabricated valves, electroosmotic pumping and electrophoretic separation were the obvious choices for early microfluidic development.

Unfortunately, electroosmotic pumping is not foolproof. When several interconnected channels are required for sample processing, phenomena such as viscous drag make it difficult to prevent electroosmotic pumping in one channel from drawing fluid from other channels. Prevention of "liquid cross-talk" requires careful design, often aided by impedance modeling and active voltage control at several points on the device (*12*). In addition, electroosmosis is not compatible with high-ionic-strength buffers or with sample components, such as basic proteins that adsorb strongly to the anionic walls of microfabricated channels.

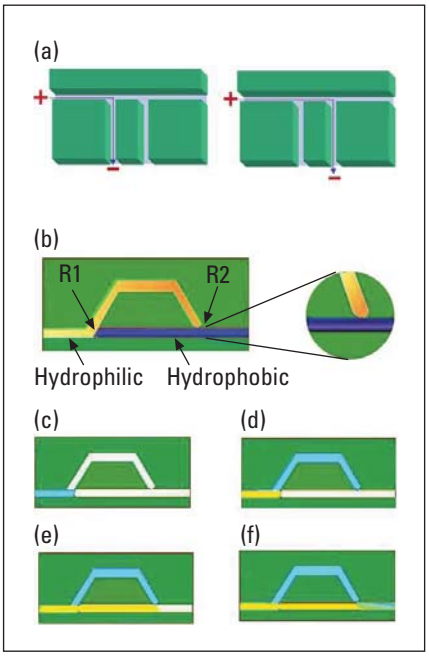


FIGURE 1. Generation and control of electroosmotic flow on microfabricated devices.

(a) The potential is applied between specific points on a microfabricated device to control the direction of flow. No valves are required. (b) R1 and R2 are restrictions. Mixing, based on hydrophobic (purple) and hydrophilic (yellow/orange) channels. (c) Two aqueous fluids (blue and yellow) are being mixed. The fluid flows to the intersection of a hydrophilic channel and a hydrophobic channel with a restriction R1. (d) The fluid prefers to flow into the hydrophilic channel until it reaches R2. Note that R2 is narrower than R1. (e) As the pressure increases, the fluid breaks through R1 and begins to fill the hydrophobic section. (f) Upon reaching R2, the contact between the two fluids breaks the surface tension at R2 and the fluids mix and continue to flow.

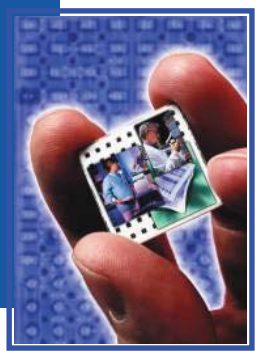
The drawbacks of electroosmosis are driving the search for alternative methods to mobilize, stop, mix, and meter fluids. Intuitively, replacing electroosmotic pumping with microfabricated valves and pressure-driven flow would seem to be the answer; however, the technical challenges of fabricating a leak-proof valve that is small enough to be incorporated into microfabricated channels have yet to be overcome. The interaction between an aqueous solution and hydrophobic patches is a technically simpler way to control fluid movement. The combination of hydrophilic and hydrophobic patches can be used to construct passive valves and mixing chambers for pressure-driven systems (Figure 1b) (*13*).

Another advantage of moving away from electroosmotic pumping is an increased flexibility in materials and fabrication methods. Fabrication methods such as injection molding, hot embossing, and laminar flow patterning are less expensive and faster than photolithography, making these methods more suitable for rapid prototyping (*14*). Investigations of alternative materials that do not have a fixed surface charge, and consequently do not support electroosmotic pumping, are leading to novel approaches for fluid movement such as laminar flow, which is the smooth flow of liquids without the turbulence that generally occurs at low velocities. As the velocity of the fluid increases, its inertia overcomes the frictional force of the fluid, and turbulence occurs.

Laminar flow occurs at Reynolds numbers (Re) below ~2000

$$\mathrm{Re} = \upsilon\rho l/\eta \qquad (3)$$

in which υ is the velocity, ρ is the density, η is the viscos-



ity, and l is the channel diameter. Contrary to macroscale devices, laminar flow is the norm in microfabricated devices because of their narrow channel diameters and the low velocity required to move fluids across their short channels in a reasonable time. Laminar flow enables individual streams of fluid to flow separately without a physical barrier between them. Mixing between the streams occurs only through diffusion, and reactions can occur at the interfaces.

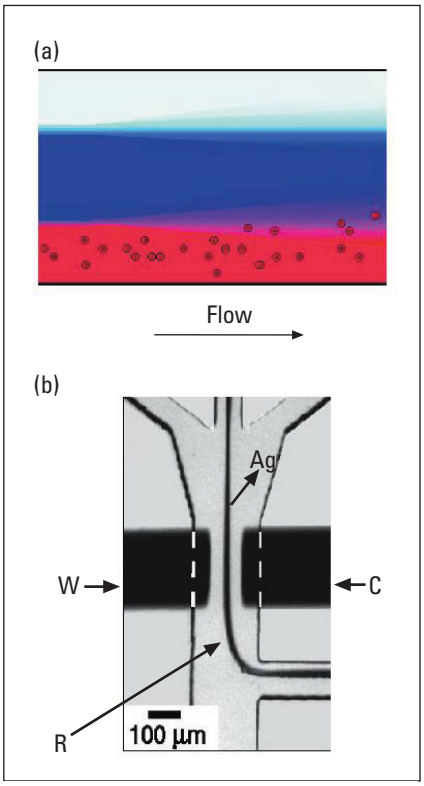


FIGURE 2. Fluorometric sensor based on laminar flow.

(a) An indicator solution (purple) is sandwiched between sample (red) and control (white) solutions. The reaction at the control–indicator interface serves as an internal standard, while the reaction at the sample–indicator interface provides the analyte signal. The circles represent large particles in the sample, such as red blood cells. These large particles diffuse slowly and therefore do not interfere with the measurement process. (b) A three-electrode microfluidics chip fabricated, in part, through laminar flow patterning. The working (W) and counter (C) electrodes were initially one continuous band of gold. The electrodes were formed by laminar flow through the channel of a gold etching compound sandwiched between two streams of water. The silver chloride reference electrode was formed by laminar flow of a two-component electroless silver-plating solution, so that the electrode formed at the interface of the two solutions. Subsequent treatment of the silver electrode with HCl formed AgCl on the electrode surface. (Adapted with permission from Ref. 14.)

Microfabricated sensors with a built-in internal standard can be constructed on the basis of laminar flow (*15*). In macro instruments, internal standards must be chosen carefully; they must not react with the analyte or interfere with measuring the analyte's signal. In the microfabricated device, the spatial separation of the internal standard and the sample by the indicator solution (Figure 2a) remove this restriction. This spatial separation of fluids also can be exploited as a fabrication technique; well-placed streams of the etching compound can be used to construct structures within microfabricated channels (Figure 2b). Undoubtedly, other novel applications of laminar flow-based analysis and fabrication are imminent.

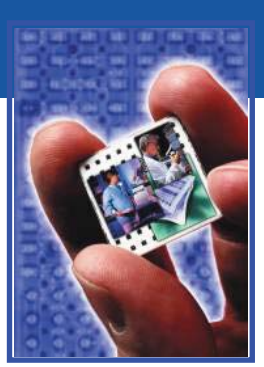
These novel approaches demonstrate that miniaturization is not just about shrinking current technology but involves opening new windows of opportunity for novel analytical systems. Miniaturization enables the use of physical processes, such as diffusional mixing, that are impractical in large instruments. Miniaturization also opens the door for placing complete analytical systems in hostile or remote environments. Events during the 1991 Gulf War dramatically illustrated the need for stand-alone, early-warning systems that can detect biological warfare agents. The key to the success of lab-on-a-chip systems does not lie solely in the development of novel microfabricated components but also in demonstrating that these systems offer novel capabilities and improved performance over current technologies. This demonstration has been achieved in the case of genomics.

The information contained in a gene (DNA) is transcribed into a message (mRNA) that is then translated and processed into a functional protein. At each step, transfer mechanisms qualitatively and quantitatively regulate the flow of information. Disturbances in this flow of information are often the cause of disease. These disturbances may be caused by genetic diseases, random mutations, environmentally caused mutations, or infectious agents. Understanding the flow of information in these processes is often the first step in directed approaches to finding cures for many diseases. However, the enormous amount of information involved in these processes prevents the application of conventional analytical techniques. Recently, large-scale approaches have been developed to rapidly study the information derived from a genome, defined as the complete set of genetic material of an organism. These approaches fall under the genomics umbrella.

Microfluidics in the context of genomics

The field of genomics has grown tremendously in recent years, in part because of the immense efforts of sequencing projects such as the Human Genome Project. Completed projects include the yeast genome (*16*) and the genome of *Borrelia burgdorferi,* the human Lyme disease pathogen (*17*). At the outset of the Human Genome Project, the current technology was not up to the task of sequencing such a large genome within a reasonable period and at a reasonable cost. The project moved forward with the hope that novel technologies and the improvement of standard technologies would soon accelerate the process.

The obvious first step was miniaturization of the standard approach to DNA sequencing, which typically uses a slab of polyacrylamide gel sandwiched between glass plates to separate DNA fragments. Miniaturization was achieved by replacing the gel slab with a gel-filled capillary (*18, 19*). Capillaries, with their relatively high surface-to-volume ratios, dissipate heat efficiently and can be run at higher voltages than their slab counterparts, resulting in increased speed. The small dimensions of the capillaries, coupled



with sensitive laser-induced fluorescence detection systems, decreased the required sample size by a few orders of magnitude. Capillary gel electrophoresis (CGE) is now a mature technique, and hundreds of multiple-capillary instruments are used at large-scale sequencing centers.

At the same time that researchers were racing to build multiplexed CGE instruments, microfabrication laboratories were already developing the next generation of sequencing machines. Microfabrication technology can go beyond CGE systems by combining separation channels with reaction chambers to perform PCR and sample cleanup, steps that currently require many instruments and considerable labor. These integrated systems could be used for high-throughput and parallel separation of double-stranded DNA, PCR products, and eventually DNA sequencing samples.

In 1994, the first single-lane microfabricated devices for the analysis of DNA restriction fragments (*20, 21*) were demonstrated, and later for DNA sequencing (*22, 23*). The devices were produced by standard photolithography patterning and etching of reservoirs and channels on a piece of glass. A second piece of glass with pre-drilled access holes to the reservoirs was bonded to the top to create a device with sealed channels and accessible reservoirs. Double-stranded DNA fragments (or a DNA sequencing sample) were pipetted into a reservoir, injected into the separation channel, separated by gel electrophoresis, and detected by laser-induced fluorescence. These initial demonstrations were an important first step; however, the full potential of microfabrication technology was yet to be exploited.

Multiplexing on a microfabricated device

Multiplexing on microfabricated systems allows for the simultaneous analysis of multiple samples or the application of a battery of analytical techniques to a single sample. Since 1994, multiplex systems with 12–96 different sample inlets have been developed (*24, 25*). Figure 3a illustrates a 96-sample device developed for rapid analysis of PCR products. In this design, two sample reservoirs share the same matrix-filled separation channel and common buffer reservoirs. PCR products are alternately injected and separated in the common separation channel. A laser-induced fluorescence detector scans across the array of 48 channels and detects the separated DNA fragments.

Such high-throughput systems can be used for rapid screening of genetic defects and rapid DNA sequencing. For example, hemochromatosis is a condition that causes the body to absorb and store excessive amounts of iron, often damaging the liver, pancreas, or heart. Despite being a common disorder that affects 1 in 250 people, many cases go undiagnosed because the cost of widespread genetic screening for this disease is prohibitive. Furthermore, many patients are asymptomatic even when at an advanced stage of the disease. Simpson et al. (*25*) demonstrated the feasibility of high-throughput population screening for the C282Y mutation in the HFE gene (cysteine at position 282 is replaced by tyrosine in the mutated protein) that leads to hereditary hemochromatosis. PCR amplification of the gene and fragmentation of the DNA produced samples with characteristic patterns of DNA fragments. Once purified, the samples were installed in the reservoirs of a 96-sample device. Samples from 48 reservoirs were simultaneously injected into the separation channels and separated according to their size by the application of an electric field along the channel. This process was repeated for the other 48 samples. The resulting patterns of DNA fragments correctly diagnosed each patient as normal or as a carrier of the defective gene (Figure 3b).

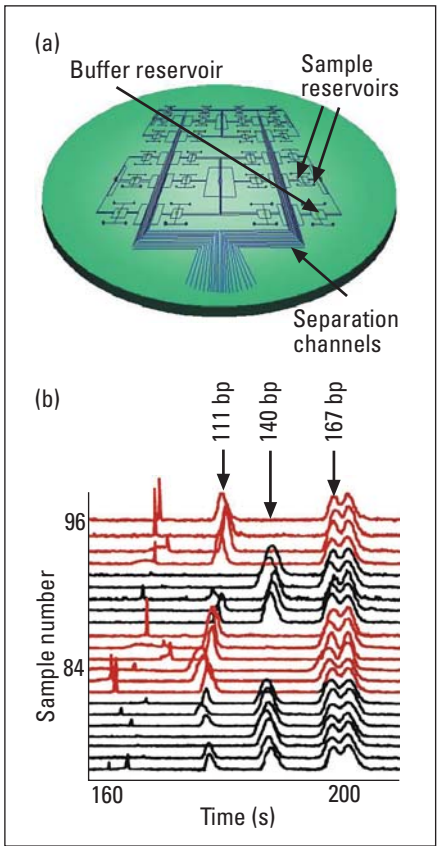
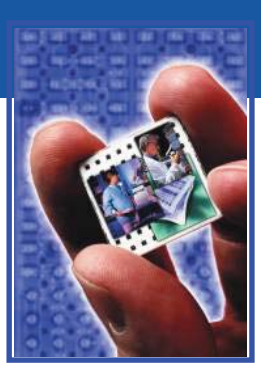


FIGURE 3. Diagram of a 96-sample device for DNA analysis.

(a) Reservoirs and channels are connected so that 48 DNA samples can be simultaneously separated by gel electrophoresis in 48 channels. (b) Electropherograms for some HFE samples. Individuals likely to have hemochromatosis exhibit two DNA fragments at 140 and 167 base pairs (bp) while individuals less likely to have this disease would exhibit either two (111 bp and 167 bp) or three (111 bp, 140 bp, and 167 bp) DNA fragments. (Adapted with permission from Ref. 25.)

Integration

True lab-on-a-chip devices offer the possibility of reducing cost by integrating processes that would otherwise require a suite of instruments and several manual manipulations in which human error and contamination can be introduced (*8, 26*). For example, a system that demonstrates the potential of integration was constructed for the analysis of nanoliters of DNA (*9*). The device is capable of DNA amplification, or digestion, and labeling and separation of the resulting products. This compact system (47 mm long, 5 mm wide, and 1 mm high) incorporates fluidics, pressure mobilization, controlled-temperature reaction chambers, sensors, gel elec-



trophoresis, and a fluorescence diode detector in a single unit.

In a typical experiment, DNA and reagents are introduced into two injection ports (Figure 4a). Sample and reagent (120 nL each) are metered, mobilized by pressure, mixed, and introduced into a reaction chamber (Figure 4b). Upon completion of the reaction, the products are mixed with a fluorescent dye and introduced into the gel electrophoresis section (Figure 4c). This narrow sample zone of DNA is electrokinetically injected and separated in <2 mm of gel. A diode detector incorporated in the device collects the fluorescence emitted by the analytes as they cross a beam of light provided by a pulsed light-emitting diode. This is one of the first systems reported that approaches a fully integrated lab-on-a-chip for identifying DNA. The only components that are not integrated on the device are the excitation source, pressure source, and control circuitry.

Figure 4d is the separation obtained on the device for a DNA ladder. The device was also used to generate and process PCR products. Each device costs $6 to produce by using low-throughput photolithography (*9*). Large-scale production of this system would decrease the cost, enabling the generation of a disposable version for diagnostic purposes.

Microfluidics in the post-genome era

The next generation of microfabricated devices will likely use novel materials and fabrication processes. This point is not to say that standard microfabrication based on photolithography on glass or silicon wafers is becoming obsolete. On the contrary, elegant prototype devices such as a drug-release microchip for in vivo drug delivery (*27*) and microfabricated chromatography columns (*28*) demonstrate the evolution of photolithography. In addition, alternative fabrication methods often require photolithography for the production of the mold or master. The most successful lab-on-a-chip systems will be fabricated by a combination of photolithography and novel fabrication methods.

Genomics-based diagnostics will probably remain the major use of these new lab-on-a-chip systems. However, with the end of several high-profile genomics projects in sight, the application of microfluidic technologies to other classes of biological molecules is gaining attention. For example, the terms transcriptome, proteome, and metabolome have already been coined for the large-scale study of RNA, proteins, and metabolites, respectively.

Proteomic studies, in which proteins are identified by MS analysis of enzymatically produced peptide fragments, are expensive and labor-intensive. An automated microfluidic system coupled with an electrospray ionization mass spectrometer has been developed for the unattended, multiplexed, and automated identification of protein samples isolated from yeast (*29*). This system consists of nine reservoirs connected via channels to a transfer capillary that leads to the mass spectrometer.

These new lab-on-a-chip systems can be used to identify large numbers of potential drug targets (typically DNA, proteins, or metabolites). Thus, the bottleneck in drug discovery will be shifting from target discovery to synthesis and screening of drugs against a chosen target. Lab-on-a-chip systems for the synthesis of combinatorial libraries are being developed to address this extremely expensive and labor-intensive bottleneck (*30, 31*).

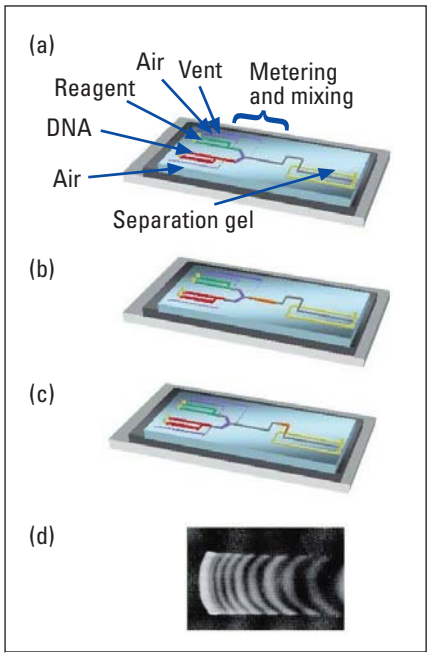


FIGURE 4. Lab-on-a-chip system for processing and analysis of 120 nL DNA.

Red is the DNA-filled channel; green is the reagent-filled channel; purple represents hydrophobic patches; gray is the air-filled channel; orange is the reaction product; and yellow is the gel-filled channel. (a) Defined volumes of DNA and reagent are measured and mixed and (b) introduced into a reaction chamber for controlled DNA amplification or digestion. (c) The products are then mobilized to a separation unit, injected on a gel, and separated by gel electrophoresis. (d) Analysis of a 50-bp DNA ladder that was separated in 2 mm of gel on the device. The band on the right side is the 350-bp band, and the remaining bands are between 400 bp and 800 bp. (Adapted with permission from Ref. 9.)

Although stimulating developments and applications of microfluidics have been reported, some serious questions still need to be addressed. First and foremost, despite the considerable publicity generated by the research community and by the influx of venture capital, microfluidics is still in the development stage.

The development of analytical techniques is a three-phase process. In the first phase, a proof of principle is established by using well-characterized standards. This phase is well under way. In the second phase, the robustness of the techniques must be demonstrated with real samples. This phase is often a major stumbling block, and the complexity of real samples often magnifies any flaws in the technique. Furthermore, laboratories that create novel devices often lack both experience with and access to real samples required for testing their systems. Most microfluidic and lab-on-a-chip systems have not yet crossed this boundary, and more multidisciplinary efforts must be directed toward this second phase of development. In the third phase of development, the technique is converted into a commercialized entity. Only a handful of products are available at this time, and the ma-

jority of companies have good ideas but no robust products. At this early stage, however, it is premature to judge the success of miniaturization by the number of commercial products.

Technical issues also need to be addressed. Sample mobilization techniques other than electroosmotic pumping are required to broaden the field of application because electroosmotic pumping can be unreliable for real samples. A broader range of materials for constructing microfluidic systems should be explored, and more components, such as miniaturized pumps and light sources, must be developed before a true lab-on-a-chip can be realized. Miniaturization can sometimes introduce technical challenges that are not present in the macro world. For example, it became apparent in CGE that the polyacrylamide gel used in slab gel electrophoresis would not work in the miniaturized capillary format. Fortunately, an intense effort resulted in a new gel formulation. Similarly, in microfluidic systems, surface effects become important because of the high surface-to-volume ratio and the low overall surface area. In addition, evaporation is a significant problem when only nanoliters of sample are used. These new challenges may be difficult to overcome.

Most importantly, the research community must acknowledge that the creation of lab-on-a-chip systems will require the wide-scale availability of basic building blocks and access to inexpensive methods for fabricating prototypes. This accessibility is particularly important for academic research groups, which typically lack both the funds and the capability to reinvent the wheel. It may be that the development of lab-on-a-chip systems for widespread use requires a level of funding that can be supported only by industrial research.

The projected market value of lab-on-a-chip technology is $1 billion to $19 billion (*8*). Such a broad range reflects the fact that most systems are still at the development stage. Numerous companies are in the race to secure a share of the market. We have attempted to give the reader a taste of some of the applications of microfabrication technology to genomics and of future applications in the post-genome era. We have described only the tip of the iceberg; numerous groups have produced or are producing novel microfabricated systems not described here. Although the full impact of lab-on-a-chip systems remains to be determined, there is no doubt that microfabrication has arrived as a valuable platform for analytical biochemistry.

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References

(1) Van den Berg, A.; Lammerink, T. S. J. *Top. Curr. Chem.* 1998, *194,* 21–49.

(2) Effenhauser, C. S. *Top. Curr. Chem.* 1998, *194,* 51–82.

(3) Qin, D.; Xia, Y.; Rogers, J. A.; Jackman, R. J.; Zhao, X.-M.; Whitesides, G. M. *Top. Curr. Chem.* 1998, *194,* 1–20.

(4) Ramsay, G. *Nat. Biotechnol.* 1998, *16,* 40–44.

(5) Harrison, D. J.; van den Berg, A., Eds. *Proceedings of the μTAS '98 Workshop;* Kluwer Academic: Dordrecht, 1998.

(6) Mastrangelo, C. H.; Burns, M. A.; Burke, D. T. *Proceedings of the IEEE* 1998, *86,* 1769–1787.

(7) Manz, A.; Graber, N.; Widmer, M. *Sens. Actuators, B* 1990, *1,* 244–248.

(8) Service, R. F. *Science* 1998, *282,* 396–401.

(9) Burns, M. A., et al. *Science* 1998, *282,* 484–487.

(10) *Nature Genetics* 1999, *21 supplement,* 1–60.

(11) Hjerten, S. *Chromatogr. Rev.* 1967, 122–219.

(12) Attiya, S.; Qui, X. C.; Ocvirk, G.; Chiem, N.; Lee, W.; Harrison, D. J. *Proceedings of the μTAS '98 Workshop;* Kluwer Academic: Washington, 1998; 231–234.

(13) McNeely, M. R.; Spute, M. K.; Tusneem, N. A.; Oliphant, A. R. *Microfluidic Devices and Systems II;* Ahn, C. H., Frazier, A. B., Eds.; SPIE: Bellingham, Washington, 1999; pp 210–220.

(14) Kenis, P. J. A.; Ismagilov, R. F.; Whitesides, G. M. *Science* 1999, *285,* 83–85.

(15) Weigl, B. H.; Yager, P. *Science* 1999, *283,* 346–347.

(16) Goffeau, A., et al. *Science* 1996, *274,* 546, 563–567.

(17) Fraser, C. M., et al. *Nature* 1997, *390,* 580–586.

(18) Karger, B. L.; Chu, Y. H.; Foret, F. *Annu. Rev. Biophys. Biomol. Struct.* 1995, *24,* 579–610.

(19) Dovichi, N. J. *Electrophoresis* 1997, *18,* 2393–2399.

(20) Woolley, A. T.; Mathies, R. A. *Proc. Natl. Acad. Sci. U.S.A.* 1994, *91,* 11348–11352.

(21) Effenhauser, C. S.; Paulus, A.; Manz, A.; Widmer, H. M. *Anal. Chem.* 1994, *66,* 2949–2953.

(22) Schmalzing, D.; Adourian, A.; Koutny, L.; Ziaugra, L.; Matsudaira, P.; Ehrlich, D. *Anal. Chem.* 1998, *70,* 2303–2310.

(23) Woolley, A. T.; Mathies, R. A. *Anal. Chem.* 1995, *67,* 3676–3680.

(24) Woolley, A. T.; Sensabaugh, G. F.; Mathies, R. A. *Anal. Chem.* 1997, *69,* 2181–2186.

(25) Simpson, P. C., et al. *Proc. Natl. Acad. Sci. U.S.A.* 1998, *95,* 2256–2261.

(26) Waters, L. C.; Jacobson, S. C.; Kroutchinina, N.; Khandurina, J.; Foote, R. S.; Ramsey, J. M. *Anal. Chem.* 1998, *70,* 159–162.

(27) Santini, Jr., J. T.; Cima, M. J.; Langer, R. *Nature.* 1999, *397,* 335–338.

(28) He, B.; Tait, N.; Regnier, F. *Anal. Chem.* 1998, *70,* 3790–3797.

(29) Figeys, D.; Gygi, S. P.; McKinnon, G.; Aebersold, R. *Anal. Chem.* 1998, *70,* 3728–3734.

(30) Hsieh, F.; Keshishian, H.; Muir, C. *J. Biomol. Screen.* 1998, *3,* 189–198.

(31) McBride, S. E.; Moroney, R. M.; Chiang, W. *Proceedings of the μTAS '98 Workshop;* Kluwer Academic: Dordrecht, 1998; pp 45–48.

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