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TRENDS

Andrew J. de Mello

Miniaturization

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In his now celebrated lecture on the 29th December 1959 Richard Feynman pondered the potential of miniaturization in the physical sciences [1]. His vision, based on known technology, examined the limits set by physical principles and proposed a variety of new nano-tools including the concept of "atom by atom" fabrication. In the intervening decades, many of these predictions have become reality; microelectronic systems have shrunk to sizes close to the molecular level, scanning probe microscopes (e.g. STM and AFM) enable us to image and manipulate individual atoms, and the molecular machinery of living systems is now being more fully understood and harnessed.

Surprisingly, it is only within the last decade that the concepts of miniaturization have been seriously applied to chemical and biological problems. Of particular focus and interest has been the development and application of lab-on-a-chip technology. These microscale analytical instruments employ micromachined features (such as channels, electrodes, reactors, and filters) and are able to manipulate fluid samples with high precision and efficiency. Microfluidic chip devices have been used in a wide variety of applications including nucleic acid separations, protein analysis, process control, small-molecule organic synthesis, DNA amplification, immunoassays, DNA sequencing, and cell manipulations [2, 3]. In a fundamental sense, chip-based analytical systems have been shown to have many advantages over their conventional (larger) analogues. These include improved efficiency with regard to sample size, response times, cost, analytical performance, process control, integration, throughput, and automation.

Much of the pioneering work in microfluidics has focused on the successful transfer of established analytical technologies from conventional to microfluidic (chip-based) formats. In particular, huge leaps in the efficiency and application of separation techniques have been facilitated by miniaturizing column dimensions and creating monolithic fluidic networks on planar substrates. Indeed, a survey of the current literature demonstrates that almost all separation methods (based on electrophoretic or chromatographic partitioning mechanisms) have been successfully transferred to micromachined formats [3].

Small volumes of sample and reagent (pL–nL) are representative of most miniaturized systems. This characteristic has clear advantages associated with cost and analytical throughput, but does pose constraints on appropriate detection methods. Consequently, much research has recently focused on the development of detection techniques that are highly sensitive, universal, miniaturized, and cost-effective. Although the vast majority still utilize fluorescent schemes (because of exceptional sensitivity) other approaches to "on-chip" detection have been introduced. These include electrochemical and electrochemiluminescent methods, absorption, indirect fluorescence, refractive index variation, plasma, and thermal conductivity methods [4]. Although many novel detection methods have been reported for on-chip applications, future studies must focus on improving concentration detection limits and complete integration of the detector with the rest of the analytical system (Fig. 1).

Of notable current interest is the use of microfabricated structures for chemical and biological synthesis. Because of the unique environments afforded within microfluidic networks, a variety of synthetic processes can be performed in continuous flow and batch formats. Increased efficiencies of mixing and separation combined with high rates of thermal and mass transfer make microreactors ideal for processing valuable or hazardous reaction components and improving reaction selectivities (thus yielding "higher quality" products). DNA amplification, combinatorial (and high throughput) chemistry, immuno- and bioassays, and tissue and cell culture are areas which have all recently benefited from advances in microfluidic chip technology [2, 5, 6].

A.J. de Mello (✉)
AstraZeneca/SmithKline Beecham Centre
for Analytical Sciences, Department of Chemistry,
Imperial College of Science, Technology and Medicine,
Exhibition Road, South Kensington, London SW7 2AY, UK
e-mail: a.demello@ic.ac.uk

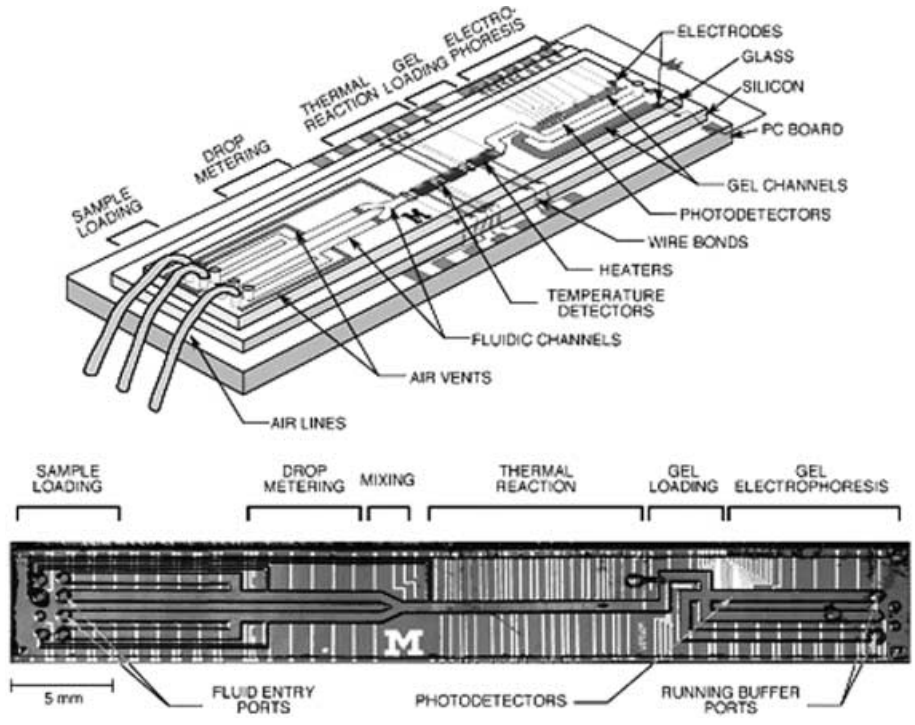

Fig. 1 An integrated analysis system in which DNA and reagent solutions are placed on the device and electronic signals corresponding to genetic information are the primary output. Image taken from Ref. [8]

One of the primary advantages and goals of microfabricating analytical instruments is the large-scale integration of functional components on a single monolithic device. Indeed, the ability to extract the required information from a chemical or biological system almost always involves performing a number of distinct analytical operations. Consequently, a complete device will ideally include all relevant steps in a complete analytical procedure (including sample handling, sample pre-treatment, reaction, analytical separation, analyte detection, and product isolation). Although, this objective is widely recognized few studies have yet embraced the concept of integration fully. Of these the focus has primarily centered on the amplification and analysis of DNA fragments [2, 7, 8]. Future work in this area will need to address integration in a more general sense and solve problems associated with materials compatibility and the handling of real-world samples. It is also likely than many future microfluidic devices will be constructed from polymeric materials (rather than silicon or glass), because of the wide availability of base materials and highly cost-effective fabrication methods (such as injection molding and hot-embossing) [9].

It is fair to say that the envisaged applications of microfluidic analysis chips have undoubtedly expanded well beyond those originally defined in the early nineteen-nineties. The first commercial devices have been introduced to market (see Table 1 in Ref. [3]), and it is almost certain that the base technologies defined over the past decade will have a high future profile in the fields of proteomics, drug discovery, cellomics, clinical diagnostics, genomics, and chemical production [10].

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