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

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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 micro fabricated 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 micro titer plates that consume hundreds of micro liters of reagents, would benefit from the use of micro fabricated arrays of nano liter volume vials. By reducing reagent consumption by a factor of 103 –104 , these devices could provide dramatic savings for the repetitive assays often performed in diagnostic laboratories.

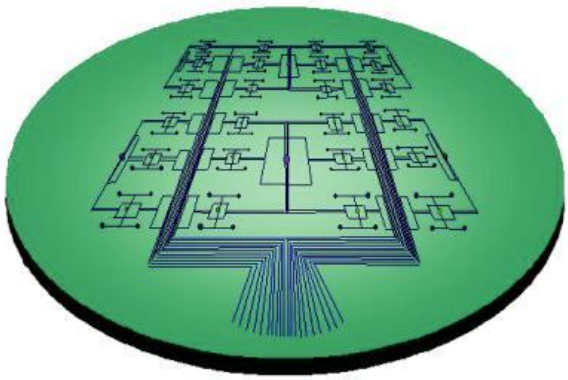
Good idea, but how?

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, Multiplexing on a micro fabricated device Multiplexing on micro fabricated 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

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 labon-a-chip (7). Many researchers greeted the revolutionary idea of a lab-on-a-chip with skepticism, primarily because of the unavailability of micro fabricated components. At that time, only channels and reservoirs could be prepared by photolithography, and the devices relied solely on electro osmotic pumping to move liquids. Over the years, new micro fluidic 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 micro fluidics, novel components used to construct prototype lab-on-achip 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 micro fluidic 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 instrument

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. Multiplexing on a micro fabricated device Multiplexing on micro fabricated 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. Technical issues also need to be addressed. Sample mobilization techniques other than electro osmotic pumping are required to broaden the field of application because electro osmotic pumping can be unreliable for real samples. A broader range of materials for constructing micro fluidic 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 polydactylamide 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 micro fluidic systems, surface effects become important because of the high surface-to-volume ratio and the low overall surface area. In addition, evaporation is a signifycant problem when only nanoliters of sample are used. These new challenges may be difficult to overcome. 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 micro fabrication 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 micro fabricated systems not described here. Although the full impact of lab-on-a-chip systems remains to be determined, there is no doubt that micro fabrication has arrived as a valuable platform for analytical biochemistry.



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