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What Can Chips Technology Offer for Next Century's Chemistry and Life Sciences?

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Abstract. Microfabrication gives access to surfaces of a few micron square, and the volumes of picoliter and femtoliter size. Integration of combinatorial synthesis, analysis speed, and small-volume handling are the main advantages. Examples of experimental results in drug discovery, analytical chemistry, and microbiology exhibit the potential of the chip-microstructure approach.

Andreas Manz graduated from ETH-Zürich and obtained his Ph.D. in 1986 with a thesis on microelectrodes for use as detectors in open-tubular liquid chromatography. He was with *Hitachi Ltd.* in Japan for a postdoc year and then joined *Ciba-Geigy Ltd.* in Basel for analytical research. Since a few months he has taken the *SmithKline Beecham* Chair of Analytical Chemistry at the Imperial College in London.

'The Incredible Shrinking Laboratory' was a recent headline in *Science* [1], when they were referring to some preliminary results of approaches to miniaturized chemical and biochemical analyzers. This overwhelming interpretation of what is happening in some of todays research labs might be a good reason to have a serious look on what has been experimentally proven and what is pure speculation.

Microfabrication techniques have been widely used in the microelectronics industry for integrated circuits, and there is a small number of physical sensors and actuators on the market, like acceleration sensors controlling airbags of automobiles and ink-jet printer heads. However, chemistry and life sciences seem to have remained nearly untouched. Is that really true? What are the future prospects?

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The Technology

Based on the experiences made in electronic chip manufacturing, photolithography is now used for the generation of micron-sized mechanical structures on flat silicon wafers. A photo negative, a so-called mask, is used to expose a photosensitive film to light which transfers the two-dimensional pattern of the mask to the photoresist. Parts of the film can be removed to give access to the substrate. The wafer is now further processed, *e.g.*, etched in solution to obtain micron-deep patterns in the silicon substrate. Other types of processes include film deposition and bonding techniques.

As a result, devices with a basically flat surface can contain cavities, channels, electrodes, windows, bridges, and many more. These features are typically 2 μm to several mm in length and width, and 100 nm to

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100 µm deep or high. The layout in the two dimensions of the flat surface can basically have any shape or complexity of integration, whereas normally one mask defines a specific depth or height. Besides silicon, amorphous glass, quartz, gallium arsenide, and other materials have been used as substrates. Surprisingly enough, only very little has been done in organic polymers to date.

Drug Discovery

Affymax has presented a microchip-based system for the synthesis of linear biopolymers (*Fig. 1a*, [2]). A photochemical reaction is carried out to selectively bind building blocks to small areas on the chip surface. A photomask serves to illuminate a specific area only, which is supposed to react with the building block (*Fig. 1b*). The mask is shifted to a next area, and the process repeated. The result is a surface with different building blocks attached to the substrate surface. Again, to attach a second set of building blocks, the photolithographic process has to be repeated over and over again. Examples of peptides and oligonucleotide libraries have been synthesized and tested using binding assays [2][3]. The repetitive use of the most complicated step, the positioning of the photolithographic mask, for a single use device, as well as the severe limitations to the available set of chemical reactions make this method an academic playground for further research activities.

A different approach has been presented recently by *Nanogen* [4]. The proposed synthesis scheme is similar to the one described above. The definition of binding areas is carried out using electrically adressable areas on the chip (*Fig. 1c*). This allows for one set of fabrication processes for a multi-use device. During the synthesis, no further photolithographic or other manual steps are involved. The addressing of pixels is done by directly applying a low voltage to the respective site on the chip. The choice of synthetic steps, however, is limited as well, but the cost effectiveness may be better as compared to the *Affymax* approach.

Surprisingly enough, no combinatorial chemistry using chips and bulk rections or split-bead techniques have been published.

Analytical

In analytical chemistry, the miniaturization has been an issue for at least the last

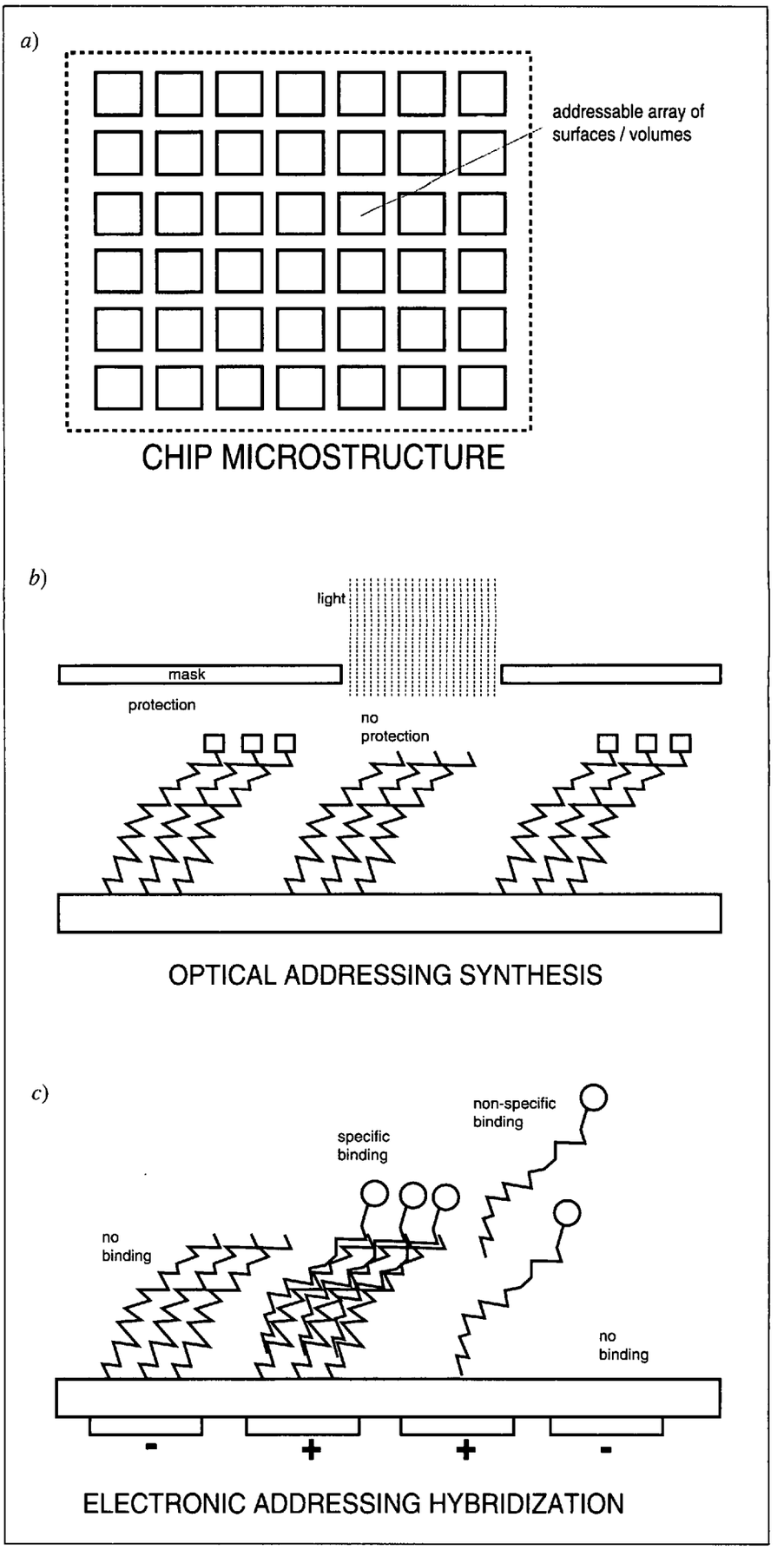

Fig. 1. *Chip-based approaches to drug discovery. a*) Schematic of a chip layout, *b*) lithographic approach to synthesis as presented by *Affymax* [2], and *c*) electronic addressing for controlled binding as presented by *Nanogen* [4].

decade. Portable chromatographs, GC-MS, ion-mobility detectors, and the whole sensor field are just a few examples of this trend. Analytical information is to be obtained *in situ* and possibly in almost real time. This can only be achieved by small instrumentation. In some cases, *e.g.* in liquid chromatography and electrophoresis, micron-sized structures are a must to obtain the separation efficiencies at a high speed [5].

The *Ciba* group has pioneered the field of chip-based separation systems and analyzers. Micromachined glass devices have been used to demonstrate that virtually all separations of small molecules with capillary electrophoresis can be achieved within 10–50 s with a good resolution (*Fig. 2*, [6][7]). Examples of amino-acid and oligonucleotide separations have been given. The amount injected was on the order of 10–100 pL, and the integrated systems would allow even to collect fractions of pure compound [8].

Several other groups have entered the field since, and the range of applications includes precolumn and postcolumn labeling [9], restriction fragmentation of DNA [10], parallel separations [11], continuous separations using free-flow electrophoresis [12] and a cyclic separation mode providing unique resolution [13].

Microsystems have been used for biosensor systems [14], chromatography and flow-injection analysis based on-line analyzers [15]. These devices exhibit extremely low reagent consumption, in some cases a short analysis time and they may be externally small.

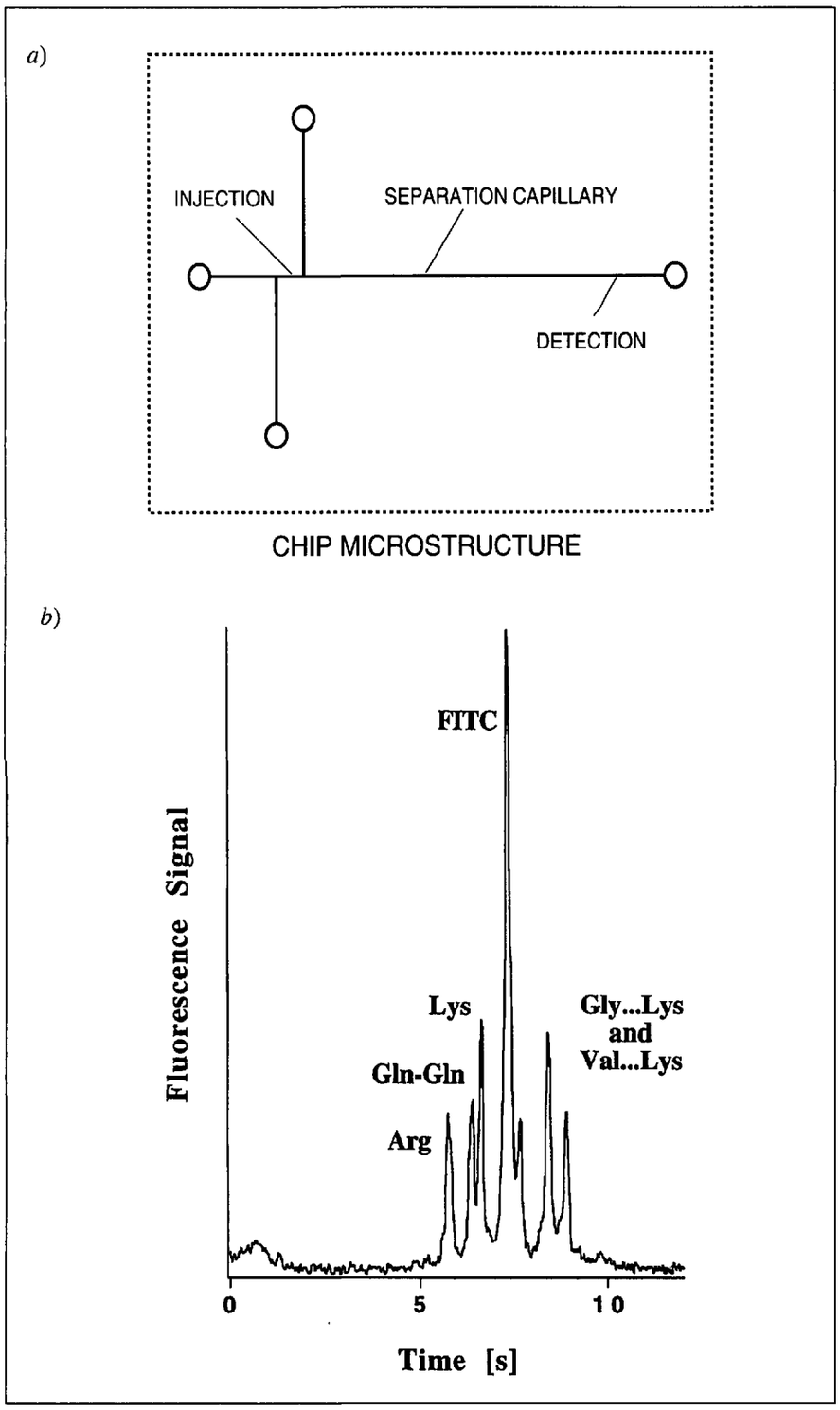

Fig. 2. *Microstructure-based approach to analytical chemistry. a*) Schematic of a capillary electrophoresis chip layout [6] and *b*) a separation of mellitin-tryptic digest obtained using a microstructure.

Microbiology

The availability of micron-sized features on a chip allows for the investigation of small objects such as single biological cells. This has been shown in many examples using conventional technology, *e.g.* microelectrodes for measuring potential, pH, or ion concentrations. Other examples include the liceing and analysis of the contents of single erythrocytes using capillary electrophoresis. What has been done with microstructures?

The *Fromherz* group has presented a number of investigations of single nerve cells, or discrete arrangements thereof, in the last few years [16]. In a typical experiment, a neuron is placed directly over a field effect transistor (*Fig. 3a*), an electronics device that is sensitive to the local change in voltage potental. Using etched channels on similar chips, the growth of neurons can be perfectly controlled. This way, small networks of live neurons can be constructed and tested.

Related to single cells in solution, there is a necessity to control and manipulate them in cavities, or during the transition to channels. The *Fuhr* group has explored the behavior of latex particles and live cells under the influence of high-frequency electric fields (dielectrophoresis). They have successfully managed to trap single cells or a group of cells in electric field cages (*Fig. 3b*, [17]). Individual cells can be spinned around one of its axes, depending on electric field conditions. In channel structures providing arrays of electrodes, the cells can be moved using travelling waves.

Conclusion

At the end, there remains the question: What is it all about?

In general terms, small volumes can be produced and handled, in very many cases, the higher speed of the processes, and the possibility to integrate a large number of identical features into a small surface allow for higher throughput in combinatorial synthesis and analytical applications. This field is still in the research phase, some commercial interest is popping up (combinatorial, bioanalytical), but the advantages are clear in specific areas. The question asked in CHIMIA five years ago 'The technology for the 21st century or just a fashionable craze' [18] has been clearly answered as the above-mentioned components demonstrate. Further developmental work has to be invested by instrument manufacturers to make the devices more user-friendly, not to say fool proof.

At this moment, more than 20 research labs are involved in this topic worldwide. The rapidly growing interest of academia might produce more applications in the upcoming five years. A broad patent socket will be produced within this time. It is definitely worth following what is going on, despite of the fact, that the access to microstructures may be a hurdle. As soon as commercial instruments are available, they may open up a whole new world in terms of speed and throughput. That is exactly what prepares us for the dramatically increasing need for biological and chemical information in next century's life science research.

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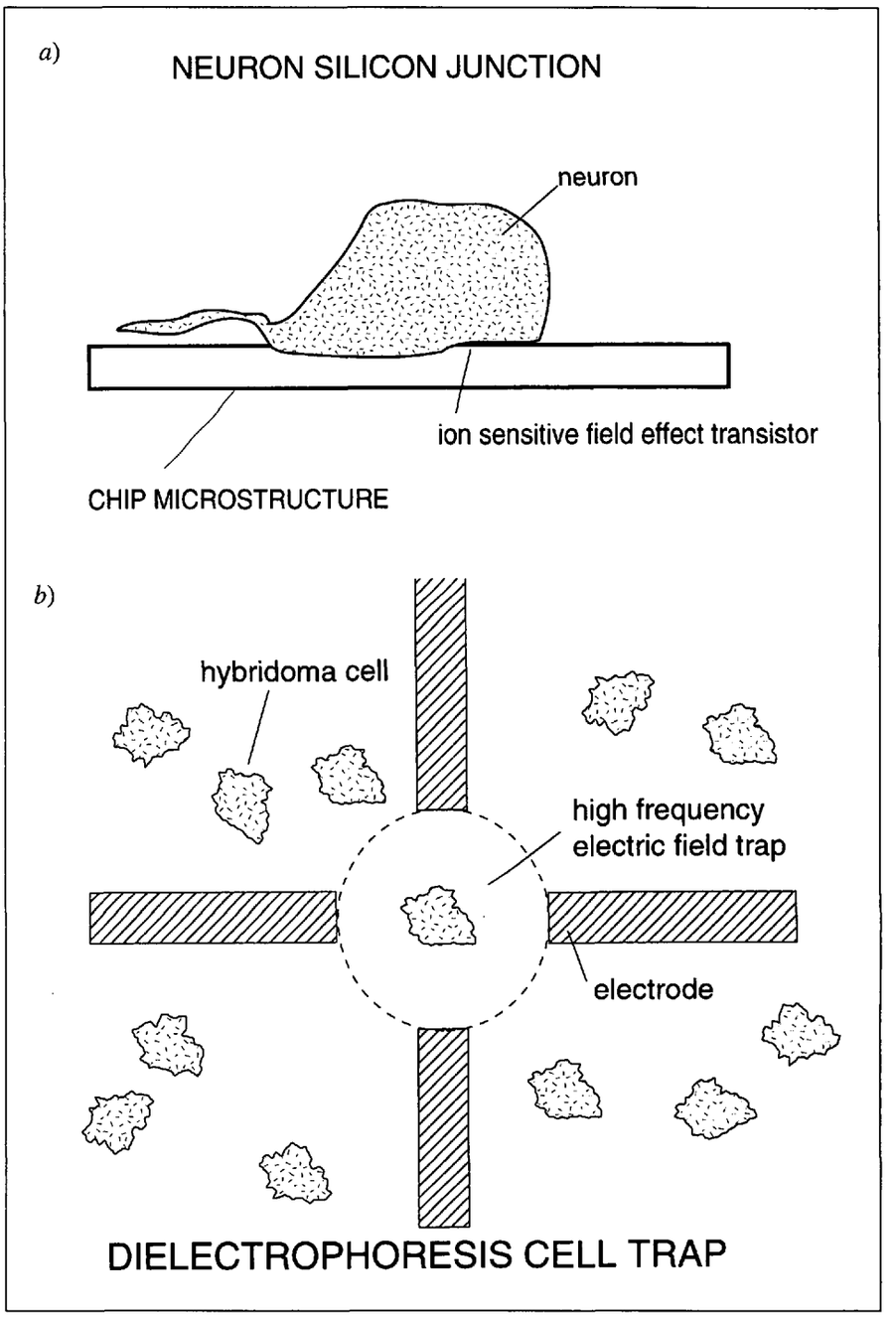

Fig. 3. *Chip-based approaches to microbiology. a)* Schematic of a neuron-silicon junction to observe single cell responses as published by *Fromherz* [16] and *b)* schematic of a cell-trapping experiment using high-frequency electric fields (dielectrophoresis) as published by *Fuhr* [17].

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