Chapter 0

Introduction to Microfluidics

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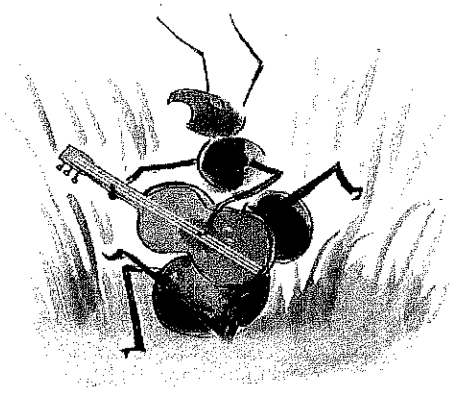

Strange things at the microscale.

Introduction

In recent years, considerable progress has been made in the field of miniaturization. It is now effectively possible to miniaturize all kinds of systems—e.g. mechanical, fluidic, electromechanical, or thermal—down to submicrometric sizes. In the 1980s, these achievements gave rise to a new field known as MEMS (*microelectro-mechanical systems*). Later, in the 1990s, this domain became considerably diversified, with MEMS devices being fabricated for chemical, biological, and biomedical applications. These systems were employing fluid flows operating under unusual and unexplored conditions, which naturally led to the need for the creation of a new discipline—microfluidics[1]—which constitutes the central subject of this book. Microfluidics can be defined as the study of flows that are simple or complex, mono- or multiphasic, which are circulating in artificial microsystems, i.e. systems that are fabricated using new technologies[2]. This description is an engineering definition that is generally accepted and understood, so we will adopt it here.

MEMS and microfluidics

Miniaturization and MEMS gave birth to microfluidics in the 1990s and today still constitute a large portion of this young discipline. MEMS are electromechanical systems whose total size varies between 1 and 300 micrometers. Alhough these numbers are rough limits (there are actually MEMS of submicrometer size and MEMS larger than 300 micrometers), the majority of MEMS devices fabricated today have typical dimensions of this order. A famous example of a MEMS is shown in Fig. 1. This MEMS is a microgear whose size is on the order of a hundred micrometers. It is held by an actual ant who seems to be questioning the usefulness of such an object. This photo, taken by a German research group, is rather striking because it represents the intrusion of a man-made machine into the micrometric world. The entry into micrometric scales is clearly not a new feat, however. Since the invention of the optical microscope

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[1] Microfluidics already existed in the 1960s, but its use was limited to developing the analogous systems of microelectronic circuits, with the electron flux being the analog to the fluid flux.

[2] The new technologies that we consider here involve several techniques, including photolithography, etching, deposition, microwetting, and microimpression, which permit the fabrication of miniaturized systems. These technologies are considered 'new' because they only first appeared in the 1970s.

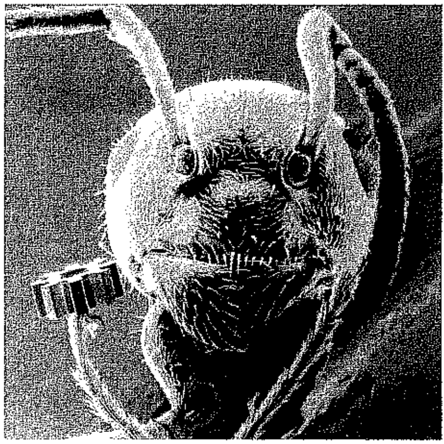

Figure 1 Ant holding a nickel micro-gear, made by LIGA technology (German for 'lithographie, galvanoformung, abformung'). This ant was metallized and placed in a vacuum in order to be photographed by electron microscopy. This image was provided by the Karlsruhe group (Germany).

in the sixteenth century, the micrometric world has been scrutinized in detail. The microscope permitted many scientific discoveries to be made, including the discoveries of protazoa, Brownian motion, and chromosomes, to cite just a few examples. However, it is far more difficult to actually *act* at a micrometric scale, which is precisely what MEMS technology allows us to do; it is thus not a far stretch to imagine that MEMS technology will lead to many technical and scientific discoveries. At the time this text was written, MEMS had essentially been created to make observations and measurements that were difficult to make using traditional methods. Some examples include the proof of the quantum nature of phonons [2], the measurement of fluid-phase chemical kinetics [3], and the characterization of the slip phenomenon in gases [4]. These are all discoveries and technical inventions that had been made possible by MEMS. In certain cases, these advances became large industrial successes such as the usage of MEMS in airbag activation (Fig. 2).

MEMS for airbags, which first appeared in the 1980s, consist of an integrated system on a silicon wafer that is just a few millimeters long, and yet are able to incorporate both electronic components and an electromechanical device capable of detecting physical impact. The detection portion is only a few hundred micrometers large and constitutes the heart of the chip. It is made of two combs, one fixed and the other mobile; the capacitance of these combs varies under the effect of an impact. As we will see in Chapter 1, the miniaturization of the capacitor element allows the creation of a highly sensitive and rapid detector. However, the industrial success of MEMS is not solely due to the improvement in sensor response and sensitivity, but also due to the ability to *integrate* detection, information analysis, and signal processing all on one single chip. Just as with integrated circuits, this chip can, in principle, be easily reproduced by the millions. The cost, which is so critical in the field of automobile manufacturing, becomes very advantageous as compared to traditional systems. For this reason, all modern automobiles now use MEMS for their airbags, and tens of millions of these devices are produced each year.

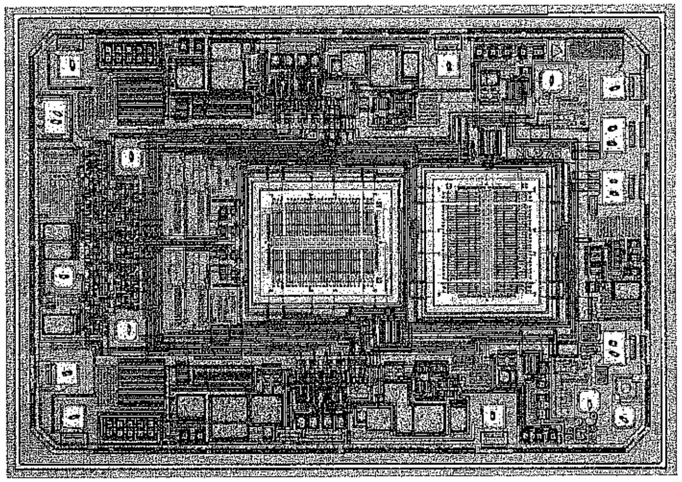

Figure 2 Device for the detection and command of airbag activation, based on MEMS technology. (Courtesy of Analog Devices, Inc. All rights reserved)

A second major industrial success came in the 1990s with the advent of MEMS usage for inkjet printer heads (Fig. 3).

The printer head consists of a portion microfabricated from silicon that serves as an ink reservoir, a heating element to put the fluid in motion, and a nozzle. The fluid is pushed through the nozzle due to the formation of a bubble near the heating element; this bubble is generated by the vaporization of the ink. The bubble propels the fluid towards the exterior, forming a jet that destabilizes under the action of capillary forces. Droplets created in this way have a size similar to that of the nozzle diameter, which is generally on the order of 50 μm. These droplets strike the paper, forming the basic spot. Smaller satellite droplets also exist, and form a sort of procession accompanying the principal drop (Fig. 3 right).

Today, the volume of MEMS activity is estimated to be worth between several billion and several tens of billions of dollars[3]. In the United States, there was on

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[3] Due to the fluctuations of worldwide activity.

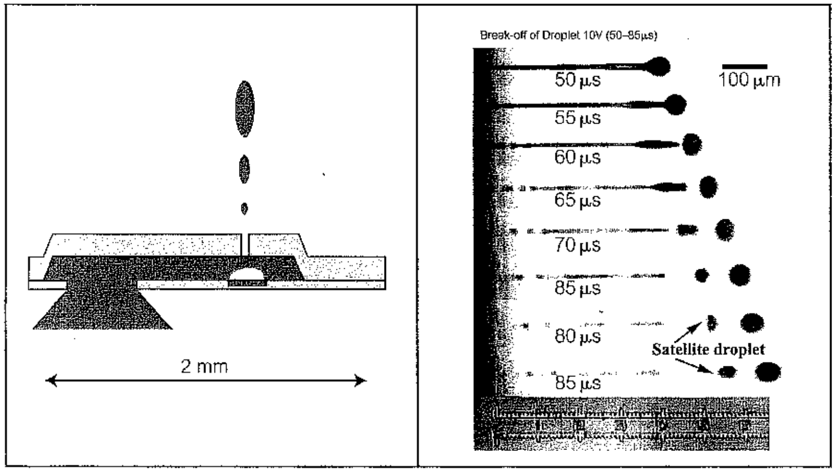

Figure 3 Figure showing a printer head of a commercial inkjet made using MEMS technology (left) and the visualization of droplets of ink projected onto a target (right). Satellite droplets, which affect the printing precision, are discernable [5].

average 1.6 MEMS per person in 2000, and this number is estimated at 4 MEMS per person now. Today, there are numerous industries involved in MEMS, as shown in Table 1, supplied by DARPA (defense)[6].

Note from the table that there are both new industries (ones that have appeared in just the last few years) as well as more traditional industries who use MEMS in a significant way in their sector of activity, or who profit from developing novel ventures by taking advantage of the potential of this young technology.

The history of the field of MEMS is an interesting one. The year 1959 is often considered to be the beginning of the history of micro- and nanotechnologies. In December of that year a visionary speech was given by Richard P. Feynman during the APS (American Physical Society) meeting at Caltech. This speech was entitled *There is plenty of room at the bottom.* The beginning of the speech went as follows:

> I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle. This field is not quite the same as the others in that it will not tell us much of fundamental physics (in the sense of, "What are the strange particles?") but it is more like solid-state physics in the sense that it might tell us much of great interest about the strange phenomena that occur in complex situations. Furthermore, a point that is most important is that it would have an enormous number of technical applications.

Table 1 Companies involved in MEMS technology in the United States (table created by DARPA)

Technological field	Typical devices/ Applications	Companies	Market 2003 ($ Millions)
Inertial measurement	accelerometers, rate sensors, vibration detectors	TI,Sarcos, Boeing, ADI, EG& GIC, Sensors, AMMI, Motorola, Delco, Breed, Systron Donner, Honeywell, Allied Signals	700–1400
Microfluidics and chemical testing/processing	gene chip, lab on chip, chemical sensors, flow controllers, micronozzles, microvalves	Battelle, Samoff, Microcosm, ISSYS, Berkeley MicroInstruments, Redwood, TiN Alloy, Affymetrix, EG& GIC Sensors, Motorola, Hewlett Packard, tl, Xerox, Canon, Epson Caliper, Agilent	3000–4450
Optical MEMS (MOEMS)	displays, optical switches, adaptive optics	Tanner, SDL, GE, Samoff, Northrop-Grumman, Westinghouse, Interscience, SRI, CoraTek, Lucent, Iridigm, Silicon Light Macines, tl, optical MEMS, Honeywell	450–950
Pressure measurement	pressure sensors for automotive, medical, and industrial applications	Goodyear, Delco, Motorola, Ford, EG& GIC, Sensors, Lucas NovaSensor, Siemens, TI	1100–2150
RF technology	RF switches, filters, capacitors, inductors, antennas, phase shifters, scanned apertures	Rockwell, Hughes, ADI, Raytheon, TI, Aether	40–120
Other	actuators, microrelays, humidity sensors, data storage, strain sensors, microsatellite components	Boeing, Exponent, HP, Sarcos, Xerox, Aerospace, SRI, Hughes, AMMI, Lucas Novasensor, Sarnoff, ADI, EG& GIC Sensors, CP Clare, Sielmens, ISSYS, Honeywell, Northrop Grumman, IBM, Kionix, TRW	1230–2470

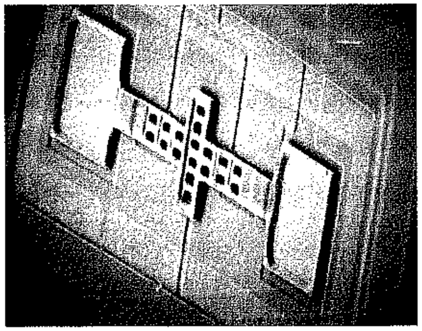

Figure 4 The first results of MEMS technology: a beam and a spiral spring. (Courtesy of Professor Richard S. Muller, Berkeley Sensor & Actuator Center, University of California, Berkeley.)

Feynman saw no physical reason why the 50 volumes of *Encyclopedia Britannica* could not be inscribed on the head of a needle. One letter would only need to consist of less than a dozen or so molecules. Confronted with the difficulty of working at micrometric scales, he suggests that we should 'train ants how to teach mites' how to construct miniaturized machines!

> How many times when you are working on something frustratingly tiny like your wife's wrist watch, have you said to yourself, 'If I could only train an ant to do this!' What I would like to suggest is the possibility of training an ant to train a mite to do this. What are the possibilities of small but movable machines? They may or may not be useful, but they surely would be fun to make.

These suggestions or predictions did not remain just as part of a fantasy world, since a few decades later, in 1995, the word 'IBM' was spelled out using only a few atoms.

The first MEMS devices were created a decade after Feynman's speech. A few examples are listed here, without an attempt to establish a rigorous chronology. The first microbeam was created in 1982, and the first microspring in 1988 (Fig. 4).

The first micromotor was created in 1989 (Fig. 5)[4]. It consists of an electrostatic motor, where the rotating electric field is generated by electrodes that have been evaporated onto a platform of polysilicon. One major difficulty in its fabrication was that of the reduction of stiction (i.e. the combined phenomena of adhesion and friction) of the rotor towards the substrate. Stiction is exacerbated by the effect of miniaturization and tends to impede the rotation of the rotor. The solution to this problem consists of reducing the surface area of the rotor/substrate contact, which obviously makes microfabrication of this machine more difficult.

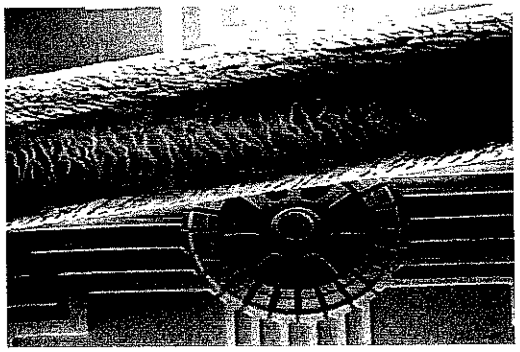

Figure 5 The first micromotor, made at UC Berkeley by Tai and Muller in 1989. This motor has been placed next to a human hair whose diameter is on the order of 200 μm. (Courtesy of Professor Richard S. Muller, Berkeley Sensor & Actuator Center, University of California, Berkeley.)

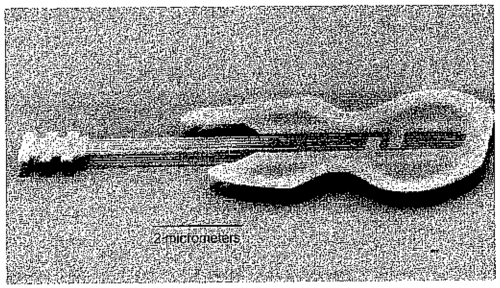

Figure 6 A microguitar with nanostrings 30 nm in diameter, made at Cornell by the group of H.G. Craighead. If this guitar could be played, it would produce a sound in the domain of MHz, which would require a particularly sharp ear to hear.

Other examples of MEMS are presented below. A microgear, a pair of microtweezers, a micro-electrovibrator, a system of inclinable mirrors that permit communication between the ground and an airborne microengine [8], and an astonishing microguitar possessing nanostrings that vibrate at a frequency of MHz, Fig. 6. Not all of these objects are necessarily practical, but they allow for exploration into a field of miniaturization where new concepts can be developed. The invention of new microsystems has been the center of activities of laboratories involved in MEMS in the 1990s. Today, a sort of maturation in the domain of MEMS prevails, resulting in less time being spent on creating new systems and more time being spent on investigating concrete applications.

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[4] We will see in Chapter 1 that this micromotor can comprise the base element of a microturbine that converts chemical energy to electrical energy. It is also interesting to note that microgears, fabricated using MEMS technology, are often used today in clock making.

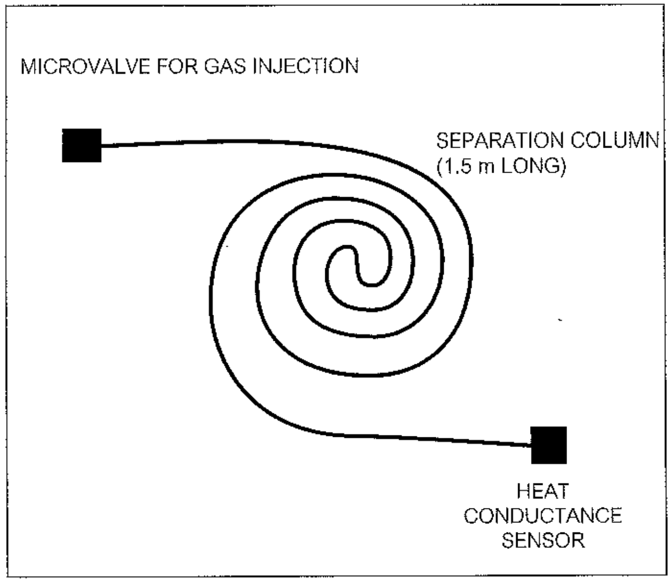

Figure 7 Diagram of miniaturized gas chromatography, created by Terray in 1975 [9].

The birth of microfluidics

We now concentrate on microfluidics. In the period when silicon-based MEMS began to take off, there were no technical obstacles in making simple microfluidic systems [11]. Thus, the first miniaturized gas chromatography system was created around 1975 [9,10].

This remarkable device circulated gas through microcanals etched in silicon. The system consisted of miniaturized electromagnetic injection as well as miniaturized thermal detection, all contained on a single chip just a few centimeters wide. This achievement was an isolated one, most likely because the separation-science community was not ready to develop silicon technologies for its own needs [12]. It was only after 1991 that the advantages of miniaturization were thrust into the spotlight, particularly for its application to chromatography [13], and then all sorts of microfluidic systems began to be fabricated. Appearing approximately chronologically were electrophoretic separation systems, [14–16], electro-osmotic pumping systems [17], diffusive separation systems [18], micromixers [19–22], DNA amplifiers [23–28], cytometers [29–31], and chemical microreactors [32,33], to cite just a few examples.

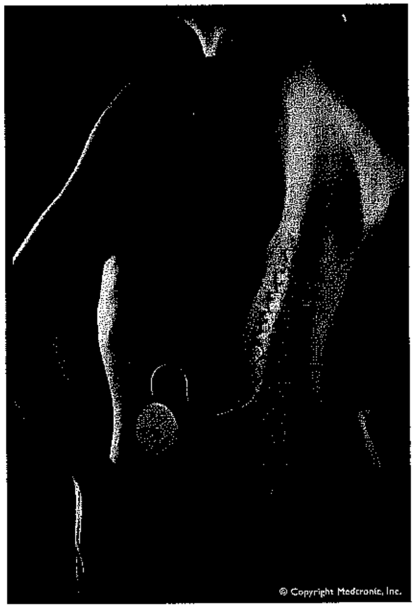
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Figure 8 Patients that have spinal cord lesions can now be healed effectively thanks to the injection of a product into the cereberospinal fluid. The efficacy of this mode of injection is far greater than by oral means. The company Medtronic has commercialized these injection pumps, which are generally implanted below the abdomen and connected to the zone to be treated using a 500 μm diameter catheter, which the neurosurgeon must manipulate with great dexterity. There are also implanted pumps for the injection of insulin into the liver for the treatment of diabetes.

During the same period of time, microfluidics was being used to tackle fundamental physical questions. For example, the first experiments involving the stretching of DNA, carried out by Chu *et al.* [34] in 1993, used a microfluidic system to control the viscous stretching force applied to the molecule; for the first time, it was possible to conduct a detailed study of the different configurations of the stretched molecule. This experiment founded a new domain of fundamental research: the study of the single molecule.

One of the amazing creations of microfluidics includes micropumps (Fig. 9). Many tricky problems arise when constructing a mechanical micropump: for example, miniaturized valves have a tendency to stick irreversibly to the substrate, making it necessary to minimize the contact surface area (as was necessary for the miniaturized motor). The micropump of the company Debiotech, schematically represented in Fig. 9, overcame this problem elegantly. This pump is destined for implantation in patients needing continuous injection of a product. Currently, insulin injection pumps in the liver and Bactofen pumps in the spinal cord are not easy to implant, particularly in children. As compared with traditional technologies, this micropump reduces its scale by an order of magnitude (Fig. 8), an important improvement from the surgeon's point of view as well as a significant gain in comfort for the patient.

The first microfluidic product commercialized on a large scale was the inkjet printer head described above (Fig. 10). Today, tens of millions of inkjet

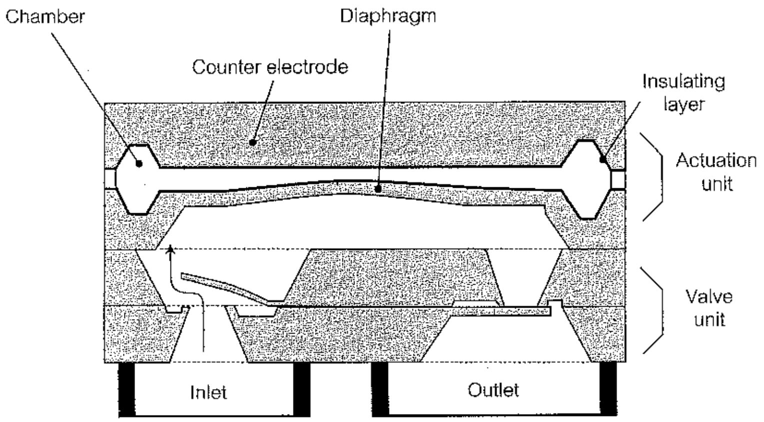

Figure 9 The future is moving towards the miniaturization of intrathecal pumps. The miniaturized pump is just a few millimeters in size, which corresponds to an improvement of two orders of magnitude over current intrathecal pumps.

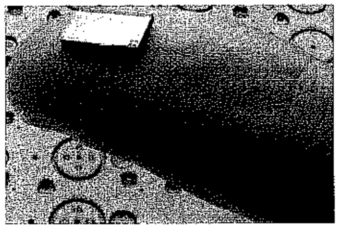

Figure 10 The Debiotech micropump can be held on the fingertip like a postage stamp.

printers use MEMS and billions of documents are written and read thanks to microfluidics. By parallelizing ejection heads, droplet dispensers can also be constructed. In this case, the destination of these droplets is not sheets of paper, but plates containing wells used for chemical or biological analyses.

Droplet dispensers at this time constitute a substantial part of commercial activity in the field of microfluidics [7]. Currently, chips are produced by the millions for chemistry and biology. These chips allow massive numbers of tests to be run in parallel, allowing large amounts of data to be delivered that aid in the precise characterization of a product. Today, this kind of technology is crucial in the search for new types of medical treatments. Microfluidic systems do not normally use moving parts (the micropump of the company Debiotech represents a rare counterexample) and this constitutes a significant simplification with respect to non-microfluidic MEMS. Consequently, it has become possible in microfluidic systems to turn to simpler technologies, ones that are faster and less expensive than silicon technology. We are generally referring to 'soft' technology, based on elastomers such as PDMS (polydimethylsiloxane) or on plastic materials, which comprise a large portion of the field today. We will return to these subjects in Chapter 6. Due to the absence of moving parts and the relative ease and accessibility of many of these technologies, it has become possible to integrate several elements on the same chip and to create lab-on-a-chip devices. The idea of constructing microfactories from MEMS often came up in the 1980s, but the difficulties involved in actually fabricating working devices using silicon technology made this dream unattainable. For microfluidic MEMS and related technologies that have no moving parts, the integration of different components has since opened up a wide range of possibilities.

Microfluidics and lab-on-a-chip devices

The rapid expansion of the field of microfluidics seems to be driven in part by the possibility of integration. The ultimate goal is to be able to detect biological molecules, and transport, mix and characterize a raw sample, all with one device. In traditional genomic analyses, it was necessary to purify and amplify a DNA fragment prior to analysis. This pre-treatment required complex labor and highlights the advantage of being able to integrate all these procedures on one chip to make it possible to directly analyse a raw sample, such as a drop of blood or a piece of gruyere cheese. Achieving this would require miniaturizing systems such as cytometers, separators, and bioreactors, and then connecting them together. The domain of integrated analysis systems has been designated as μTAS (*micro-total analysis systems*) [35], or also 'lab-on-a-chip' systems. The two terms are essentially synonymous. Lab-on-a-chip devices or μTAS delineate an abundant field that includes analysers of air and water quality, diagnostics of illnesses, and devices that replace the many functions of the nose, the tongue, etc. The economic possibilities of this field have been estimated at tens of billions of dollars per year.

Today, these possibilities have ceased to become just a dream. Already, in 1994, a group of researchers succeeded in fabricating a chip integrating three different functions: the mixing of reactants, enzymatic reaction, and separation [36]. Four years later, one single device capable of titrating aqueous solutes and then performing the mixing, amplification, enzymatic digestion, electrophoretic separation, and detection was published in the journal *Science* [37]. During the last few years researchers have come up with all sorts of solutions to improve and simplify the manipulation of fluids on-chip. There is still an enormous amount of progress to be made in this domain, which is precisely one of the tasks allocated to microfluidics.

In the meantime, lab-on-a-chip devices accomplishing a small number of functions have already been commercialized. For example, the company Biosite

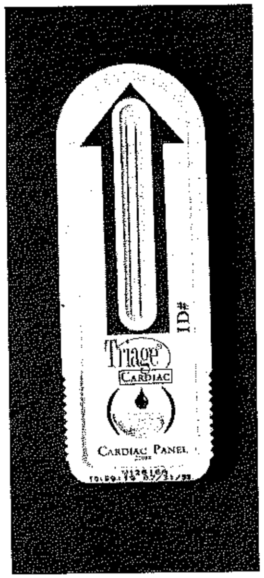

Figure 11 Biosite chip. A droplet of blood is placed in an opening on the chip. This drop is pulled towards the microfilter and the microseparator (in the direction of the arrow) by capillarity. The results of the analysis are given after data is analysed on a microcomputer. In just 15 min, this diagnostic can determine whether or not a heart attack has taken place.

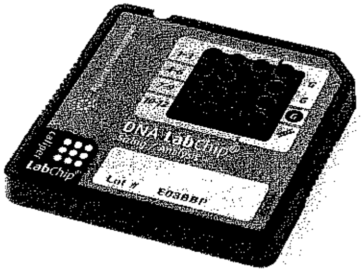

Figure 12 This chip, commercialized by Agilent Technologies, is a few centimeters long, and permits the identification of specific genetic sequences in a 1-μl sample of roughly purified DNA. This process takes place in just 10 min.

has commercialized systems that can take a drop of blood from a patient and transport it by capillary force across a filter, analyse the blood in a functionalized microcanal, and then diagnose whether or not the patient had suffered a heart attack. The principle of the test is founded on the detection of three myocardial proteins that are produced in abnormal quantities once a heart attack has taken place. This system is shown in Figs. 11 and 12.

This system is not completely integrated because a computer is required to analyse data produced by the chip, although the data-acquisition system itself is portable. In this case, the interest of miniaturization is not just to allow for portability, but also the rapidity of achieving results[5]. For the Biosite chip, a

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[5] Note that in this case, the reduction of diagnostic time is not only related to the physical phenomena in play. It is also due to the reduction of necessary human involvement, since physico-chemical processes are almost completely integrated.

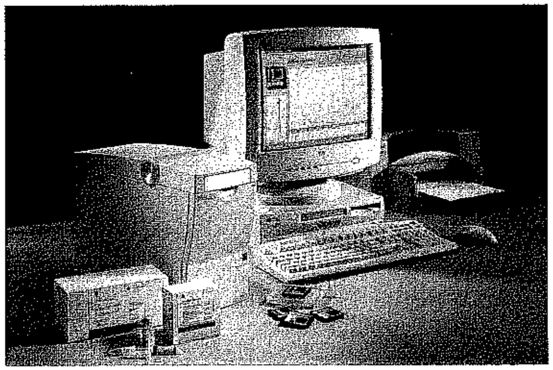

Figure 13 Agilent 2100 Bioanalyzer. The Agilent chip in the preceding figure is small in size, but it still requires a non-miniaturized computer environment to analyse the acquired data.

diagnosis is given in 15 min, while traditional systems need several hours. Not knowing the true nature of a patient's condition, doctors needing to make quick decisions sometimes end up treating non-existent cardiac problems. Furthermore, patients can be unnecessarily alarmed by a false diagnosis, believing they have a fatal condition when in fact the problem may be much less serious.

It is worthwhile to mention other commercialized systems that are precursors of the lab-on-a-chip systems of the future. Figure 12 represents a remarkable miniaturized system commercialized by Agilent. Among other functions, this system can perform genotyping, i.e. the identification of an object (a virus for example) from characteristic sequences of genes. It is not necessary to sequence the whole genome of a strand of DNA, but just to identify fragments. The chip is made of a network of gel-filled microcanals, and uses a powerful separation technique known as CEC (*capillary electro-chromatography*). This chip can also idenfity RNA and proteins.

Just as for the Biosite system, integration is not complete; the device must be used in tandem with a system for data analysis, as shown in Fig. 13[6].

Microfluidics and chemical engineering

Another problem in microfluidics is that of miniaturization of processes for chemical engineering. We will see in Chapter 1 that miniaturization favors heat

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[6] This fact can sometimes lead to a discussion of whether it is more appropriate to call these systems 'chip-in-a-laboratory' instead of 'laboratory-on-a-chip.' Clearly, there remains much progress to be made for the complete miniaturization of a chain of analysis.

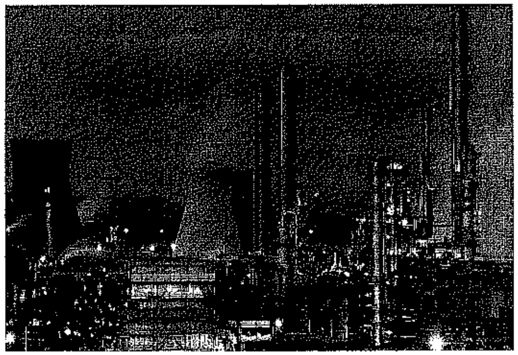

Figure 14 Can a refinery be miniaturized? The problem of production volume would require massive parallelization of lab-on-a-chip systems for chemical engineering (© J. Walker/S.P.L./Cosmos).

exchange, and allows the control of strongly endo- or exothermic reactions that can be difficult to manage in traditional chemical engineering systems. By improving control, selectivity is also improved (by avoiding the formation of unwanted chemical species). Emerging from all this came the idea of the miniaturization of chemical factories, as shown in Fig. 14.

It is not clear whether it is possible to miniaturize the factory shown in Fig. 14. The obvious problem that arises is whether there would be sufficient production volume[7]: can enough volume be produced using a miniaturized system? Is it possible to displace a mountain with a small spoon? One possible idea would be to multiply the system using massive parallelism, an approach known as *numbering up*. It is undoubtedly necessary to rethink modes of production in this domain so that it can best profit from the advantages of miniaturization, especially to break down units of production or install them near the users. The latter would present many advantages, such as the reduction of transport and the reduction of chemical-contamination risks. The appeal of microsystems for chemical engineering has been perceived at least since 1996, as cited by several references [38, 39]. Today, microsystems are seen as an important source of innovation; international conferences organized on this subject, such as the IMRET series, have seen a strong vitality in research activity on the theme of miniaturization. A recent review of these subjects is given in [40].

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[7] A related issue in the domains of biology and analytical chemistry is how to obtain a large amount of data by parallelizing many miniaturized analysis units. These systems are called *high-throughput* devices.

Astonishing microfluidic systems in nature

The framework in which we have placed ourselves—that of 'systems made by man'—is obviously restrictive. Nature produces astonishing micrometric and nanometric systems that have impressive characteristics, and these include the controlled circulation of fluids. We mention the tree as an example, where a hydrodynamic problem involving these types of scales appears: how can a tree bring water and nutrients to the leaves? Nature found an amazing solution using a complex network of capillaries (Fig. 15).

Tens of thousands of leaves are nourished by a capillary network containing hundreds of thousands of microcanals of diameters between a hundred micrometers (in the trunk) and several tens of nanometers (in the leaf). Despite the complexity of the network, the supply of sap is homogeneous[8]. To understand the hydrodynamics of this system, it is necessary to consider the *deformability* of the canals (the ability of the capillaries to deform under the effect

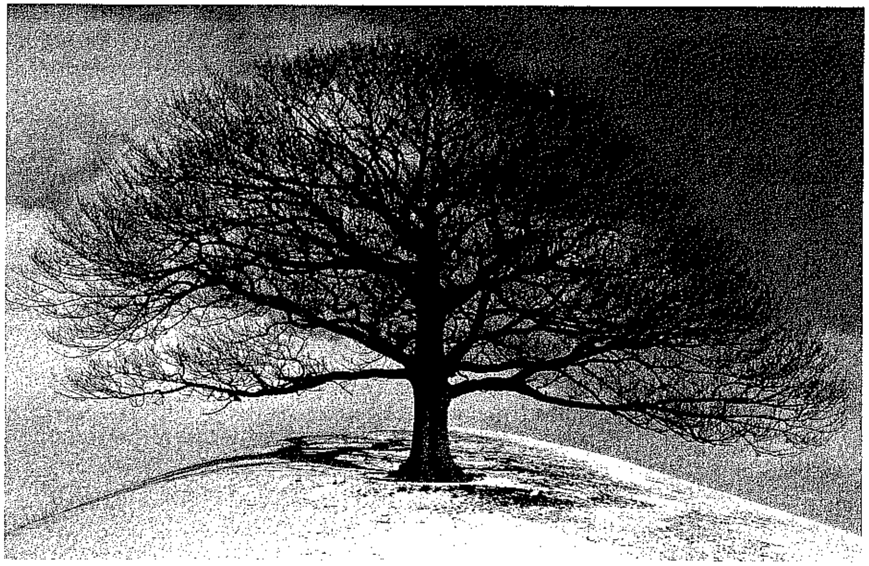

Figure 15 This tree possesses a complex network of capillaries that allows it to supply water homogeneously to the tens of thousands of leaves that it carries on its branches. This system also involves flows in micro- and submicrometric-sized canals (© Packwood/OSF/Bios).

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[8] It is interesting to note that the pressure drops that develop in the network are significant (several tens of bars); implying that the sap is subjected to negative pressures.

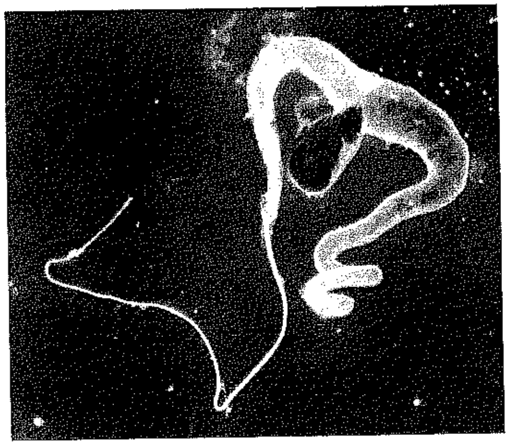

Figure 16 One of the silk glands of a *nephila clavipes* (photo graciously provided by J. Bico, M.I.T.).

of pressure), the considerable significance of capillary effects (which originate from the drainage of fluid), and the role of redundancy (if one capillary dies, another takes its place). A second example of how nature extraordinarily handles complex micrometric flows appears in the spider web. To spin its sticky trap, the spider produces a long silken thread a few dozen micrometers in diameter, and despite its slenderness this thread has exceptional mechanical properties. The silken thread is the result of a protein that is synthesized in a gland mixed with a solution. This system is shown for the spider *nephila clavipes* in Fig. 16.

We will describe in Chapter 3 microfluidic reactors where chemical reactions take place under well-controlled conditions. However, these man-made systems are still far from being able to compete with this animal.

It would be easy to continue listing examples of microfluidic systems from nature. However, despite the many interesting characteristics of these systems, this text will be limited to mono- and polyphasic fluid flows, and the associated transport phenomena, of microsystems *made by man*. This 'engineering' definition is simplified but generally accepted.

Different aspects of microfluidics

There are several different aspects of the field of microfluidics. The first major set of questions involve issues of microplumbing, i.e. how to circulate fluids in microsystems. It is necessary to resolve problems of fluid outlets, valves, and tubes, which, in macrometric systems, are taken care of by a plumber. These issues most notably involve:

- **Fluidic interconnects.** These accomplish the coupling between two microfluidic systems, or between a microfluidic system and the exterior world. It is desirable that the linkage is made in a simple, standardized way, without leaks, similar to how two electronic circuits are connected. Multiple fluidic interconnect systems have been conceived in research laboratories, but they are rarely useful industrially. It would be useful to have a simple and universal interconnect available, but such an interconnect does not yet exist. This difficulty presents an obstacle to integration;
- **Pumps and valves.** Control elements such as valves and pumps, when made using silicon technology, are complicated to fabricate and then difficult to integrate onto lab-on-a-chip systems. However, the use of 'soft' technologies based on elastomers offer elegant possibilites for valves and pumps that we will describe in more detail in Chapter 6. The question of the choice of material and how this choice relates to the possibilites of microfabricating control elements is still an open problem today in the field of microfluidics;
- **Fluid injection.** The injection of fluids is a practical difficulty that does not always have a simple solution, especially when the sample is very small and is not amplifiable (for example, proteins extracted from a single cell). The sample can be diluted in a large volume so that it can be manipulated more easily, but this creates a series of difficulties, including the need for sensitive instrumentation. The injection of minute quantities of fluid remains an open problem in the management of fluid volumes.

These microplumbing problems are subtle, and are systematically examined during microfluidic conferences, but they are not all that make up microfluidics! There are also situations involving physical or physico-chemical phenomena in unusual contexts that cannot be attributed to microplumbing problems; for example, the situation of gas flowing in microcanals, where ordinary hydrodynamic boundary conditions no longer apply. Also, the intensification of the coupling between the flow and the electric field at the micrometric scale gives rise to novel methods for the movement of fluids that are impossible to apply in the macrometric world. In addition to this, there exists the possibility of using microfluidics to manipulate rapid chemical kinetics, an achievement that is generally outside the range of ordinary systems. Another aspect of microfluidics involves the idea of building complex integrated systems whose functioning is qualitatively different from those based on more modest integration. This text will use several examples to show that microfluidics goes far beyond difficulties related just to microplumbing.

Possibilities offered by nanofluidics

To manipulate objects of nanometric size in solutions, one may think of eventually developing 'nanofluidics', i.e. the field involving the study of flows in nanometer-sized systems. This topic currently includes the activity of several research groups interested in the flow of fluids in submicrometric-sized canals [41–42], the implementation of nanojets [21, 43], and the confinement of objects of a submicrometric scale. Nanofluidics can undoubtedly contribute to the field of physics of the single molecule, as well as to mesoscopic physics (i.e. studies involving scales intermediate between micro- and macroscopic). To illustrate this aspect of nanofluidics, it is worthwile to look at a few suggestions offered by Fujita [44] that are pertinent to this field:

- confining molecules produced by a cell or an enzyme in a nanometric space for detection purposes,
- following the rapid kinetics of chemical reactions,
- characterizing the activity of individual molecules,
- intensifying and analysing the role of surfaces in a catalytic reaction,
- applying local or intense electric or magnetic fields that can control chemical reactions,
- manipulating molecules directly and physically,
- labelling molecules and following their conformational changes during a chemical reaction,
- constructing hybrid systems by assembling biomolecules in NEMS (*nano-electromechanical systems*).

At this time, the domain of nanofluidics is still largely unexplored; it is acceptable to think that a growing effort will develop in the future on this subject.

Specialized publications

Microfluidics is a young science, and as a consequence of this (at the time of the writing of this book), there are not a large number of works and reviews written on the subject. We mention that the first text on microfluidics can be considered to be '*Microflows*' [4], which appeared in 2002. This book most notably dealt with the phenomena of slip, the modelling of flows, and electrokinetics. A more

recent book is 'Fundamental and Application of Microfluidics', by N.T. Nguyen and S. Wereley [46], which uncovers a broader part of the subject. There are also collections of papers, edited as books: 'Lab on a Chip', edited by E. Oosterbroek and A. Van den Berg [45], Microfluidique, edited by S. Colin [47], and the MEMS Handbook by G. el Had *et al.* [48]. In addition, a journal on this topic, entitled 'Micro and NanoFluidics', appeared in 2003. Reviews on the research carried out in the field of microfluidics also exist: we cite Ho and Tai [49] on control[9], Gad el Hak [50] on the control of rarefied gases, Giordano and Cheng [41], Tabeling [51], Stone and Kim [52] on physical aspects, Beebe *et al.* [53] on the physics and biomedical applications, Sanders and Verpoorte [54, 55] on biochemical analysis, Lichtenberg *et al.* [56] on sample pre-treatment, the review prepared by the group of A. Manz [12, 57] on μTAS, and a recent review by Ajdari *et al.* [58] on the hydrodynamic aspects of microfluidics. In general, research articles in microfluidics are dispersed in journals such as *Analytical Chemistry*, *Physical Review Letters*, *Physics of Fluids*, *Sensors and Actuators*, *Journal of Chromatography*, *Electrophoresis*, *Nature*, *Science*, *Applied Physics Letters* and *Lab on a Chip*; the *Proceedings* of conferences such as μTAS, and, to a lesser extent, *MEMS* and *Transducers* are also an important source of information on the research efforts in the field. Courses on microfluidics are currently dispersed in notes that can sometimes be found on the Internet. We also refer to microfludic courses proposed during international conferences, or organized on a regular basis [59].

Organization of the text

This text consists of seven chapters.

- In the first chapter, entitled 'The physics of miniaturization', consequences of the miniaturization of the 'ordinary' world are described from a physical point of view. Miniaturization often leads to the disturbance of force equilibria: volumetric forces such as gravity cease to prevail in the micrometric world. Instead, this world tends to be dominated by surface forces like capillarity. This fact leads to situations that are sometimes surprising, and go

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[9] The problem of flow control involves finding activation methods that allow the influence of a flow to limit or heighten unstable modes, reduce or augment turbulence, etc. In this context, MEMS are particularly useful, because they allow one to act at the center of a flow from where vortices originate. For example, the group of C.M. Ho showed that it is possible to maneuver a Delta airplane without a mobile centerboard, instead controlling it by activating hundreds of MEMS. These MEMS are placed in a line along the edge of the wings; these microsystems act on the formation of spiral vortices, which play an important role in the lift force developed by the wing [49].

against physical intuition. The consequences of these surface forces are often cleverly exploited by nature, for example by small insects. Miniaturization also gives more importance to phenomena that are negligible in the macrometric world[10]: one example is the mean free path of gases, often neglected in ordinary hydrodynamics, but which must be explicitly taken into account in microfluidic flows.

- The second chapter tackles microfluidics itself, and low Reynolds number flows (the regime defining microhydrodynamics) are presented. The effects of solid/liquid and solid/gas slip are also discussed. Then, capillary phenomena in the microfluidics of droplets and bubbles are detailed. Also, the role of surfactants in miniaturized systems, including the production of emulsions, is studied.
- In the third chapter the phenomena of diffusion, dispersion, mixing, adsorption, and separation are described. Taking the importance of chromatographic questions in microfluidics into account, this text proposes an introduction to separation techniques with several examples of miniaturized separation systems. Other basic notions on chemical kinetics in the context of microsystems are also given.
- The fourth chapter describes the electrohydrodynamics of microsystems; electrophoresis and electro-osmosis, two extremely important phenomena for understanding lab-on-a-chip devices, are discussed in detail. Dielectrophoretic effects allowing the micromanipulation of neutral particles are also presented.
- The fifth chapter is dedicated to heat exchanges in microfluidic systems: after a discussion of the limits of macroscopic approach, the equations governing velocity and heat fluxes are introduced, and some basic solutions relevant to microfluidics are derived. The results obtained in this part are applied to the particular problem of temperature control in the next generation of microprocessors.
- In the sixth chapter, microfabrication methods are introduced. Today, it is difficult to tell which technologies will dominate in the coming years. Currently, microfabrication technologies include a diversity of technological approaches. In this spirit, silicon technology is described in this chapter; a substantial portion of the chapter is also dedicated to soft technologies based on elastomers and also plastic MEMS, accounting for their ever-growing importance.

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[10] The term macrometric will often be used in this book. The term designates the range of scales above the dimensions of MEMS.

- Finally, the seventh chapter gives a few examples of the products and devices of microfluidics, interconnects, valves, and pumps.

Perspectives on microfluidics

Today, we expect a lot from microfluidics: we hope that the complete control of the flows at micrometric scales will allow the construction of highly complex microsystems, where fluids can circulate in a controlled manner, performing a large number of tasks in a maze of microcanals[11]. This is the dream of integrated systems of the future, whose capabilities are difficult to imagine, just as fifty years ago it was difficult to imagine the level of performance of computers today. Living systems provide a sort of perspective on the level of complexity that could be attained in artificial systems. We tend to consider today that the path leading to such complexity is partly obstructed by problems of flow control; the definitive solutions to these problems could very well be provided by microfluidics. The field of microfluidics is abundant; all sorts of solutions, elegant or crude, fragile or robust, simple or sophisticated, are brought to the problem of fluid management in microsystems. This book does not intend to be exhaustive, as the number of microfluidic achievements are in the thousands. Thus, the title of the book *Introduction to Microfluidics* is appropriate. We hope that while reading, the reader will acquire a frame of reference as well as pertinent knowledge that will enable the reader to tackle a large number of situations involving fluid flows through miniaturized systems, which in essence defines the field of microfluidics.

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[7] The company Yole, based in Lyon, carries out analyses on the industrial situation of domains such as MEMS and microfluidics. The evaluations mentioned in this text are taken from a recent report (see www.yole.com).

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