Chapter 1
Introduction

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Micro/nano biosystems are miniaturized systems able to handle and detect or analyze biological samples for medical, environmental and biological applications. They are most often considered as a subset of MicroElectroMechanical Systems (MEMS) and called bioMEMS even when they do not include mechanical micro or nanotructures because they often share similar technological processes. They are usually designated as micro total analysis systems (μTAS) when they include all steps required to perform biological sample collection and its chemical or biochemical analysis as usually done in a laboratory. A lab-on-chip (LoC) is an highly integrated version on a single chip of a μTAS function or of a whole μTAS.

From the end of seventies up to the beginning of nineties integrated sensing systems were mainly based on microactuators and on microsensors of physical quantities (pressure, acceleration, magnetic field, temperature,…). They were typically fabricated by processes coming from microelectronics completed by dedicated bulk and surface micromachining of silicon or Silicon-On Insulator (SOI) wafers and eventual assembly with a glass wafer. Since about 1990, these integrated sensing systems were designated as MEMS and this denomination is now commonly used for all kind of miniaturized sensing and/or actuation systems. Later on, at the end of nineties, optical functions and/or components were added to build optical MEMS and Micro OptoElectroMechanical Systems (MOEMS). Finally at the beginnning of 21st century, nanostructures and nanomaterials began to be integrated, and NanoElectromechanical Systems (NEMS) were born.

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Nowadays, MNOEMS have reached a high level of sophistication and maturity and are fabricated by using a large variety of materials and processes and mobile communication devices such as cell phones enjoy MEMS technology for radio frequency signal reception and transmission. MNOEMS represent 80% of the industrial market of sensing and actuating miniaturized systems with an annual growth rate larger than 10% for 10 years.

Microfluidic devices in glass technology and labs-on-chip appeared later than physical microsensors but with a rapid growth since the beginning of nineties. Since, a very broad range of specific fabrication technologies largely based on polymers, and of various sensing principles were developped. BioMEMS have a wide variety of applications for biology, medicine and agriculture. In 2000, microfluidics systems and bioMEMS represented only a few % of the MEMS industrial market but it is now more than 20% and a compound annual growth rate of 25% is predicted up to 2023. Nevertheless, μTAS and labs-on-chips still represent a small fraction of this market and the challenge is to overcome the commercialization, ethic and legal barriers to benefit of the high potential of these bioMEMS.

The size of biological objects is ranging from a few nm to a few hundreds of μm (Fig. 1.1). So a basic requirement of bioMEMS is the ability to handle and detect objects at micro/nanoscale: manipulation methods to separate, concentrate, filtrate, and identify cells, proteins, viruses and DNA using electrophoresis, electroosmosis, and electrowetting. This is notably achieved by integrating biosensors as depicted in Fig. 1.2, A biosensor typically includes a microfluidic system with micro/nano channels, pumps, valves, filters and electrodes to transport, concentrate, separate, mix, localize,… the biological objects or micro/nano particles carrying them. It also usually includes biofunctionnalized surfaces or traps to capture targeted species with a high selectivity. Detection is often performed in research works by optical microscopy or by other external means but to benefit from the full potential of bioMEMS, miniaturized transducers or indicators should be integrated to detect captured species and to convert the result into an electrical or optical signal, or to a specific color. As detailed in the different chapters of this book, various electrical, optical, mechanical, magnetical and coupled phenomena can be used for fluids and bio species handling and detection at micro/nanoscale.

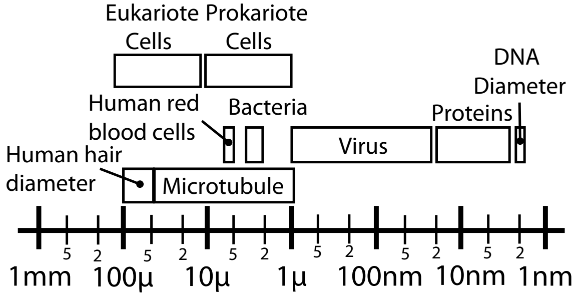

Fig. 1.1 Typical size range of biological species and comparison with hair diameter

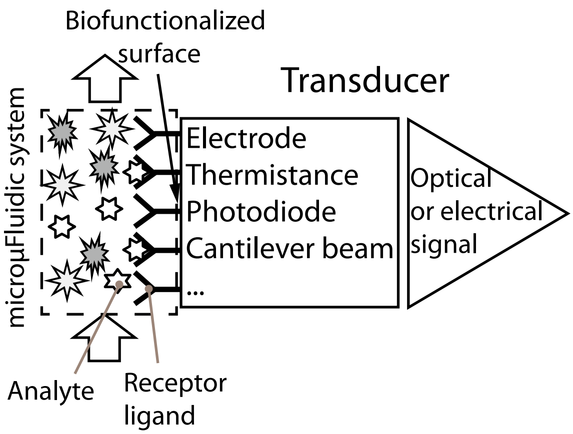

Fig. 1.2 Schematic drawing of a bio sensor

Owing to micro/nano fabrication technologies, bioMEMs integrating biosensors like in Fig. 1.2 can be highly miniaturized and fabricated at low cost by batch processing on various substrates (glass, silicon, polymers). This offers the possibility to get disposable systems that avoid maintenance operations like cleaning, purge, calibration, etc…and reduces the need of trained staff for their operation. BioMEMS have also many other proven or potential benefits when compared to conventional systems [1–25]:

– BioMEMS have the ability to handle small amounts of expensive chemical or pharmaceutical products and are sufficiently sensitive to detect small concentration of biological objects. This contributes to cost reduction and faster biochemical analyses but also reduces waste generation and minimize exposure to hazardous products. For human diagnostics, it reduces, for example, the amount of critical corporal liquids like blood that must be collected. For fundamental research, it also allowed, for the first time, operations at the single cell level.
– BioMEMS can allow faster measurements than with conventional systems because diffusion of chemicals, flow switching and diffusion of heat are faster at micro/nano scale. Eventually faster measurements can provide real-time process control and monitoring. As an example, integration of Polymerase Chain reaction (PCR) in a lab-on-chip allows a ten times faster DNA amplification.
– BioMEMS are able to integrate a large number of fluidics and biochemical functions on a single system and to perform parallel measurements. This largely reduces the cost of individual analysis and makes easier complex operations. For medical applications this allows a faster diagnosis of possible deseases and identification of the best suited antibiotic or antiviral.
– BioMEMs contributes to the reduction of human errors. Indeed, ease of use, reduced handling and automation of complex analyses should greatly reduce the risk of human errors.
– The small size and weight of bioMEMS favours a low consumption and make them more transportable.

All these abilities make BioMEMS suitable for point-of-care diagnostic that could revolutionize medicine by reducing the cost and time of bioanalyses as well as the training and infrastructure needs. This will make them usable by doctors in their offices, by nurses at hospitals and even by patients themselves. A rather unique successful example of the later case, is glucose monitoring for diabetics. For this application, portable systems based on lab-on-chip are already commercially available. Biosystems connected to smartphones begin to emerge.

This high potential of labs-on-chip and μTAS has been been largely recognized worlwide. As evidenced by the numerous review published in the last 15 years [1–25], a large amount of works, mainly focused for applications to human diagnostics and DNA analysis, or for the characterization of biological objects or bioprocesses, have been done. These works already demonstrated the large benefits of these miniaturized sensing systems. Some striking examples are the following one:

For DNA/RNA amplification and detection and for proteomics, labs-on-chip offer high gains in terms of speed. For example, LoC are able to sequence the human genome several order of magnitude faster than conventional systems and immunoassays with labs-on-chips can be done in a few tens seconds instead of a few tens minutes. Likewise, by integrating all steps, protein analyses can be reduced from hours to a few minutes. The small sise of fluidic microchannels in LoC is well suited for cell analysis and operations at the single cell level was demonstrated for the first time owing to labs-on-chip. Such a capability is demanded for physico-chemical modelling of biological processes and for the evaluation of parameters for cell changes identification. LoCs also provide high speed flow cytometry and cell sorting.

One holy grail of BioMEMs is to realize a low cost lab-on-chip able to perform a very large number of fully automated multiplexed bio chemical analysis of real complex biological samples like blood or saliva, A lot of work remains to be done to fully exploit the potential of bioMEMS and reach this goal. This tutorial book is intended for graduate students and researchers readers motivated by this challenge and having different backgrounds in physical science and electrical/mechanical engineering.

It provides the basic and advanced knowledge required to design, realize and test new LoCs or μTAS dedicated to the handling and sensing of biological samples. It is clear from Fig. 1.2 that building a state of the art fully integrated LoC or μTAS is demanding. Indeed, it is necessary to master micro/nanofluidics, biochemistry and bio analysis, sensing techniques, microfabrication processes and associated characterization and testing techniques. Practical and up-to-date information on all these topics is gathered in this book: First, Chap. 2 provides the basics of micro/nano fluidics and biology as well as information on the main ex-situ and in-situ characterization techniques. Then, fabrication and packaging technologies useful for BioMEMS are examined in Chap. 3. The four following chapters provide a detailed analysis of the main phenomena used in micro/nano fluidics systems and for bioanalysis. Finally the limitations of bioMEMS and current challenges will be presented in the concluding chapter.

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