Edited by Oliver Geschke,
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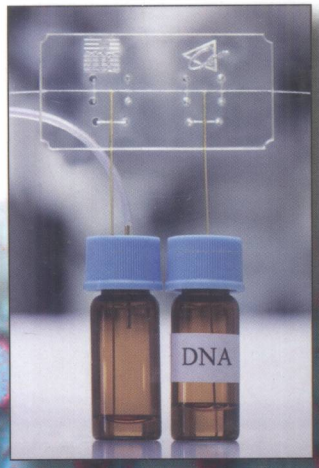
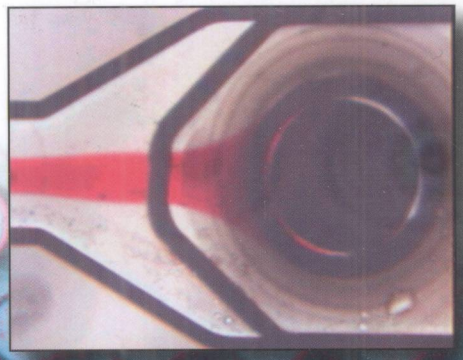
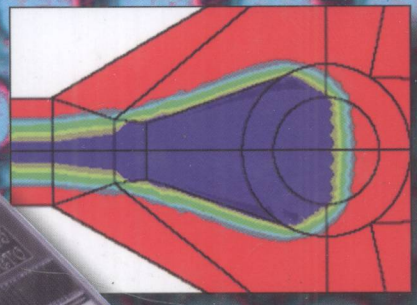
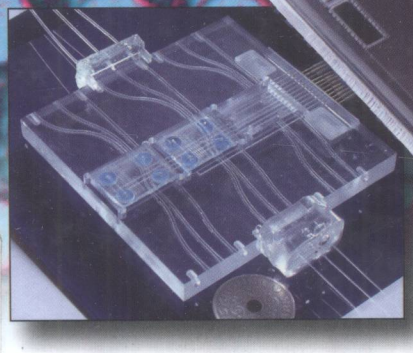
Microsystem Engineering of Lab-on-a-Chip Devices

Second, Revised and Enlarged Edition









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Preface

We live in a world that is influenced by technological developments. One of the clearest examples of this is microtechnology. The use of microtechnology to miniaturize and functionally integrate electronic components has changed our world, and hardly any facet of our lives is not in some way affected by microelectronics. Building on the experience of microelectronics research and industry we have started to apply microtechnology to chemistry and biochemistry. We stand to gain many advantages including improved performance, portability, and reduction of cost. The application of microtechnology to chemical and biochemical analysis is a very multidisciplinary topic which needs input from scientist and engineers with different backgrounds. This book combines the experience of a group of engineers, chemists, physicists, and biochemists who are applying microtechnology to chemical and biochemical analysis at the Department of Micro- and Nanotechnology at the Technical University of Denmark (DTU Nanotech). The various stages in the development of such microsystems are described in this text book: from concept to design, to fabrication, and to testing. There is little doubt in the international research and industry community that the application of microtechnology to chemistry and biochemistry will revolutionize our lives in a way that is comparable to what we have seen with microelectronics. Our aim with this book is to allow a broad range of scientists and engineers to get interested and familiarized with this very exciting topic.

Lyngby, March 2008

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Introduction

Pieter Telleman

1.1
Learning from the Experiences of Microelectronics

Try to think back to the time that your parents were your age and imagine the technological developments that have taken place since then. Sometimes it is hard to imagine that only 2 decades ago personal computers, mobile phones, compact disks (CD) players, and digital video disks (DVD) players did not exist. What made these technological developments possible? One of the major contributing factors is microelectronics. The first breakthrough from electronics to microelectronics was the invention of the transistor in 1947 at Bell laboratories. Transistors provided a better, cheaper alternative to mechanical relays, which were the standard electronic component for switching and modulating electronic signals. With improving semiconductor technology, transistors became progressively smaller, cheaper, and better. A second breakthrough was the introduction of the integrated circuit in 1959, by which numerous transistors and other electronic components together with the necessary wiring were organized on a thin silicon disk or wafer. In 1965, only 4 years after the introduction of the integrated circuit, Gordon Moore predicted an exponential growth of the number of transistors in an integrated circuit (Moore's Law). Although the pace has slowed down a bit in recent years, experts agree that the current rate of a doubling every 18 months will continue at least for 2 more decades. If we should summarize the process that made microelectronics so successful, we could say that it was the combination of miniaturization, i.e., microfabrication of transistors and other electronic components, and functional integration, i.e., the organization of many different miniature electronic components to form integrated circuits with complex functions. Since the application of miniaturization and functional integration to electronics, the same strategy has been applied to a range of other disciplines, e.g., mechanics and optics. One example of a microelectromechanical system (MEMS) is the accelerometer. The deployment of airbags in cars depends on signals from a number of accelerometers, i.e., miniaturized mechanical sensors that measure the g forces on the car. Other examples of MEMS are pressure sensors and microphones. The promise of faster and better data transfer offered by optical communication has resulted in the application of microtechnology to develop microstructures for the manipulation of light, e.g., micromirrors and optical switches.

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In 1979, S.C. Terry et al. presented "A gas chromatographic air analyzer fabricated on silicon wafer using integrated circuit technology" [1]. This was the first publication that discussed the use of techniques borrowed from microelectronics to fabricate a structure for chemical analysis. The introduction of the concept of micro total-analysis systems (μTAS) by Manz and coworkers in 1990 [2] triggered rapidly growing interest in the development of microsystems in which all the stages of chemical analysis such as sample pre-preparation, chemical reactions, analyte separation, analyte purification, analyte detection, and data analysis are performed in an integrated and automated fashion. The aim of this textbook is to provide you with a comprehensive understanding of the concept of μTAS. We will introduce you to microfluidics, i.e., the manipulation of small amounts of reagents and sample on microchip, simulation and modeling of microfluidics, fabrication of microsystems for chemical analysis in silicon, glass, and plastics, packaging of microsystems, and several examples of chemical analysis in microstructures.

1.2 The Advantages of Miniaturizing Systems for Chemical Analysis

Why is it that, when the concept of μTAS was introduced in the early 1990s, it attracted so much interest from the scientific and the industrial community? It was because the conventional approach to chemical analysis can no longer meet all the requirements that many applications demand. Let us look at some of these requirements and see how μTAS can offer unique solutions.

With rapid developments and growing interest in, e.g., medicine, drug discovery, biotechnology, and environmental monitoring, we have become more and more dependent on chemical analysis. Traditionally, chemical analyses have been performed in central laboratories because they require skilled personnel and specialized equipment. However, the trend is to move chemical analysis closer to the 'customer'. Some examples are pregnancy tests, blood glucose concentration tests for diabetes patients, and analysis of soil and water samples. These chemical test kits can be acquired off the shelf and can be used in the home by persons with no special training in chemistry. This trend of decentralization of chemical analyses is expected to continue. For this to happen we need to make analytical equipment smaller and thus portable, easier to operate, and reliable. The results of the chemical analyses must be processed so that it is easy for the user to interpret. The concept of μTAS builds on performing all the necessary steps that are required for a chemical analysis on a miniaturized format and thereby offers portability. Because the microfabricated components in a μTAS can be operated with very low power consumption, battery-operated analytical equipment opens up the possibility of performing chemical analyses in the field independent of a power grid. Automation of the entire chemical analysis process and data processing is also part of the μTAS concept. In its extreme case μTAS can be represented as a black box where the user needs only to apply the sample and push a start button

to perform the chemical analysis and retrieve the results. Microfabrication allows us to reproduce the same carefully designed μTAS many times with the same specifications. When care is taken to address reliability at the stage of designing a μTAS, reliability can be warranted for large batches. At the heart of each μTAS is a chip in which fractions of microliters of samples and reagents are moved around with very high accuracy. Traditionally chemical analyses are performed by mixing milliliters of samples and reagents in conventional test tubes and analyzing the product in an analytical instrument, e.g., a spectrophotometer. Especially when the samples and reagents are in short supply or very expensive, μTAS offers a significant decrease in costs by dramatically reducing the volume of samples and reagents that are needed to perform a chemical analysis. We already mentioned that once a μTAS has been successfully developed, it can be reproduced faithfully in very large numbers. This opens up the possibility of processing samples in parallel, which is very useful when the same chemical analyses must be performed many times over. This is exactly what drug discovery is about. A drug candidate often needs to be identified from a pool of many thousands of samples by performing a particular chemical analysis on each sample (this process is referred to as high-throughput screening or HTS). Today HTS is implemented by performing the chemical analysis in microtiter plates in combination with robotic handling of the samples and reagents. The possibility μTAS offers of parallelizing chemical analyses is seen as an interesting alternative to the use of microtiter plates and will eventually allow an increase in throughput.

Often, we want to know how the concentration of an analyte changes in time, i.e., online monitoring. It is better to continuously monitor the concentration of glucose in the blood of a diabetes patient than to measure the glucose concentration once every so many hours. Continuous analysis of ammonium in wastewater is more valuable for controlling a sewage-treatment plant than a measurement only 2 or 3 times a day. With conventional methods of chemical analysis is it difficult to implement online chemical analyses. Handling and processing of the sample is, at least in part, done manually and often in specialized laboratories. But with μTAS, we can bring the chemical analyses close to the place where they need to be performed, independent of a laboratory and laboratory personnel. Sample handling and processing, the chemical analysis, and data processing are integrated in μTAS, which makes it very well suited for online measurements.

The advantages of μTAS can be summarized as follows: μTAS offers portability, reliability, reduction of sample and reagent consumption, automation of chemical analysis, high-throughput screening, and online analysis. Keep in mind however, that μTAS has been around only since the late 1980s and that a much research and development still has to be performed in order to fully benefit from all its advantages. Several issues that are essential to the widespread use of μTAS have received little attention so far. The most prominent of these issues are interconnection and packaging. Regardless of how skilled we are in designing and fabricating μTAS, the chip at the heart of the μTAS must be interfaced to the macroworld of the user. For μTAS, this requires fluidic, mechanic, optical, and electronic interconnections. Furthermore, μTAS must be packaged so they can be handled safely

without damaging the delicate microstructures on the chip. Both issues must be dealt with to allow for successful commercialization and thereby wider use of the technology.

1.3 From Concept to μTAS

When you received this book you most likely started to flip through the pages to see what you can expect in the coming days or weeks. And you discovered that this book addresses a wide range of subjects that belong to many different disciplines, including physics, chemistry, and computer sciences. μTAS is a truly multidisciplinary activity that requires input from scientists having many different backgrounds.

The process of developing a μTAS consists of several discrete steps, starting with determining the specifications for the μTAS (Fig. 1.1). These specifications depend mainly on the nature of the chemical analysis and must answer questions such as: which reagents are used? what are the reaction kinetics? at what temperature are the reactions performed? what means of detection will be used? what is the desired range of detection? what is the required limit of detection? The chemistry in turn determines what material can be used for fabrication of the μTAS, for example: should it be transparent? are the reagents aggressive? is the μTAS intended for single use or multiple use? Inherent to combining mechanics, fluidics, optics, and electronics in μTAS is the formation of interfaces between these media. One must be aware of the fact that the sensor function of μTAS is actually based on the interfaces between 2 or more media, e.g., for absorption measurements you need an interface between light and a chemical. The interface of μTAS and the user, i.e., interconnection and packaging, must be also considered during

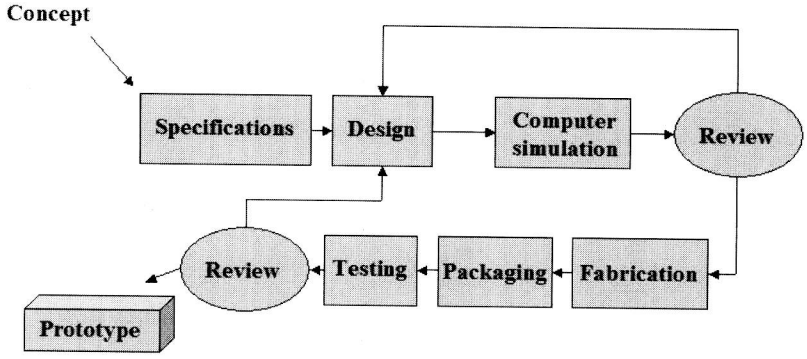

Fig. 1.1 From concept to μTAS. The successful development of a μTAS involves a number of discrete steps: specifications of the chemical analysis, design, modeling to evaluate performance, fabrication, and testing. Reviews of the modeling and test results enable optimization of the performance of the μTAS.

the specification phase. Defining the specifications for μTAS is a process that should involve all project members because it affects the overall μTAS performance.

With the specifications in place, the next step is to design the μTAS. Design constitutes the most important block in the flow sheet from μTAS concept to prototype and is discussed in more detail in chapters 3 and 4. It is here that considerations of μTAS concept, definition of interfaces, and specifications are translated to a fabrication plan. Developing a sequence of process steps for individual μTAS components, e.g., micropumps, is challenging in itself, but aiming at μTAS, where the entire process sequence involves a variety of integrated components, raises questions of process sequence and compatibility. How does one combine, from a process point of view, for example, microfluidic components with optical components without loosing the properties of the individual structures due to process incompatibility somewhere along the way? Is the choice of a particular process sequence compatible with demands for packaging? One of the first steps in establishing a complete and effective μTAS platform must be the categorizing of all process steps that are involved in making individual components, investigating process compatibility, and finding alternative processes or process sequences in cases of incompatibility. Design is in many ways a matter of experience and intuition and, with a design that satisfies the demands of the different partners involved, it is in principle possible to start fabricating the μTAS. However, depending on the complexity of the design, it is often very difficult to predict the performance of the μTAS intuitively. In these cases computer simulations may provide a means to study the performance of a μTAS prior to fabrication.

Computer simulations can significantly shorten the possibly long process of μTAS design, fabrication, and testing. The behavior of individual components, as well as the interplay between integrated components, can be predicted by computer simulations. By including a review step after computer simulation, structures can be optimized for their geometry and operational parameters based on the simulation results prior to actually fabricating the components or devices. This rational approach constitutes a significant improvement over the approach in which computer simulation is omitted and structures are optimized by numerous rounds of fabrication and testing. Important aspects of computer simulations are addressed in chapter 5. Key to the development of μTAS is microfabrication: the fabrication of structures down to micrometers in size. Aspects of microfabrication in silicon, glass, and polymers are discussed in chapters 6, 7 and 8. The explosive growth of microelectronics has led to a wide range of microfabrication tools for silicon, and consequently, much higher levels of experience and expertise exist for working with silicon as a material for microtechnology. Silicon presented an obvious choice as a material for the microelectronics industry due to its semiconductor properties. Few materials can surpass silicon when it comes to fabricating microstructures: silicon is suitable for the fabrication of electronic, mechanical, and optical components and thereby allows for high levels of functional integration. However, the superiority of silicon as a material for μTAS is debatable because the chemical stability of silicon is not very good. In fact, many of the microfabrication

methods available today are based on the controlled removal of silicon by chemical treatments. Although the surface of silicon can be treated to withstand harsh chemical environments, other materials may be more suitable for certain applications. Another important argument for investigating alternative materials is the relatively high cost of silicon, especially in applications where μTAS that have been in contact with biohazardous materials like blood are discarded after a single use. For these reasons polymers and glasses offer interesting alternatives to the use of silicon for μTAS. Because the use of polymers and glasses for mechanical, optical, and electronic components is still very much under development, fabrication of these materials carries with it concessions as to the level of functional integration that can be achieved. Hybrid solutions, in which microstructures of different functions and fabricated of different materials are assembled to make up a complete μTAS, will most likely arise.

With fabrication complete, structures must be tested in the laboratory to assess to what extent they live up to the previously defined specifications and how well computer simulations were able to predict the performance of the μTAS. When the device does not perform according to the specifications, all aspects downstream from the specifications need to be reconsidered. Modeling tools will have to be modified if they cannot predict the behavior of μTAS accurately enough.

As mentioned earlier, the aim of μTAS is a complete integration of all necessary steps for conducting a complete chemical analysis. Depending on the duration and complexity of the entire process of design and fabrication of μTAS, you can imagine that the final μTAS can be very expensive. In applications where the μTAS offers a significant improvement over conventional chemical analysis techniques and where the expected useful lifetime of the μTAS is long, the potential high cost of μTAS may not be the decisive factor that prevents its use. However, in applications where the μTAS is discarded after a single use, the cost of μTAS is very important. In some cases we may be simply unable to realize a true μTAS because we lack the technology to integrate certain essential components, e.g., lasers. The formal concept of functional integration in μTAS and all the accompanying advantages must therefore be balanced against complexity, cost, and feasibility. Undoubtedly we will see many examples of μTAS that result from the assembly of a microfabricated chip with conventional, possibly miniaturized, components, e.g., pumps, light sources, electronics. The assembly of these hybrids between microtechnology and conventional technology can be adjusted so that the level of integration makes sense for the individual application. With hybrid technology, you can discard certain parts of the hybrid while keeping expensive functional units like pumps and light sources.

At the time of writing this textbook, the commercial market for μTAS-based products is still rather small. However, market research reports predict consistent growth in the global market for μTAS-based products. These reports also agree that chemistry and the life sciences continue to be the major users of microsystem technology. With the anticipated future technological developments in chemistry and the life sciences, it is clear that microtechnology in general and μTAS specifically will play an essential role in these developments. Many fundamental