

# 4

## BIOMEMS

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### **Executive Summary**

This chapter provides information regarding bioMEMS market drivers for those who would like to utilize market drivers in their own roadmaps. In-vivo and in-vitro applications that make up the bioMEMS family of products are currently utilizing considerably different front-end and packaging technologies. Material requirements suggest that many differing technologies will be used in the future for this dynamically growing microsystems market area. The applications of MEMS in the medical-biochemical realm are presently poised to surpass MEMS applications in other areas, in terms of market revenue. Until the mid 1990's, MEMS techniques in the medical-biochemical field were usually associated with blood-pressure sensors. In the past 5 years, a host of other less-publicized bioMEMS-based devices are being used in medical equipment or have

been prototyped and ready to enter the market. Thus, the percentage occupied by bioMEMS in the total MEMS market is expected to be close to 40% in 2003 from 20% it enjoyed in 1996.

The bioMEMS market can be divided into in-vivo and in-vitro segments. The in-vivo or “Inside-the Human Body” includes bioMEMS devices like micromotors, retinal implants, microcatheters etc., and are significantly small compared to the in-vitro segment or “Outside-the Human Body”. In-vitro devices range from body fluid microanalysis devices to microsurgical equipment and account for the bulk of the present bioMEMS market. The only bioMEMS device that can be expected to have a billion dollar revenue is the biochip, an in-vitro device in which bio-molecules are chemically analyzed on a credit-card-sized chip as if it were a full-fledged laboratory. The value of the biochip market in 2000 was \$ 500 million and is expected to be \$ 3 billion in 2004 according to our contributors and their sources. The DNA array market, a subset of the biochip market, expanded from \$45 million in 1997 to \$330 million in 2001. The increasing interest displayed by pharmaceutical makers to find new drugs through genetic information is expected to drive its demand to \$ 800 million in 2006. An ancillary DNA instrumentation and equipment market, that accompanies the DNA array market, accounts for an additional 50% of the DNA market during any given period of time. BioMEMS devices such as pacemaker accelerometers, electronic noses and blood-pressure sensors had a combined market share of around \$300 million in 2001. This figure is expected to increase exponentially, and the total bioMEMS market could rise to \$4 billion in 2004.

These figures could give rise to skepticism since the estimated market figures for MEMS devices have always fallen well short of expectations. The automotive market share was wrongfully estimated in 1992 to be around \$500 million for the year 2000. The aggressive competition intrinsic to the automotive industry that drives down prices was not considered and the actual market revenue turned out to be \$150 million. Optical MEMS suffered a huge setback due to exaggerated predictions based on the dot-com surge and the over 100% annual growth predicted that trickled down to single-digit growth. In contrast, bioMEMS applications satisfy very important requirements in a rapidly improving medical field, which is not as volatile as the automotive industry. In addition, most bioMEMS products are disposable, ensuring sustained replacement, and the estimated market figures for bioMEMS have accounted for a sustained

reduction of cost in the future. Thus, the estimated market figures for bioMEMS will not be as way off the mark as that predicted for the automotive or optical MEMS markets.

Unlike other MEMS markets that use silicon as the primary material, bioMEMS devices encompass both IC and non-IC-compatible technologies. Countries like Germany, Switzerland, Taiwan, Korea, Japan and the U.S. are among the leaders in non-IC-compatible bioMEMS technology.

A few bioMEMS devices have captured the imagination of the biochemical industry and have weaned them from conventional devices. Chemical industries and manufacturers of R&D analytical equipment have displayed immense interest in microreactors, since they reduce research costs substantially. The demand for microreactors is expected to grow rapidly considering mounting pharmaceutical R&D costs. The “Electronic Nose” is one of the very few MEMS devices that have overreached market expectations. The market for electronic noses in 1996 was \$0.1 million with 1000 units sold. Nexus predicted in 1998, that this market in 2002 would be \$5 million with sales of 50,000 units. In 1999 however, the electronic nose market was already \$15 million per year. The popularity of electronic noses is expected to increase tremendously due to increasing security concerns, and pioneer companies in this field expect the market to be \$50 million in the next 2-3 years.

The bioMEMS market is relatively new and has not reached maturity and there is enough room for new players. The only bioMEMS product that has a significant number of competitive companies is the DNA array. The majority of other bioMEMS devices are one-company dominated. Niche hi-tech markets that were not visualized before are being developed continuously. This necessitates development of awareness of the end-user by bioMEMS companies about the benefits of their devices to adequately capture existing market segments in the ever-demanding and highly regulated medical field.

There is significant variation among MEMS/MST market size predictions projected by various organizations. Irrespective of these variations, the compound annual growth rate (CAGR) for medical applications has turned out to be the highest in comparison to any other MEMS/MST market, since the figures predicted for optical MEMS have not materialized. BioMEMS devices that do not have equivalent substitutes in the non-MEMS realm look the most promising, unlike other MEMS/MST application segments.

Anytime a roadmap is attempted concerning a new and unique technology, it becomes a living document, subject to constant change. The purpose of this document is to provide a roadmap of where the technology currently exists and where we anticipate it being in both the near and distant future. We look forward to continually updating the information in this document, as it will undoubtedly change.

## 1.0 Introduction

The term bioMEMS, i.e. biological MEMS, in this chapter, refers to all MEMS or MST devices that have applications in medical, biochemical or any non-medical biological applications. Medical devices include blood-pressure sensors, catheter micromotors, pacemakers, etc. Biochemical applications include microreactors, DNA arrays, etc., while non-medical biological applications comprise tensile sensors, micropipettes, etc. A roadmap as a rule consists of information pertaining to the adoption of technology nodes on a time scale. The roadmap for semiconductors from SEMATECH gives the expected values of important parameters of semiconductor devices like minimum feature size, DRAM pitch, gate length etc., on a time scale. The bioMEMS industry is still young (except for medical pressure sensors) and is not as generic as semiconductor technology. Hence this chapter gives a detailed description of bioMEMS devices both available on the market and under development, so the reader can have a better grasp of the large product range in the bioMEMS industry. We have provided product definitions in detail and have projected important device characteristics of a few bioMEMS devices.

BioMEMS is one among the few microsystems focus areas that have initiated the search for device materials other than silicon. Any in-vitro medical device would have much more functionality if it were made from a carbon-based material such as plastic. BioMEMS companies have adapted sensors with polymer or metallic coatings to make sure their devices are biocompatible. In addition, ceramics and quartz have long been used in bio-medical devices. In this chapter we discuss the bioMEMS industry according to:

- (a) IC-compatible and potentially IC-compatible bulk micromachining, sacrificial surface micromachining, and some high-aspect-ratio micromachining technologies.
- (b) Non-IC-like technologies like LIGA and other HARM technologies, which use plastic, nickel, etc.

Table 1 lists thirty-eight IC and non-IC devices that can be described as bioMEMS.

**Table 1. IC and Non-IC BioMEMS Devices**

<b>Product</b>	<b>Sense</b>	<b>Think</b>	<b>Act</b>	<b>Communicate</b>
<b>Active transdermal patches (microneedle-based)</b>	X	X	X	
<b>Biliary stents</b>			X	
<b>Cardiovascular stents</b>			X	
<b>Catheter-based pressure sensor</b>	X		X	
<b>Data knife (a surgical knife with sensors)</b>	X	X	X	
<b>Dendrimer drug delivery</b>	X	X	X	
<b>Disposable blood-pressure sensors</b>	X	X		X
<b>DNA microarray chips</b>	X	X		X
<b>Electronic nose</b>	X	X		X
<b>Gas sensors</b>	X	X		X
<b>Glucose-monitoring sensor</b>	X	X		X
<b>Hearing-aid / Cochlear implants</b>	X	X	X	X
<b>Heart pacemaker</b>	X	X	X	X
<b>Immunoligand assay</b>	X	X		X
<b>Implantable defibrillators</b>			X	
<b>Implantable pumps for drug delivery</b>	X	X	X	X
<b>Intra-cranial pressure sensors</b>	X	X		X
<b>In vitro fertilization (IVF) embryo chip</b>				
<b>Lab-on-a-chip</b>	X	X		X
<b>Micro actuator for minimally invasive surgery</b>	X	X	X	
<b>Micro linear stepper motor for intra-ocular lens</b>		X	X	
<b>Microcatheter</b>			X	
<b>Microgripper</b>			X	
<b>Micromotor for endoscopes and catheters</b>			X	

<b>Microphysiometer</b>	X	X		X
<b>Micropipette for nanodispensing</b>			X	
<b>Micropump for asthma inhalers</b>			X	
<b>Microreactors</b>	X		X	
<b>Microspectrometer</b>	X	X		X
<b>Micro teeth</b>	X		X	
<b>Minimally invasive arthroscopic tools</b>			X	
<b>Nanomotor</b>		X	X	
<b>Non-invasive surgical tools (lancets, microneedles, microtweezers)</b>			X	
<b>Protein chips</b>	X	X		X
<b>Retinal implants</b>	X	X	X	X
<b>pH sensor used for dialysis</b>	X	X		
<b>Smart cataract surgical sensor</b>	X	X	X	
<b>Strain sensor for artificial leg</b>	X	X	X	X
<b>Ultrasound transducers</b>	X		X	
<b>Wobble motors</b>			X	

One of the most complex devices targeted in the bioMEMS section to help drive the roadmap effort is the lab-on-a-chip, a device that can be used in a variety of biochemical analyses. A lab-on-a-chip can be used to test biological fluids (biofluidic chips) or aerosols (electronic noses). The applications for lab-on-a-chip devices include: drug screening, disease identification, critical-care patient monitoring, and bio-agent identification. Lab-on-a-chip devices are in a group of bioMEMS devices that are no longer just sensible, but are being pushed to either become or be part of intelligent systems that can sense, think, act, and communicate. The most well known bioMEMS product is the DNA microarray chip. The DNA chip can be considered a part of microfluidic chip technologies that includes lab-on-a-chip and electronic nose devices. There are 25 major companies manufacturing DNA microarrays, the pioneer being Affymetrix, Micralyne along with Cepheid and Aclara Biosciences. The latter two, which also make DNA microarrays, are major lab-on-a-chip companies. There are more than 15 companies around the

globe catering to the increasing needs of olfactory sensing requirements through different electronic nose technologies, for industries ranging from food packaging to medical diagnostics. This is an important market driver for the bioMEMS industry second only to DNA arrays.

BioMEMS companies have chosen a variety of manufacturing technologies, packaging efforts and systemization strategies mostly dependent on application. This chapter gives a detailed explanation of specific bioMEMS products and the technology adopted. The following pages discuss of some of the bioMEMS efforts by IC and non-IC manufacturing realms and focus on lab-on-a-chip technologies. They are stressing current MEMS-based manufacturing technologies, packaging technologies, interconnect technologies and systemization efforts.

## **2.0 Bulk Micromachined, IC-Compatible bioMEMS**

### **2.1. Product Information**

The earliest and most popular bioMEMS device is the blood-pressure sensor. The piezoresistive blood-pressure sensor is used in many diagnostic and therapeutic devices and is made using piezoresistive semiconductor technology, which uses bulk micromachining and surface etching techniques. The most recent development in piezoresistive pressure sensors is the use of bulk micromachining of a silicon-on-insulator (SOI) wafer. A hole can be formed from the backside of the wafer to make a silicon diaphragm. Wheatstone bridges consisting of piezoresistors are located on the edge of the diaphragm to sense the differential pressure. SOI technology ensures that pressure sensors are electrically insulated from the bulk substrate, increasing the operating-temperature range (S. Renard, 2001). MST based blood-pressure instruments that use miniature pressure sensors cost about \$10 and are disposable. These have made conventional reusable \$500 devices that cost \$50 for every additional usage, obsolete.

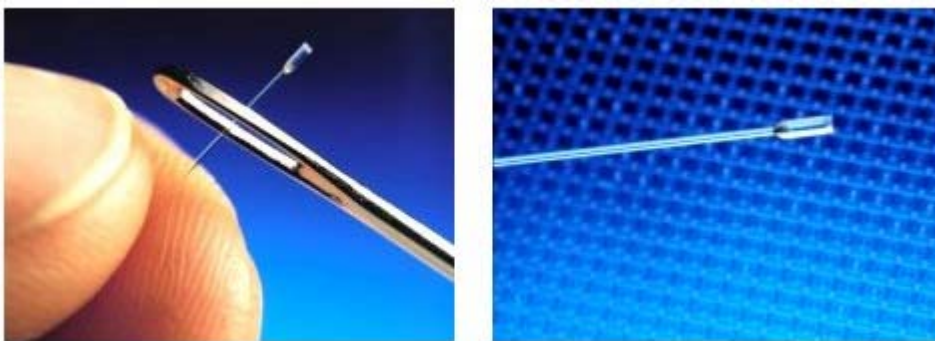
MST components in most MST-based implantable infusion pumps are pressure sensors and microvalves. Implantable pumps can range from popular insulin pumps to unwanted intrathecal pumps. Infusion pumps and drug-delivery systems meter medication through a disposable plastic set or tube inserted into the patient. For infusion applications, a silicon bulk micromachined microstructure flow restrictor can provide the precise low-flow-rate control required. A silicon insulin micropump can replace a bulky and cumbersome conventional insulin pumping system completely, and cuts down the volume required by more than 80%.

Silicon-based tactile sensors are used for biomechanics research, clinical evaluations of hand functions, and in rehabilitation devices. A tensile sensor consists of a silicon diaphragm and is instrumented with ion-implanted piezoresistors in a Wheatstone bridge configuration. A solid dome on the top of the silicon diaphragm acts as a force-to-pressure transducer. The applied force is distributed across the diaphragm via the dome. When the distributed force deforms the diaphragm, it gives rise to an output voltage proportional to the applied force for small deflections. Medical uses of tactile sensors are twofold: To detect tumors and guide microcatheters; and spatial and temporal pressure distribution from the pulse of a human wrist, which is used for biomechanics information in telesurgery or surgical training.

Bulk micromachining has a major role to play in nanodispensing techniques. Micropipettes are used to fill microscopic cavities, e.g. the wells of microtiter plates or even micromachined nanotiterplates. Micropipettes can be integrated easily in standard laboratory environments and are mostly used in pharmaceutical drug research, gene insertion and biochemistry.

## 2.2. Status of Bulk, IC bioMEMS Technology and Manufacturers

Invasive blood-pressure sensors are based on the piezoresistive principle and use bulk micromachining techniques. Companies like Tronics Microsystems employ SOI bulk micromachining to make piezoresistive pressure sensors to measure blood pressure. Some of the most advanced and tiniest in-vivo blood-pressure sensors make use of fiber-optic interferometric principles (Figure 1).



**Figure 1. A Fiber-optic In-vivo Biomedical Pressure Transducer (0.5-mm O.D. and 0.5-mm long) made with Silicon Micromachining Technology. The Transducer is at the Tip of an Optical Fiber. (Source: FISO Technologies).**

There are no major manufacturers of bulk micromachined-based insulin micropumps, though a few companies in Europe have developed a prototype. Another potential MEMS/MST

micropump, the intrathecal pump, is surgically placed under the skin of the abdomen to deliver morphine directly into the intrathecal space. Commercially available non-MST intrathecal pumps consist of a catheter and a micropump. Constant-rate implantable intrathecal infusion drug pumps are manufactured by using high-precision microsystem technology to develop a glass capillary of extreme compactness. The use of microsystems in micropump technology to make innovative choke paths, i.e. constrictions in an outlet that restricts fluid flow, has resulted in an 85% reduction in building space in comparison with choke paths made of conventional drug infusion instruments. Although many manufacturers make micropipettes for laboratory use, only a few can be considered truly MST like those from GeSiM GmbH of Germany.

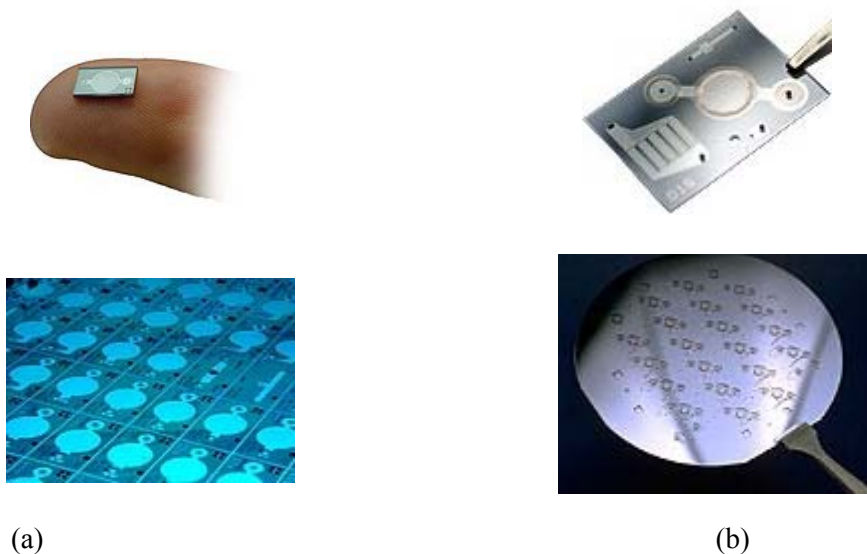
There are few companies that make tactile-sensing systems used for biomechanics in addition to industrial, aerodynamics and robotics, but none are MST based. The U.S. Government is currently funding a new project to develop a MST-based haptic glove that uses sophisticated tactile sensors to collect surgical data.

### **2.3. Bulk, IC bioMEMS Vision: The Coming 3 Years**

Presently, the wafer fabrication process for most silicon-based pressure sensors combines conventional bipolar IC technology with bulk micromachining. This process etches away most of the diaphragm making the silicon wafers susceptible to breakage during handling. To reduce in-process damage, some manufacturers have recently changed the blood-pressure sensor fabrication process by performing the etch process as the last major photolithography step. In addition, the adoption of electrochemical etch-stop techniques ensures smaller variations in wafer thickness and has enabled Motorola to reduce pressure-sensor dimensions by more than 10% (Bitko, 2000). All medical pressure-sensor companies are expected to accept these process technology changes in the next 3 years.

Debiotech, a major micropump player based in Switzerland, plans to create a bulk micromachined micropump chip, the Chronojet<sup>TM</sup> that is capable of infusing insulin in doses as small as 150 nanolitres. Debiotech also intends to adopt surface micromachining techniques to make insulin micropumps in collaboration with Tronics Microsystems, France.

The technologies used for both of the micropumps shown in Figure 2 are standard silicon bulk micromachining and anodic wafer bonding. The overall wafer processing is a 5-mask process for the Chronojet™ and a 12-mask process for the implantable pump.



**Figure 2. The Chronojet™ Pump has a Flow Rate of 10  $\mu\text{l}$  /min. and a Chip Size of 6 mm x 10 mm (a). An Implantable Pump has a Flow Rate of 0 to 100  $\mu\text{l}$  /hour from a Chip just 16 x 12 x 1.86mm (b). (Source: Debiotech)**

Inverness Medical, Inc., which was recently acquired by Johnson & Johnson, had entered into a licensing agreement with Debiotech to develop a miniature insulin pump that can be completely taped onto the skin. The cost of production of insulin pumps could be reduced considerably, if MEMS techniques are used. Companies offering intrathecal drug pumps are developing programmable versions and plan to obtain regulatory approval by the end of 2002.

#### **2.4. Bulk, IC bioMEMS Vision: 3 to 5 Years From Today**

For applications where miniaturization is required (e.g., catheter tip pressure measurement), manufacturers of bulk micromachined blood-pressure sensors will try to transfer to surface micromachining technology. Two Swedish institutions, the Royal Institute of Technology and RADI Medical Systems, have teamed up to design, fabricate and commercialize very small piezoresistive surface micromachined silicon-pressure sensors for use in catheter-based medical equipment for intravascular pressure measurements (Figure 3).



**Figure 3. An Ultra-miniaturized Medical Pressure Sensor Chip just 0.1 mm x 0.14 mm x 1.3 mm (Source: Melvås P., Royal Institute of Technology, Sweden).**

Miniature wireless capacitive-based pressure-measurement in-vivo devices, for disposable and implantable applications, will become available. The adoption of SOI technology will be virtually universal for MEMS pressure sensors. According to current research trends, it can be assumed that there will be a migration to surface micromachining from bulk micromachining in the area of implantable micropumps within the next 5 years due to its inherent advantages.

MIT and Carnegie Mellon University have joined forces under a DARPA project to develop new tactile interfaces that exploit advances in MEMS to create high-bandwidth displays for stimulating the human tactile sense. The project foresees a major bioMEMS application wherein tactile interfaces attached to the human body, through a glove or wristband, could be used with wearable computers or communication devices to enable remote communication in a hostile environment. A rudimentary version of a military communication link based on tactile sensors will be developed within 5 years for the U.S. Army. Head-pressure analysis systems that provide fit, comfort, and seal information for headgear such as gas masks, helmets, goggles, etc., for military personnel could also be developed in the near future. The most significant future application of tactile sensors will be in developing haptic gloves that will revolutionize medical surgery. These tensile sensors will provide the surgeon information regarding the pressure to be applied during surgery in a simulation environment.

Porous silicon is obtained by electrochemical etching of silicon in HF-based solutions and can be used in HARM applications since it can have aspect ratios up to 250. Silicon can be made either microporous (20 Å) or macroporous (10 µm) and the pores follow crystallographic orientation. Porous silicon oxidizes readily and etches at a very high rate. It has been used in a number of applications including electrochemical reference electrodes, high-surface-area gas

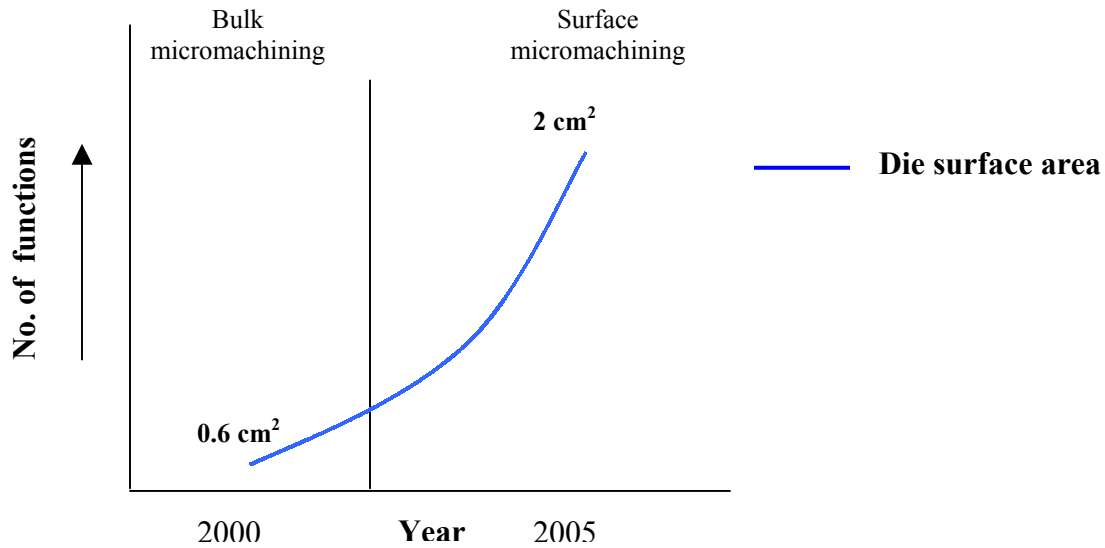
sensors, humidity sensors, and sacrificial layers in micromachining. Recent research has focused on using porous silicon as a substrate for chemical sensors.

Biosilicon™ from psiMedica(U.K.), is wafer-thin, porous silicon. It can be used to make temporary scaffolds to promote bone healing that later dissolves away. It could also function both as a reservoir for drugs and house a tiny computer system to control timing and dosage. Porous silicon sensors have been built before, but their practicality has been limited because of high resistance in the electrodes connected to the porous silicon and power requirements of as much as 5 volts. A unique metallization process lets researchers at the Georgia Institute of Technology dramatically reduce the resistance of the electrodes built into the silicon. Sensors can thus operate between one and 10 millivolts. The sensors can detect ammonia, hydrochloric acid and nitrogen oxides at concentrations between 10 and 100 ppm, compared to 100 to 1,000 ppm for the higher-voltage ones. Applications include biological /chemical weapons detection, blood analysis, glucose detection, pathogen testing and analyzing allergic reactions. Porous silicon for drug delivery and in low-voltage biosensors will be widespread in the next 5 years.

## **2.5. Bulk, IC bioMEMS Vision: 5+ Years From Today**

If current trends continue, die sizes of single-function blood-pressure sensors will be reduced up to 50% which will lead to smaller packages. The ultimate goal of advanced IC-based biosensors is a multi-functional microchip that can measure blood pressure; partial pressure and concentration of blood gases; the pH of blood, etc. Manufacturers will try to incorporate as many functions as possible, for monolithic integration on a chip, resulting in larger die sizes (Figure 4).

Recent developments in wireless technology can make a major impact in blood-pressure sensing and other medical devices. Bluetooth™, the short-range 2.4-GHz radio networking technology, is currently used by a start-up high tech firm to monitor body pulse and temperature of Alzheimer patients and to identify the location of lost kids and pets. This is enabled by a synergy of advanced biosensor technology and Web-enabled wireless telecommunications linked to Global Positioning Systems (GPSs). Future products using this technology, expected within 5 years, include remote human blood-pressure monitoring.



**Figure 4. Trends in IC-compatible Medical Sensors.**

The visually impaired could use tactile channels for sensory substitution and accretion by 2010. It could be used in any situation where vision and hearing are impossible, or in tandem with vision and hearing to provide multi-sensory information. Thus, tensile sensors can be used for both civilian and military applications, such as pilot alerting systems, geo-spatial information for scuba divers, real-time communication between infantry soldiers in military actions, etc. Beckman Institute at the University of Illinois at Urbana-Champaign, is developing oral tactile interfaces on the tongue, lips or mouth cavity that can be used to complement the functions of the hand during man-to-machine interaction. But, complete technical feasibility, let alone commercial feasibility, is distant. Three-dimensional tensile sensors will increasingly be used in robots during space exploration (Mea, 2000). This will advance the capabilities for remote medical surgery.

## **2.6. Market Information**

The current worldwide market for blood-pressure sensor products is 18 million to 20 million units a year (Forbes, 2001). Treatment costs, for those diagnosed with diabetes mellitus globally, exceeds \$100 billion annually. Diabetes mellitus affects more than 16 million Americans. The estimated intrathecal drug pump market in 1998 was \$100 million worldwide and is growing annually at 30 to 40%.

### **3.0 Surface Micromachined, IC-Compatible bioMEMS**

#### **3.1. Product Information**

The blend of surface micromachining on SOI and telemetry has helped in the development of a new miniature capacitive pressure sensor clinical data-acquisition microsystem that can be placed as close as possible to an organ (Renard S., et. al., 2001). By adopting this in-vivo pressure sensor microsystem, there will be a vast improvement in therapies and diagnostic methods since vital clinical data can be obtained. A 100-mm wafer can be used to make over 5,500 miniature SOI telemetric capacitive pressure sensors. The sensors have a sensitivity of a few picoFarads for every 100 kPa of pressure change.

The MEMS device in modern pacemakers is a surface micromachined accelerometer. The FDA has approved to-date only one MEMS based implantable pacemaker, Medtronic's' InSync, in July 2001. A pacemaker is usually surgically implanted near the shoulder with three leads, or wires leading to the heart. It protects patients from abnormal heartbeats. The heart must beat faster during periods of increased physical exertion for pacemaker users since they suffer from bradycardia. The accelerometer ensures this by monitoring the heart's activity level and works alongside a microprocessor to deliver more electricity to keep the heart in rhythm when heart-beat levels go above or below the required heart-rate range.

An integrated capacitive pressure sensor consists of an array of single circular pressure-sensitive elements switched in parallel. Fraunhofer-IMS, Germany, can produce pressure sensors for any pressure range fabricated in a surface micromachined technique, fully integrated in a standard 1.5- $\mu\text{m}$  CMOS process. The absolute pressure sensor is built as a capacitor and consists of a polysilicon membrane separated by a vacuum-sealed cavity over a highly-doped area in the silicon substrate.

A 400-microneedle array of 10 mm<sup>2</sup> in size built by researchers from the Georgia Institute of Technology, can act as a micro insulin bank. This array is placed under a silicon chip containing insulin and a microprocessor pump. The entire cartridge area is 2 cm<sup>2</sup> with a height of a few millimeters. The silicon chip is etched with valves, channels, and reservoirs that hold concentrated insulin. A micropump controls the release of insulin into a dilution channel prior to filtering through the microneedles.

Both gas sensors and medical imaging products can be based on ultrasonic transducers. Sensant Corp. (U.S.) offers MEMS-based ultrasonic gas sensors commercially. Surface micromachined-based ultrasonic transducers are built on the surface of a silicon wafer and resemble tiny percussion drums. When activated electronically, the drums generate high-frequency sound waves. Conversely, when sound waves impinge upon the drums, they vibrate the drum membrane and produce an electrical signal. Ultrasound transducers provide new improvements in medical ultrasound imaging. They also offer the potential for significantly improved 1D array image quality in addition to reduced connection and cabling requirements.

Electronic noses can be based on many types of sensors. The metal MOS sensors in electronic noses use tin-oxide-based thick films deposited onto two different types of substrates: alumina and silicon micromachined substrates. The other types of IC-compatible micromachined sensors in electronic noses include:

- Field-effect (FE) sensor technology based on the field effect generated by ambient gases in MOSFETs with catalytic metals as gates. The manufacturing techniques for these types of sensors are very similar to surface micromachining.
- MOS sensor technology based on changes in resistance of a sensitive metal-oxide layer induced by the surface interaction with ambient gases. CMOS and bulk micromachining techniques are used to make these MOS sensors.

Microsystem technology is playing a major role in the miniaturization of hearing aids. In a microsystem-based hearing aid developed by the University of Michigan-Ann Arbor, the microphone uses a low-stress polysilicon diaphragm suspended above a perforated p<sup>+</sup> silicon backplate. It was fabricated by a combination of surface and bulk micromachining. Sacrificial surface micromachining techniques are also being used by researchers at the Center for Microelectronic Sensors and MEMS, the University of Cincinnati, to make a fully implantable hearing aid which is based on a magnetic microactuator. A combination of bulk and surface micromachining techniques including chemical vapor deposition methods can be used to make microphone arrays.

The Digital Micromirror Device or DMD<sup>TM</sup> from Texas Instruments is an array of micro-mirrors and acts as a light modulator for high-definition projection television systems. This array, which consists of more than 400,000 micro-mirrors, is made by thin-film and surface

micromachining technology and can process DNA information. DNA chip processing requires photolithography to synthesize small regions on the chip by photomasks. A mask is required for each option A, C, T and G and for each position on the probe. Therefore, a probe 25 bases long requires 100 masks. These numbers soon multiply as the number of probes contained on a DNA chip increase to hundreds of thousands. Researchers at the University of Wisconsin in Madison, led by Professor Franco Cerrina, found a better way of synthesizing the chips using the DMD™ called a Maskless Array Synthesizer (MAS) based on TI's Digital Light Processor (DLP™) technology. The micro-mirrors reflect light onto particular regions of a DNA chip by tilting the mirrors  $\pm 10^\circ$ , eliminating the need for an inordinate number of photolithographic masks. By using MAS, high-density custom-built DNA chips can be made in 3 hours, without the need for costly high-speed robots currently being used.

### **3.2. Status of Surface, IC bioMEMS Technology And Manufacturers**

Industry leaders in pacemaker accelerometer technology use an epi-SOI surface micromachining process. A single crystal epitaxial silicon layer is grown up to several tens of  $\mu\text{m}$ . It is then etched by deep RIE techniques to form a 20- $\mu\text{m}$ -thick silicon layer and 2- $\mu\text{m}$  minimum pattern width. This process allows the production of thick structures with very high aspect ratios, low stress, and high Q factors, which leads to smaller pacemaker accelerometers. Miniature capacitive pressure sensors from Tronics have an area less than 1  $\text{mm}^2$  and a quick response time of less than 5 ms and can be used for medical applications with few modifications. At present, Medtronic produces about half the number of pacemakers sold in the US. Integrity®  $\mu$ , the world's smallest, dual-chamber implantable pacemaker, has a volume of 8 ccs and weighs 18 gms and is available through St. Jude Medical, Inc. Single-chamber pacemakers have reached levels of 5.9 ccs and 17 gms. Younger and healthier patients are likely to get a double-chamber pacemaker and the older and sicker patients are usually prescribed a single-chamber pacemaker. The latest pacemaker designs provide closed-loop rate adaptation. The closed loop stimulation restores the coupling of the pacing rate to the natural control loop, constantly guaranteeing an adequate heart rate.

Acreo, Sweden, manufactures a pressure sensor 1.3 x 0.1 x 0.1 mm for Radi Medical Systems, and claims it's the world's smallest blood-pressure sensor. It developed this pressure sensor with the Royal Institute of Technology, Sweden. Swedish MEMS/MST manufacturer

Silex (a spin-off from Acreo), which raised 2.7 million Euros in November 2001, now produces the sensor.

Currently there are only a few hearing-aid companies using MEMS to make microphones, but many universities have developed surface micromachining techniques to reduce microphone sizes. The approaches adopted by them vary considerably. Sacrificial surface micromachining techniques are being used by researchers at the Center for Microelectronic Sensors and MEMS, the University of Cincinnati, to make a fully implantable hearing aid that is based on a magnetic microactuator. The Research Center for Integrated Microsystems at the University of Windsor, Canada, has developed MEMS deposition and etching methods to make a 4-mm x 4-mm MEMS microphone array. A combination of bulk and surface micromachining techniques including CVD methods are used to make the array. MEMS A/S, Denmark, uses a combination of bulk and sacrificial surface techniques to make microphones.

It is expected that MAS technology will replace conventional photolithographic mask technology used by most DNA array manufacturers. Nimblegen, the company that introduced MAS commercially is in direct competition to Affymetrix, which holds a 62% share of the current DNA chip market.

Redeon, Inc., Cambridge, MA, is trying to commercialize an invention of its founders Mark Prausnitz and Mark Allen from the Georgia Institute of Technology. They invented a 10-mm<sup>2</sup> array of silicon needles (each 150- $\mu$ m long) that make microscopic holes in the skin and can painlessly pump drugs into the body (Figure 5). These silicon microhypodermic needles were fabricated with a combination of bulk and surface micromachining techniques. The painless needle is actually a very small patch, about the size of a human eye's pupil that is covered with 400 microneedles (Henry, 1998).

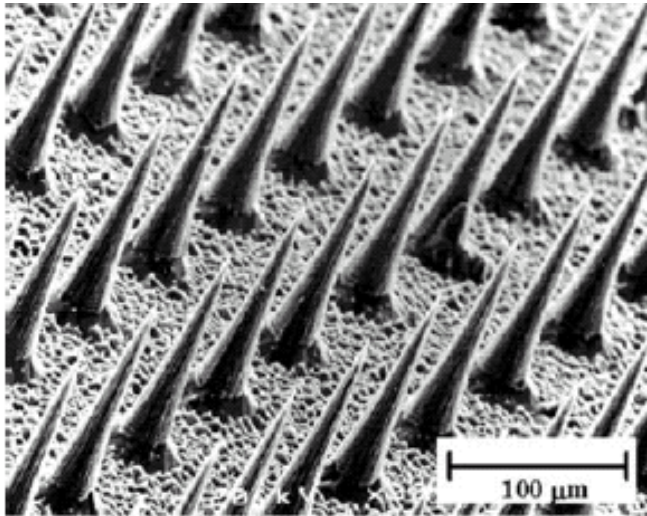


Figure 5. Micromachined Needles for Transdermal Drug Release (Source: Henry S, 1998, Georgia Tech).

### 3.3. Surface, IC bioMEMS Vision: The Coming 3 Years

All major hearing-aid manufacturers around the globe are expected to switch completely to MST or MEMS technology within the next few years. MST-based technologies will affect in-the-ear (ITE) and completely-in-canal (CIC) types of hearing aids significantly. Figures 6 and 7 and Table 2 provide market and technology information on hearing-aid devices.

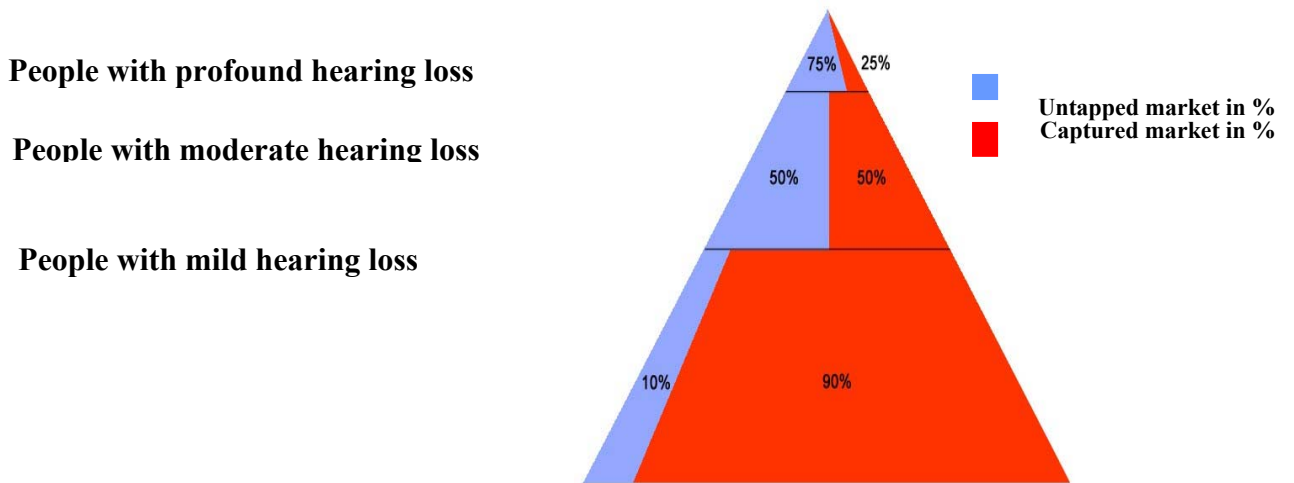
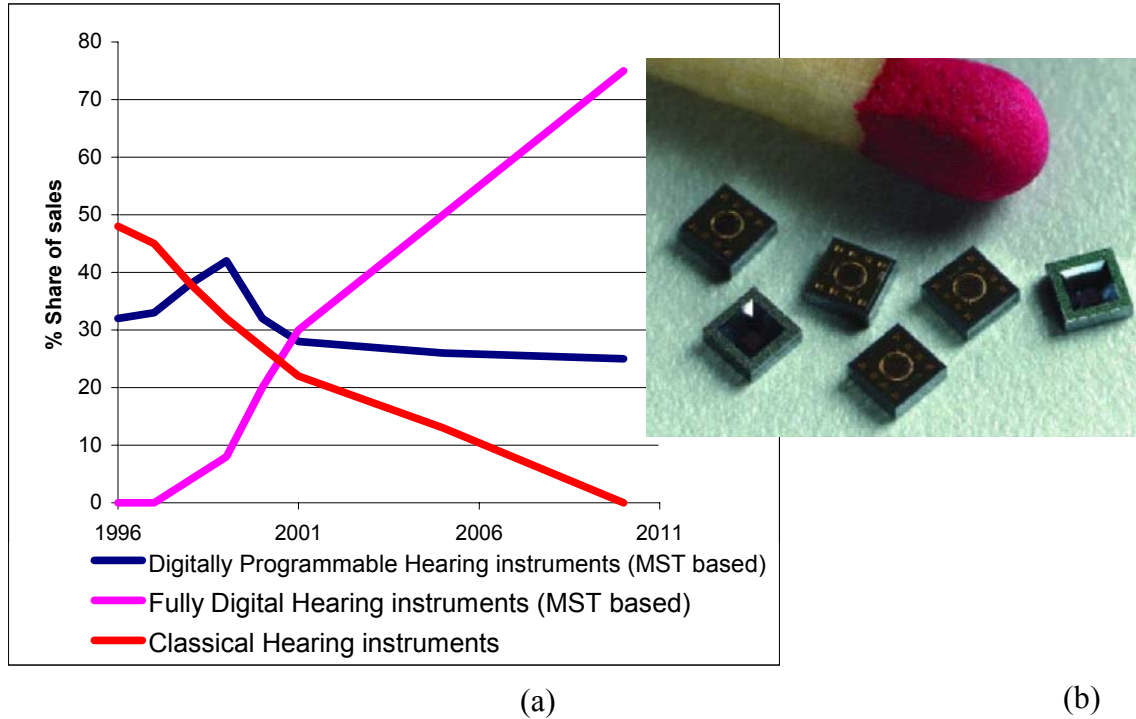


Figure 6. Present Market Potential of Hearing-aid Instruments.

**Table 2: Types and Market Share of Hearing-aid Instruments**

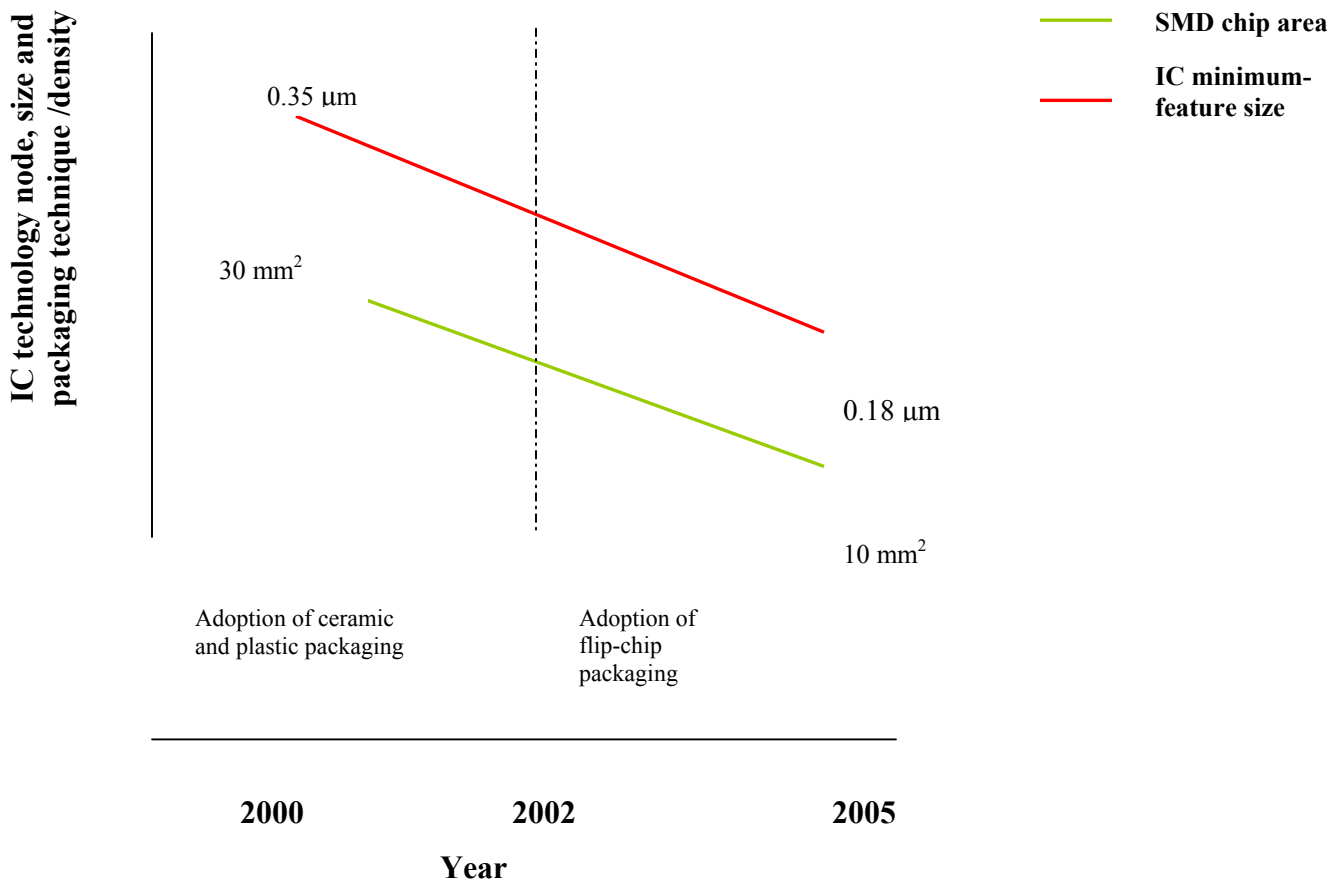
Instrument type	Behind-the-ear (BTE)	In-the-ear (ITE)	Completely in canal (CIC)
% Market share	45	44	11
Price (US\$)	\$400-\$600	\$500-\$700	\$1400-\$2000



**Figure 7. Percentage of Global Sales for Hearing Aids According to Technology (a). A Silicon-based Condenser Microphone (b). (Source: Knowles Electronics, Inc.)**

The fabrication of silicon microphones using MST allows the integration of mechanical and electrical circuits on the same chip. This offers the option of creating a digital output signal, which is much less susceptible to electromagnetic interference and allows direct communication with a microcontroller or Digital Signal Processor (DSP), the latter introduced in 1998. A further benefit is the possibility of packaging the microphone as a surface-mounted device (SMD) and assembling it on a printed-circuit board (PCB) using standard CMOS processes. The high temperature of a solder process would destroy the conventional non-MST electronic microphones, during SMD mounting. A blend of surface and bulk micromachining processing steps to make microphones allows its fabrication in a standard CMOS production line. In

addition to hearing aids, these MST-based silicon microphones have applications in cellular phones, PCs, laptops, PDAs and MP3 players, etc., due to the ability to incorporate additional electronics in the SMD package and its reduced sensitivity to vibration, shock and temperature (Figure 8). Microtronic A/S, a hearing-aid company that has applied microsystems technology to manufacture digital hearing aids, estimates return on microsystems investment to be more than 280% over the next 4 years. Hearing aids are a prime example of the benefits of adopting microsystems in medical applications. MST-based hearing-aid companies have an opportunity to focus on producing fully digital hearing instruments for the untapped hearing-aid markets as shown in Figure 6.



**Figure 8. Trends in Microphones.**

### **3.4. Surface, IC bioMEMS Vision: 3 to 5 Years From Today**

The introduction of multiple sensors for pressure and O<sub>2</sub> saturation will allow the pacemaker of the future to improve its speed of response at the onset of exercise, to provide a proportionality of the heart rate to the work load, and to offer differential sensitivity to physiological changes. New packaging and interconnect technologies, such as chip-scale packaging and flexible laminates, are being developed by the Fraunhofer Institute, Germany, to provide higher-density electronics for future pacemaker designs.

Pacemaker users cannot undergo Magnetic Resonance Imaging (MRI), a diagnostic technique used to produce high-quality images of the interior of the human body. Biophan Technologies, Inc., a New York-based company started by the inventor of the cardiac pacemaker, Wilson Greatbatch, developed a solution in 2001 that, for the first time, allows cardiac patients with implantable pacemakers to safely undergo MRI diagnosis. When a patient with an implantable pacemaker needs to undergo an MRI procedure, the pacemaker's performance is disturbed or interrupted by exposure to the MRI's magnetic field. Deaths have been reported when pacemaker wearers used MRIs. As a result, both the U.S. Food and Drug Administration (FDA) and many pacemaker manufacturers have issued warnings against pacemaker wearers undergoing MRI. All future pacemakers will be designed to avoid damage during an MRI within the next 5 years.

In 2000, a new packaging solution for pacemakers was introduced. A French pacemaker accelerometer manufacturer, Tronics, now uses chip-size packaging, a technology with the following considerable advantages (Renard, 2000) compared over existing ones:

- Packaging at the size of the chip
- Realization at the wafer level
- Low-cost production with batch processing
- No thermal mismatch between the chip and its package
- Easy testing and handling of the chip
- Soldering with traditional surface-mountable technologies
- Reworkability of the chips after mounting

The trend has been towards the adoption of biaxial accelerometers in pacemakers as shown in Figures 9 and 10.

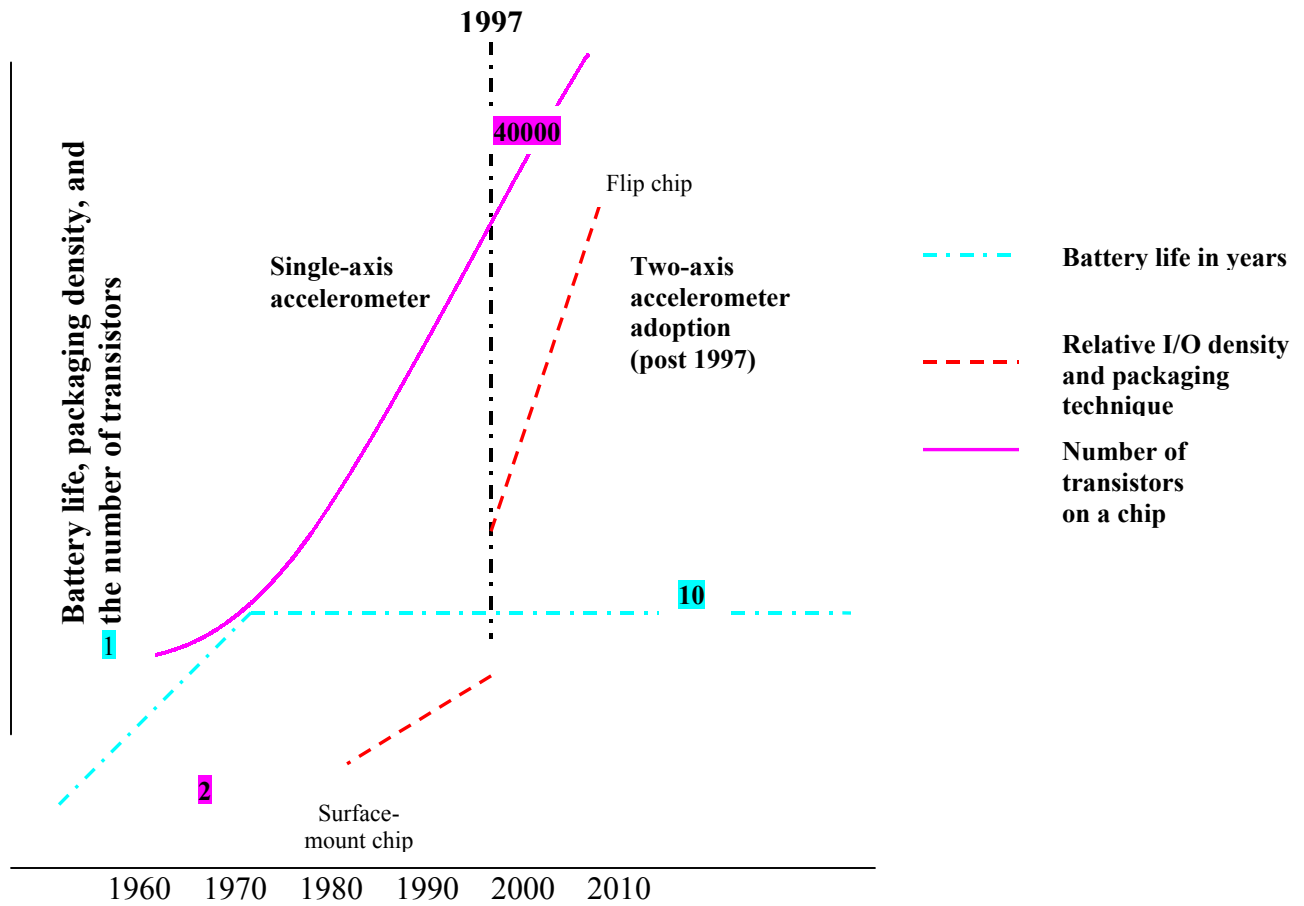


Figure 9. Trends in Accelerometers used in MST-based Pacemakers.



Figure 10. A Chip-size-packaged Twin-axis Accelerometer (Source: Tronics).

### **3.5. Surface, IC bioMEMS Vision: 5+ Years From Today**

The price of MST-based pacemakers, electronic noses, and hearing aids will be cheaper. They'll achieve greater market penetration. MOSFET-based electronic noses will have better sensor response and very low power consumption. Common difficulties with electronic noses like drift and repeatability will be reduced. Microneedles will replace needle-based injection systems almost completely.

### **3.6. Market Information**

Reuters predicts that the MEMS-based implantable pacemaker market will be \$1.1 billion by 2005 (Small Times, 2001). The market for microsystem-based pacemakers in 1996 was \$ 1 billion with sales of about half a million units. About 40% of the entire pacemaker market was microsystem-based in 1996 and it is predicted that all companies will use microsystem-based technologies by 2003. At present, approximately 500,000 pacemakers are being implanted annually. In the year 2000, around 3,000,000 people around the world were living with functional pacemakers and approximately 600,000 units were implanted. As the population ages, the number of patients receiving pacemakers is increasing at a rate of about 8% per year.

The average selling price of a pacemaker is presently \$5,500. The current market potential for cardiac pacemakers is, therefore, over \$3.36 billion per year based on the potential 600,000 customers at present. But the worldwide pacemaker sales in 2000 were just \$138.9 million with pacemaker sales in the U.S. being \$87.2 million, due to the expensive procedure involved in implanting them into the body.

## **4.0 LIGA Micromachined, Non-IC Compatible BioMEMS**

### **4.1. Product Information**

The adoption of LIGA by manufacturers to make bioMEMS products is recent and has not spread beyond Germany. LIGA provides materials selection that other MEMS-based technology find impossible to achieve and will help increase its market potential. In addition, it provides the highest aspect ratio possible in microsystems technology.

At present, LIGA-based bioMEMS products available commercially are:

- Micromotors

- Micropumps
- Microreactors
- Microspectrometers
- Non-invasive bilirubin analyzers

A few companies have elicited interest in using LIGA to make other bioMEMS products, but are a long way from commercially manufacturing them. Specifically, these products include:

- Capillary electrophoresis (CE) chips using moving mask LIGA techniques
- PZT (Lead Zirconate Titanate) columns used in medical imaging equipment

Motors that range from 1.9 mm to 5 mm in diameter are termed “Micromotors” and are used in applications as diverse as space exploration and drug-delivery systems. The LIGA-based 1.9-mm micromotor is used in minimally invasive surgical techniques, such as endoscopic vein harvesting and catheter-based procedures. LIGA-based micronozzles are showing strong signs of being used in the next generation of nebulizers, revolutionizing asthmatic treatment.

Microreactors are miniaturized reaction systems containing one or more reaction channels with sub-millimeter dimensions. These LIGA-based devices enable the introduction of new reaction procedures in chemistry, molecular biology and pharmaceutical chemistry. The LIGA-based micromixer, similar to the microreactor, enables the reduction of mixing times to the millisecond range and the production of highly uniform emulsions with non-miscible substances.

LIGA techniques are used to make commercial medical diagnostic devices like miniature microspectrometers, essentially waveguides, integrated with an echelette grating (Figure 11). A spectrum is generated by directing light through a silica fiber into the center layer of the three-layer waveguide housing the molded grating. The bilirubin analyzer, a LIGA microspectrometer-based device, is used to detect dangerous levels of bilirubin in babies. The non-invasive analyzer is based on the analysis of spectroscopic information from light reflected from human skin.

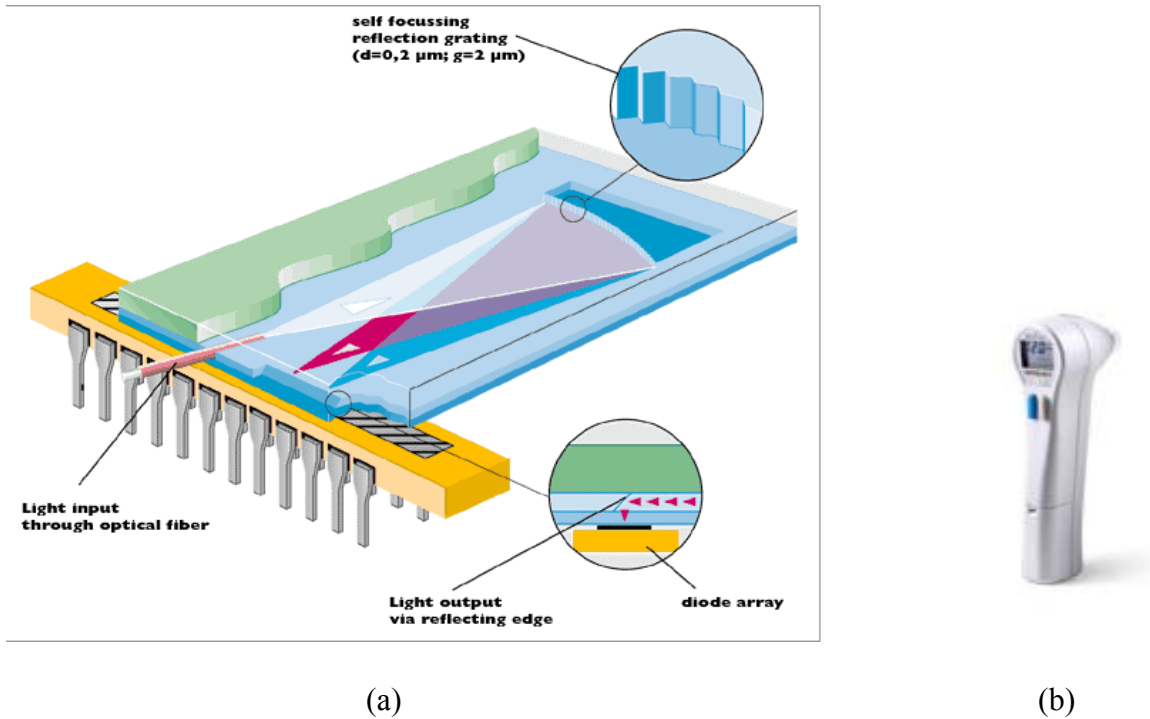


Figure 11. A VIS-LIGA Microspectrometer Chip (a) (Source: STEAG microParts GmbH.)  
 A Bilirubin Analyzer (b) (Source: SpectRyx Inc.).

#### 4.2. Status of LIGA, Non-IC bioMEMS Technology and Manufacturers

Conventional microengineering technologies consistently failed to make DC motors smaller than about 2 mm in diameter with viable output power. In 1999, LIGA techniques enabled the fabrication of 60-milliwatt-output, 1.9-mm-diameter motors. LIGA mitigated the complications arising out of extremely small wires, the armature, and bearings with the quality needed to ensure reliable commercial production. Dr. Fritz Faulhaber GmbH, Germany, made these 6-mm-long motors having 30- $\mu\text{m}$  gears and is considered to be the smallest micromotor to-date. The BL 1900 Series of brushless motors from Dr. Fritz Faulhaber GmbH along with its matching planetary gear head, is targeted at applications such as medical endoscopes and microsurgical tools. The required precision for micro gears with a toothface width of less than 2300  $\mu\text{m}$  can be obtained only using LIGA technologies.

Microreactors are well positioned to completely change the future of industrial-scale chemistry. Their ability to perform new chemistries in a novel controllable manner has the potential to extend applications beyond current capabilities, and has fueled commercial interests.

LIGA-based microreactors are successfully being used in the European chemical R&D industry. They're manufactured by the Institut für Mikrotechnik Mainz GmbH (IMM), and Ehrfeld Mikrotechnik GmbH. Most microreactors fabricated by silicon micromachining and LIGA technologies have channel widths in the range 25-300  $\mu\text{m}$ . The reactors can be made from a variety of materials like glass, silicon or noble metals. The choice of material is determined by factors such as ease of machining, chemical inertness and temperature stability. The sidewalls of cavities of LIGA-based microstructures are parallel in the nanometric range. This results in non-turbulent, laminar flow that is not achievable in conventional microreactors. Thus mixing of fluids in LIGA-based microreactors is precise. Material selection choices afforded by the use of LIGA ensures chemical inertness of the microreactor chamber, even if highly reactive chemicals are being processed. Chemical companies who have used micromixers, micro-heat exchangers and microreactors to optimize reactions have found it profitable and are keen on continuing to use them. More than 20 of IMM's corporate partners have moved beyond the proof-of-principle stage including 8 of who have decided to use LIGA microreactors for chemical process development.

#### **4.3. LIGA, Non-IC bioMEMS Vision: The Coming 3 Years**

For LIGA-based bioMEMS products available now, there will not be any major technological changes in the next 3 years. Available products are the culmination of decades of research work, and the companies who made them are now looking to get government clearances to make them more popular in the market and thus reap monetary benefits. These companies are not currently involved in making their products smaller in size.

Major pharmaceutical firms in the asthmatic-inhaler business are expected to use LIGA- or EDM-based micronozzles in their inhalers, which are bound to make a major impact. Such inhalers use only one-third of the medication used by conventional non-MST inhalers, do not use any propellant gases, and are reusable several times. Worldwide clinical tests of this product are expected to be over in the 2003. LIGA allows the use of material infusion pumps, which can be used inside the human body. Infusion-pump components are fabricated in polycarbonate using microinjection molding since polycarbonate has the advantage of being sufficiently biocompatible and is presently used in a large number of medical applications.

There will be a substantial increase in awareness about the benefits of using microreactors, among the chemical industry R&D community in the next few years. Microreactors will have established a presence in the pharmaceutical R&D market. BASF has modified two fine chemical production processes: a gas-phase partial oxidation of an alcohol to an aldehyde and a liquid-phase cyclization following the company's first microreactor demonstrations. Many such organic chemical manufacturers will take the same route as BASF and adopt microreactors to accommodate them to specific processes.

Microspectrometers are extensively used only as a part of non-invasive bilirubin analyzers. Germany will remain the only country manufacturing LIGA-based microspectrometers over the next few years. LIGA foundries in the U.S. have expressed interest in manufacturing microspectrometers and could come up with a prototype. Biophotonics, the ability to diagnose and monitor a disease based on the way it interacts with tissue, is the principle behind the bilirubin analyzer. By adopting this extremely fast diagnostic technique, treatments can begin almost immediately. This technology can be used to continuously monitor glucose and detect cervical cancer and diabetes, and is expected to get some market share in the next few years.

#### **4.4. LIGA, Non-IC bioMEMS Vision: 3 to 5 Years From Today**

Micromotors that can be used to power catheters and endoscopes are at present produced only by German companies or their subsidiaries in the U.S. Catheters and endoscopes have to be invariably powered by miniature micromotors in the future, since catheter diameter sizes are getting smaller and will entail the use of LIGA-based micromotors. The aerospace and space industry will fuel the reduction of the diameter of the LIGA-based micromotors to around 1 to 1.5 mm in the next five years.

Pharmaceutical companies offering asthma inhalers will be willing to embrace MEMS-based micronozzle technology if Boehringer Ingelheim achieves initial successes in its latest nebulizer system manufactured by Steag microParts GmbH. The asthmatic inhaler market will have reached a stage where consumers will demand that the inhaler needs be compact, reusable and non-polluting.

At present, major chemical producers, like BASF, view microreactors as R&D tools for optimizing rather than replacing plants. Currently, microreactors are viewed as analytical tools to

support larger plants. This perception will change and companies will adopt microreactors to produce chemicals in large quantities. Dow Chemical has invested in two startup firms, Aclara BioSciences (Hayward, CA) and Caliper Technologies (Palo Alto, CA) that have commercialized microreactor assay systems. Merck KGaA (Darmstadt, Germany) is using IMM's technology for commercial chemical production and many more companies are bound to follow within the next 5 years. DuPont has used microreactors to produce several hazardous chemicals like phosgene, butyl isocyanate, and methyl isocyanate (Fairley, 1998).

SpectRx. Inc. is planning to build the world's first non-invasive diabetes detection device. It is designed to identify the estimated 75 million undiagnosed Type II diabetics worldwide. Using this device, diabetes can be detected by shining a blue light into the lens of the eye. The returned light is collected and analyzed by a microspectrometer. The light emitted from the eye of a person with diabetes is more intense than that of a person without diabetes. Non-invasive diabetes detection using MEMS-based devices could see the light at the end of the commercialization tunnel within the next 5 years.

#### **4.5. LIGA, Non-IC bioMEMS Vision: 5+ Years From Today**

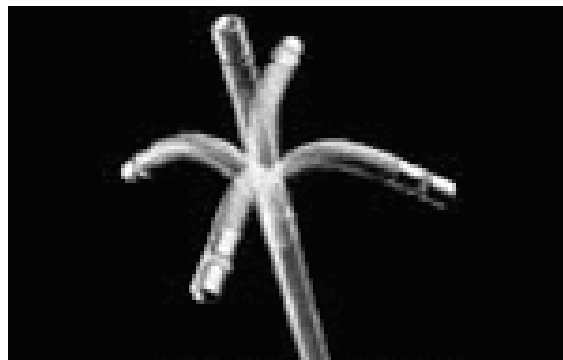
A group of researchers from Ritsumeikan University, Shimadzu Corp., Minolta Co., Ltd., and the University of Tokushima, Japan, pioneered the use of LIGA techniques to make micro Capillary Electrophoresis (CE) chips. The X-ray mask is moved in a circular motion, on a PMMA substrate, to create an inclination in the sidewalls of micro capillary channels. Electroplating and molding follows the Moving Mask lithography process. This fabrication technique is called Moving Mask LIGA ( $M^2$  LIGA) technology.

In this application, conventional LIGA methods cannot be used, since wall inclination has to be incorporated to allow accurate release of the replicated plastic chip from the mold chip. Due to the reduction in price and faster production time,  $M^2$ LIGA micro CE chips will be in a vantage position to grab a huge portion of the market for all other types of biochips and conventional biochemical analytical instrumentation systems within the next 10 years. A miniaturized analytical system for separating and detecting toxic organophosphate nerve agent compounds can be made by the coupling of a micromachined CE chip with a thick-film amperometric detector and can be used as a nerve-gas detector (Wang, 2001). Similar biochemical applications that need highly precise CE channels will drive the commercialization of LIGA-based CE chips.

Lead Zirconate Titanate (PZT) columns can be manufactured by the “Lost Mold” technique using a plastic mold manufactured by a LIGA process. PZT has been used most extensively in transducers, among all piezoelectric materials. Sumitomo, using deep X-ray LIGA, was able to reduce PZT transducer dimensions by 80%. The use of a micro-structured piezoelectric composite in the field of medical ultrasonic diagnosis can be foreseen in the near future.

Within the next 10 years, a non-invasive cervical cancer device that uses biophotonics to determine chemical and structural changes in tissue that is cancerous or prone to cancer will be available. The light reflected back from the cervix (a part of the uterus) could be analyzed using a LIGA-based microspectrometer, providing a full image, or map of the cervix and pinpointing the exact location of cancers and precancers.

Endoscopes used in surgery today are utilized only for diagnostic purposes and as a visual aid, but not for direct operations. In commercially available endoscopes, the orientation of only the last ten centimeters can be controlled (Figure 12).



**Figure 12. The Motion of the Tip of an Endoscope (Source: Korz).**

This type of control has two main drawbacks: first, a change in the orientation of the tip of the endoscope means also a translation of this tip, which may not always be possible if the diameter of the pipe is too small. Second, an accurate positioning of the tip is not possible due to the friction in the wire guide and potential energy storage in the pipe that acts like a spring. A solution is to add at the tip of the endoscope a micro-robot that will offer accurate mobility locally. The mini robot, prototyped by INRIA, a research institute in France, has a diameter of 1 cm, 3 degrees of freedom and an accuracy of less than 0.1 mm (Merlet, 2000). INRIA decided to

use three LIGA-based micro-electrical motors 1.9 mm in diameter from MicroMotor Inc., whose rotation motion will be converted into linear motion with a screw. The use of endoscopes to both manipulate and view surgical tools in MIS procedures can be expected to occur over the next five years. This will have a direct impact for the approximately 4 million minimally invasive procedures performed worldwide. Table 3 shows the trend in micro-motor dimensions.

**Table 3. Trends in Micro-motor Dimensions**

<b>Characteristic</b>	<b>1996 *</b>	<b>1999</b>	<b>2005</b>
<b>Diameter (mm)</b>	5	1.9	1
<b>Length (mm)</b>	11	6	4
<b>Diameter of gear</b>	2.6 mm	50 µm (plastic)	20 µm (plastic)

\* Non-LIGA micromotor from Toshiba used in endoscopy

#### **4.6. Market Information**

Ideally, predicting the market for micro-motors of diameters less than 5 mm can be done by looking at the markets for devices that use them like catheters, endoscopes, arthroscopic devices, etc. The U.S. endoscope market totaled an estimated \$300 million in 1999 and is expected to reach \$375 million by 2006. U.S. medical device manufacturers dominate the catheter industry, producing 70% to 80% of catheters used around the world. Market forecasts for catheters are shown in Table 4. Table 5 shows the market for micropumps, encapsulates, aerosols and implantable drug-delivery systems.

**Table 4: Forecasts for Catheters by Product Type (\$ millions)**

<b>CATHETER TYPE</b>	<b>1996</b>	<b>1998</b>	<b>2003</b>
<b>Coronary</b>	2.5	3.0	5
<b>Renal</b>	0.75	0.9	1.5
<b>Infusion</b>	3	4.5	7
<b>Totals</b>	6.25	8.4	13.5
1996–2003 ANNUAL GROWTH RATE = 10%			

**Table 5: Forecasts for Inhalation Drug-delivery Systems**

Year	2000	2002	2004	2006
US \$ billions	3	3.5	5.0	6.0

The U.S. market for asthma medications, which is about \$4.4 billion, has been growing 12% annually over the last five years. Nebulizer sales jumped from \$20 million in 1992 to \$60 million in 1999 (Table 6).

**Table 6: Forecasts for Inhalation Drug-delivery Systems**

Year	1999	2000	2001	2002	2003	2004	2005
US \$ billions	1.2	1.3	1.4	1.7	2.0	2.5	3.0
1999 –2005 annual growth rate = 17%							

Industrial branches with promising application fields for microreactors are:

- Chemical industries
- Pharmaceutical industries
- Cosmetics and personal care (IMM, 2001)
- Food and beverages
- Refineries
- Chemical engineering suppliers

Microspectrometers can be used in the following applications:

- Medical diagnostics: Near Infra Red (NIR) microspectrometers can be used in blood-sugar and cholesterol measurement and cervical cancer diagnosis. Diabetes affects an estimated 150 million people worldwide, of who half do not know they have the disease.

Worldwide, there are approximately 371,000 cases of cervical cancer diagnosed annually and approximately 190,000 deaths per year.

- Environmental monitoring: The microspectrometer offers a quick and easy way of identifying airborne and marine toxic pollutants. The market for MST-based environmental-monitoring devices is expected to increase from \$200 million in 1998 to \$900 million in 2002.

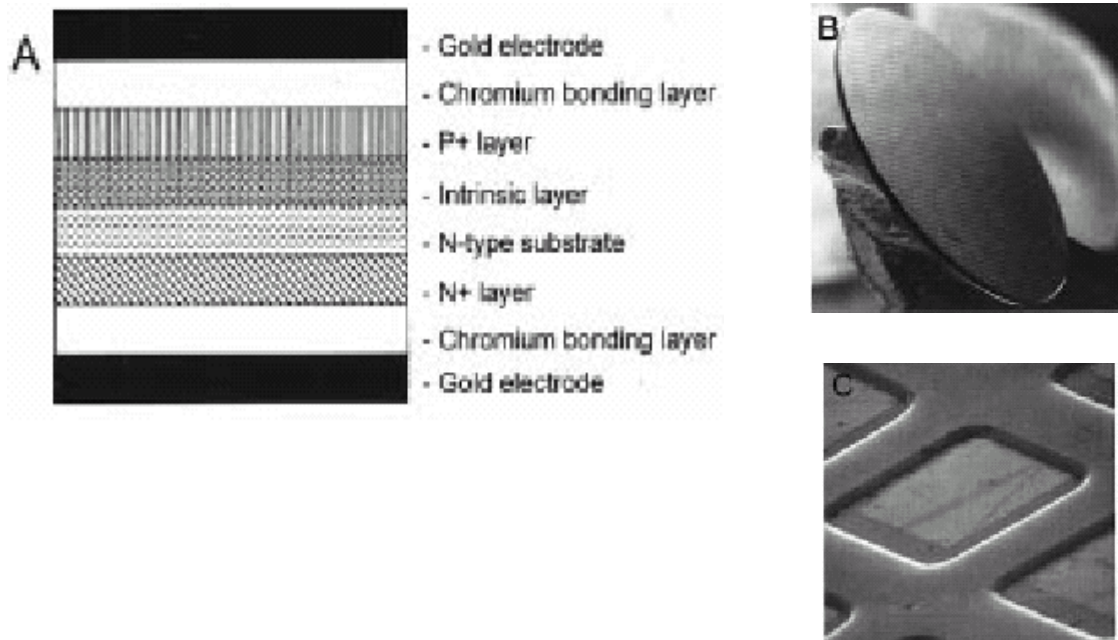
The market potential for bilirubin analyzers has not yet reached its full potential. Up to 60% of all new-born babies develop infant jaundice. In March 2001, the U.S. FDA granted expanded claims for use of BiliChek™ from SpectRx, Inc. during and after treatment of infant jaundice as well as for screening. As a result, more hospitals, doctors' offices and home health-care systems will be ready to check more babies with the BiliChek™. The global market for bilirubin analyzers was expected to be \$50 million in 1999 and \$100 million in 2004. The product revenue for BiliChek™ was up by 36% in the second quarter of 2001 compared to the second quarter of 2000, reflecting its increased demand.

## **5.0 Other Non-IC Compatible bioMEMS**

### **5.1. Product Information**

This section discusses the wide array of devices that cannot be classified under surface, bulk or HARM technologies and are not IC compatible. A brief explanation of these devices is given.

Microelectronic retinal implants currently under development are of two types, subretinal and epiretinal. The subretinal device or implant is designed to replace photoreceptors in the retina and is a microelectrode array powered by approximately 3,500 microscopic solar cells. A subretinal device from Optobionics, Inc., called the Artificial Silicon Retina™, is approximately 50- $\mu\text{m}$  thick with a diameter of 2.0 to 2.5 mm. The epiretinal implant consists of several subsystems and is designed to communicate directly with the ganglion and bipolar cells of the brain through its components, which includes a camera, image-processing systems, telemetry, etc. (Figure 13).



**Figure 13. A Subretinal Implant. Schematic Diagram of Implant Cross-section. Each Layer of the Microphotodiode Array Device is Indicated. Layers are not drawn to Scale (A). Low magnification image of scanning electron micrographs of an MPA-type implant that's 2 mm in diameter (B). A high-magnification image showing the individual 20- $\mu\text{m}$  x 20- $\mu\text{m}$  subunits separated by 10- $\mu\text{m}$  channel stops (C). (Chow, 2001, ©Optobionics Corp. 2001).**

A micro catheter is a fine tube made to pass mainly through small blood vessels (1-2 mm in diameter). It facilitates X-rays using contrast media, injections of anti-cancer drugs for liver cancer, intravascular treatment of embolization, etc.

Lasers can be used to help micromachine ceramic structures or bodies made from piezoelectrics, alumina, or aluminum nitride to manufacture ultrasound transducers. Laser micromachined micro holes of less than 0.01 mm in diameter allow accurately metered and distributed drug delivery. Precise micro-holed catheters are also used to measure the oxygenation level of blood in premature babies. Catheter stents of biocompatible materials like stainless steel, titanium, and tantalum can be made by laser micromachining techniques like those used by Resonetics, Inc. The stent diameters range from several millimeters down to less than one millimeter. Manufacturing such stents requires a laser kerf of around 35  $\mu\text{m}$  in 100 to 150- $\mu\text{m}$ -thick material, and 15  $\mu\text{m}$  in thinner sections.

Surgical scalpels based on a silicon substrate (which acts as a passive carrier) can include a diamond edge cutter. To reduce the surface roughness of the diamond cutter, a bias-enhanced

nucleation process can deposit highly oriented diamond coatings. However, high raw material price and limitations in the shaping and complicated mechanical polishing procedures, have limited the use of diamond-edged scalpels. This problem was recently solved by CVD. It uses diamond on silicon substrates from the gas phase with a carbon containing a hydrogen mixture. A subsequent plasma polishing process permits the production of scalpels into virtually any shape. Highly Oriented Diamond (HOD)-based diamond scalpels differ from conventional diamond scalpels in that the diamond tips are structured down to the atomic detail, hitherto not possible. By using a special plasma polishing process, cutting-edge thicknesses of a few atoms can be reached—a physical property limit. Gesellschaft für Diamantprodukte (GFD), Germany, produced the first commercially available CVD-based nanostructured diamond-edged scalpels.

Surface Acoustic Wave (SAW)-based chemical sensing is used as a sensing technology in electronic nose products. The unique properties of SAW technology produce sensors that measure physical parameters such as particulate contamination, tire pressure, torque and dew point. Osmetechs has used electronic noses to detect microorganisms for healthcare diagnostics. Currently, the application of its multi-sensor array technology is focused on diagnostics for urinary tract infections, bacterial vaginosis, pneumonia in intensive-care-unit patients, and bacterial pharyngitis. These sensors can be used in automated multi-sample instruments for use in a central laboratory setting or in a small point-of-care device in a doctor's office.

An embryo chip from Micro Agri Systems, Inc., is designed to automatically carry out all the steps involved in in-vitro fertilization (IVF), from fertilizing eggs to preparing embryos for implantation. This device mimics conditions inside a female's reproductive tract. It is made of a transparent elastomer and contains a network of microscopic channels, each around 0.2 mm in depth and width. The channels are connected to programmable syringe pumps, which can move embryos around and add or remove fluids. This microfluidic system was found capable of transporting individual, pre-implantation mouse embryos (100  $\mu\text{m}$  to 150  $\mu\text{m}$  in diameter) through the network of channels. The ova, embryos, and cells are transported and manipulated in channels using microfluidics where a fluid, such as a culture medium, flows through channels with sub-millimeter cross-sectional dimensions. The channels are produced using microelectronics fabrication technology (Glasgow, 2001). The embryos are gently forced to travel along with the flowing fluid. Embryos can be retained at constrictions that are strategically

fabricated in the desired locations. The functions of the IVF embryo chip include in-vitro maturation of Oocytes and the culture of pre-implantation embryos.

A microvalve is defined as a valve whose fluid control barrier is less than a millimeter and has a width between 0.05-0.5 mm. Microvalves are a prerequisite to the operation of most microfluidic systems since they control the transport of samples and reagents in different parts of the system. Each of these valves requires an independently operating microactuator. To perform complex or parallel functions in the microsystems, many valves (>10) are needed. Microvalves are used in analytical, medical instrumentation and industrial process-control equipment. A large percentage of drug-delivery devices make use of microvalves. The MEMS fabrication process for microvalves relies on both silicon-to-silicon fusion bonding and silicon-to-pyrex anodic bonding. The vertical dimension of a three-layer microvalve device is typically 1.6 mm with a pyrex layer of 0.8 mm, a silicon membrane layer of 0.4 mm, and a silicon flow channel layer of 0.4 mm. The membrane itself measures 4.0 x 4.0 mm with a thickness of 50  $\mu\text{m}$ . Dimensions for flow channels and inlet/outlet ports range from 25 to 1000  $\mu\text{m}$ .

A number of companies are developing chips that use microfluidics technology for genomic analysis. These devices enable the manipulation of small amounts of fluids, often through small channels cut into a chip. The goal of many of these products is to integrate the various processes of experiments, from sample preparation to analysis, into a single, miniaturized format that allows miniscule volumes of chemicals and test material to be used, thus reducing costs. Fluids like chemical reagents and biological samples are moved in a controlled way through various forces, including electrokinetics and pressure dynamics. In addition, microfluidic devices offer a high degree of experimental control and automation, accelerating the rate of genomic analysis.

The fabrication of micro devices with conventional plastic molding technologies such as reaction injection, thermoplastic molding, and hot embossing should not be overlooked. These continue to be by far and away the cheapest alternatives to making microstructures in materials. Many of the microfluidic devices currently appearing on the market are made using this technique and are designed to be inexpensive and disposable.

## **5.2. Non-IC bioMEMS Vision: 5+ Years From Today**

Retinal implants have made considerable progress over the last two years. The six recipients of the retinal implant in 2000 are able to see only flashes of light but have yet to suffer implant rejection, infection, inflammation, or erosion of the chip. It can be assumed that by 2010, a retinal implant offering a 30-50 % vision compared to the normal eye will be available.

ChipRx, Inc., is developing a fully integrated, self-regulated therapeutic system that can eliminate the need for telemetry and human intervention. The plastic capsules, called "Smart Pills," are not meant to be swallowed but are implanted beneath the skin. Each implantable capsule is about the size of a matchstick perforated with microscopic holes, each opened or closed by a small ring of artificial muscle. The muscles contract and swell on command, acting like tiny trapdoors to release variable amounts of medication. The smart pill is based on hydrogels, which are full of microscopic holes and are capable of expanding to several times their normal size. An artificial muscle is created by attaching a piece of hydrogel to a backbone of conductive plastic. Current flowing through the plastic makes the drug-illed hydrogel shrink or swell. Applying a voltage makes the muscle contract, releasing the drug. By reversing the voltage, the muscle expands cutting off drug flow. The technology for this is still experimental and the availability of the first such pill is anybody's guess.

MEMS strain sensors that sense the load in artificial legs for humans have been quite successful commercially. These legs are able to function even under extreme duress since the sensor senses the weight load of the artificial leg recipient 50 times a second. But the costs of these artificial legs are prohibitively costly (\$30-50K). Companies like Otto Bock, Germany, are trying to reduce the price of these legs within the next 5 years to expand market presence.

## **6.0 DNA Arrays**

A DNA array is a matrix containing multiple gene-specific sequences that permits simultaneous evaluation of hundreds to thousands of individual genes. It focuses on increasing the number of genes that can be studied in a single experiment. In DNA arrays, gene-specific sequences are immobilized on solid-state matrices and tested with labeled copies of biological samples. This term includes:

- Nylon-membrane-based arrays (so-called macroarrays)

- Microscope-slide-based arrays (DNA microarrays)
- Silica chips with high-density oligonucleotides constructed in situ (the Affymetrix GeneChip TM)
- Microelectronic arrays (a unique combination of addressable electrodes and gene-specific fragments)

The human genome has approximately 35,000 genes and approximately 3 billion base pairs. The immediate applications for DNA arrays are large-scale genomic (genetic) and functional genomic (gene-expression) analyses. Researchers are interested in ascribing functions to thousands of anonymous expressed sequence tags (ESTs) in the human genome and identifying genes responsible for diseases. New approaches are driven by the need to identify genetic polymorphisms and gene functions in human, animal, and microorganism genomes. DNA arrays are essential for achieving high throughput analysis of genetic material. Table 7 shows the status of DNA arrays.

**Table 7: Status of DNA Arrays**

<b>DNA array type</b>	<b>DNA macroarrays</b>	<b>DNA microarrays</b>	<b>High-density oligonucleotide arrays</b>	<b>Micro-electronic arrays</b>
<b>Year of introduction</b>	1995	1996	1996	2000
<b>Physical scale</b>	8 x 12-cm membranes  200 to 5,000 genes	2.5 x 7.5 cm with thousands to tens of thousands of genes	1 x 1 cm  >40,000 genes	0.7-cm <sup>2</sup> chip  Array area 2-mm <sup>2</sup>
<b>Fabrication method</b>	Spotting or printing robots or ink-jet/piezoelectric Methods	Spotting or printing robots or ink-jet/piezoelectric methods	Photolithography	Semiconductor fabrication
<b>Hybridization, detection method</b>	Radioactivity	Fluorescent (pre-hybridization)	Fluorescent (post-hybridization)	Fluorescent

<b>Applications</b>	Brain disorders and polygenic diseases which involves very small changes in gene expression	Identifying disease-causing genes	Single-nucleotide polymorphism (SNP) identification	Single-nucleotide polymorphism (SNP) identification  Protein identification
<b>Number of major manufacturers</b>	Three	Many	One (Affymetrix: product is the GeneChip)	One (Nanogen: product is the Nanochip)

### 6.1. Forces That Determine Demand For DNA Arrays

- DNA arrays can examine tens of thousands of genes to identify disease-causing polymorphisms in a single experiment.
- Significant reduction in labor and reagent costs.
- Exponential increase in speed and throughput of genetic experiments.
- Initial success in hitherto impracticable experiments. Effects of a biological/chemical war on genes, drug development specific for certain populations.

### 6.2. Challenges The DNA Arrays Industry Faces

- High R& D costs.
- Limitations in accessing existing complex data about the human genome.
- Regulatory hurdles.
- The need for a standard format to represent array data obtained from various research centers, irrespective of array format used.
- Major players embroiled in patent litigation.

### 6.3. System Integration Issues

Integration covers a whole spectrum of issues from the semiconductor and fluidic level, to the control, information display and treatment, to user-interface levels. Integration must address electronic, mechanical and optical interfaces, materials and packaging issues, as well as chemical compatibility and functionality.

## **Interfaces**

Fluid interconnects do not exist for microfluidic devices and those that have been used vary widely from pipette tips and glue to gas-chromatographic fittings and microfabricated fittings (Mourlas et al., 1999; Nicolas et al., 1999). In general, “Macro-to-micro” interface issues have not been well resolved.

## **Fluidics And Electronic Integration**

Monolithic integration places all components on the same device. Typically, actuators and sensing elements are made in the same process and little or no assembly is required. Monolithic systems are highly reliable and low in cost. Limitations include incompatibilities with process steps, low overall yield due to many points of failure, and high costs for small quantities. Several layers, each with its own processing requirements, can be sandwiched together to make a final assembly in a collective system. Benefits of collective integration include the ability to segregate chemical and processing step incompatibilities. Higher individual step yields, encountered by final assembly requirements, are often highly variable. As in collective integration, hybrid integration results in a sandwich construction. The layers of silicon, glass or plastic can either be fluidic, control, or electronic and are assembled and bonded together. DNA sequencing by hybridization (Drmanac et al., 1993) (SBH) and other oligonucleotide hybridization protocols rely on a time-consuming hybridization step. Although there are many variables to control for a successful hybridization, migration of the DNA to the fixed complementary probe tends to be slow. Often, this step requires hours to overnight reaction times. Recently, Nanogen commercialized a chip that electronically drives the target DNA to the probes, greatly speeding up this process (Cheng et al., 1998a). After hybridization, the chip is washed and detection occurs, reducing a typical experiment that takes several hours to less than 30 minutes.

Nanogen’s microelectronic array technology allows small sequences of DNA capture probes to be electronically placed at, or “Addressed” to specific sites on the microchip. A test sample can then be analyzed for the presence of target DNA molecules by determining which of the DNA capture probes on the array bind, or hybridize, with complementary DNA in the test sample. In contrast to nonelectronic or passive hybridization with conventional arrays on paper or glass “Chips,” the use of electronically mediated active hybridization to move and concentrate target DNA molecules accelerates hybridization. Hybridization thus may occur in minutes rather

than the hours required for passive hybridization techniques. In addition to DNA applications, this technology can be applied to a number of other analyses, including antigen antibodies, enzyme substrates, cell receptors, the isolation of cancer cells from peripheral blood cells (Cheng et al., 1998a), and cell-separation techniques.

### **Integral Detection Systems**

Sample measurement in chips presents new challenges to detection systems. The most popular modalities are fluorescence, absorbance, luminescence and chemiluminescence. Other methods include mass sensors such as mass spectrometry and acoustic-wave devices, electrochemical sensors such as potentiometric, amperometric, and conductivity types, and DNA Macroarrays, and finally, thermal sensors such as bolometers and thermopiles. All are handicapped to an extent by the small sample sizes encountered on chips and therefore must be very sensitive or coupled to chemistries that exhibit amplification.

#### **6.4. Future Trends In DNA Arrays**

Presently, DNA macroarrays are not being used much due to low functionality in comparison to the other 3 techniques. It is relatively cheap (\$500 to \$2000) and is easy to use. Its usage could virtually disappear from the DNA array industry in the next 5 years.

### **DNA Microarrays**

At present, the absolute amount of DNA sample present on the chip varies from spot to spot irrespective of the method used to construct the DNA microarray. This kind of variation affects the accuracy of quantitative results generated by microarray analysis. Considering current research trends, by the end of 2003, this will be rectified. There are limited choices of fluorescent dyes that can be used in microarrays. As demand increases in the future, more fluorescent dyes will be developed for this technology to improve the sensitivity of the assays and reduce background signals.

### **High-Density Oligonucleotide Arrays**

The GeneChip from Affymetrix can also be considered a microsystem. Affymetrix is endeavoring to reduce its size and put more genes onto it (Table 8).

**Table 8: Trends for High-density Oligonucleotide Arrays**

Specifications	2001	2003	2006	2011
Wafer size (in.)	1 x 3	1 x 3	0.75 x 2	0.75 x 1.5
No. of probes on a wafer (in millions)	60	65	80	100
Probe Pair/Genes	16	14	6	4
Cost	\$5000	\$5000	\$4000	\$3000

**Microelectronic Arrays**

The microelectronic array is considered to be the latest in DNA microarray technology. Its functionality is drawn from advanced molecular biology and semiconductor fabrication. It is a MEMS device consisting of an electronic chip, which in turn holds an array having 99 test sites. These sites consist of sets of electrodes covered by a thin layer of agarose (a polysaccharide obtained from agar). Each microelectrode is less than  $100 \times 10^{-15}$  m in diameter and can generate a controllable electric current that can be used to draw probes, samples, and reagents to specific locations on the chip surface. Table 9 summarizes microelectronic array trends.

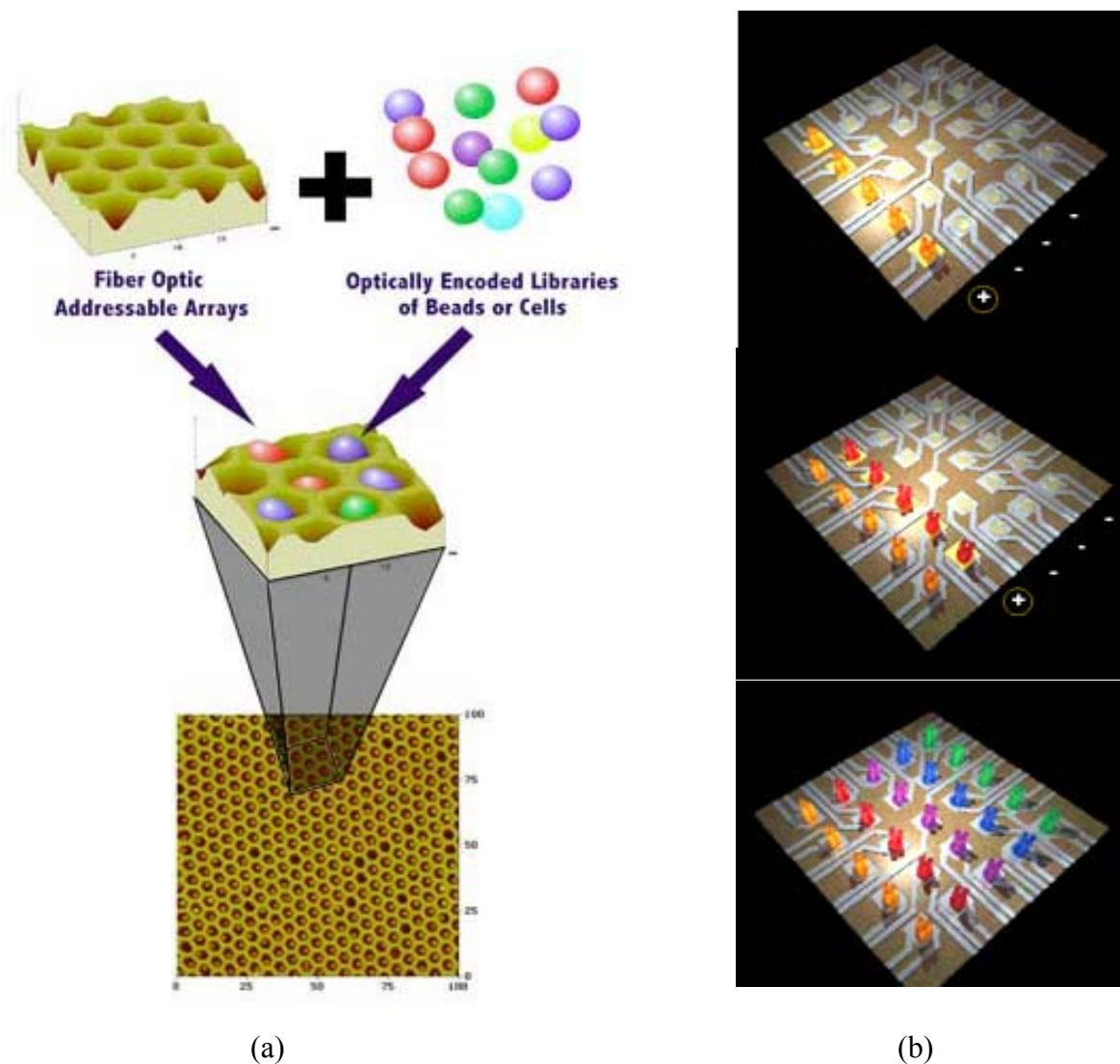
**Table 9: Microelectronic Array Trends**

Specifications	2001	2003	2006	2011
Chip Area (cm <sup>2</sup> )	0.7	0.7	0.5	0.3
Number of Test Sites	99	99	198	297
Array Site Size (microns)	80	80	40	20
Cost per chip	\$100	\$80	\$60	\$40

**Bead-based Fiber-Optic Arrays**

The ability to etch silicon materials has predictably given rise to an interesting DNA array technology based upon fiber optics. The fibers can be made in outside diameters of 3 to 7  $\mu$ m.

One thousand of these fibers can be bundled together into a 1-mm-diameter bundle. The ends are then etched with hydrofluoric acid to produce micron-sized or femtoliter-sized pits. It is possible to insert individual microspheres into these wells. The beads are sized so that they self-assemble, one to a well, when the fiber bundles are dipped into 20% solids slurry. One milliliter of such slurry can contain 100 million beads. Each individual bead can be optically encoded with fluorescent dyes so that it reports a unique optical “Bar Code” when interrogated with a laser. Moreover, it is possible to construct an array of 384 of these fiber bundles on a 4.5-mm pitch to fit into a standard 384-well microtiter well plate. This increases the amount of information gathered in a single experiment to around 3 million data points. Illumina, Inc., is currently commercializing this BeadArray™ technology to support applications in genotyping, gene-expression profiling, and proteomics. With unique segments of DNA attached to each bead, the BeadArray™ technology can be used for SNP genotyping (Figure 14).



**Figure 14. (a) A Self-assembled Array of Optically Encoded Microbeads into Femtoliter-sized Wells on the Ends of Individual Optical Fibers. The identity of the bead is first determined followed by a measurement of the concentration of analyte attached to the bead by selective chemistries (a). (Source: Illumina Inc.) A test site or a row of test sites on the microchip is electronically activated with a positive charge. A solution of DNA probes is introduced onto the microchip. The negatively charged probes rapidly move to the positively charged sites, where they concentrate and are chemically bound to that site. The microchip is then washed and another solution of distinct DNA probes can be added. Site by site, row by row, an array of specifically bound DNA probes can be assembled or addressed on the microchip (b). (Source: Nanogen)**

### 6.5. Future DNA Array Technology Competitors

All the aforementioned microarrays will face stiff competition from the protein chips in the years to come. Proteins are the ultimate product of genes and, therefore, are at the heart of understanding biological functions and the way these functions vary between states of health and disease. They could be used to study protein-protein interactions and the interactions between

arrayed proteins and potential drugs. Specifically, arrays of a series of protein targets could be used to identify binding of particular proteins or small molecules (e.g., potential therapeutics) to these targets. Productivity demands have not been met by DNA microarray high-throughput screening, in terms of new drug compounds reaching the market. Hence the Protein Chip, which has been commercially available since 2001, is the natural successor to the DNA array.

In the next three to four years, financial pressures may force pharmaceutical companies to reduce research spending on genomics. Bioinformatics is at present a non-starter and pharmacogenomics has not turned out to be 100% error-free, which is a prerequisite for U.S. FDA approval. Increasing losses incurred by firms in these fields reflect these facts.

A key FDA requirement for new drugs is that metabolization of all drug compounds by the enzymes (a type of protein) of the body should be understood completely, irrespective of genetic makeup of individual patients. A new field of study, chemogenomics, that has captured the interest of drug discovery and pharmacogenomics companies, will help in fulfilling this requirement. Chemogenomics refers to the study of the discovery and interaction of drug compounds directed at all possible drug targets, i.e. the 30,000 proteins coded by the human genome. The chemogenomics approach towards drug discovery is considered to be more efficient than genomics, since it enables us to identify all of the possible drug classes for a given molecular target, simplifying the drug-discovery process in its entirety. Many venture capital firms predict chemogenomics and protein-on-a-chip technologies will be more successful in the near future than genomics or DNA arrays.

## **6.6. Market Information**

DNA diagnostic testing was worth \$540 million in 1997 and is estimated to reach \$1.5 billion by 2003. The lab testing market is currently moving downstream and by 2007, human diagnostics will be done non-invasively in patients' homes without having to go to a lab.

The entire DNA array market is expected to grow from \$322 million in 2000 to \$1.2 billion in 2006. The market for protein arrays alone is expected to grow from approximately \$45 million in 2000 to \$500 million in 2006, which will eat into the DNA array market share.

## 7.0 Conclusion

BioMEMS is an exciting field and is poised to reach much of its promise. Complexity in design and in the nature of materials required for in-vivo versus in-vitro application has complicated product introduction. In addition, regulatory organizations such as the U.S. FDA do not have a large history with MEMS-based medical devices, further complicating the matter. We depict in Figure 15 the manner in which device complexity affects bioMEMS devices and commercialization timing. Furthermore, in Figure 16, we provide an industry value chain for a selected number of bioMEMS opportunities.

BioMEMS has the opportunity of redefining the supply chain in many application arenas. The task for advanced bioMEMS devices is not only to be more efficient in performing tasks already performed by current technologies, but also to redefine existing distribution networks to increase market expansion. Finally, bioMEMS is more widespread in applications than many know since many bioMEMS devices have been used in superior solution sets, which are opaque to the larger pharmaceutical systems suppliers who provide these solutions to end users.

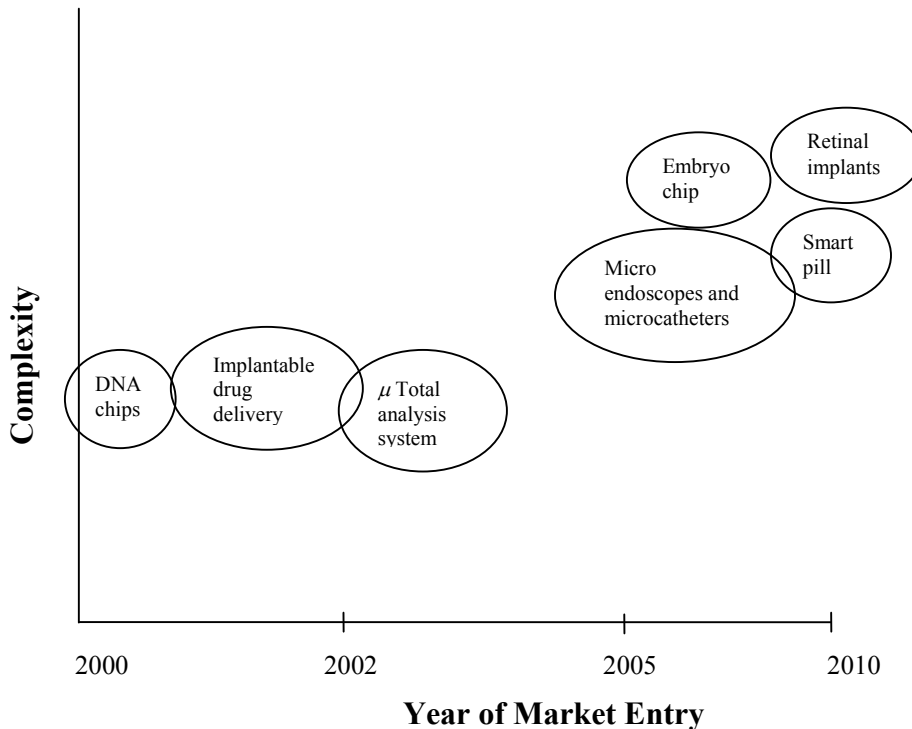


Figure 15. Time-to-market for Complex bioMEMS Devices.

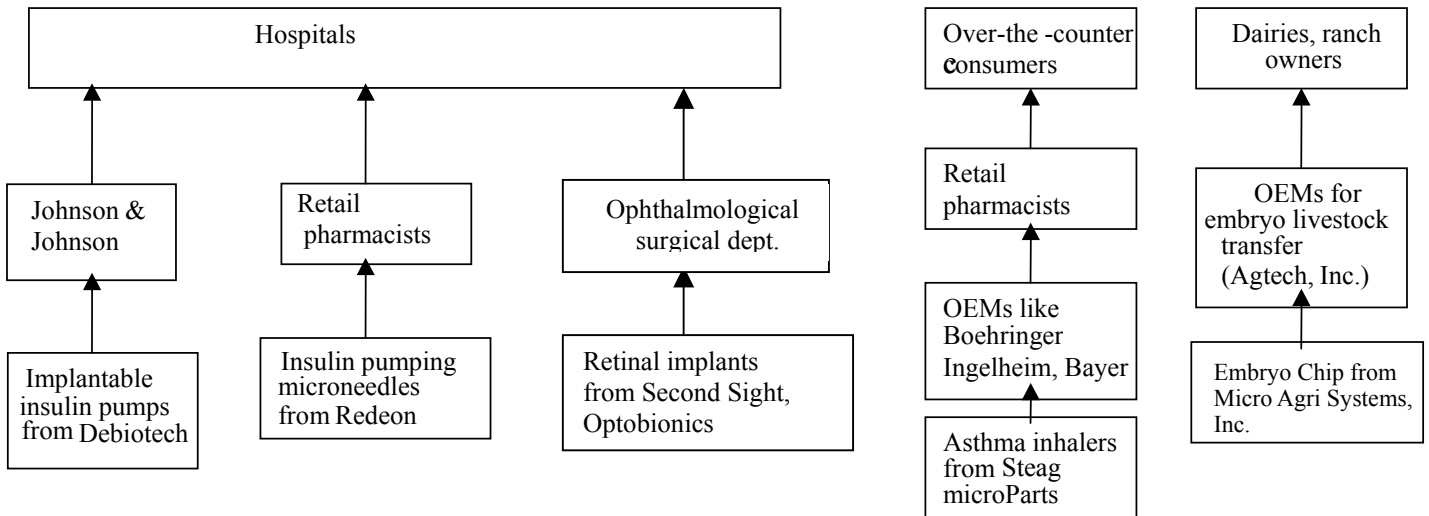


Figure 16. Future Distribution Network for bioMEMS Devices.

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