Emerging Technologies

MEMS in medicine and biology

Dorin Panescu

Microelectromechanical systems (MEMS) is a technology developed from the integrated circuit (IC) industry to create miniature sensors and actuators. Originally, these semiconductor processes and materials were used to build electrical and mechanical systems but have now expanded to include biological, optical, fluidic, magnetic, and other systems as well. MEMS, the term originated in the United States, typically contain moving or deformable objects. Engineers in other parts of the world may refer to these devices as *microsystems technology* or *microstructures technology* (MST). MEMS merge the functions of sensing and actuating with computation and communication to locally control physical parameters at the microscale level. Figure 1 shows the main components of MEMS [1]. In addition to reducing size and mass, other advantages of MEMS-based systems include low cost through mass production.

In order to understand the design of MEMS devices, a review of fabrication technologies, materials, and power supplies is provided.

Fabrication of MEMS comprises steps similar to those used by semiconductor manufacturing processes and falls into three categories:

- surface micromachining
- bulk micromachining
- molding process.

Surface micromachining involves the buildup of micromechanical structures on the surface of a substrate by deposition, patterning, and etching processes. One of the processing steps involves the selective removal of an underlying film referred to as a *sacrificial layer*, without attacking the overlying film, referred to as the *structural layer*. Figure 2 illustrates the typical surface micromachining process [1].

As an example, surface micromachining can be used to manufacture inertial sensors—primarily devices for measuring linear and rotational acceleration [2]. Figure 3 illustrates the structure of a MEMS rotational accelerometer device that can be used in hard disk drives to compensate for vibrations or in vehicle stability control systems to detect unwanted yaw axis movements.

Compared to rival technologies, silicon MEMS sensors achieve much greater sensitivity and uniformity of performance.

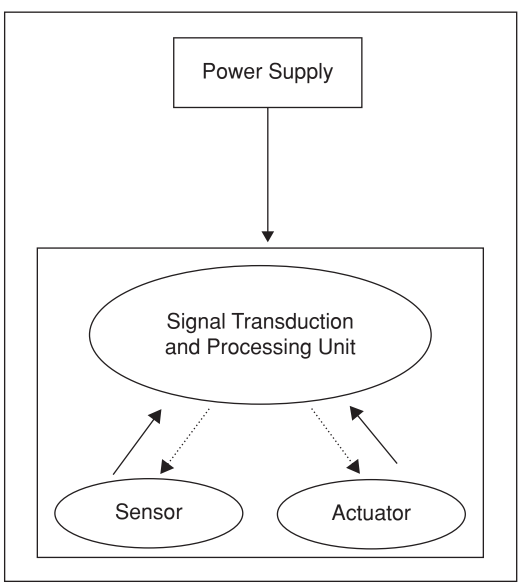

Fig. 1. The main components of a MEMS (1).

The micromachined structure consists of a "rotor" free to move a small fraction of a degree within a stator structure. When the device is rotated, the rotor tends to remain where it was so it moves relative to the stator, changing the capacitance of the rotor/stator combination. A sensitive capacitance measuring circuit translated the capacitance into a digital output signal. Inertial MEMS devices, such as the one presented in Figure 3, are typically manufactured by the same basic process highlighted in Figure 2. Generally the process begins with the growth of a layer of silicon dioxide on the silicon wafer. This layer is called *sacrificial* because later it will be mostly removed to free the moving parts. Into the sacrificial layer holes are etched at points corresponding to the supports for fixed elements and anchors for mobile elements. A thicker epitaxial polysilicon layer is grown on top of this and into this layer the form of the fixed and moving elements is etched. Finally the sacrificial oxide layer beneath the structures is removed by an isotropic etching operation to free the moving parts. The open space around the MEMS structures is filled with gas, usually dry nitrogen, to avoid the stiction effects due to humidity or variations in gas density that would affect the resonance frequencies. The steps above are shown in more detail in Figure 4 [2].

Compared to rival technologies like piezoelectric materials, silicon MEMS sensors achieve much greater sensitivity and uniformity of performance while at the same

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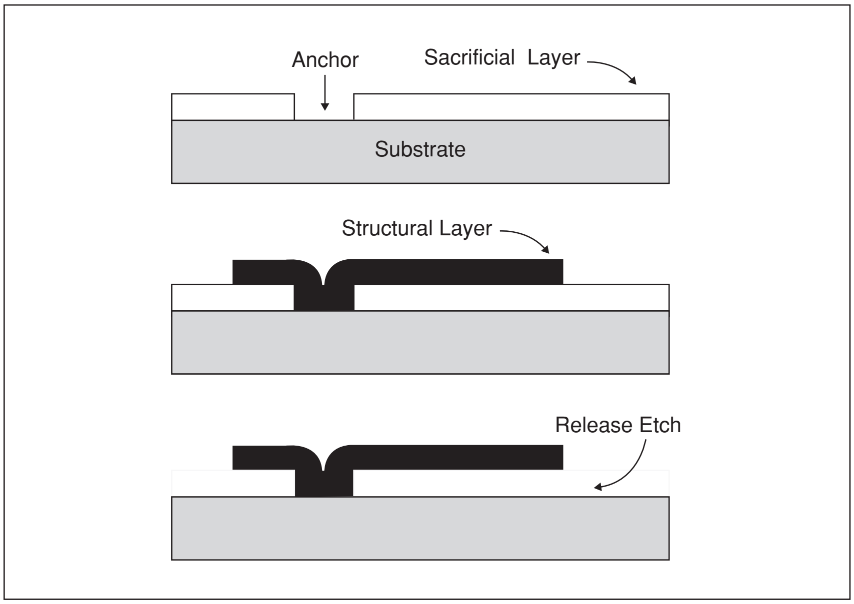

Fig. 2. Typical steps of MEMS surface micromachining (1).

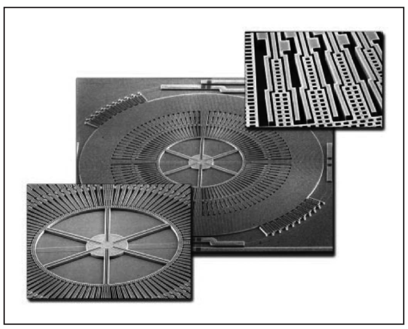

Fig. 3. Scanning electron microscopy picture of an angular accelerometer produced in MEMS technology (2).

time they can be manufactured at very competitive cost, in large quantities. As a consequence it is likely that MEMS accelerometers will be adopted much more widely in medical devices that detect the patients' level of activity to effectively control their heart rate, such as cardiac pacemakers and implantable cardioverter defibrillators (ICDs). Bulk micromachining uses wet or a dry plasma processes to etch into the substrate to produce MEMS structures. The etching can be isotropic or anisotropic. By exploiting the predictable anisotropic etching characteristics of single-crystal silicon, many high-precision complex three-dimensional shapes, such as V-grooves, channels, and nozzles, can be formed. Figure 5 is an example of bulk micromachining along crystallographic planes. Deep reactive ion etching is a plasma process that is used increasingly to make MEMS, with structures that are over ten times as deep as they are wide. This is an important consideration in MEMS, where higher mechanical power of force levels is desired or in applications involving fluids such as nozzles.

The third fabrication process used in the creation of the mechanical elements of the device is the deposition of material into microfabricated molds. The most widespread use of this process is the LIGA (German acronym—lithography, galvanoforming, molding). It involves X-ray lithography for mask exposure; galvanoforming to form metallic parts; and molding to produce microparts with plastic, metal, ceramics, and their combination. Laser-induced etching and deposition of materials as well as ultrasonic and electron discharge milling are other alternative technologies that can be used as part of this process [1].

The principal materials used in MEMS manufacturing include doped single crystal silicon wafers as the semiconductor substrate and deposited layers of polycrystalline silicon for resistive elements; aluminum (or copper or gold) as the principal conductor; and silicon oxide, silicon nitride, and titanium nitride for electrical isolation and protection. Recently, new materials have been developed: the shape memory alloys that are used for actuators are one example. Piezolectric materials have become very useful in MEMS devices because of their electrical-mechanical reciprocity. Piezoelectric materials are capable of very high energy and power densities at microscales. The high frequency of operation inherent in MEMS devices matches well with the relatively high-frequency capability of piezoelectric materials. The most commonly used

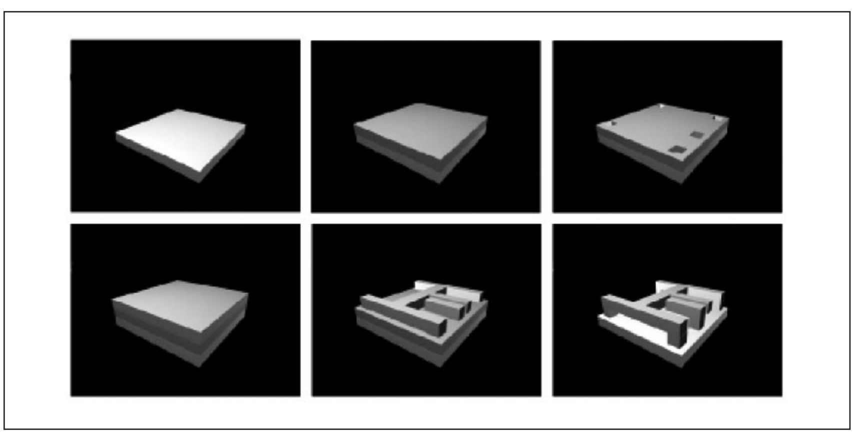

Fig. 4. More detailed surface micromachining MEMS fabrication steps (2).

piezo-materials in MEMS devices are lead zirconate titanate (PZT), zinc oxide (ZnO), and aluminum nitride (AlN). Recent advancements in environmental monitoring, especially in the area of chemical and biological sensors, have given rise to new materials applications in MEMS design. Biocompatibility testing is at the forefront of evaluating new materials for MEMS applications in medicine. Voskerician et al. studied biocompatibility of materials used for MEMS drug delivery devices [3]. They found that gold, silicon nitride, silicon dioxide, SU-8 photoresist, and silicon were biocompatible. Gold, silicon nitride, silicon dioxide, and SU-8 photoresist also showed reduced biofouling.

The need to provide energy to effect sensing and actuation calls for the integrated power supply into the MEMS device. The application of embedded microsensors entails burying them in the structures with no physical connection to the outside world. In such cases, electric power can be obtained from the environment by extracting energy from mechanical motion and vibration by using piezoelectric materials; air/liquid flow by using a miniature air turbine generator; temperature gradients by using thermopiles; pH gradient by using chemical electrodes; and particle radiation by using p-n junction or other converters [4]. Efficient MEMS power

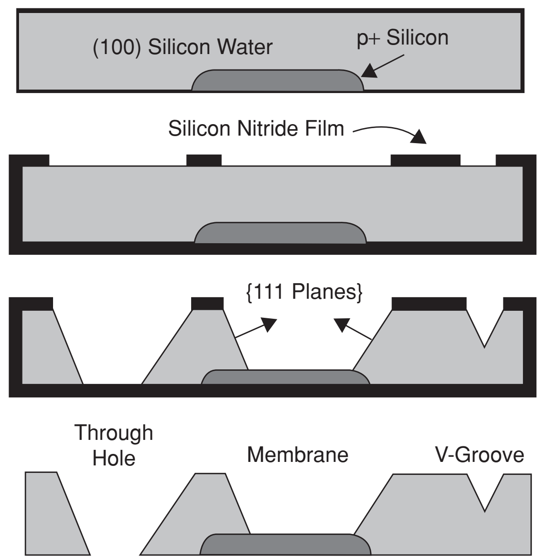

Fig. 5. Typical steps of MEMS bulk micromachining (1).

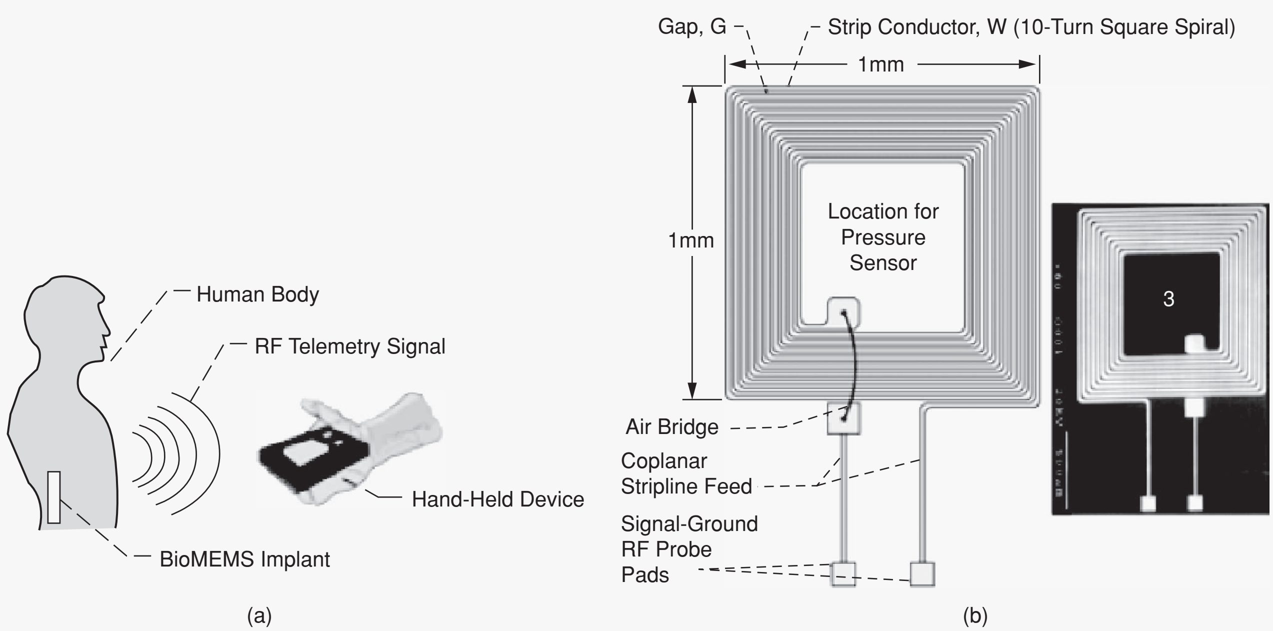

Fig. 6. (a) RF telemetry signals can communicate and power MEMS devices. (b) An example of an antenna for a wireless MEMS pressure sensor (6).

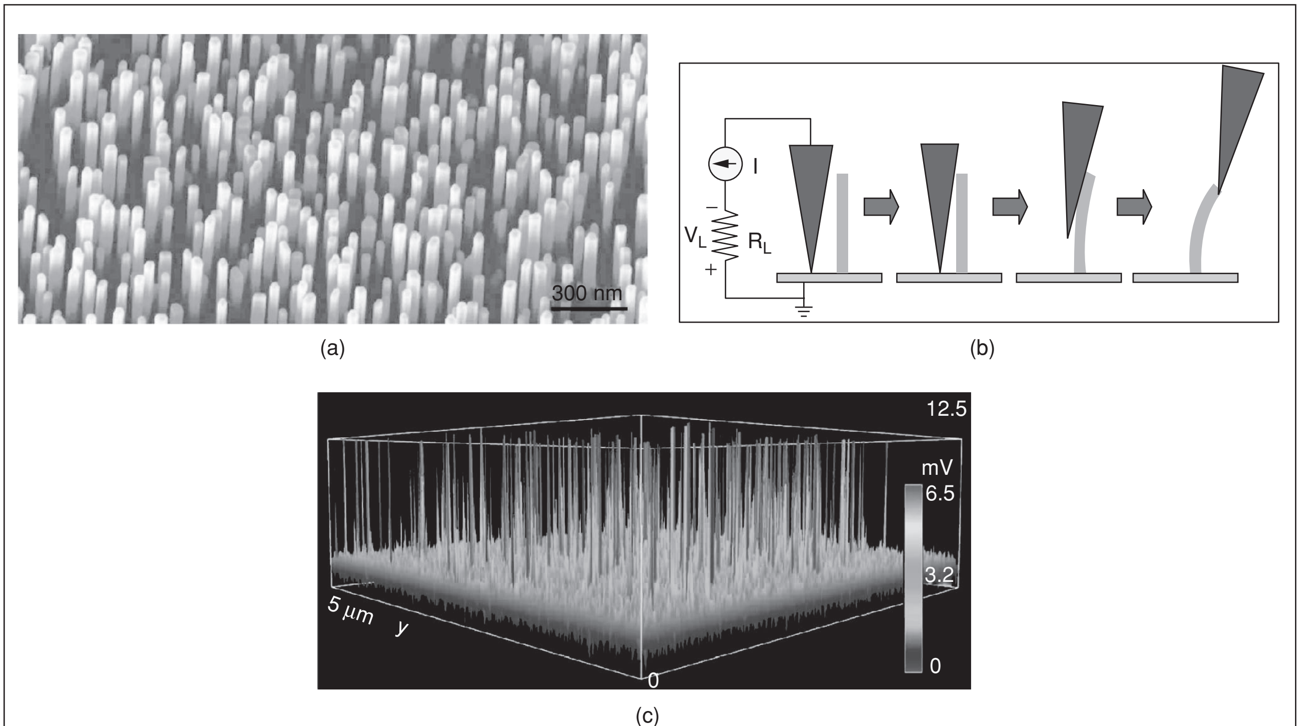

Fig. 7. (a) A scanning electron microscope image of zinc oxide nanowires. (b) Schematic of an AFM tip scanning and bending nanowires to produce current. (c) Output voltages produced by the array as it is scanned by the probe (7).

supplies should have a low recurring cost, a usable service life that commensurates with the instrumented structure, and the ability to accommodate a varying number of different types of sensors in close proximity. Efforts have been dedicated to develop wireless technologies that can communicate with and also provide power to MEMS biodevices [5], [6]. Figure 6 illustrates this concept [6].

The frequency range for the device presented in this example is from 200–700 MHz, within a distance of up to 10 cm [6].

Nanogenerators represent a different and new concept of providing power to batteryless MEMS device [7]. The nanogenerators developed at the Georgia Institute of Technology produce current by bending and then releasing zinc oxide nanowires—which are both piezoelectric and semiconducting. The concept behind nanogenerators is illustrated in Figure 7. Arrays of zinc oxide nanowires are grown. Atomic-force microscope (AFM) tips deflect individual wires. As a wire is contacted and deflected by the tip, stretching on one side of the structure and compression on the other side creates a charge separation—positive on the stretched side and negative on the compressed side—due to the piezoelectric effect. The charges are preserved in the nanowire because a Schottky barrier is formed between the AFM tip and the nanowire. The coupling between semiconducting and piezoelectric properties results in the charging and discharging process when the tip scans across the nanowire. By converting mechanical energy from body movement, muscle stretching, or water flow into electricity,

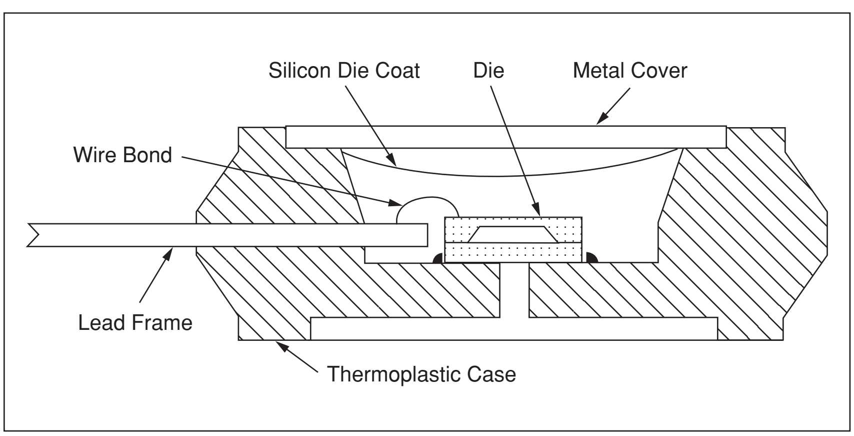

Fig. 8. MEMS pressure sensor by Motorola.

these nanogenerators could make possible a new class of self-powered implantable medical devices, sensors, and portable electronics.

MEMS Applications in Medicine and Biology

While a comprehensive list of MEMS uses in medicine is beyond the scope of this article, several more recent applications are discussed below.

Pressure Sensors

MEMS technology has been utilized to realize a wide variety of differential, gauge, and absolute pressure microsensors based on different transduction principles. Typically, the sensing element consists of a flexible diaphragm that deforms due to a pressure differential across it. The extent of the diaphragm deformation is converted to a representative electrical signal, which appears at the sensor output. Figure 8 shows a manifold absolute pressure (MAP) sensor manufactured by Motorola. The microfabricated sensor integrates on-chip, bipolar op-amp circuitry, and thin-film resistor networks to provide a high output signal and temperature compensation. The sensor die/chip consists of a thin Si diaphragm fabricated by bulk micromachining. Prior to the micromachining, piezoresistors are patterned across the edges of the diaphragm region using standard IC processing techniques. After etching of the substrate to create the diaphragm, the sensor die is bonded to a glass substrate to realize a sealed vacuum cavity underneath the diaphragm. Finally, the die is mounted on a package such that the top side of the diaphragm is exposed to the environment through a port. A gel coat isolates the sensor die from the environment while allowing the pressure signal to be transmitted to the Si diaphragm. The ambient pressure forces the diaphragm to deform downward, resulting in a change of resistance of the piezoresistors. This resistance change is measured using on-chip electronics; a corresponding voltage signal appears at the output pin of the sensor package.

Pressure microsensors have found their way into cardiac implanted devices. Recently, two companies announced the development of products that use such sensors to monitor and alert patients to the progression of heart failure (HF). Heart failure is a debilitating disease that enlarges the ventricles, increases the blood pressure, and significantly reduces their efficacy to pump blood. Patients affected by this illness have little or no effort capacity [8].

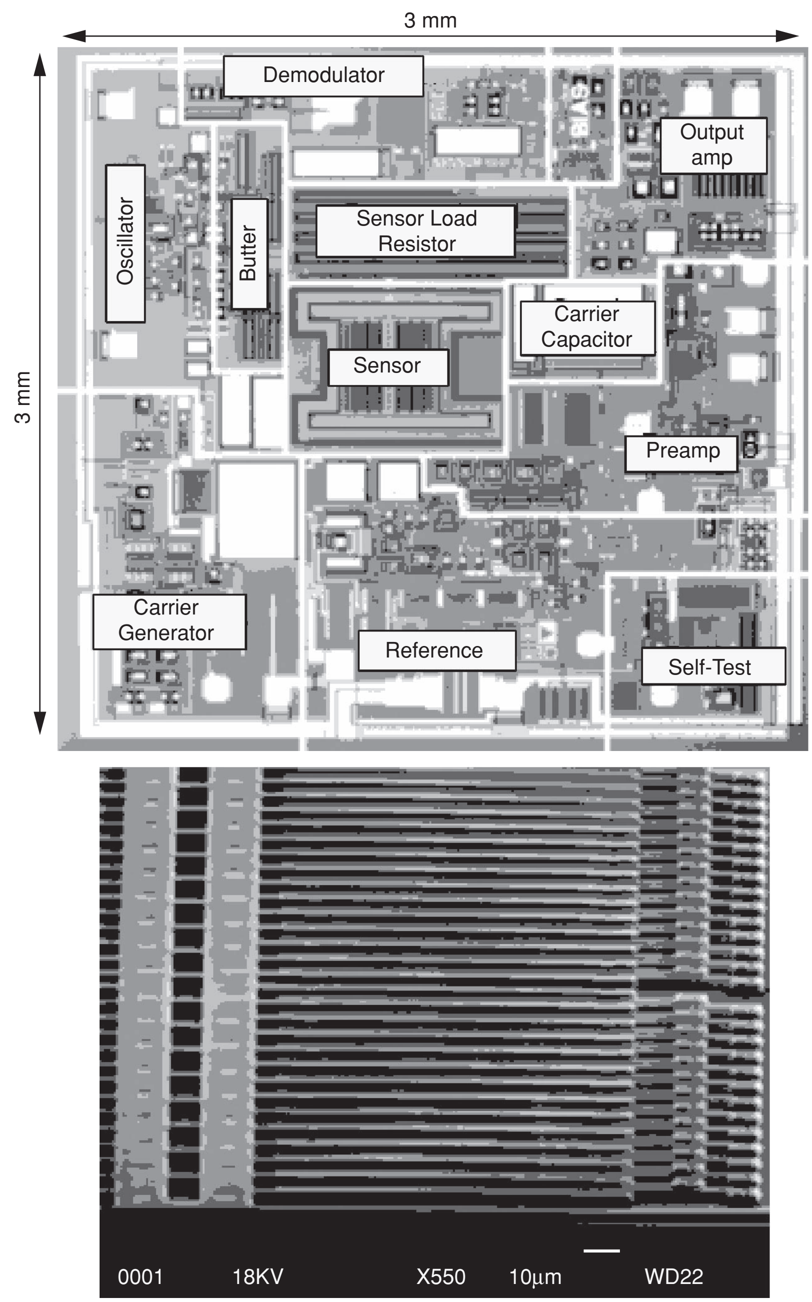

Fig. 9. MEMS accelerometer by Analog Devices Inc.

Medtronic has launched Chronicle, an implantable blood pressure monitor [9]. A pressure microsensor is placed at the tip of the device lead. The lead is implanted in the right ventricle. Pressure data is monitored and recorded by the device, and patients (or their physicians) can be alerted when the blood pressure in the right ventricle increases to limits that may represent a concern in HF progression. Since most HF patients first display symptoms associated with their left heart, St. Jude Medical and Savacor, Inc. are developing the HeartPOD system, which includes an implantable device that can record pressure in the left atrium (LA) [10]. The HeartPOD system uses a lead that has its tip implanted in the interatrial septum. The tip of the lead crosses the thickness of the septum and is exposed to the conditions in the LA. The lead tip carries a pressure microsensor that can monitor the evolution of the LA pressure. As with the Chronicle, patients and physicians could be alerted to concerning trends detected in the LA pressure.

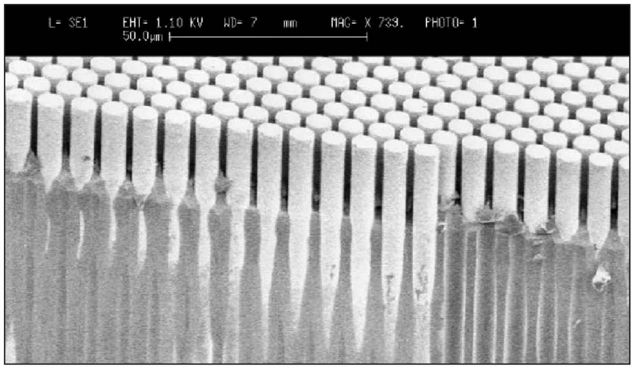

Fig. 10. Retinal prosthesis interface microelectrode array (12).

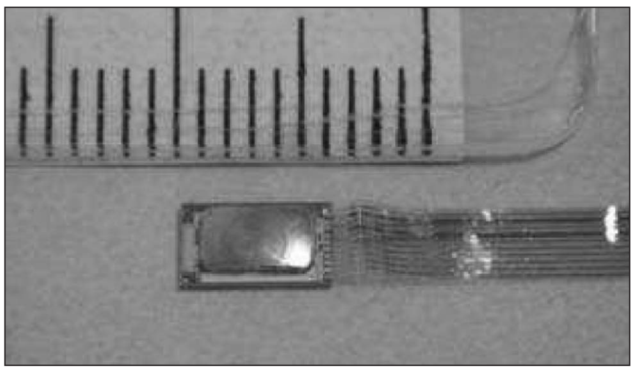

Fig. 11. Retinal prosthesis device with curved microwire glass on top (12).

Accelerometers

Acceleration sensors are relatively newer applications of MEMS technology. Typically, the sensing element consists of an inertial mass suspended by compliant springs. Under acceleration, a force acts on the inertial mass, causing it to deviate from its zero-acceleration position, until the restoring force from the springs balances the acceleration force. The magnitude of the inertial-mass deflection is converted to a representative electrical signal, which appears at the sensor output. Figure 9 shows a monolithic accelerometer manufactured by Analog Devices, Inc. The device is fabricated by surface micromachining and BiCMOS processes. The inertial mass consists of a series of 150-μm-long fingerlike beams connected to a central trunk beam, all suspended 2 μm above the substrate by tether beams. The device uses a capacitive measurement method to determine acceleration. The deflection of the inertial mass changes the capacitance between the finger beams and the adjacent cantilever beams. The sensor structure is surrounded by supporting electronics, which transduce the capacitance changes due to acceleration into a voltage, with appropriate signal conditioning. The analog output voltage is directly proportional to acceleration and is fully scaled, referenced, and temperature compensated, resulting in high accuracy and linearity over a wide temperature range. Internal circuitry implements a forced-balance control loop that improves linearity and bandwidth. Internal self-test cir-

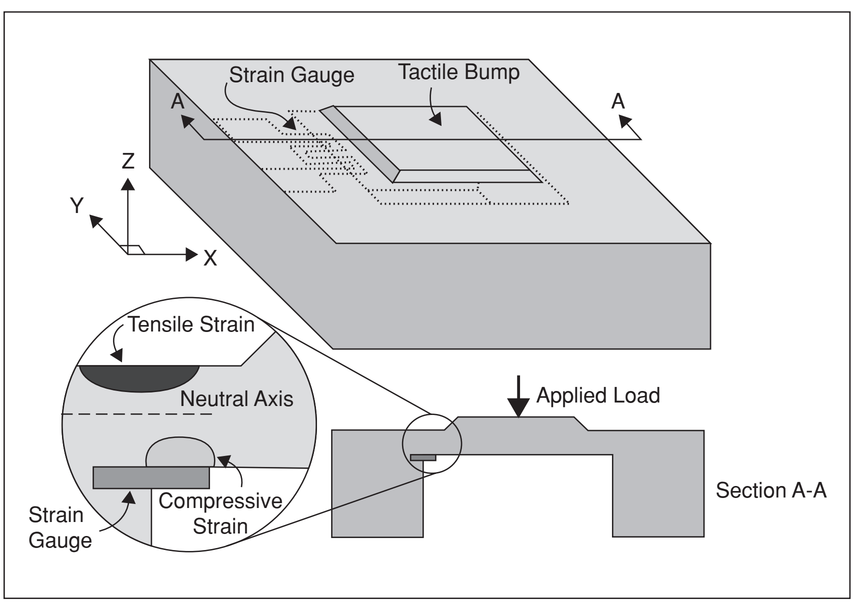

Fig. 12. Illustration of a taxel and resistive sensors located at the edge of membranes (13).

cuitry can electrostatically deflect the sensor beam upon demand in order to verify device functionality.

Most modern implantable cardiac pacemakers and ICDs employ a MEMS accelerometer. Their function is to detect the level of patient activity and provide feedback to the device microcontroller. In turn, the microcontroller adjusts the heart pacing rate to best match the patient's level of physical effort [11].

Human Retinal Prosthesis

Partial restoration of visual function (e.g., facial recognition or navigation through a building) involves the development of implantable retinal prosthesis devices with sophisticated image processing and neural interfaces. Skeath et al. developed such a device, including a curved array of 3,200 electroformed independent stimulating microelectrodes that conform to the retinal surface on the inside of the human eye [12]. The retinal prosthesis package had the following characteristics: 1) the device fit through a 4-mm incision in the eye wall, 2) the microelectrode array independently transmitted each pixel of a 40 × 80 array from the flat surface of the image-processing IC to the curved surface of the retina, 3) each microelectrode made intimate contact with the retinal surface without damaging delicate retinal tissue, 4) each microelectrode had less than 1 MΩ impedance at 1 kHz, 5) the package exposed the eye only to biocompatible materials, 6) the package interfaced with control instrumentation external to the eye, and 7) the entire prosthetic device survived steam sterilization. The microelectrode array was constructed by electroplating metal through the entire 1-mm thickness of microchannel glass plates (over 200,000 microchannels per device, with an aspect ratio 200:1). The result, shown in Figure 10, was a highly ordered array of individual uniform parallel microwires captured in a glass matrix (microwire glass). The microwires had a diameter of 5.5 μm and a pitch of 8 μm.

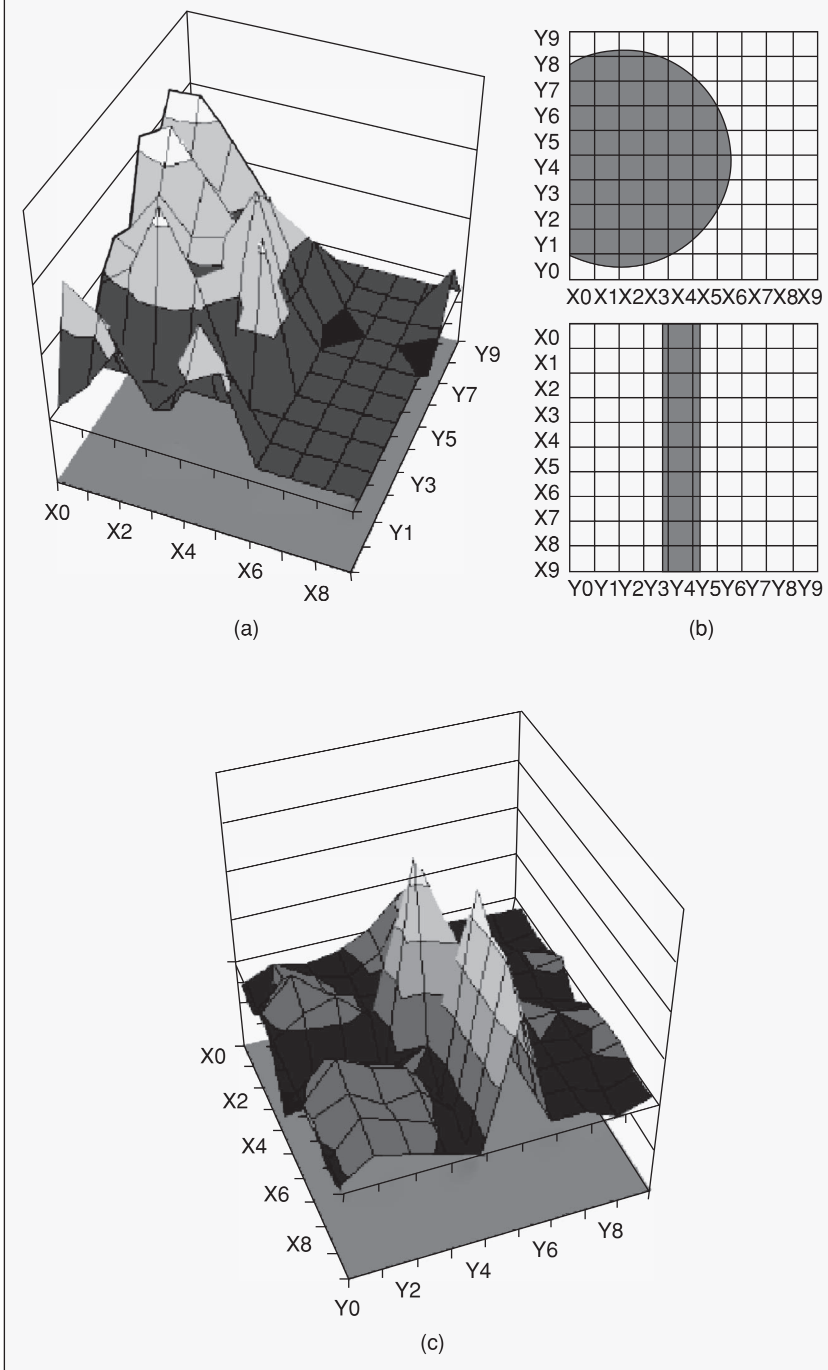

Fig. 13. Response of a 10 × 10 tactile array to contact with a 5-mm-diameter rubber probe and 22-gauge PVC insulted wire (approximately 1 mm in diameter). The charts in (b) show area of contact and (a) and (c) charts show measured responses (13).

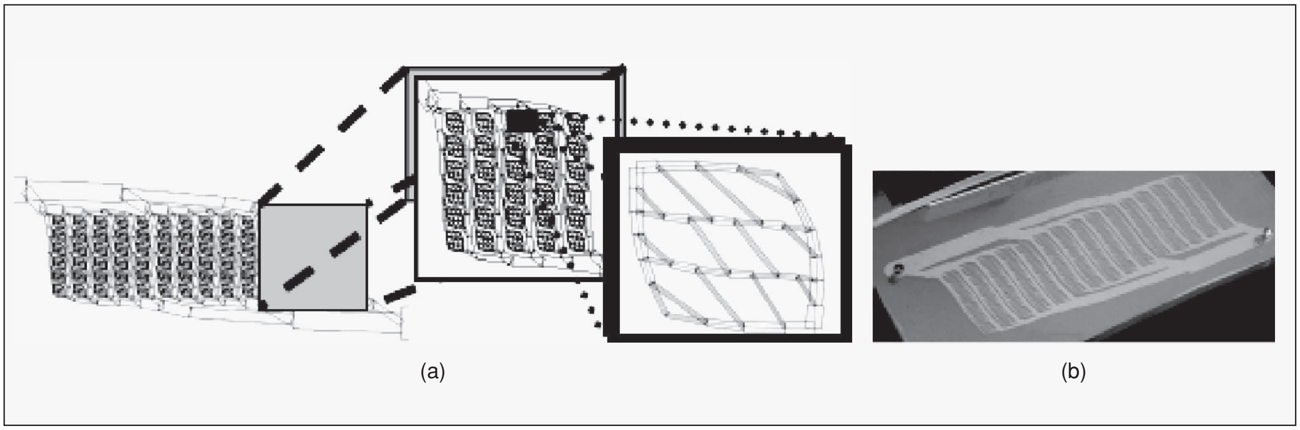

Fig. 14. (a) Design process for generation of microvascular networks and (b) PDMS layer cast in the inverse image of the designs above(14).

Major difficulties in the electroplating process included obtaining nearly perfect filling of all microchannels with metal throughout the microchannel glass and electroplating metal 1-mm thick with sufficiently low stress so the glass matrix does not crack. Overcoming these difficulties required not only control of the plating process but also proper selection and preparation of the microchannel glass for electroplating. The microelectrode impedance for each unit cell was minimized by maximizing surface area (each pixel is connected to multiple microwires) and by exposing additional microwire surface by etching to remove a portion of the glass matrix near the surface.

Assembly of the microelectrode array and the image-processing chip was accomplished using an indium bump-bonding technique. Each pixel had a 20 μm $\times$ 30 μm, 10 μm-high indium bump for connection to the package. The microwire glass package was joined to the image-processing chip by pressing the ends of the microwires into the indium bumps. Shown in Figure 11, the package also incorporated an electroplated ten-trace microcable. A surgical incision in the eye wall would be needed to pass the microcable from the image processing chip to external instrumentation. The Washington National Eye Center is seeking FDA approval to conduct human clinical trials.

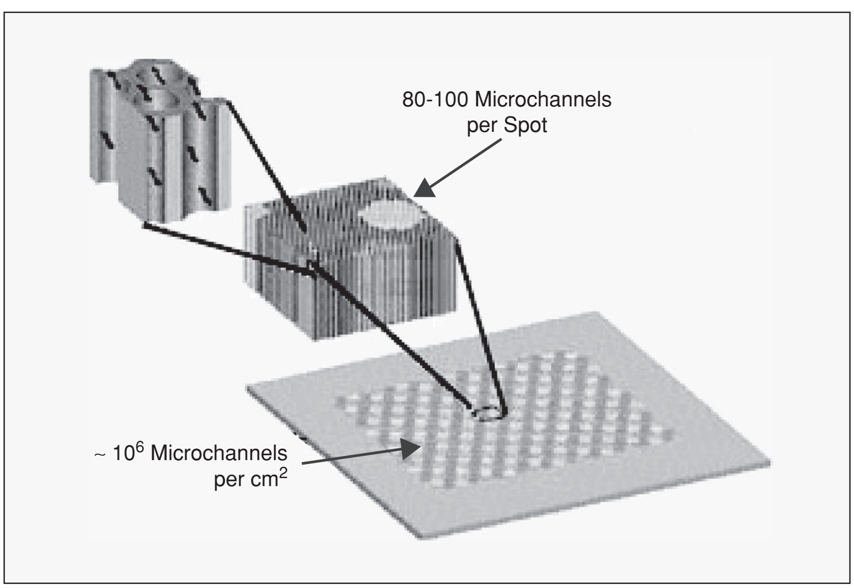

Fig. 15. Conceptual schematic of the Flow-thru Chip (15).

Tactile Sensor Skin

Tactile sensing is an area of MEMS research that has the potential to impact a large number of industries and disciplines. Key among these is application to robotics in medicine and industrial automation. Robust, reliable tactile feedback of forces and torques, contact shape and location, and dynamic slip sensing are required for dexterous, dynamic gripping and manipulation by robots and by humans through haptic interfaces. Lack of such suitable commercial tactile sensors will limit development in robotic handling of fragile or irregular objects for applications including minimally invasive surgery. Engle et al. developed a polyimide-based two-dimensional tactile sensing array realized using a novel inverted fabrication technique [13]. The sensor skin contained an array of membrane-based tactile sensors (taxels), such as the one illustrated in Figure 12.

Micromachined thin-film metal strain gauges were positioned on the edges of polyimide membranes. The change in resistance from each strain gauge resulting from normal forces applied to tactile bumps on the top of the membranes was used to image force distribution. The effective gauge factor of the taxels was found to be approximately 1.3. The output of a 10 × 10 sensor array output was characterized and shown in Figure 13. The demonstrated devices were robust enough for direct contact with humans, everyday objects, and contaminants without undue care.

MEMS-Based Renal Replacement System

End-stage renal disease (ESRD) is a significant cause of morbidity and mortality in the United States, with 72,000 ESRD deaths reported annually. Standard clinical care for most of the 250,000 renal failure patients is three 4-h hemodialysis sessions per week, costing nearly US$12 billion each year. However, these treatments only provide intermittent filtration and reabsorptive functions, and patients are at higher risk for further complications. Moreover, life expectancy drops to less than 20% for patients on renal dialysis treatments for periods of five years or more. Recent advances have been reported in bioartificial kidney technology, nanofabricated ultrafiltration membranes, and MEMS-based microdegassing devices for dialyzers. Mofrad et al. reported early design, fabrication, and ultrafiltration results for a novel MEMS-based system for renal replacement that incorporates fractal microvascular network designs and micromolded flow chambers [14]. Figure 14 illustrates the microvascular network concept. Bilayer devices have been fabricated using silicon micromachining and polymer replica molding processes. Vascular and dialysate layer designs were produced as transparencies on high-resolution 5,080-dpi printers. Transparency masks were used to pattern silicon wafers, which were then etched to a depth of 35 μm using an isotropic silicon etching recipe in a standard plasma etcher (STS). Passivation layers were deposited in a deep reactive ion etcher (STS) to promote release of replica-molded polymer films. Thin polydimethylsiloxane (PDMS) films were repeatedly produced using solvent casting against the silicon wafer masters. Thicknesses of PDMS films as low as 100 μm were routinely produced from these molds, consistent with high packing densities for multilayer devices.

For the single bilayer device demonstrations, however, PDMS thicknesses of about 2 mm were targeted for ease of handling during flow studies. This microfabricated device could ultimately provide a smaller, less invasive, and less expensive therapy for ESRD. Preliminary studies showed that the high surface area and precision of this MEMS-based

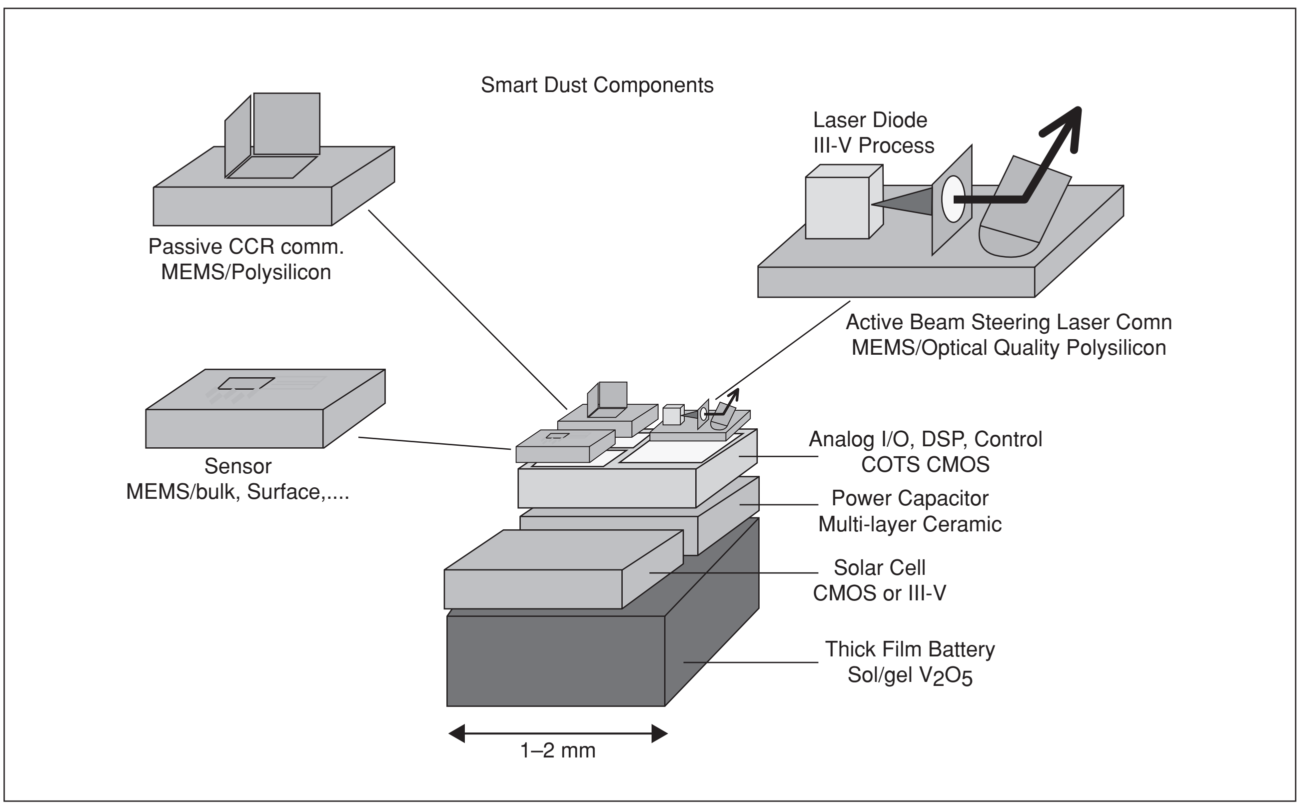

Fig. 16. Illustration of MEMS "smart dust" concept (16).

hemofiltration system offered a significant improvement in the clearance efficiency of uremic wastes over current hemodialysis technologies. Additionally, the miniature aspect of this system enabled it to be portable and potentially wearable.

Analytical Systems

Analytical systems can be used for a variety of multiplexed molecular diagnostic assays, including gene expression profiling, DNA analysis, pathogen detection and typing, genotyping, and immunobinding.

The MetriGenix Flow-Thru Chip (FTC) is an advanced microarray device for bioanalytical analysis in which molecular interactions occur within a three-dimensional matrix of microchannels rather than on a two-dimensional surface [15]. As shown in Figure 15, microchannels connect the upper and lower faces of the device such that fluid can flow through them. Binding reagents are attached to the walls of distinct groups of these microchannels, and target molecules are captured as they pass through. Multiple binding reagent spots are deposited in a regular grid to permit parallel analysis of up to 400 spots (biomolecular targets) per sample. The chip is composed of an ordered array of microscopic channels that traverse the thickness of the substrate. Arrays of probes are deposited on the chip in spots that incorporate several microchannels. Fluid flows through the chip and biological recognition reactions occur within the confined volumes of the microchannels.

Smart Dust

"Smart dust" devices are tiny wireless MEMS sensors, or sensor arrays, that can detect everything from light to vibrations. Thanks to recent breakthroughs in silicon and fabrication techniques, these motes could eventually be the size of a grain of sand, though each would contain sensors, computing circuits, bidirectional wireless communications technology, and a power supply. Motes would gather scads of data, run computations, and communicate that information using two-way band radio between motes at distances approaching 1,000 ft. Figure 16 illustrates the concept of smart dust MEMS, as developed at University of California, Berkeley. Current motes are about 5 mm on a side, but the goal for researchers at UC Berkeley is to get these chips down to 1 mm. The cost of motes has been dropping steadily. Prices range from US$50–100 each today but are anticipated to fall to US$1 within five years [16].

Future of MEMS

MEMS in medicine have already made an impact. The BioMEMS market was already at US$215 million in 2001 and is projected to grow at more than 20% a year to US$550 million in 2006 and finally top US$1 billion by 2011, according to In-Stat-MDR estimates. In the not-so-distant future, molecular biology will blend with computational systems at the atomic scale to create bionanoelectromechanical systems that could become a major factor in nanotechnology. While the significant impact of nanotechnology and its applications is expected to be in the future, the U.S. Food and Drug Administration has already approved many products such as imaging agents and nanoparticle ingredients in sunscreens. There are also cosmetics currently on the market that claim to contain nanoparticles. Borrowing a scene from the classic 1966 science-fiction movie *Fantastic Voyage*, the time may come when MEMS microrobots will enter patients' bodies to clear arteries or make microsurgical repairs.

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