

# **BioMEMS**

***Nabiollah Abolfathi***

**Mechanical Engineering Department  
Of  
North Dakota State University**

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### **MEMS Technology for Biological applications**

#### **1- INTRODUCTION**

Since the beginning of micro-electro-mechanical systems in the early 1970s, the significance of the biomedical applications of these miniature systems were realized [1,2]. Biomedical or Biological Micro- Electro-Mechanical Systems (BioMEMS) are now a heavily researched area with a wide variety of important biomedical applications [3]. In general, BioMEMS can be defined as “devices or systems, constructed using techniques inspired from micro/nano-scale fabrication, that are used for processing, delivery, manipulation, analysis, or construction of biological and chemical entities”. These devices and systems encompass all interfaces of the life sciences and biomedical disciplines with micro- and nanoscale systems. Areas of research and applications in BioMEMS range from diagnostics, such as DNA and protein micro-arrays, to novel materials for Bio-MEMS, micro-fluidics (not dealt with in this review), tissue engineering, surface modification, implantable BioMEMS, systems for drug delivery, etc. Microelectromechanical systems (MEMS) devices are manufactured using similar microfabrication techniques as those used to create integrated circuits. They often have moving components that allow a physical or analytical function to be performed by the device in addition to their electrical functions. Microfabrication of silicon-based structures is usually achieved by repeating sequences of photolithography, etching, and deposition steps in order to produce the desired configuration of features, such as traces (thin metal wires), vias (interlayer connections), reservoirs, valves, or membranes, in a layer-by-layer fashion. Interest in using MEMS and microfabrication technologies for *in vivo* applications, however, is growing. MEMS can be aseptically fabricated and hermetically sealed, and the biocompatibility of materials used in MEMS fabrication is being investigated. The manufacturing techniques used in the microelectronics industry

may lead to greater uniformity and reproducibility of implantable devices than is currently available to the biomedical and pharmaceutical industries. MEMS offer great potential advantages over other types of implantable systems for certain applications due to their small size scale, electrical nature, and ability to operate on short time scales. The development of retinal implants to treat blindness, neural implants for stimulation and recording from the central nervous system, and microneedles for painless vaccination are examples of applications in which features unique to MEMS, such as optical and electrical sensitivity or feature size comparable to relevant biological structures, are being leveraged for maximum impact. The ability of MEMS to act on a short time scale and under physiologically relevant conditions, coupled with their ability to deliver an electrical stimulus and/or drugs from a device, offer the potential for these devices to actuate systems in the body.

## ***2- Detection methods, BioMEMS, and biochip sensors.***

Much has been done in the application of MEMS technology to biosensors and the adaptation of various types of sensors to *in vivo* diagnostics. Long-term *in vivo* sensing is a critical component of the ideal closed-loop drug delivery or monitoring system, but the issue of implant biocompatibility and biofouling must be addressed in order to achieve long-term *in vivo* sensing. Biosensors are analytical devices that combine a biologically sensitive element with a physical or chemical transducer to selectively and quantitatively detect the presence of specific compounds in a given external environment [4]. During the last decade, BioMEMS and devices have been used as biosensors and the resulting biochips can allow sensitive, rapid, and real-time measurements [5, 6]. These BioMEMS sensors can be used to detect cells, proteins, DNA, or small molecules. Many demonstrations to date are on one sensor and these sensors can potentially be integrated into an array format. There are many detection methods used in BioMEMS sensors and biochips, including (i) mechanical, (ii) electrical, (iii) optical, etc.

### ***2-1- BioMEMS and mechanical detection:***

Mechanical detection for biochemical entities and reactions has more recently been used through the use of micro- and nano-scale cantilever sensors on a chip. These cantilever sensors (diving board type structures) can be used in two modes, namely stress sensing and mass sensing. In stress sensing mode, the biochemical reaction is performed selectively on one side of the cantilever. A change in surface free energy results in a change in surface stress, which results in measurable bending of the cantilever. Thus, label-free detection of bimolecular binding can be performed. In the mass sensing mode, the cantilever is excited mechanically so that it vibrates at its resonant frequency (using external drive or the ambient noise, for example). The resonant frequency is measured using electrical or optical means, and compared to the resonant frequency of the cantilever once a biological entity is captured. The change in mass can be detected by detection of shift in resonant frequency, assuming the spring constant does not change. One of the main advantages of the cantilever sensors is the ability to detect interacting compounds without the need of introducing an optically detectable label on the binding entities. Direct, label-free detection of DNA and proteins have been demonstrated using silicon cantilevers [7]. Hybridization of DNA and detection of single based mismatches on DNA strands has been demonstrated on cantilevers with a thin Au gold layer on one side [8, 9]. This isolated capture DNA strands are attached to the Au layer and the deflection of cantilevers can be detected when the target strands bind to the capture strands. These sensors can also be used to detect proteins and cancer markers such prostate specific antigen, which have also been detected at 0.2 ng/ml in background of human serum albumen in clinically relevant conditions, [10]. Cantilevers coated with environmentally sensitive hydrogels such as pH-sensitive (poly) methacrylic acid (PMAA) can also be used to induce a stress on the cantilever surface since these polymers are known to expand (or contract) upon change in pH.

Since the stress detection method used with cantilevers is based upon a change in surface energy, it can be speculated that the DNA or protein layers are continuous over the area of gold-coated cantilevers, as is the case with Self-Assembled Monolayers (SAMs), and hence result in a uniform surface stress change, resulting in the cantilever bending.

## ***2-2- BioMEMS and electrical detection***

Electrical or electrochemical detection techniques have also been used quite commonly in biochips and BioMEMS sensors. These techniques can be amenable to portability and miniaturization, when compared to optical detection techniques, however, recent advances in integration optical components on a chip can also produce smaller integrated devices [11, 12]. Electrochemical biosensors include three basic types, they are as follows: (i) amperometric biosensors, which involves the electric current associated with the electrons involved in redox processes, (ii) potentiometric biosensors, which measure a change in potential at electrodes due to ions or chemical reactions at an electrode (such as an ion Sensitive FET), and (iii) conductometric biosensors, which measure conductance changes associated with changes in the overall ionic medium between the two electrodes. There are more reports on potentiometric and amperometric sensors, specially, due to the established field of electrochemistry, and many of these sensors have been used as the micro- and nano-scale. The most prevalent examples of amperometric biosensors employ an enzyme-catalyzed redox reaction, where the resulting redox electron current is measured at a working electrode. The most widely used examples are that of detection of glucose, based on glucose oxidase, which generates hydrogen peroxide and glycolic acid in the presence of oxygen, glucose, and water [13]. Then, hydrogen peroxide is reduced at  $-600$  mV at Ag/AgCl anode reference electrode. These devices are designed either for monitoring formation of hydrogen peroxide formation or consumption of oxygen. At the micro-scale, these sensors require the formation of the working and reference electrodes on a chip, and an enzymatic layer on the working electrode, as demonstrated for the detection of glucose, lactose, and urea [14,15] and for the detection of glucose [16]. More recently, hydrogels and conducting electroactive polymers have been integrated to develop electroactive hydrogels that physically entrap enzymes within their matrices for biosensor construction and chemically stimulated controlled release. In addition, amperometric biosensors on a chip have been applied towards detection of gases [38], metabolic parameters in human blood [18], lactate [19], and even DNA hybridization [20]. The DNA hybridization was detected by measuring the field effect in silicon by the intrinsic molecular charge on the DNA, using a buffer of poly-L-lysine later. Conductance techniques are attractive due to their simplicity and ease of use since a specialized reference electrode is not needed, and have been used to detect a wide variety

of entities such as agents of biothreat [21], biochemicals , toxins , and nucleic acids . Measurement of impedance (or admittance) was used to measure the metabolic activity of microorganisms within micro-fluidic biochips. As bacterial cells are grown within micro-fluidic channels and wells, the impedance changes in the medium can be detected using electrodes placed appropriately within the channels [22]. Electrical measurements of DNA hybridization using conductance techniques have been demonstrated where the binding of oligonucleotides functionalized with gold nanoparticles leads to conductivity changes associated with binding events [23]. Neurons have been cultured on micro-fabricated surfaces and changes in their electrical signals upon exposure to harmful chemicals and toxins have been measured on a chip. Significant challenges exist for long-term operation since the cells need to be kept alive and healthy under various harsh operating conditions and much work has been done towards this front, as this technology has been extended to demonstrate automated portable cell based biosensors platform that have been field tested . Liver cells have also been used as biosensors by culturing them in 3-D culture environment for over 14 days and the toxicity of the target compounds was determined optically [24,25]. Microorganisms have also been used as biosensors for the detection and monitoring of environmental pollutants. Whole cell-based sensors will potentially offer tremendous benefits for the evaluation of drug candidates and effects of biochemical on multi-cellular organisms since the response of these sensors is directly predictive of the physiological response of an organism.

### ***2-3- BioMEMS and optical detection:***

Optical detection techniques are perhaps the most common due to their prevalent use in biology and life sciences. Optical detection techniques can be based on fluorescence or chemiluminescence. Fluorescence detection techniques are based on fluorescent markers that emit light at specific wavelengths and the presence and enhancement, or reduction (as in Fluorescence Resonance Energy Transfer) in optical signal can indicate a binding reaction, Recent advances in fluorescence detection technology have enabled single molecule detection [4]. Fluorescence-based detection in BioMEMS has been applied to detection of cells within micro-chips, using antibody-based (ELISA type) assays.

Majority of the detection schemes in microarray and numerous lab-on-a-chip devices and applications (as described in the next section) utilize optical detection schemes. Detection of proteins [26] and detection of DNA using PCR on a chip are among a few examples. Bioluminescent light generated from a 1-mM ATP with firefly luciferase/ luciferin solution was placed inside the channels and chambers, coated with metal, and the light output was observed through a close up lens by a CCD, with maximum light enhancement obtained by silver coated microchannels and chambers. Similar enhancements in optical sensitivity can be achieved when chemiluminescence is combined with three-dimensional channels in biochips for quantitative detection of hybridization [27] and for capillary electrophoresis in PDMS. One of the challenges for optical detection within biochips is the ability to integrate the detectors in a miniaturized portable format.

### ***3- Drug Delivery Systems:***

An area of rapidly increasing interest is the use of microfabricated devices and structures for drug delivery. The digital capabilities and short response times of MEMS make them attractive for drug delivery applications in which trigger pulsate drug release is desired. Further, the reproducibility of the microfabrication processes may minimize batch-to-batch variation of the devices in comparison to current biomedical and drug delivery implants, which is highly desirable from the regulatory and quality control viewpoints. Incorporation of sensing components, such as the hydrogels discussed earlier, may allow for the achievement of a “smart” or responsive MEMS drug delivery system. The use of MEMS for drug delivery requires the existence of a drug depot or supply within or on the device. A number of approaches are being pursued in an effort to devise new reservoir-containing structures fabricated from traditional MEMS materials such as silicon as well as polymeric materials.

#### ***3-1-Microparticles:***

One straightforward approach to realize a microfabricated drug reservoir is the fabrication of silicon microparticles that contain an internal reservoir loaded with drug [28], [29]. Standard microfabrication techniques (photolithography and wet or dry etching) are used to pattern wells ranging in size from 25 to 100 nm inside silicon squares ranging from 80 to 150 nm in size. The reservoirs can be filled using a microinjector attached to a micromanipulator, and the devices are small enough to be injected or ingested. Devices injected intravenously could have a slow dissolving cap, fabricated from gelatin or starch, for example, over each reservoir to prevent burst release of the drug upon injection. Grafting of fibroblast growth factor (FGF) to the surface of the device could provide a high-affinity ligand for proliferating vascular endothelial cells, which are often found in tumors, and enable the microparticles to target delivery of their drug load to cancerous cells [30]. Oral drug delivery could be achieved from these devices by ingestion of an enteric capsule that contains the drug-loaded microparticles. Upon dissolution of the capsule in the gastrointestinal tract, release of the drug could be triggered by the binding of a surface-functionalized molecule to cells in the digestive tract.

### ***3-2- Silicon Microreservoir Devices for Drug Delivery:***

Another microfabrication approach for drug delivery is a silicon-based MEMS device consisting of an array of microreservoirs [31]. Each dosage of drug is contained in a microreservoir that is covered with a gold membrane. Application of an anodic voltage to the membrane of interest causes electrochemical dissolution of the membrane in the presence of chloride ions. This causes the membrane to weaken and rupture, allowing the drug within the reservoir to dissolve and diffuse into the surrounding tissue. This device allows the release of potent substances in a “digital” manner, such that small pulses of drug can be combined to produce a complex release profile or one with tight dosage control [32]. Each microreservoir can be individually filled, so multiple substances can be delivered from a single MEMS device. This device contains no moving parts, and when packaged with a power source and programmable clock would be approximately the size and weight of a pacemaker. A simpler version of the device could be an ingestible

platform for a few releases at timed intervals along the gastrointestinal tract. Release of fluorescent dye and radiolabeled compounds has been demonstrated from these microreservoir devices *in vitro* in saline solution and serum [31]. Additionally, a great amount of effort in the pharmaceutical industry is targeted toward ensuring that the drug formulation is optimized to prolong the stability of the drug, but formulation optimization may be restricted by the fact that the polymer matrix must necessarily be part of that formulation. The mechanism or formulation that controls the release of drug from the silicon microreservoir devices described here, in contrast, is simply the gold membranes that seal the reservoirs. It is expected that for most drugs, the formulations within the reservoirs can be changed without causing any effects on the gold membranes or release mechanism. Another important reliability issue for this microreservoir device is its long-term stability, which is currently being investigated through a long-term implantation study.

### ***3-3- Polymer Microreservoir Devices:***

Most polymer drug delivery systems currently in commercial development or research are based on the depot principle. These systems often are composed of a physical mixture of the drug of interest and a polymer, as was described above. Delivery of the drug is typically achieved by diffusion of the drug through the polymer substrate or pores in the implant, or by degradation of the polymer and subsequent release of the drug. However, other researchers are exploring the use of nontraditional MEMS fabrication techniques and materials that could be used to form microwell- or microreservoir-based drug delivery devices. For example, microwells of varying sizes (as small as 3 fL/well) have been fabricated by micromolding of poly (dimethylsiloxane) (PDMS) on a photoresist-coated silicon wafer that is photolithographically patterned [33]. These microwells can be filled with solutions by using the principle of discontinuous dewetting. Either the array can be immersed in a bulk solution and then removed in order to fill the reservoirs or the liquid can be spread over the surface of the array to fill the wells and then allowed to drain off the array due to gravity. The use of ultraviolet laser micromachining (ablation) has been explored for micropatterning of biodegradable polymer substrates [34]. Grooves

and holes were patterned in multilayer poly (D-lactic acid) and poly (vinyl alcohol) (PVA) films and single-layer PVA films, respectively. The grooved structures are designed to provide guidance to neurons (peripheral nerve regeneration), while the PVA films with 5- to 10-  $\mu$ m holes could be used for ultrafiltration applications. This technique of laser ablation could also be used for micromachining of drug reservoirs in polymeric devices.

#### ***4- MEMS Material Biocompatibility:***

Thus far we have focused on how the application of microfabrication technology can improve the integration and function of implantable devices. Understanding the interaction between the implanted MEMS materials and the local cellular environment, and assessment of the immune response, are critical, however, for optimizing the performance of MEMS *in vivo*. In this section we review the current understanding of the biocompatibility of some common materials used in MEMS fabrication. Biocompatibility testing of implant materials is becoming increasingly complex, and MEMS devices have unique biocompatibility issues. The biocompatibility requirements vary considerably depending on the device function and design; biocompatibility is defined by *The Williams Dictionary of Biomaterials* as “the ability of a material to perform with an appropriate host response in a specific application” [35]. The performance of sensors (glucose, pH, etc.), for example, is limited by biofouling and isolation of the sensor surface. However, neural electrodes must remain in intimate contact with the neurons that they are stimulating or recording. The ISO 10 993 standards outline minimum tests of material characterization, toxicity, and biodegradation that may be augmented depending on actual device usage. Biocompatibility can be assessed using several types of tests. *In vitro* assays include leaching of material, corrosion testing, protein adsorption testing, and cell culturing on material samples. *In vivo* biocompatibility assays typically involve the implantation of material or a device at the eventual site of use (intramuscular, subcutaneous, etc.).

The biocompatibility of MEMS materials was not addressed until recently because these materials were packaged or encapsulated away from direct contact with tissue and fluids; biocompatibility is a surface-mediated property, and the biocompatibility of a device depends only on those materials in contact with tissue. The biocompatibility of silicon and other MEMS materials has become much more important with the advent of implantable MEMS devices that interact directly with the body. The biocompatibility of some MEMS electrode materials has been studied, however, because of their use in other devices such as pacemaker electrodes and dental implants. Silicon substrates are the basis for most MEMS devices, and silicon compounds commonly enable device function. A comprehensive evaluation of silicon materials was completed by Kotzar *et al.*, who performed the baseline ISO 10 993 tests on single crystal silicon, polycrystalline silicon, silicon dioxide, silicon nitride, single-crystal silicon carbide, titanium, and the photo epoxy SU-8 [36]. This basic information will be valuable to guide future device design and materials selection, although slight variations in processing and composition may change the results of biocompatibility tests. The biocompatibility of MEMS materials for the silicon microreservoir drug delivery device has been studied using a cage system that was previously used for polymers [37]. Material samples were placed within a stainless steel wire mesh cage and implanted in rats. The lymphocyte concentration and adherent macrophages and foreign body giant cells (FBCG) were measured out to 21 days to characterize the acute and chronic biocompatibility. The advantage of this technique is that it is both *in vivo* and quantitative. The results indicated that silicon, silicon nitride, silicon dioxide, gold, and SU-8 were biocompatible, and all but silicon and SU-8 had reduced biofouling. In a similar study, silicon nitride was implanted in Teflon containers in rabbits [38]. The biocompatibility of silicon-based microelectrode arrays was evaluated *in vitro* using brain slice cultures [39]. Silicon microelectrodes with silicon nitride and platinum-coated tips were found to support cell cultures similarly to conventional semiporous membranes. These microelectrode arrays may be used *in vitro* to study defined neural networks and perform neurotoxicological screening. The biocompatibility of silicon membranes with well-controlled pore sizes to encapsulate pancreatic islet cells has been studied [40], [41]. These biocapsules allow nutrients and small molecules to pass freely through the membranes while isolating transplanted cells

from rejection by the patient's immune system. The porosity and pore size of silicon has been found to affect the bioactivity of silicon [42, 43]. Low-porosity microporous films induced hydroxyapatite growth *in vitro*; high-porosity mesoporous films exhibited substantial dissolution *in vitro*, while planar silicon was inert in the same medium. These characteristics may be used to aid MEMS implant design to select bioactivity or bioinertia depending on device function. The electrode materials for implantable MEMS devices are typically gold, platinum, or titanium. The noble metals have a long history of successful use in dentistry, and more recently as electrodes for pacemakers, while titanium is successfully used for many orthopedic implants. Higher noble metal content in dental alloys has been shown to increase biocompatibility [44]–[45].

## ***5- CONCLUSION***

MEMS have many characteristics that make them appealing for biological applications, including the ability to control their physical and chemical characteristics on the micrometer and nanometer scale. Additionally, the exact temporal control that can be achieved over MEMS operation makes the devices particularly attractive for drug delivery applications where precise dosing is required. The microchip for drug delivery developed in our laboratory [82], for example, is capable of pulsatile release of drugs by opening various reservoirs on command. The addition of hydrogels, biosensors, and other features that are responsive to the local environment of the device will allow MEMS to operate in a more closely integrated manner with the biological surroundings. Further, the application of MEMS technology in novel areas such as stent fabrication and immunoisolation capsules offers the potential for significant improvements in biological integration of a wide range of implantable devices. The growing interest in combining living cells with microfabricated devices, and in using microfabrication technology for tissue engineering and drug delivery, may ultimately lead the way to fully integrated, MEMS-based devices that could augment or replace entire biological systems in the human body.

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