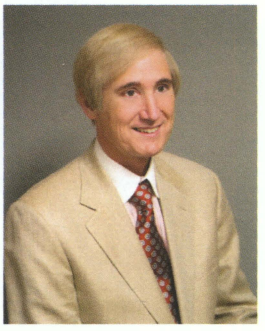

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Education, bioMEMS and the medical microdevice revolution

'We are on the threshold of a medical microdevice revolution that will change how we diagnose and treat patients. Our educational programs must rise to the challenge of providing the required diverse curriculum.'

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It is with great honor that I have accepted this opportunity to address the emerging field of biomedical microelectromechanical systems (bioMEMS), the science of medical microdevices, and to reflect on the skills required to conceive, design, fabricate and apply these devices to biomedical research and clinical medicine. BioMEMS is concerned with devices that have at least one dimension between 100 nm and 200 µm, while other dimensions may be several mm or more. Applications include lab-on-chip (LOC) devices, micro-total-analysis systems (µTAS), DNA and protein microarrays, and a host of diagnostic, interventional and therapeutic devices. BioMEMS may also be the platform for delivery of future nanotechnologies, such as stem cell research and microsphere-encapsulated drug-delivery systems.

We are on the threshold of a medical microdevice revolution that will change how we diagnose and treat patients. Our educational programs must rise to the challenge of providing the required diverse curriculum. The promise of these technologies is the delivery of sensitive, selective, fast, low-cost, less invasive and robust methods for diagnosis and pathogen detection; individualized treatment directed at specific targets and genetic inadequacies; and methods of therapy incorporating novel drug-delivery devices and other actuator systems.

The multidisciplinary nature of the field is reflected by the diversity of students who are taking the 'Introduction to BioMEMS' course at the University of Minnesota, MN, USA. This includes senior undergraduate students and graduate students in biomedical, chemical, electrical and mechanical engineering programs and health-related fields, such as biochemistry, cellular biology, pharmacy and medicine.

Among the advantages of miniaturization of analytic devices are lower manufacturing costs, reproducibility, small sample size and reagent use, improved signal-to-noise ratio, improved response time, precise control of mixing, reacting and discarding of waste products, in-line and embedded detection methods and high throughput. DNA and protein microarrays allow for large-scale genetic and pathogen screening, which is unobtainable by traditional methods.

Devices intended for real-time diagnostic monitoring or therapeutic intervention may operate *in vivo* or *in vitro*. These include handheld point-of-service instruments, topically applied sensors and drug-delivery systems, and implanted medical microdevices. These may be smart systems with integrated microprocessors, which have onboard or external power sources and operate as either open-ended (sensor or actuator) or closed-loop systems (autoregulation). BioMEMS are typically integrated with other components and perform one or more functions in a chain of operations. Implanted devices may be part of a distributed system, such as fiberoptic sensors, providing continuous information via light from various parts of the body to a central implanted device. BioMEMS also include polymer microspheres that may be used to encapsulate drugs and utilize controlled biodegradation of the polymer for drug delivery [1].

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An emerging field

BioMEMS as a science includes traditional MEMS/microstructure technology (MST) and an expansion into a host of new polymer materials, microfluidic physics, surface chemistries and modification, soft fabrication techniques (including polymers and biologic components), biocompatibility and cost-effective solutions to biomedical problems. BioMEMS is also the quintessential science for genomics, the study of sets of genes, gene products and their interactions and proteomics, the study of proteins and the expression of genes in health and disease. Applications include diagnostics, health screening, individualized treatment, drug-delivery systems, tissue engineering and minimally invasive procedures.

LOC devices and μTAS, including DNA and protein microarrays, will be the basis of most, if not all, diagnostic tools within the next 10 years. Transport of samples, reagents and buffers through microfluidic systems based on electrokinetic and active pumping techniques will be at the heart of these systems. Actuator systems, including environmentally sensitive hydrogels, electrically active polymers (EAPs) and piezoelectric devices, will be used for drug-delivery systems and to fabricate impressive biomimetic systems. Homeland security will also benefit from novel sensors for the detection of biologic and other terrorist weapons [1].

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Training

The anticipated growth of medical microdevices places an enormous burden upon traditional biomedical engineering programs which alone may be unprepared to handle the diverse subject matter. The necessary preparatory training includes the following subjects:

- Microfabrication of silicon, glass and polymer devices
- Microfluidics, transport processes and electrokinetics
- Sensors, actuators and drug-delivery systems
- μTAS and LOC devices
- Introduction to clinical laboratory medicine
- Detection and measuring systems
- Genomics, proteomics, DNA and protein microarrays
- Understanding of emerging applications in medicine, research and homeland security
- Packaging, power systems, data communication and radio frequency (RF) safety
- Biocompatibility and international standard ISO 10993 biologic evaluations

Microfabrication

The majority of MEMS/MST devices are made from the same materials used for microelectronics, including for example, single crystal silicon wafers; deposited layers of polycrystalline silicon (polysilicon) for resistive elements; aluminum, copper and other metals for conductors; silicon oxide for insulation and as a sacrificial layer (to allow release of moving parts) and silicon nitride and titanium nitride for electrical insulation and passivation. An advanced integrated circuit fabrication center with a clean-room environment is required for silicon, ceramic and glass micromachining. This includes precision lithography and mask production etching techniques, thin-film application with physical and chemical vapor deposition, sputtering, electroplating and substrate bonding. Integration of electrodes for application of electrokinetic techniques, electrochemical detection and metal contacts for ultrasonic bonding of lead wires is necessary for many bioMEMS devices. Hybrid packaging with integrated electronics, including application-specific integrated circuits (ASICs) for control and communication is also essential.

Soft fabrication techniques are used for bioMEMS that incorporate synthetic polymers, natural polymers such as DNA, RNA and proteins, and other biologic materials. These techniques require altogether different facilities and may be distributed among various departments and laboratories in an institution. Fabrication methods include micromolding and embossing, 3D construction with photopolymerization (microstereolithography), smart polymers and hydrogels (that can be formed *in situ* and respond by changing shape to environmental stimuli), self-assembled monolayers (SAMs) and thick-film techniques. Also, surface treatment with plasma, chemical or biologic modification serves to alter hydrophobicity, transport processes, electrokinetic phenomena, binding properties and biocompatibility of materials.

Microfluidics, transport processes & electrokinetic phenomena

Microfluidics is the study of transport processes in microchannels. Microfluidic devices are the primary component of LOC devices and μTAS, and may consist of channels, valves, mixers, pumps, filters and heat exchangers. These components allow metering, dilution, flow switching, particle separation, mixing, pumping, incubation of reaction materials and reagents, and sample dispensing or injection. Eventually, such devices will improve throughput of samples, increase accuracy and lower analysis cost. Microfluidic devices offer the possibility of reducing entire laboratory operations onto single chips with the advantage of smaller reagent volumes, shorter reaction times and parallel operation.

Transport processes involve an understanding of fluid mechanics, including laminar flow and fluid kinematics. In microfluidics, channel flow is primarily laminar and passive mixing is by diffusion. Chaotic mixing may be achieved by special geometries and active pumping systems. Surface area-to-volume (SAV) increases significantly as dimensions are reduced for microfluidic channels. As the SAV increases, processes such as capillary electrophoresis becomes more efficient due to easier removal of heat, and transport due to electrokinetic flow decreases because of rapid diffusion of macromolecules and adsorption to channel surfaces.

Electrokinetic phenomenon in microfluidics includes electroosmosis (movement of fluid relative to a stationary charged or conducting surface through the application of an electric field), electrophoresis (charged species in a fluid are moved by an electric field relative to the fluid molecules), streaming potential (an electroviscous effect) and dielectrophoresis (forces exerted on dielectric materials). Harnessing electrokinetic phenomenon in microfluidic devices for moving fluid and particles (including proteins, cells, bacteria and viruses) is essential for μTAS and other LOC applications.

Sensors, actuators & drug-delivery systems

A sensor converts one form of energy to another, and in doing so, detects and conveys information about some physical, chemical or biologic phenomena.

More specifically, a sensor is a transducer that converts the measurand (a quantity or a parameter) into a signal that carries information. Types of sensors that respond to different stimuli include acoustic, biologic, chemical, electrical, magnetic, optical, mechanical, radiation and thermal. Many established sensing techniques can be used internally and externally with bioMEMS, and microfabrication allows direct integration with LOC and μTAS. Dynamic characteristics of the sensor are important for continuous flow monitoring, and special design consideration needs to be given to prevent biofouling or interference with function from contact with biologic material. Other important sensor characteristics include interchangeability, lifetime, limit of detection (especially with smaller volumes and lower analyte concentrations), reproducibility, resolution, response time and selectivity.

'BioMEMS offer a number of advantages to drug delivery, including controlled release, reliable dosing, targeted therapy, precise delivery and automated or semiautomated feedback control.'

Actuators serve a variety of functions in bioMEMS, including microfluidic valve control and pumping, positioning and alignment of detectors, and even for dispensing of medications. In MEMS/MST, we typically think of an actuator as doing some form of work, or more specifically, converting electrical, optical, magnetic or chemical energy into mechanical energy. In bioMEMS, we can also consider actuation as the work performed by an efferent limb of a control system. In this sense, electrical, optical, magnetic and chemical systems may directly do the work. For example, if it is desirable to create a device that delivers a precise amount of medication in an oscillatory manner, a polymer material could be fabricated so as to alter its diffusivity based on some form of control signal, such as a change in pH, allowing dispensing from a reservoir source. In addition to traditional mechanical techniques, activation may be performed by harnessing electrostatic, electrostrictive, piezoelectric, magnetic, thermal and optical phenomenon.

Medications are currently administered topically, sublingually, orally, nasally, subcutaneously, intramuscularly, intravenously, intrathecally, rectally, vaginally and by perfusion to arteries and target organs via catheters. Some medications may be administered from implanted reservoir devices including analgesics and insulin. Various transdermal systems (patches) using reservoir gels have been developed for delivery of nitroglycerin, hormones, scopolamine and other drugs, in which gradual release is beneficial. Dose, frequency, duration, oscillatory behavior, toxicity, drug interaction and allergies must all be considered and customized for patients based on their illness and history. BioMEMS offer a number of advantages to drug delivery, including controlled release, reliable dosing, targeted therapy, precise delivery and automated or semiautomated feedback control.

Micro-total-analysis systems & lab-on-chip devices

The goal of μTAS and LOC devices is to achieve increased efficiency through smaller scales and to undertake analysis that could not be performed conveniently by other means. Advantages of smaller scales include improved transport through the use of electrokinetic effects and miniaturized pumps; efficient cell, molecular and particle separation and immobilization; smaller sample requirements and carrier volumes; reduced reagent consumption; and integration of channels, mixers, separators, reactions chambers, electrodes and detectors into single devices. Improved throughput of analytes occurs as a consequence of miniaturization and integration. LOC devices may incorporate microfluidic components, microsensors, microactuators and customized surfaces created by chemical modification or coatings with inorganic and organic materials. Microspheres and beads are also integral to numerous LOC devices.

Surface science for LOC devices includes chemical and biologic modification of glass, polymer and silicon surfaces. Chemical surface modification may enhance electrokinetic effects and create areas of hydrophobicity, hydrophilicity and adhesion that assist in fluid handling. Covalent chemical modification, ultraviolet and plasma exposure, self-assembly of molecules, array patterning, protein and surfactant coatings and application of blocking agents are all examples of surface modification that may be applied to glass, silicon and polymer materials.

Detection & measuring systems

Electrochemical detection (ECD) in liquid solutions is concerned with the measurement of electrical quantities, such as potential, current and charge in order to gain information about the composition of the solution and the reaction kinetics of its components. Capillary electrophoresis (CE) devices were among the first to incorporate microfabrication of integrated electrodes.

Choosing a detection and measurement system for a specific application may depend on the preference for a labeled versus a label-free methodology. Labeled systems make use of chemiluminescence, fluorescence and radioactive markers, and include molecular beacons (single-stranded oligonucleotide hybridization probes that undergo conformational

changes that change them from dark to fluorescent) and aptamers (artificial nucleic acid ligands that can be generated against amino acids, drugs, proteins and other molecules). Nonlabeled techniques include mass spectrometry for identification based on measurement of atomic and molecular mass.

Measurement instrumentation includes confocal laser microscopy (illumination of a labeled sample to visualize target-probe fluorescence), interferometry, ellipsometry (characterizing surface properties with polarized light), surface plasmon resonance spectroscopy (for the study of thin-films), Raman microscopy (based on laser light scattering upon a material), transmission and scanning electron microscopy (use of focused beams of electrons rather than light for much higher resolution) and atomic force microscopy (topography measurement with a probe).

Genomics, proteomics, DNA & protein microarrays

Genomics includes understanding the mechanism of DNA replication, protein synthesis, gene expression and the exchange and recombination of genetic material, understanding of restriction endonucleases and DNA ligases capable of cutting and rejoining DNA at sequence-specific sites; technical advances such as the PCR and automatic DNA sequencing; and bioinformatics, the storing, analyzing and interpreting of data [2]. Functional genomics is the overall effort of deconstructing the genome to assign biologic function to genes, groups of genes and particular gene interactions.

'The past few years have seen an emergence of DNA, protein, cell and tissue microarrays with significant commercial potential.'

Proteomics is the study of all proteins, including their relative abundance, distribution, post-translational modifications, functions and interactions with other macromolecules, in a given cell or organism within a given environment and at a specific stage in the cell cycle [3]. BioMEMS applications for proteomics can be divided into LOC devices for specific tasks such as protein isolation, purification, digestion and separation, and microarray devices for high-throughput study of protein abundance and function. The past few years have seen an emergence of DNA, protein, cell and tissue microarrays with significant commercial potential.

Microarray analysis allows for the simultaneous study of genes and gene products, including DNA, messenger RNA (mRNA) and proteins. There are basically two formats: complimentary DNA (cDNA) microarrays and oligonucleotide microarrays. A cDNA microarray is an orderly arrangement of spots of DNA probes printed onto a solid matrix, such as glass, nylon or silicon. Hybridization is the base pairing between target and probe, and is limited by the sensitivity and specificity of the microarray. There are three basic types of oligonucleotide microarrays: gene expression, genotyping (single nucleotide polymorphisms [SNPs]) and resequencing. Genomic DNA may be used for the study of SNPs, while expressed DNA sequences (cDNA clones, expressed sequence tags [ESTs]) are used for gene expression.

Biocompatibility & ISO 10993 biologic evaluations

Biocompatibility and packaging compliment one another, and are important to the success of future medical devices. It is important that biocompatibility be considered at the onset of the design phase so as to minimize the number of biocompatibility tests that need to be run later.

It may be necessary to perform material and chemical characterization on all materials inside and outside the device, including materials encountered during the manufacturing and preservation process that have a potential to cause cytotoxicity, sensitization, irritation, toxicity, genotoxicity, carcinogenicity and reproductive or developmental abnormalities. Adverse effects are generally chemical effects produced by material components, contaminants and breakdown products. Biocompatibility testing answers two fundamental questions: is the material safe, and does it have the necessary physical and mechanical properties for its proposed function? The extent to which a material needs to be characterized depends on the type of material, the end use of the device and the function of the material within the device [4].

The ISO 10993 International Standard pertains to the Biological Evaluation of Medical Devices, and is applicable to surface devices on the skin, mucosal membranes, breached or compromised surfaces, external communicating devices with blood, tissue, bone, dentin and implantable devices. Its purpose is to protect humans and serve as a framework for selecting tests to evaluate biologic responses.

Prospects

The outlook for training in bioMEMS and medical microdevices is superb owing to a number of driving forces. The first is student demand and recognition that 'small is better' in terms of future technologies, and a desire to be at the forefront of future vocational opportunities. Many engineering faculties have come to the realization that bioMEMS funding is surpassing traditional MEMS/MST funding, and that they are more likely than ever to become involved in joint projects with faculties in the health sciences. Homeland security and the growing awareness of biochemical threats is also a driving force. There should be ample government incentives for numerous bioMEMS projects, with anticipated spinoffs as a result of these efforts.

However, there are obstacles ahead. There is a dearth of individuals who have the clinical, research and engineering skills necessary to match applications with solutions. The boundaries are so entrenched between these disciplines that one almost needs to plead for the opportunity to teach across the void. Also, the patent system seems at times more of a battleground for corporate giants, than a method to foster and reward individual and corporate achievement. Finally, there is not a good understanding of biocompatibility testing. Few researchers in the field have even heard of the ISO 10993 International Standard, let alone considered what matrix of biocompatibility studies should be considered early in their work.

References

1 Saliterman S. *Fundamentals of BioMEMS and Medical Microdevices.* SPIE Press, Bellingham, WA, USA (2006) (In Press).

2 Baldi P, Hatfield GW. *DNA Microarrays and Gene Expression.* Cambridge University Press, NY, USA (2002).

3 Pardanani A, Wieben ED, Spelsberg TC, Tefferi A. Primer on medical genomics. Part IV: expression proteomics. *Mayo Clin. Proc.* 77(11), 1185–1196 (2002).

4 Albert DE. The important role of material and chemical characterization in device evaluation. *Med. Device Technol.* 15(5), 15–18 (2004).

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