Introduction to BioMEMS & Medical Microdevices

Introduction to BioMEMS

Companion lecture to the textbook: Fundamentals of BioMEMS and Medical Microdevices, by Prof. Steven S. Saliterman, http://saliterman.umn.edu/
BioMEMS

- **Bio**medical **Micro** **Electro-Mechanical** **Systems.** (The science of very small biomedical devices.)
- Subset of **MEMS**/**MST** (**Microsystem Technology**).
- At least one dimension from ~100 nm to 200 μm.
- New materials, understanding of the microenvironment, and biocompatibility.
- Harnessing any phenomenon that accomplishes work at the microscale.
- **Work** may be at the microscale alone, or through some multiplication process at the macroscale.
The “Micro” Realm

Steven S. Saliterman

Gardner JW et al, Microsensors, MEMS and Smart Devices, John Wiley & Sons, Chichester, NY (2001)
BioMEMS Applications

- Laboratory Diagnostic Tools:
  - Microsensors & Microactuators,
  - Lab-on-a-Chip Devices (LOC),
  - Micro Total Analysis Systems (μTAS),
  - DNA and Protein Microarrays.
- Individualized Treatments
- Tissue Scaffolding Devices
- Medication Delivery Devices
- Minimally Invasive Procedures
- Platform for Nanomedicine Technologies
- Homeland Security

Image Courtesy of Sandia National Laboratories
Specialized Sensors

Sub-µm IDEs (proteins, DNA)

Surface Acoustic Wave (proteins)

Polymer FETs (pH, glucose)

Magnetic-bead Biosensor (proteins, DNA)

Transmission Plasmon Biosensor (proteins, DNA)

GaAs MESFETs (neurons, proteins)
Actuators

- Valve control and pumping
- Positioning and alignment of detectors
- Dispensing of medications
- Harnessing chemical, electrostatic, electrostrictive, piezoelectric, magnetic, thermal and optical phenomenon

Lee, KB et al., Frequency tuning of a lateral driven micromotor using an electrostatic comb array of varied length., Transducers pp. 113-116 (1997)
Microfluidics & Transport Processes

- Science of fluid behavior in microchannels.
- In lab-on-a-chip and µTAS devices, the following features are often seen:
  - Microchannels,
  - Microfilters,
  - Microvalves,
  - Micropumps,
  - Microneedles,
  - Microreservoirs,
  - Micro-reaction chambers.

Courtesy of Micronit
Transport Processes

- **Fluid Mechanics:**
  - Laminar flow,
  - Fluid kinematics.

- Mixing by diffusion, special geometries and mechanical means.

- Effects of increased surface area-to-volume as dimensions are reduced in microfluidic channels.
Electrokinetics

- Electrokinetic phenomenon:
  - Electro-osmosis,
  - Electrophoresis,
  - Streaming potential,
  - Dielectrophoresis.

- An important tool for moving, separating and concentrating fluid and suspended particles.

Lab-on-a-Chip

- Improved transport, efficient cell, molecular and particle separation and immobilization; smaller sample requirements and carrier volumes; and reduced reagent consumption.
- Improved throughput of analytes occurs as a consequence of miniaturization and integration.

Surface Modification

- Advantages of surface modification.
- Techniques for surface modification:
  - Covalent chemical modification,
  - UV and plasma exposure,
  - SAMs,
  - Coatings.
Drug Delivery Systems

- Current methods of drug delivery:
  - Topically, orally, injection, insertion, and perfusion.

- Parameters of administration:
  - Dose, frequency, duration, oscillatory behavior.

- Benefits of bioMEMS:
  - Reliable and precise release of targeted therapy.

Images courtesy of Microchips
“Application of the principles of biology and engineering to the development of viable substitutes which restore, maintain, or improve the function of human tissue.”

Tissue scaffolding devices, various sensor and stimulating electrodes and electroactive polymers as muscle substitutes are but a few of the new technologies.

Dario 2000
Minimally Invasive Surgery

- Onset in 1988 when Dr. J. Barry McKerman performed a laparoscopic cholecystectomy through a 1 cm incision.
- Reduced tissue damage, scarring and pain; shorter recovery time and hospital stays.
- May use thin tubes called trocars, miniature cameras, specialized instruments and CO\textsubscript{2} to inflate the area.
- Opportunities for bioMEMS and MEMS devices.
May provide for the next generation of synthetic organs and organ assist devices.

Synthetic hearts, livers, kidneys and endocrine glands may in the future be produced by assembly of large numbers of microfabricated components.
Traditional Microfabrication

- **Microfabrication:**
  - Precision lithography and mask production.

- **Micromachining:**
  - Etching techniques - subtractive processes.
  - Thin-film application and other additive processes with physical and chemical vapor deposition, sputtering, and electroplating.

- Substrate bonding.

- Dicing and packaging.
Silicon Wafers
Micromachined Microneedles

Image Courtesy of Micronit
“Soft” Fabrication Methods

“Soft” fabrication includes:

- Polymers, environmentally sensitive hydrogels and biological materials,
- Soft-lithography,
- Micromolding,
- Microstereolithography,
- Thick-film deposition,
- Self-assembled monolayers (SAMs),
- Other surface modifications.

Genomics

- **DNA** replication, protein synthesis, gene expression and the exchange and recombination of genetic material;
- **Restriction endonucleases** and **DNA ligases** capable of cutting and rejoining DNA at sequence specific sites;
- Technical advances:
  - Polymerase chain reaction (PCR),
  - Automatic DNA sequencing.
- **Bioinformatics:**
  - Storing, analyzing and interpreting of data
- **Functional Genomics**
DNA Microarrays

Image Courtesy of Affymetrix
DNA and protein microarray chips offer the ability to screen for numerous genetic traits rapidly and inexpensively:

- Genetic screening for detection of mutations,
- Gene expression profiling,
- Diagnosis and prognosis of cancer,
- Drug safety for pharmacogenetics,
- Monitoring of pathogens and resistance in infections,
- Stratification of patients in clinical trials.


Image Courtesy of Affymetrix
DNA Probe Array

[Diagram showing DNA probe array with labels:
- 1.28 cm x 1.28 cm
- Actual size of GeneChip™
- 500,000 cells on each GeneChip™ array
- Millions of DNA strands built up in each cell
- Actual strand = 25 base pairs

Image Courtesy of Affymetrix]
Expression Profiling

RNA fragment hybridizes with DNA on GeneChip

Shining a laser light at GeneChip causes tagged DNA fragments that hybridized to glow

Non-hybridized DNA

Hybridized DNA

Image Courtesy of Affymetrix
“Proteomics is the study of all proteins, including their relative abundance, distribution, posttranslational 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.”

- Lab-on-a-Chip devices for protein isolation, purification, digestion and separation.
- Microarray devices for high throughput study of protein abundance and function.
Protein Chip Surface Interactions

- Hydrophobic
- Cation exchange
- Anion exchange
- Metal affinity
- Normal phase

- PS-10 or PS-20
- Antibody–antigen
- Receptor–ligand
- DNA–protein

Individualized Treatment

1. Molecular diagnostics, particularly single nucleotide polymorphism (SNP) genotyping.
2. Integration of diagnostics with therapy.
3. Monitoring of therapy.
4. Pharmacogenomics.
5. Pharmacogenetics.
6. Pharmacoproteomics.
Detection Schemes

- Electrochemical detection:
  - Capillary electrophoresis.

- Labeled systems:
  - Chemiluminescence,
  - Fluorescence,
  - Radioactive markers,
  - Molecular beacons,
  - Aptamers.

- Non-Labeled systems:
  - Mass spectrometry.
Measurement Systems

- Confocal Laser Microscopy,
- Interferometry,
- Ellipsometry,
- Profilometry,
- Surface Plasmon Resonance Spectroscopy,
- Raman Microscopy,
- Transmission and Scanning Electron Microscopy,
- Atomic Force Microscopy.
Biocompatibility

- Biocompatibility testing answers two fundamental questions: is the material safe, and does it have the necessary physical and mechanical properties for its proposed function?
ISO 10933 Standards

- Criteria to meet for biological evaluation of medical devices.
- To protect humans and to serve as a framework for selecting tests to evaluate biological responses.
- Represented here by the American National Standards Institute.
- 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.
- Adverse effects are generally chemical effects produced by material components, contaminants and breakdown products.
- 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.
- The standards are applicable to surface devices on the skin, mucosal membranes, breached or compromised surfaces; external communicating devices with blood, tissue, bone, dentin; and implantable devices.
Summary

- **Biomedical Micro Electro-Mechanical Systems.**
- At least one dimension from \(~100\) nm to \(200\) µm.
- Topics for study:
  - Microfabrication of silicon, glass and polymer devices,
  - Microfluidics and electrokinetics,
  - Sensors, actuators and drug delivery systems,
  - Micro total analysis systems (µTAS) and lab-on-a-chip devices (LOC),
Clinical laboratory medicine,
Detection and measuring systems,
Genomics, proteomics, DNA and protein microarrays,
Emerging applications in medicine, research and homeland security,
Packaging, power systems, data communication and RF safety,
Biocompatibility, FDA and ISO 10993 biological evaluations.