Introduction to BioMEMS & Medical Microdevices

Introduction to BioMEMS  www.tc.umn.edu/~drsteve

Companion lecture to the textbook: Fundamentals of BioMEMS and Medical Microdevices, by Dr. Steven S. Saliterman
BioMEMS

- **Biomedical 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 at the microscale alone, or through some multiplication process at the macroscale.
The “Micro” Realm

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Gardner JW et al, Microsensors, MEMS and Smart Devices, 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
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 at al. 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.
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.

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LI (left) and Ahn (right)
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.
“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.
Minimally Invasive Procedures

- An alternative approach to traditional surgery.
- Specific targeting of tumors and other organs for drug delivery.
- Micro-visualization and manipulation.
- Implantation of microsensors, microactuators and other components of a larger implanted device or external system.
Minimally Invasive Surgery

Da Vinci Surgical System
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
“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.
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

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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.
DNA Probe Array

Actual size of GeneChip

1.28 cm

500,000 cells on each GeneChip array

Actual strand = 25 base pairs

Millions of DNA strands built up in each cell

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Image Courtesy of Affymetrix
Expression Profiling

RNA fragment hybridizes with DNA on GeneChip

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

Non-hybridized DNA

Hybridized DNA

Image Courtesy of Affymetrix
GeneChip®

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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 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 Subparts

1. Overview of evaluation and testing,
2. Animal welfare requirements,
3. Tests for genotoxicity, carcinogenicity and reproductive toxicity,
4. Selection of tests for interaction with blood,
5. Test for in-vitro cytotoxicity,
6. Tests for local effects after implantation,
7. Ethylene oxide sterilization residuals,
8. Selection and quantification of reference materials for biological tests,
9. Framework for identification and quantification of potential degradation products,
10. Tests for irritation and delayed-type hypersensitivity,
11. Tests for systemic toxicity,

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12. Sample preparation and reference materials,

13. Identification and quantification of degradation products from polymeric medical devices,

14. Identification and quantification of degradation products from ceramics,

15. Identification and quantification of degradation products from metals and alloys,

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16. Toxicokinetics study design for degradation products and leachables,
17. Establishment of allowable limits for leachable substances,
18. Chemical characterization of materials
19. Physiochemical, mechanical, morphological and topographical characterization of materials.
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.