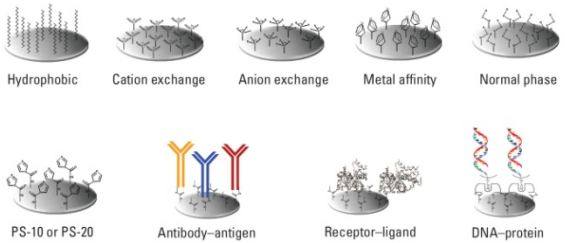
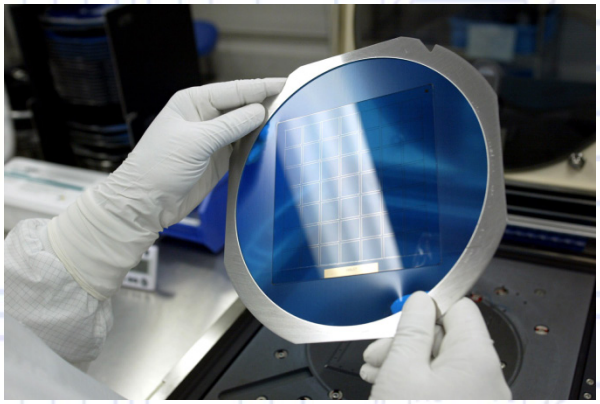
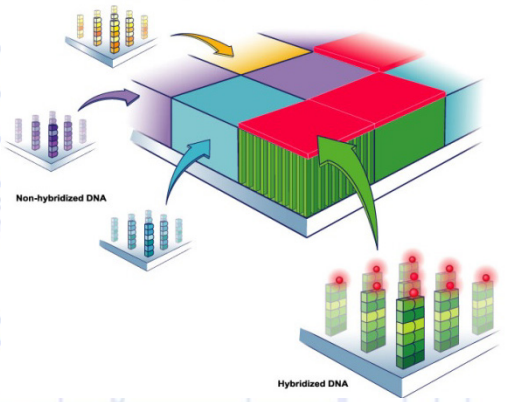
Introduction to BioMEMS & Medical Microdevices

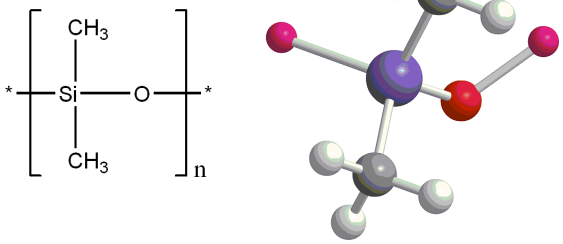
Introduction to BioMEMS

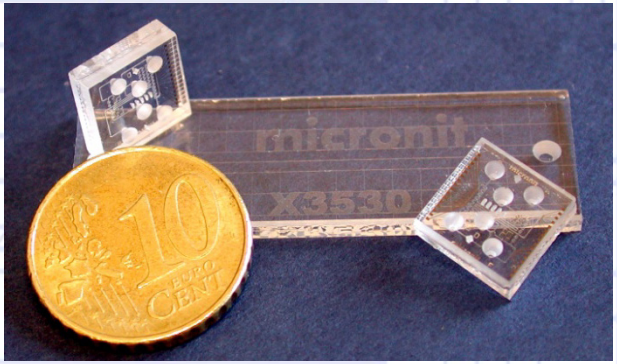
Companion lecture to the textbook: *Fundamentals of BioMEMS and Medical Microdevices,* by Prof. Steven S. Saliterman, http://saliterman.umn.edu/











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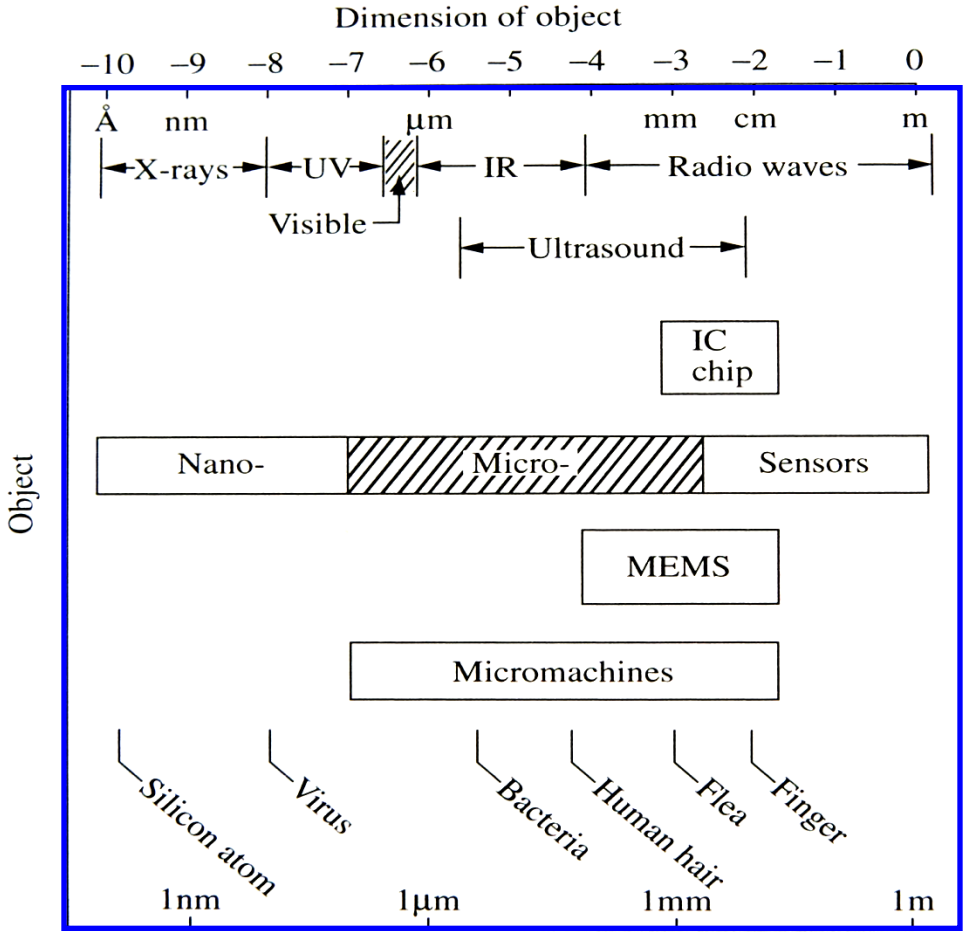
BioMEMS

- 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 be at the microscale alone, or through some multiplication process at the macroscale.

The “Micro” Realm



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

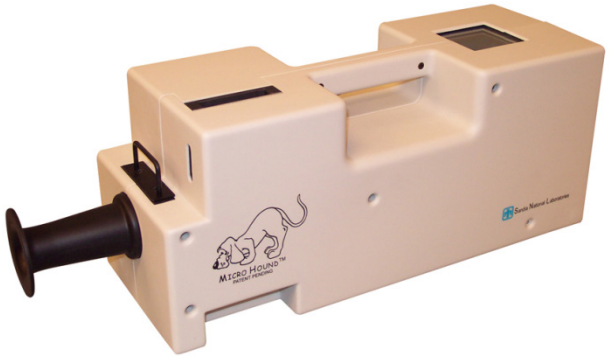
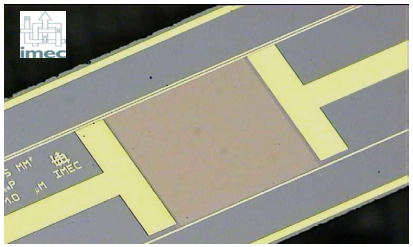
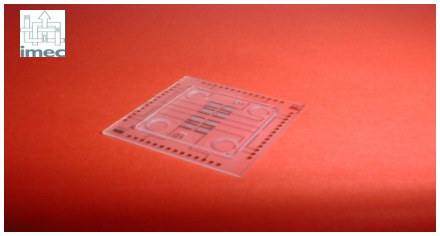


Image Courtesy of Sandia National Laboratories

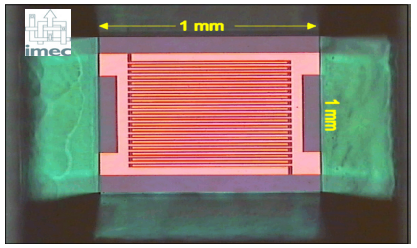
Specialized Sensors



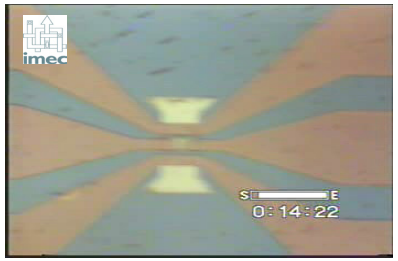
Sub-µm IDEs
(proteins, DNA)



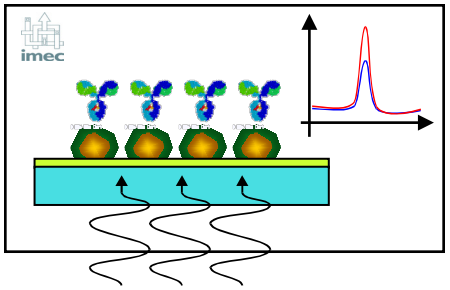
Surface Acoustic Wave
(proteins)



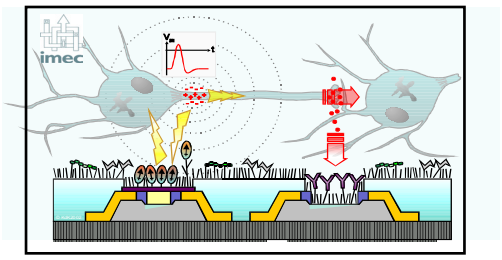
Polymer FETs
(pH, glucose)



Magnetic-bead Biosensor
(proteins, DNA)



Transmission Plasmon Biosensor
(proteins, DNA)

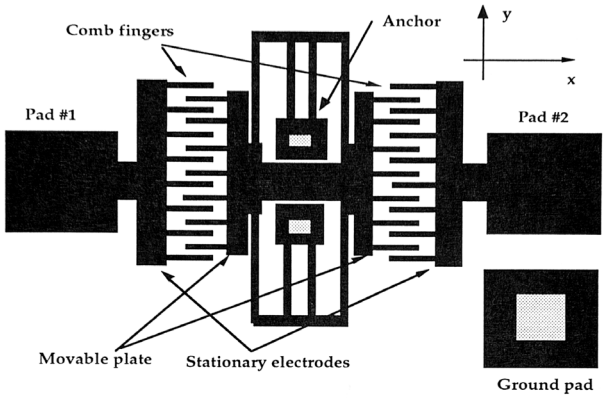


GaAs MESFETs
(neurons, proteins)

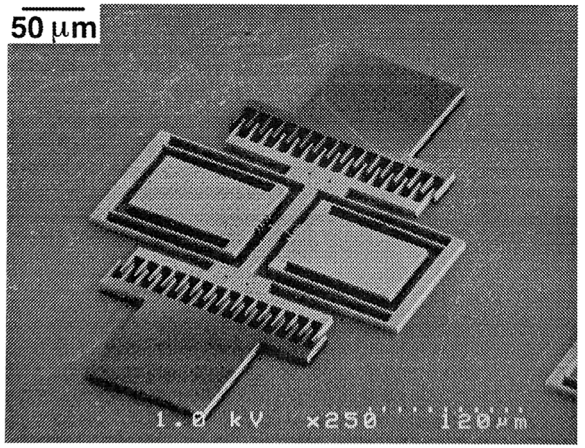
Image Courtesy of Campitelli A, IMEC

Actuators

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



(a)

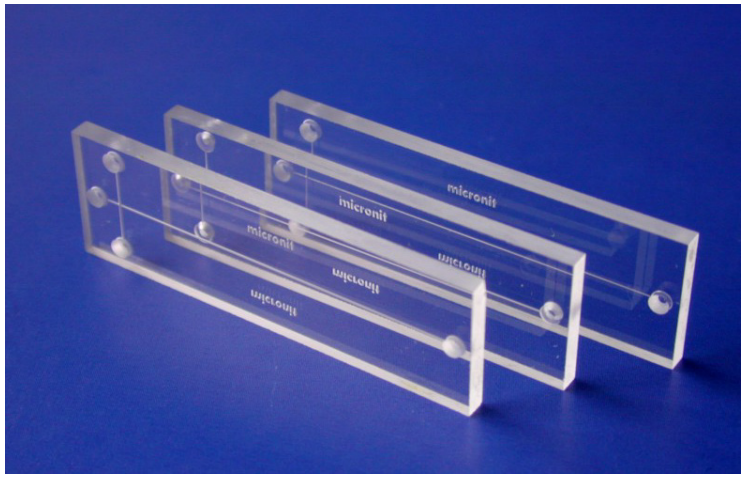


(b)

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

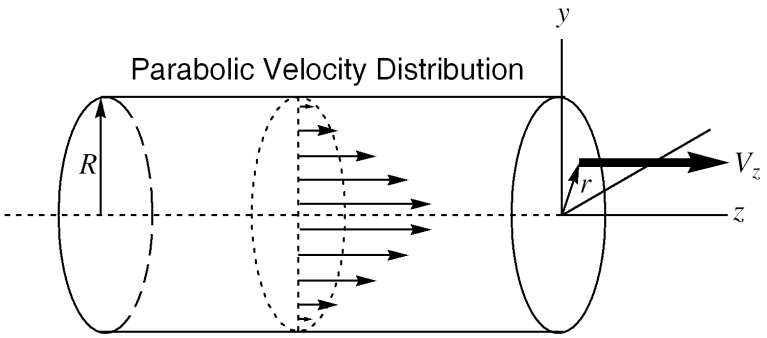
- Science of fluid behavior in microchannels.
- In lab-on-a-chip and μTAS devices, the following features are often seen:
  - Microchannels,
  - Microfilters,
  - Microvalves,
  - Micropumps,
  - Microneedles,
  - Microreserviors,
  - Micro-reaction chambers.



Courtesy of Micronit

Transport Processes

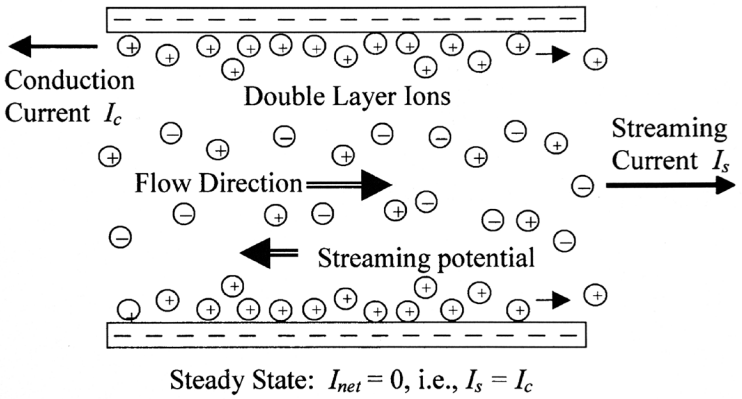
- Fluid Mechanics:
  - Laminar flow,
  - Fluid kinematics.



- 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.

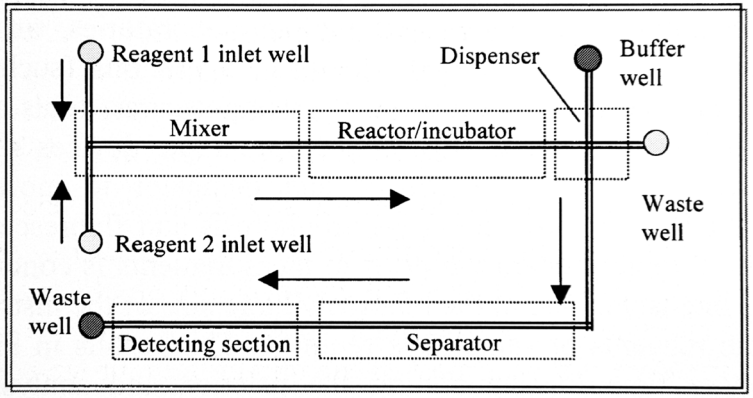


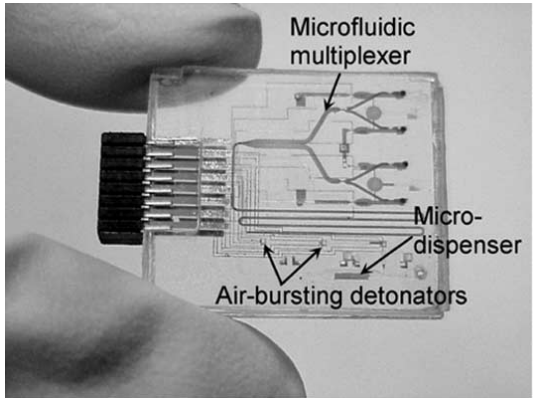
- An important tool for moving, separating and concentrating fluid and suspended particles.

Li, D., Electrokinetics in Microfluids, 1st ed., Vol 2., Elsevier, Amsterdam (2004).

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.

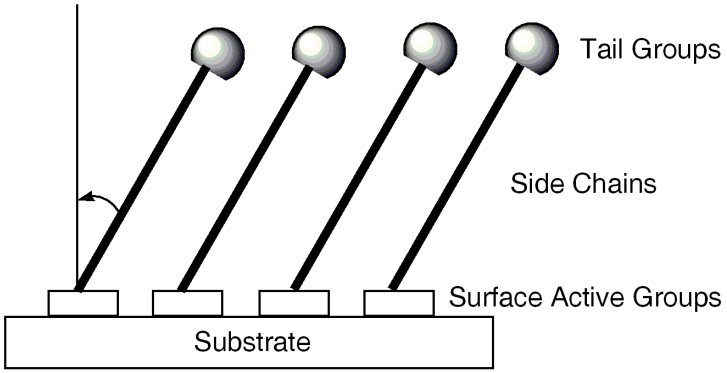




(Left) Li, D., Electrokinetics in Microfluids, 1st ed., Vol 2., Elsevier, Amsterdam (2004).
(Right) Ahn, CH, Disposable smart lab on a chip for point of care clinical diagnostics. Proceedings of the IEEE 92(1) pp. 154-173 (2004)

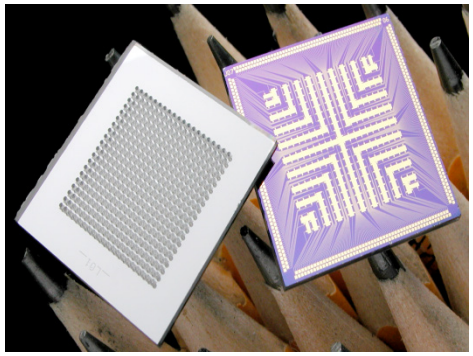
Surface Modification

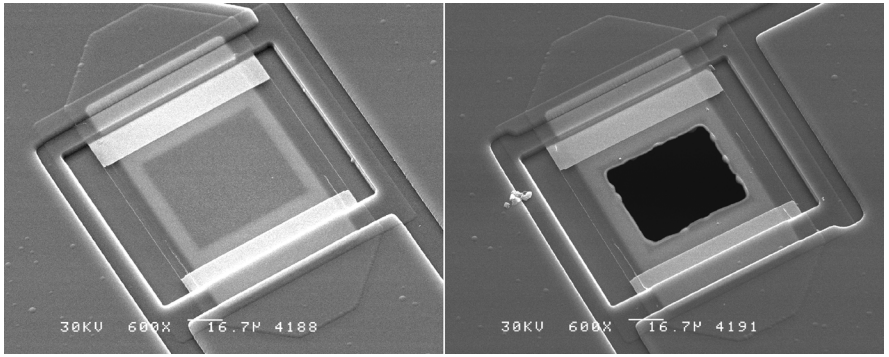
- Advantages of surface modification.
- Techniques for surface modification:
  - Covalent chemical modification,
  - UV and plasma exposure,
  - SAMs,
  - Coatings.



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.

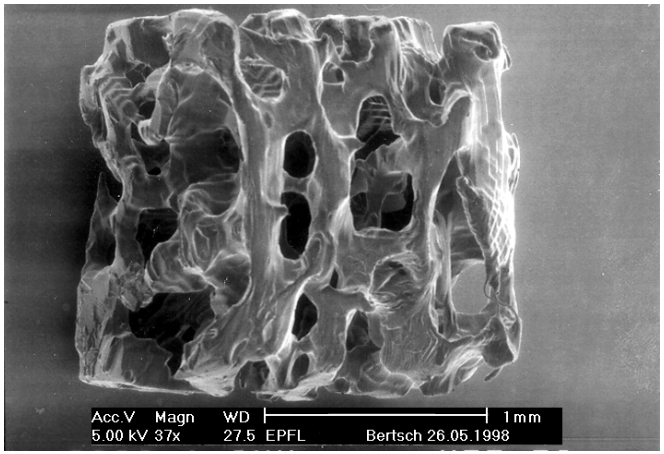




Images courtesy of Microchips

Tissue Engineering

- "Application of the principles of biology and engineering to the development of viable substitutes which restore, maintain, or improve the function of human tissue."

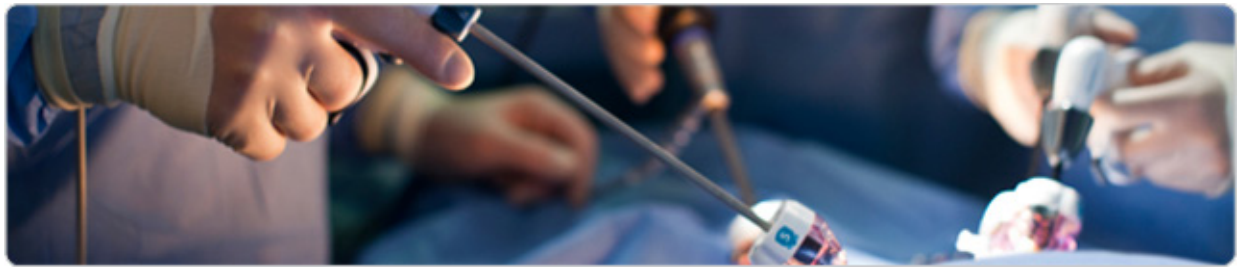


- Tissue scaffolding devices, various sensor and stimulating electrodes and electroactive polymers as muscle substitutes are but a few of the new technologies.

Dario 2000

Bertsch A. , et al., Microstereolithography using a liquid crystal display as dynamic generator. *Microsystem Technologies* 3(2), pp. 42-47 (1997)

Minimally Invasive Surgery

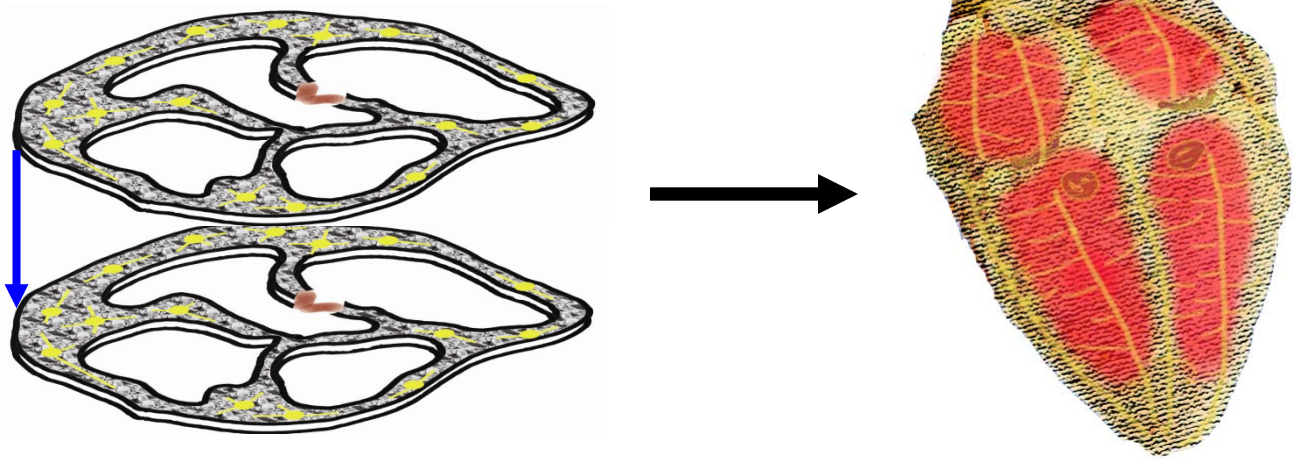


- Onset in 1988 when Dr. J. Barry McKerman performed a laparoscopic cholecystectomy through a 1 cm incision.
- Reduced tissue damage, scarring and pain; shorter recovery time and hospitals stays.
- May use thin tubes called trocars, miniature cameras, specialized instruments and CO_2 to inflate the area.
- Opportunities for bioMEMS and MEMS devices.

Image Courtesy of Ethicon

Large-Scale BioMEMS Integration

- 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

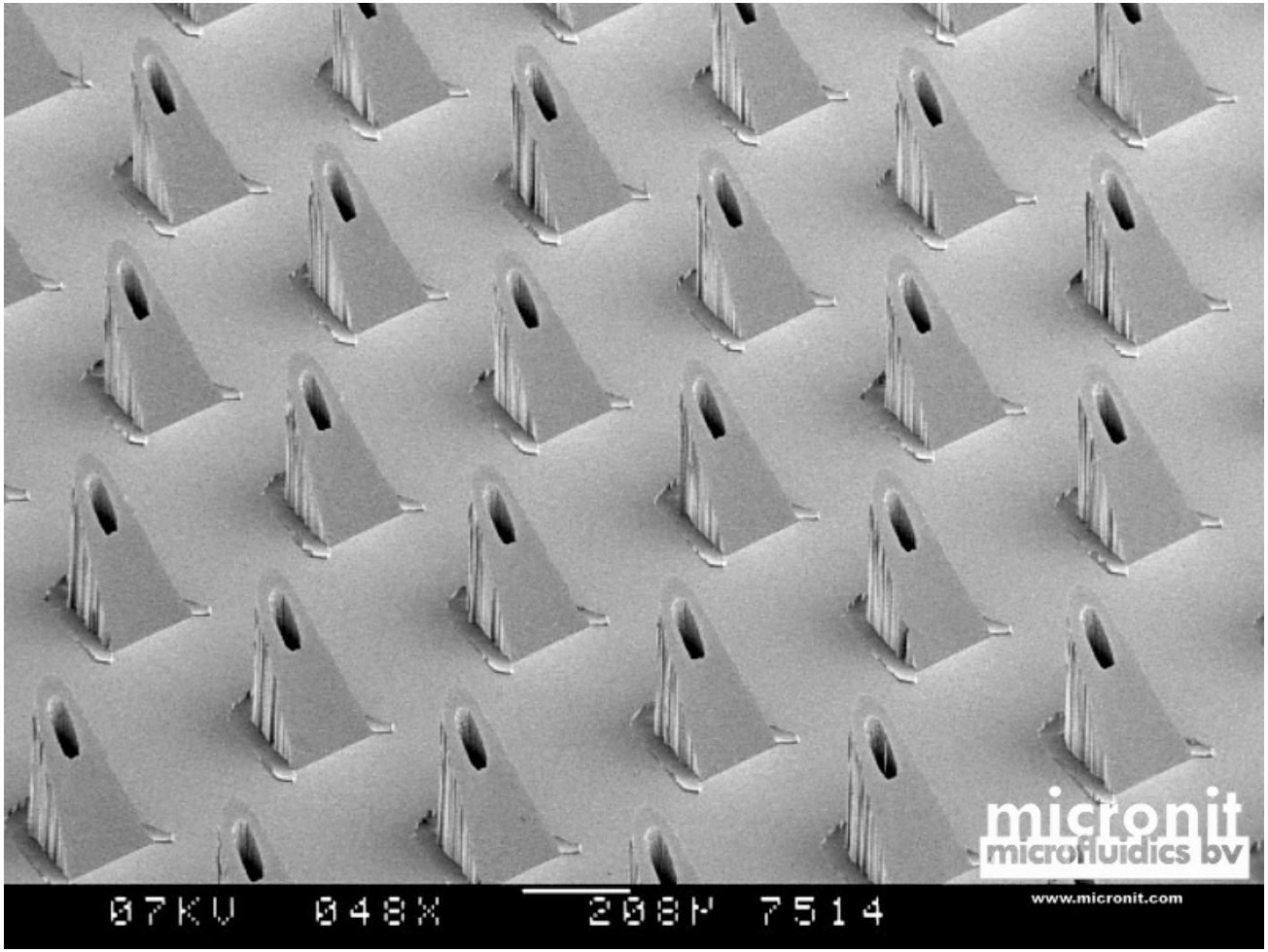
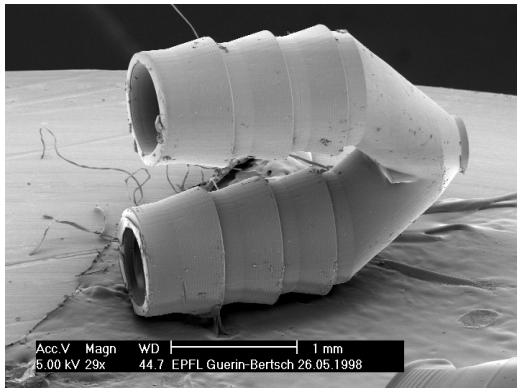


Image Courtesy of Micronit

“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.



Bertsch A. , et al., Microstereolithography using a liquid crystal display as dynamic generator. *Microsystem Technologies* 3(2), pp. 42-47 (1997)

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

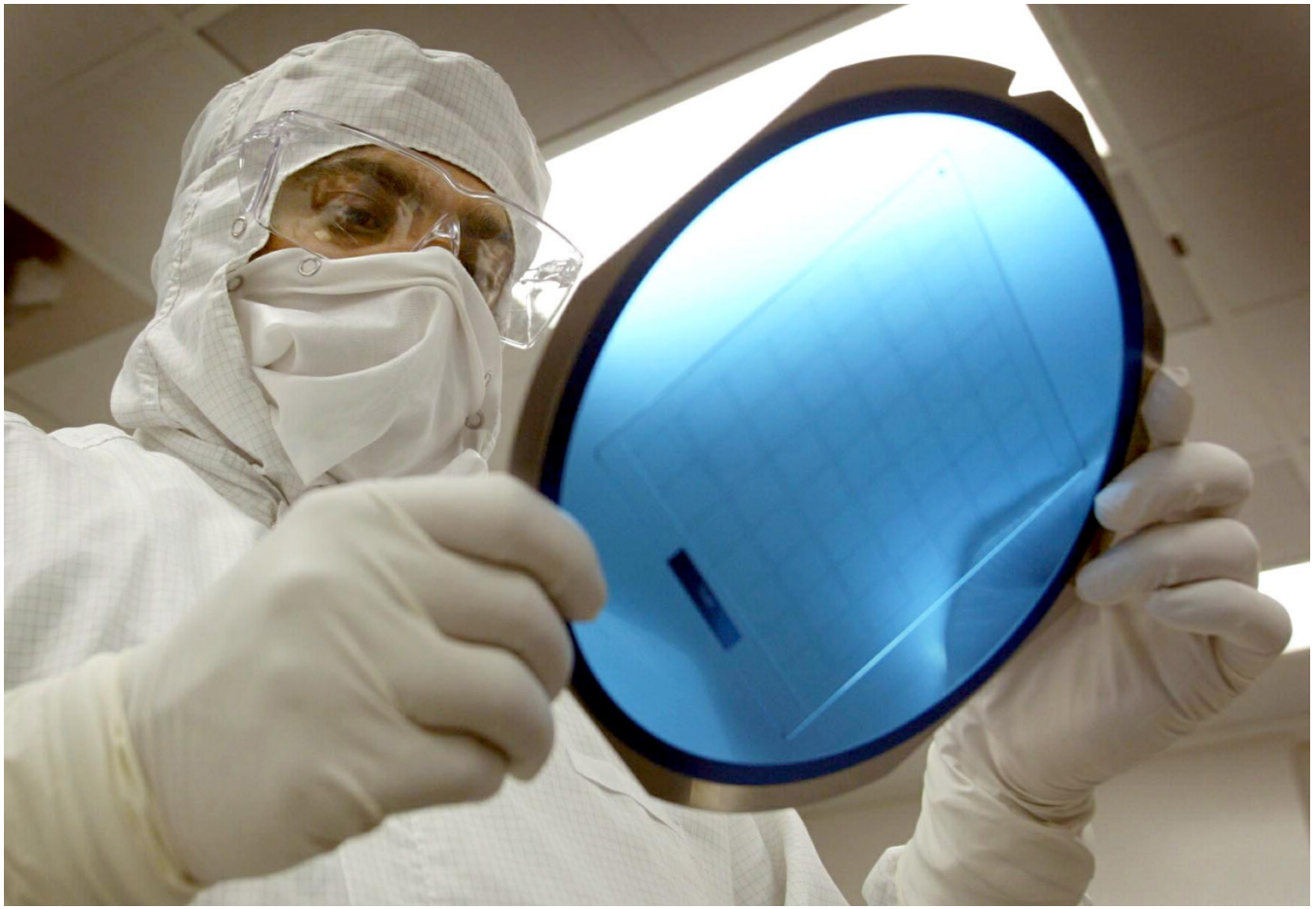


Image Courtesy of Affymetrix

- 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.

Jain KK, Personalized Medicine, *Current Opinion in Molecular Therapeutics* 4(6). Pp. 548-558 (2002)
Image Courtesy of Affymetrix

DNA Probe Array

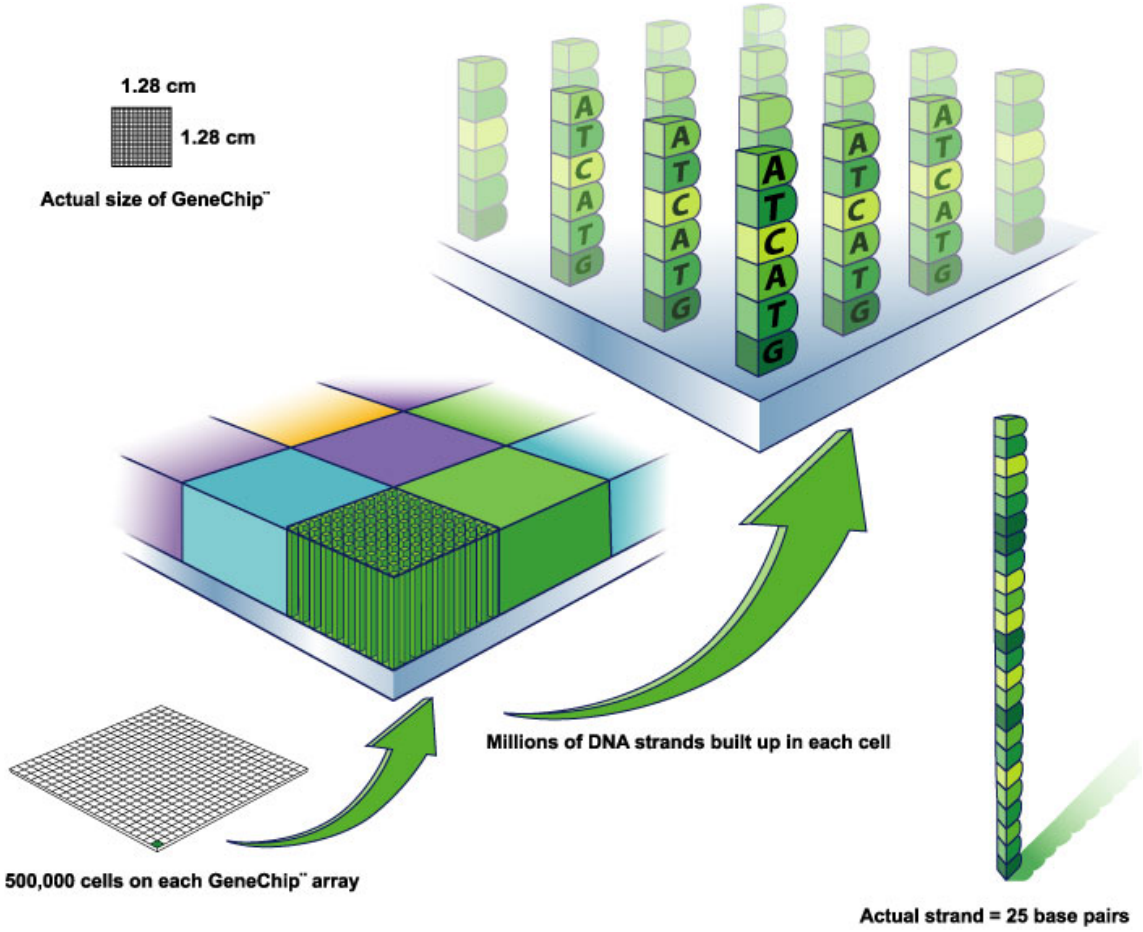
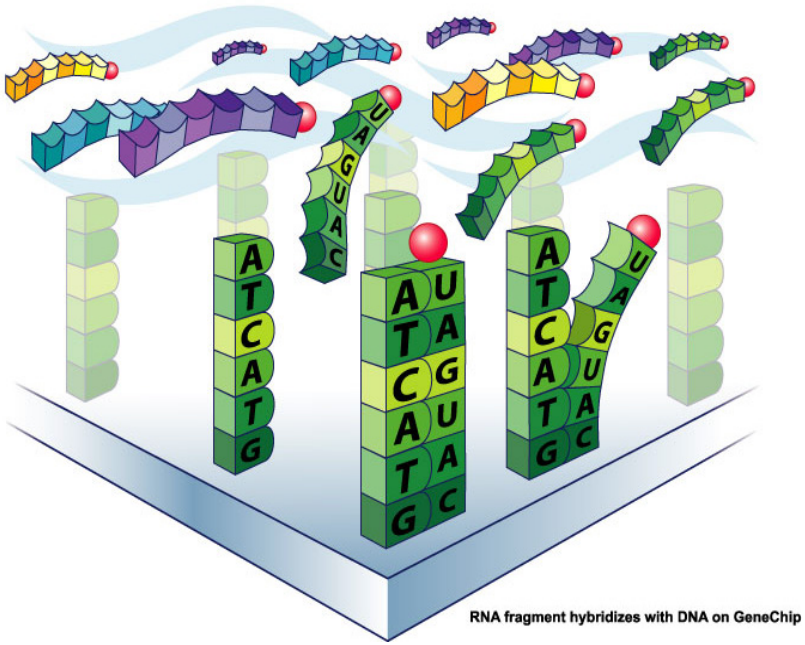


Image Courtesy of Affymetrix

Expression Profiling



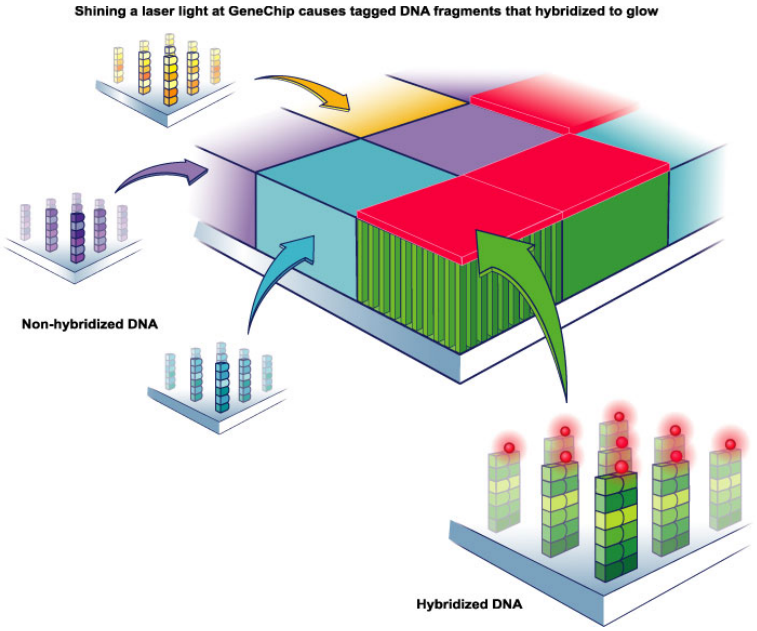


Image Courtesy of Affymetrix

GeneChip®

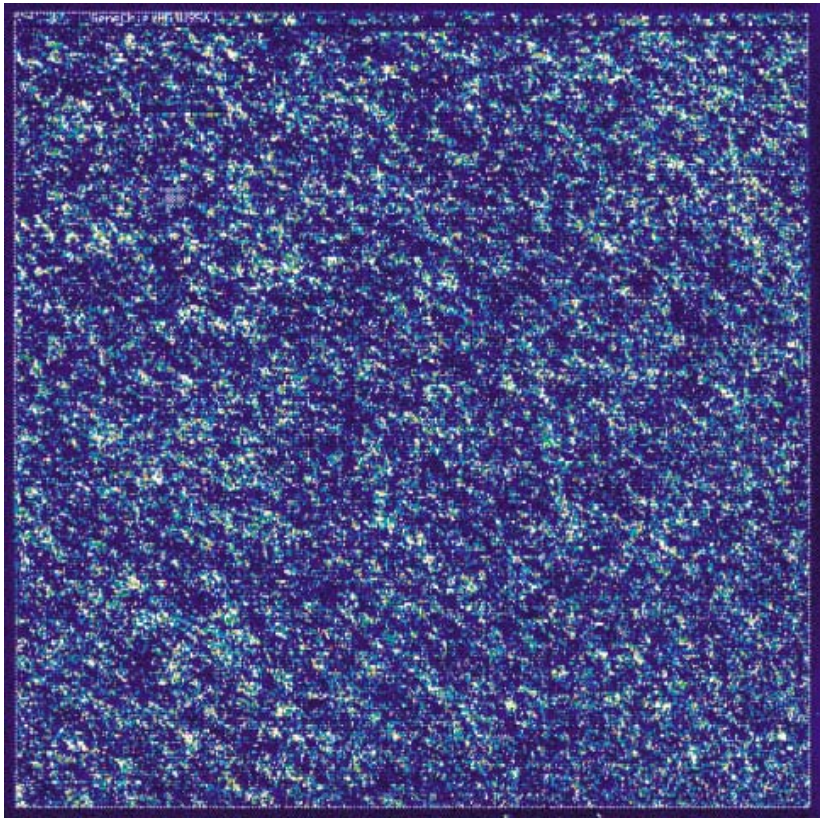


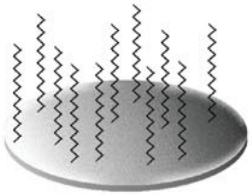
Image Courtesy of Affymetrix

Proteomics

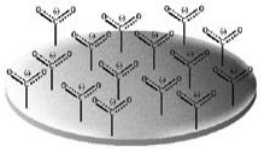
- “Proteomics is the study of all proteins, including their relative abundance, distribution, posttranslational modifications, functions, and interactions with other macromolecules, in a given cell or organism within a given environment and at a specific stage in the cell cycle.”
- Lab-on-a-Chip devices for protein isolation, purification, digestion and separation.
- Microarray devices for high throughput study of protein abundance and function.

Pardanani, AE et al. Primer on medical genomics. Part IV: expression proteomics. *Mayo Clinic Proceedings* 77(11), pp. 1185-1196 (2002)

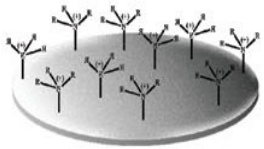
Protein Chip Surface Interactions



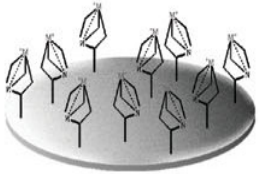
Hydrophobic



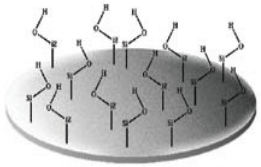
Cation exchange



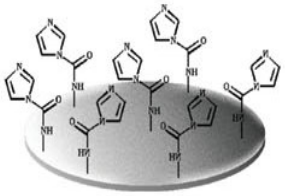
Anion exchange



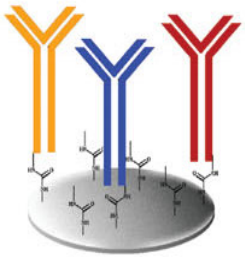
Metal affinity



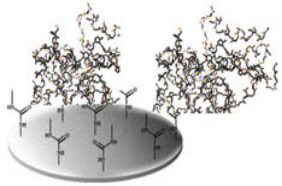
Normal phase



PS-10 or PS-20



Antibody–antigen



Receptor–ligand

DNA–protein

Issaq, HJ, et al. , SELDI-TOF MS for diagnostic proteomics. *Analytical Chemistry* 75(7), pp. 148-155 (2003)

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.

Jain KK, Personalized Medicine, *Current Opinion in Molecular Therapeutics* 4(6). Pp. 548-558 (2002)

Detection Schemes

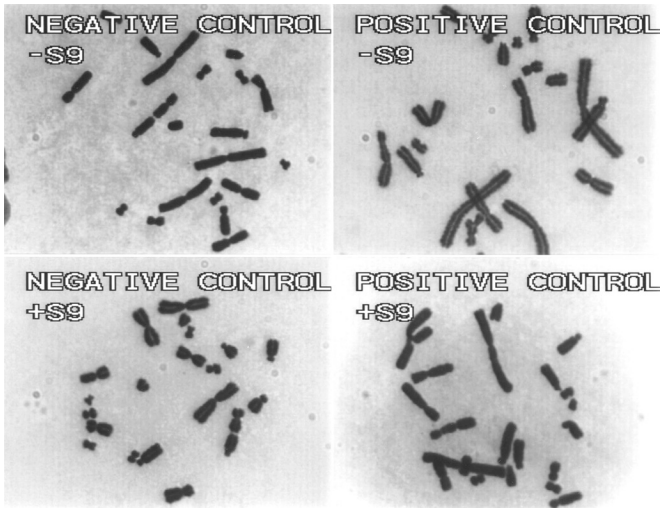
- Electrochemical detection:
  - Capillary electrophoresis.
- Labeled systems:
  - Chemiluminescence,
  - Fluorescence,
  - Radioactive markers,
  - Molecular beacons,
  - Aptamers.
- Non-Labeled systems:
  - Mass spectrometry.

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?



Images Courtesy of North American Science Associates (NASMA)

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.