BioMEMS (and Microfluidics)
MEMS Technology

- BioMEMS
  - Microfluidics & Implantable sensors
- ‘Traditional’ MEMS
  - Accelometers & Inject Heads
- RF MEMS
  - Filters & Varactors
- Optical MEMS (MOEMS)
  - Mirrors & Switches
- MEMS Technology
History of MEMS Technology

BioMEMS is a relatively new field...

Image taken from: http://www.rfmems.net/a/MEMS/20100411/58.html
SILICON & ITS DERIVATIVES
- Silicon (Si)
- Silicon Dioxide - SiO₂ (glass)
- Silicon nitride (Si₃N₄)

- Mechanical Reliability
- Performance
- IC compatibility

METALS
- Platinum
- Silver
- Chrome and Gold
- Indium Tin Oxide (ITO)

POLYMERS
- Photosensitive Polymers (e.g. SU-8)
- Polydimethylsiloxane (PDMS)
- Parylene
- PS
- PMMA

- Biocompatibility
- Cost
- Surface Modification
- Disposability (e.g. single use devices)
- Rapid Prototyping

BioMEMS Materials
- Increased Functionality
- Integration (sensors & actuators)
- Biocompatibility
- Cost
- Surface Modification
- Disposability (e.g. single use devices)
- Rapid Prototyping
Microfabrication Consists of 3 Major Steps: **Deposition, Patterning, Removal**

1. **Select a Substrate** (e.g. a silicon wafer)

2. **DEPOSIT** the *Structural* Material
   (usually a few-microns thick film)

3. **DEPOSIT** PhotoResist (PR)
   (PR is photosensitive to UV radiation)

4. **PATTERN** PR using light (LITHOGRAPHY)

5. **REMOVE** the structural material

6. **REMOVE** PR
Etching is performed in cycles of 3 steps:

**Deposit Polymer (step 1):** $C_4F_8$-based plasma is used to conformally deposit a few monolayers of PTFE-like fluorocarbon polymer across all surfaces.

**Etch polymer (step 2):** The plasma gas is then switched to SF$_6$ that isotropically etches silicon (like typical RIE). Ions from the plasma bombard the surface of the wafer, removing the polymer. Increased ion energy in the vertical direction results in a much higher rate of removal of fluorocarbon from surfaces parallel to the wafer surface.

**Etch silicon (step 3):** Following selective polymer removal, the silicon surface at the base of the trench is exposed to reactive fluorine-based species that isotropically etch the unprotected silicon. The remaining fluorocarbon polymer protects the vertical walls of the trench from etching.
Soft- Lithography: Creating a ‘Soft’ (e.g. PDMS) Mold

1. Start with a Master Mold

Master Mold

2. Cast and Cure PDMS

e.g. cure at 100°C for 45 min

3. Peel off and you're DONE!

Soft Mold

It can be reused
What can you do with the ‘Soft’ Mold?

1. Micro Contact Printing (μCP)
2. Replica molding (REM)
3. Micromolding in capillaries (MIMIC)
4. Microtransfer molding (μTM)
5. Microfluidics
& Multilayer Soft Lithography

...From Simple Valving...

a. Control channel
Flexible membrane
Flow channel (PDMS)
Glass or silicon substrate

b. Flow channel
Flexible membrane
Control channel

c. Upper control channel
Flow channels
Lower control channel

...to Complex Systems:
A microfluidic Chemostat

A. Image of microfluidic chemostat

B. Diagram of input ports, supply channels, growth chamber loop, and waste

C. Diagram of lysis buffer, medium, supply channels, growth chamber loop, and peristaltic pump

D. Diagram of lysis buffer, medium, supply channels, growth chamber loop, peristaltic pump, and Nth dilution compartment
BioMEMS in the Medical Field

Ex vivo...

In vivo...

Image taken from: http://mems.colorado.edu/c1.res.ppt/ppt/g.tutorial/ppt.htm
Micro Needles

Solid MicroNeedles (coated, first generation)
Saw-tooth style

Ultrasharp Si (Citadel style) with a hole at the side
Polymer-based (PDMS)
Optical Pressure Sensors

Concept: A deformable membrane acts as a mirror in a Fabry–Pérot cavity

The Measuring Setup
The CardioMEMS Sensor

Materials
- Copper-clad Liquid Crystal Polymer (LCP)
- Expanded polytetrafluoroethylene (PTFE)

Microfabrication Process
- Photolithography/ Wet Etching
- Bonding: The layers are aligned, assembled and laminated at 180°C under pressure

Final Device: A self-packaged structure in which only a polymer outer surface is exposed to the environment
BioMEMS Actuators

The image shows a diagram of a BioMEMS actuator, which consists of a 'Hot and cold arm' actuator. The actuator is composed of different layers:

- **Cr/Au layer (heating element)**: This layer acts as a heating element and is shown at a scale of 30 μm.
- **SU-8 layer (structural element)**: This layer provides structural support and is also shown at a scale of 30 μm.
- **Cell holder**: This component is used to hold cells for biological studies.

The actuator dimensions are 650 μm in width and 100 μm in height.
Microfluidics/Lab-on-Chip Systems

**Sample Prep**
- Fluid Handling
- Amplification
- Derivatization
- Lysis of cells
- Concentration
- Extraction
- Centrifugation

**Sample Separation**
- Lab-on-a-chip concept for capillary electrophoresis
- Sample input
- Dilution buffer
- Chemical reagent
- Reaction chamber
- Sample channel
- Separation channel
- Buffer waste
- Sample waste

**Sample Detection**
- Fluorescence
- UV/vis Absorption
- Amperometric
- Conductivity
- Raman

**Electrophoresis, liquid chromatography**
In most microfluidic cases, Inertial & Gravity forces are negligible compared to Pressure & Viscous forces.

\[ \rho \left( \frac{\partial \mathbf{V}}{\partial t} + \mathbf{V} \cdot \nabla \mathbf{V} \right) = -\nabla p + \rho \mathbf{g} + \mu \nabla^2 \mathbf{V} \]

N-S: \[ 0 = -\nabla p + \mu \nabla^2 \mathbf{V} \]
EOF and Electrophoresis

EOF and Electrophoresis might compete each other...

Do not forget to calculate absolute velocities:

$$\vec{u}_{abs} = \vec{u}_{ep} + \vec{u}_{EOF}$$
Capillary Electrophoresis for DNA Separation

Concept:
Use microfluidic channels (capillaries) to separate DNA fragments

Operation Principle

a) Fill the channel intersection with sample solution
b) Apply potential between buffer and waste inlets to initiate electrophoresis

Electric Field applied: 200-400 V/cm, Separation time: 1-2 min, Limiting factor: Joule Heating
Dielectrophoresis

An **Non-uniform** Electric Field exerts a **force** on a **uncharged**, **dielectric** object (e.g. particle)

The object does not have to be charged, **all** dielectric objects exhibit dielectrophoretic activity!

**Application**

*To move, trap, separate, neutral, dielectric objects (e.g. cells)*
Fluidic Operations in Digital $\mu$fluidics

1. Droplet formation/injection

2. Cut & Merge (Split & Mixing)

[Diagram of fluidic operations with images of experimental results]
Microfluidic Components

Used to manipulate (transport, mix, separate, etc) fluids

- µ-Valves
  - Passive vs Active

- µ-Pumps
  - Displacement vs Dynamic

- µ-Mixers
  - Passive vs Active

- µ-Separators
- µ-Filter
- µ-Dispensers
- Other...
The Herringbone Mixer

Concept:
Use set of ridges to create transverse vortices, (parallel to the cross section of the channel

2-Flow Mixing

• Channel Width = 200 µm, Channel Height = 70 µm ,Ridge Depth = 40 µm, Ridge Width ridge = 200 µm
• Mixing length 1-3 cm, Re \( \sim 10^{-2} \)
Integration. μ–lenses on μ–Actuators

Concept
Integrate electrostatic μ-actuators with μ-lenses (e.g. for scanning...)

- μ-lenses are simply dispensed on the actuator ring and UV cured...
- Electrostatic actuators (comb drives) are used as they require minimum power
The biochip integrates two modules:

- the **TIR-CT module** for isolating, trapping and illuminating single WBCs
- the **µCSA module** for imaging/counting the trapped WBCs
Some other exciting stories...
1. Single Molecule Real Time (SMRT) Sequencing

Motivation: The $1,000 Genome Project

What if you could sequence the entire human genome in a single day, in a single experiment — for less than $1,000?
Nanopores for DNA SMRT Sequencing

**Concept**

*Flow DNA through a (∼1nm) nanopore and measure the electric current*

...The amount of current which can pass through the nanopore at any given moment depends on whether the nanopore is blocked by an A, a C, a G or a T

Currently under development by several companies (Oxford Nanopore Technologies, Noblegen)
Zero-mode waveguides (ZMW) guide light into a volume that is small in all dimensions compared to the wavelength of the light:

→ Minimize background noise  → Single Molecule Imaging
2. Large Scale Microfluidic Handling
Large-Scale Integration of μ-valves

**SPECS**
- 3574 on-chip μ-valves
- 22 outside control interconnects
- 1,000 individually addressable picoliter reaction chambers
- A column and row multiplexor are used to address each chamber

**The microfluidic Multiplexor**

Fluidigm Dynamic Array
Integrated Fluidic Circuits (IFCs)

On-chip High-throughput Polymerase Chain Reaction (PCR)
Fluidigm chips have an on-chip network of microfluidic channels, chambers, and valves that automatically assemble up to 2,304 unique PCR reactions, decreasing the number of pipetting steps required by up to 100 fold.

Applications
• Gene Expression
• SNP Genotyping
• Targeted Resequencing
• Single-Cell Gene Expression
• Protein Crystallization
• ...

3. Centrifugal Microfluidics

Commercialized by GYROS:
The GYROS BioDisk

Key Idea:
Use hydrophobic Patches to block fluid flow. Use Centrifugal Forces to overcome these pads.
GYROS for Protein Quantification

CD for protein quantification

- 112 parallel measuring structures per CD
- 200 nL of sample and reagent per measurement
- time-to-result < 1h

Applications: Point-of-Care Immunoassays
BioMEMS: The future is Bright!

MEMS products phase of development

Number of microfluidic patents issued per year (in the USA)
Hope you got Inspired!

...And please do not forget to evaluate the class...