BioMEMs
Micro and Nano Fabrication

Biological Micro Electro-Mechanical systems
BioMEMs & Microfabrication

- Techniques from electronics field
  - Computer chips
  - Mini-sensors: pressure, acceleration, etc...
- Measure cell forces
- Impart cell forces
- Microfluidics
- Total systems
Mechanotransduction

- Cell Forces
  - Cell-Material Interactions
  - Cell-Cell Interactions
- Examine Cells
  - Develop measurement tools
  - Discovery of how cell parts interact with each other
- Cell stiffness response
  - (A) Soft PA .03% Bis
  - (B) Hard PA .26% Bis

[Adapted from Pelham]

(Even-Ram, 2006 from Engler, 2006)
Measurement

• First detection: (A) Heat cured silicone membrane wrinkling
• Next breakthrough: (B) Traction force microscopy, bead displacement
• Refinement: (C) Patterned bead displacement
• Coupled displacements

[Harris, Muneevar, Balaban]
Lithography

- Spin Photoresist
- Soft Bake
- Align Mask
- Expose
- Post Exposure Bake
- Develop

- Positive Resist: Photoactivated compound becomes soluble in developer

- Negative Resist: Light causes resist to polymerize
Lithography – Bulk Micromachining

- Isotropic (universal direction) etch:
  - XeF2 gas, HNA

- Anisotropic (directional per crystalline plane):
  - KOH, ion etching
Lithography - Etching

- Masks created using high-raster printers or direct write lasers
- ~100/50nm resolution for DUV/ExtremeDUV systems
- RIE, Deep-RIE

Etching (SF6 gas)
Passivation (C4F8 gas)
Feature Creation

- Multiple layers can be stacked to create complex systems
Measurement

- MEMs cantilever in silicon
- (A) Horizontal displacement, with varying pad area
- (B) Discovers front of cell pulls, rear of cell pushes

[Adapted from Galbraith]
Measurement

- Microposts
- (A) Megaposts:
- (B) cardiac myocytes
- (C) clumps of platelets
- (D) Nanoposts:
- (E) Higher precision

[Kajzar, Liang, Yang]
Electron Beam Lithography

- JEOL JBX electron beam writer
  - Minimum field resolution: 1.25 angstroms
- Resolution is sensitive, special challenges
  - Temperature, humidity
  - Ground vibration
  - EM field noise
  - Special room
Electron Beam Lithography

- Slow, but accurate writing.
- Like writing an image 1 pixel at a time
- Electron Scattering
Apply Force

- Most basic: micromanipulator + pulled glass tips
- Magnetic twisting cytometry: (A) Adhere bead, (B-C) twist or pull on bead

[Adapted from Matthews]
Apply Force

- MEMs cantilever in silicon
- Expansion of glass needle concept
- Incorporates reference point during pulling, better accuracy

[Adapted from Yang]
Apply Force

- Magnetic microposts
- Embedded ferromagnetic wire
- Global field applied

- Apply local force, see whole cell response simultaneously

[Adapted from Sniadecki]
Soft Lithography – Polymer Replication

- (A) Features are created in silicon or photoresist, a negative is cast, then a positive is case
- (B) Negative features are created, then a positive is cast
Microfluidics

- Shear forces for cells
- Many variations, single channel, multi channel, channel + stretch, channel + microposts, etc...

Duffy et al. 1998

[Adapted from chau]
Microfluidics

- Single cell sorting
  - (A) flow setup
  - (B) channel setup
  - (C) a single cell

- Why single cell?
  - If you measure behavior through averages, you can miss modal behaviors

[Adapted from Di Carlo]
Apply Force w/ Microfluidics and Optics

- Optical traps, tweezers can manipulate beads on cells, proteins
- Stretch cells without contact with (A) divergent beams, (B) sort in microfluidics, (C) unstretched (D) stretched
- Check non-adherent cell properties

[Adapted from Arsenault]

[Adapted from Guck]
Microfluidics – Lab on Disc

- Lab on chip / Lab on disc assays for high throughput detection of biomarkers
- In this example, ELISA immunoassay for hepatitis (Enzyme-linked immunosorbent assay)

[Adapted from Lee]
Microfluidics – Organ on Chip

- Organ on chip: Lung
- (A) Construction
- (B) Dual cells on PDMS membrane
- (C) Stretch and chemical exchange

[Adapted from Huh]
Questions?