Alternative MicroFabrication and Applications in Medicine and Biology

Massachusetts Institute of Technology

6.152 - Lecture 11

Fall 2005

These slides prepared by Dr. Hang Lu (Georgia Tech)

Outline of Today's Materials

- Intro
- Alternative materials and fabrication techniques
- Applications in biology and chemistry
- Applications in medicine
- A real MTL example of rapid prototyping

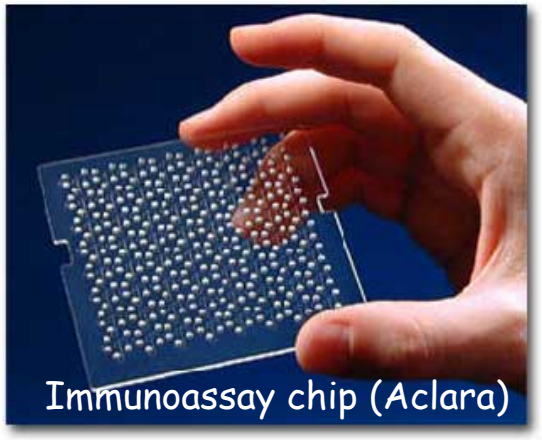
Micro Systems for Bio / Med

- Micro systems have characteristic length scale in the order of microns. (Human hair width is ~100 microns.)

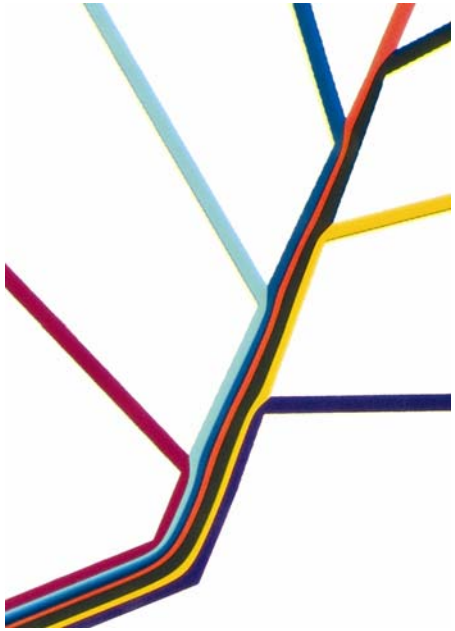
- The applications of these systems span
  - Biological analysis
  - Medical diagnosis
  - Chemical analysis and synthesis
  - Drug discovery
  - Drug Delivery
  - …

Advantages of Micro Systems

- Small length scale
- Laminar flow (good and bad)
- High surface-to-volume ratio
- Small thermal mass


Immunoassay chip (Aclara)

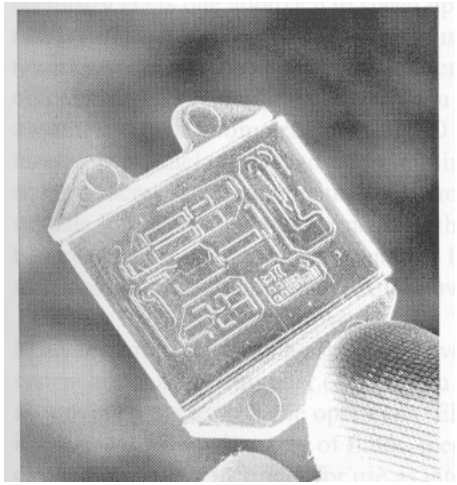
- Close to some biological length scale
- Shorter processing time
- Less sample / reagent required
- Disposable
- Automation possible
- Parallel operation possible – high throughput
- Integration possible


Whitesides (Harvard U.);
Photo credit: Felice Frankel

Alternative Materials

- Materials requirement for bioMEMS is different from that for MEMS.

- Desired properties of bioMEMS materials
  - Biocompatible
  - Chemically modifiable
  - Easy to fabricate
  - Economic
  - Soft and compliable
  - Smart

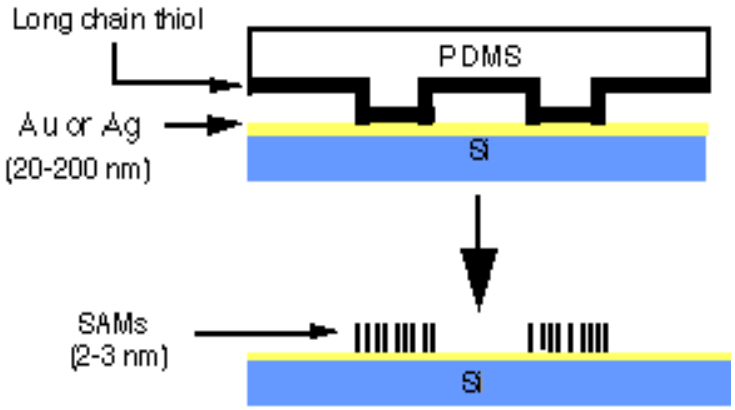


- If not Si and glass, what then?
- *Polymers* (e.g. PDMS, PMMA) are good materials especially for biological applications.

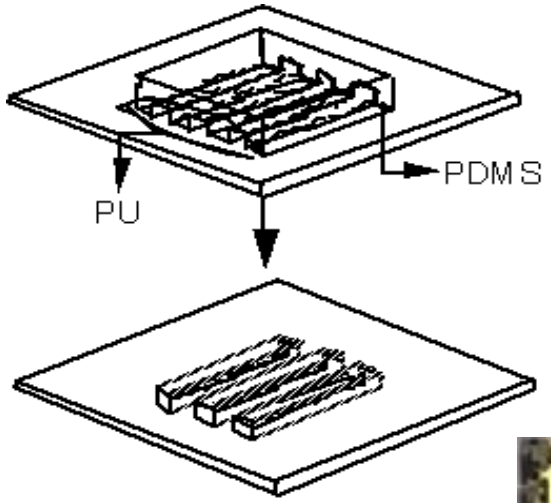
Alternative Fabrication Methods

- Soft lithography

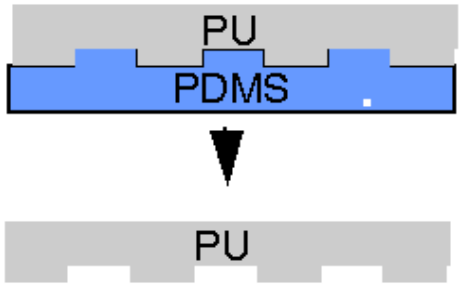
Micro contact printing



Micro molding in capillaries (MIMC)

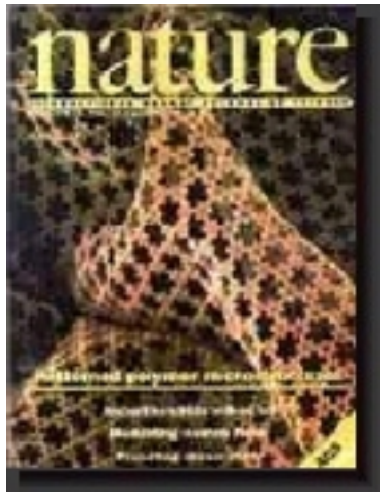


Replica Molding



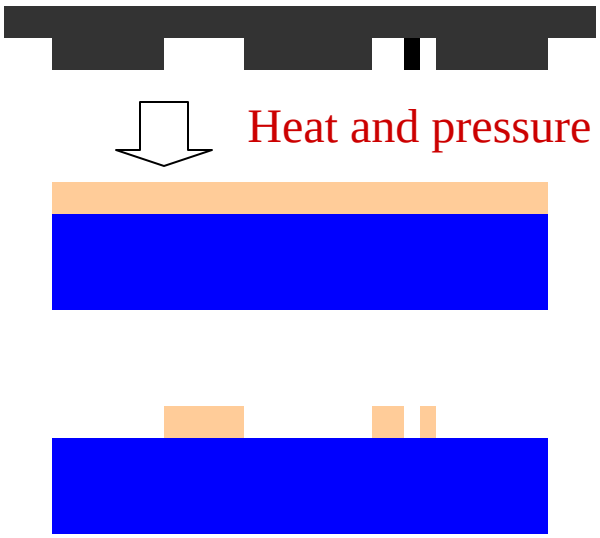
Y. Xia and G.M. Whitesides (Harvard U.)

Photographed by Felice Frankel



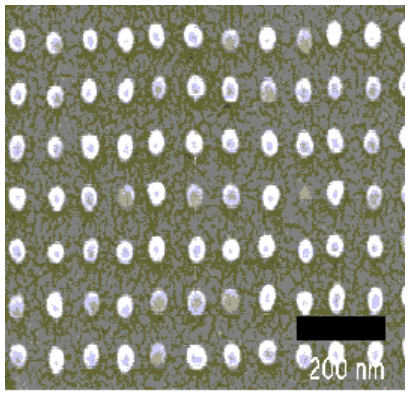
Other Polymer Methods

- Hot embossing



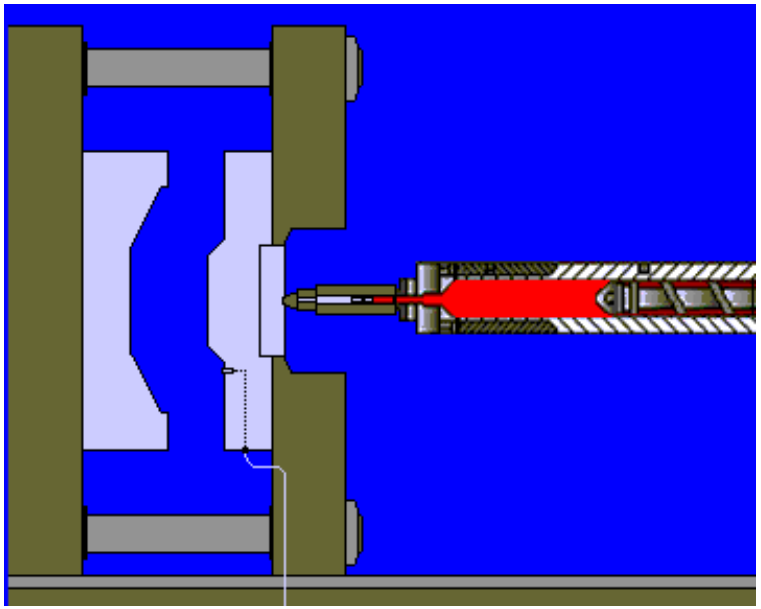
Stamp (master)

Thermoplastic Substrate

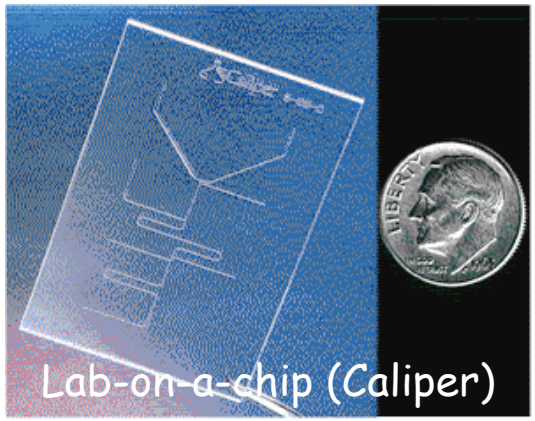


Schift et al (PSI)

- Injection molding

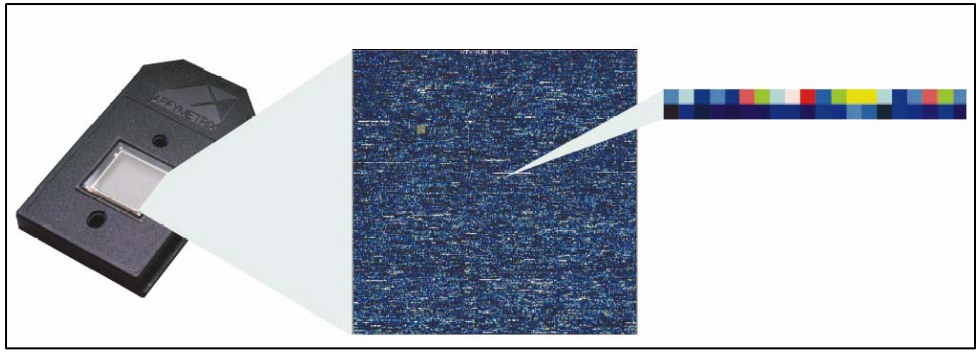


Examples of bioMEMS Systems



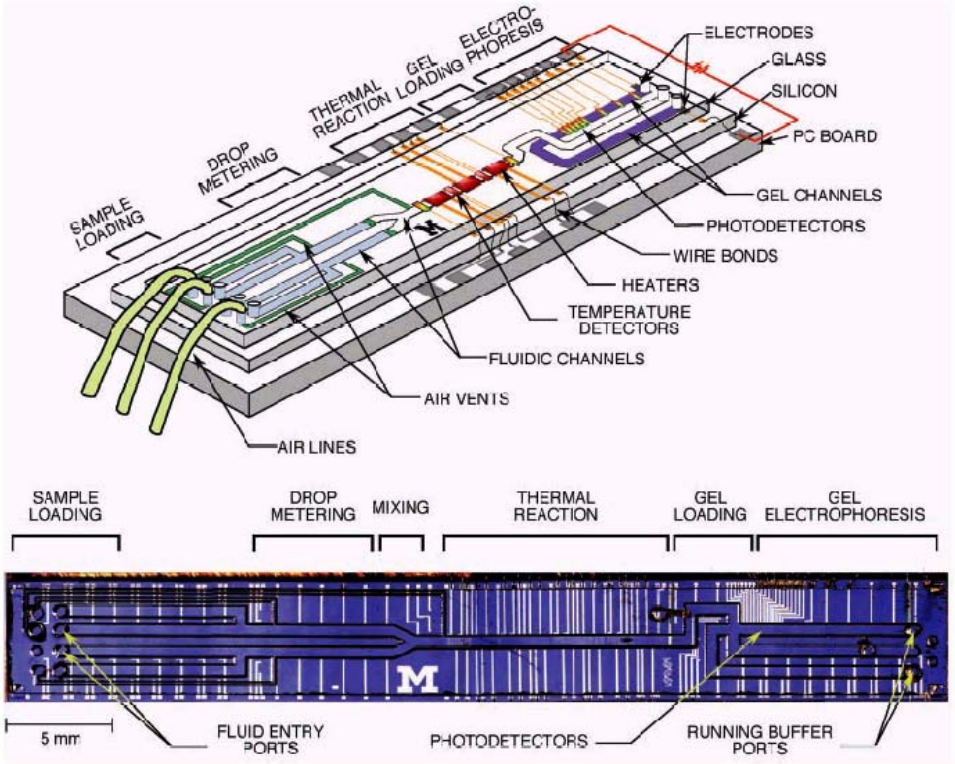
Lab-on-a-chip (Caliper)

- Detection and diagnosis
- Synthesis and analysis
- Interaction and interrogation
- Treatment


GeneChip (Affymetrix)

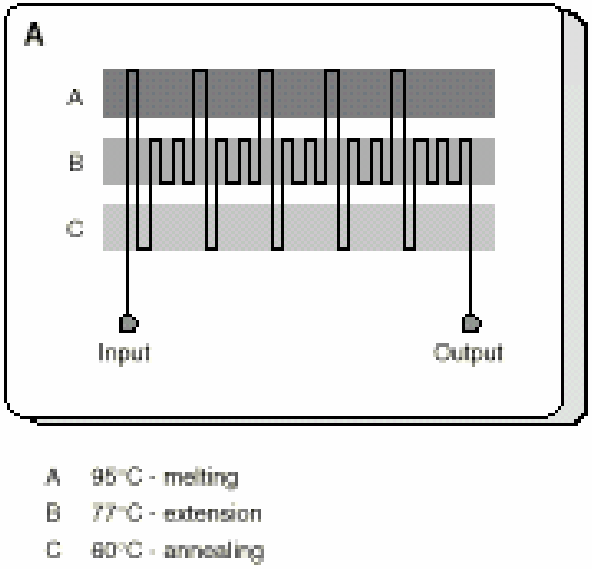

Immunochip (Aclara)

DNA electrophoresis I



DNA analysis chip (M. A. Burns, U Mich)

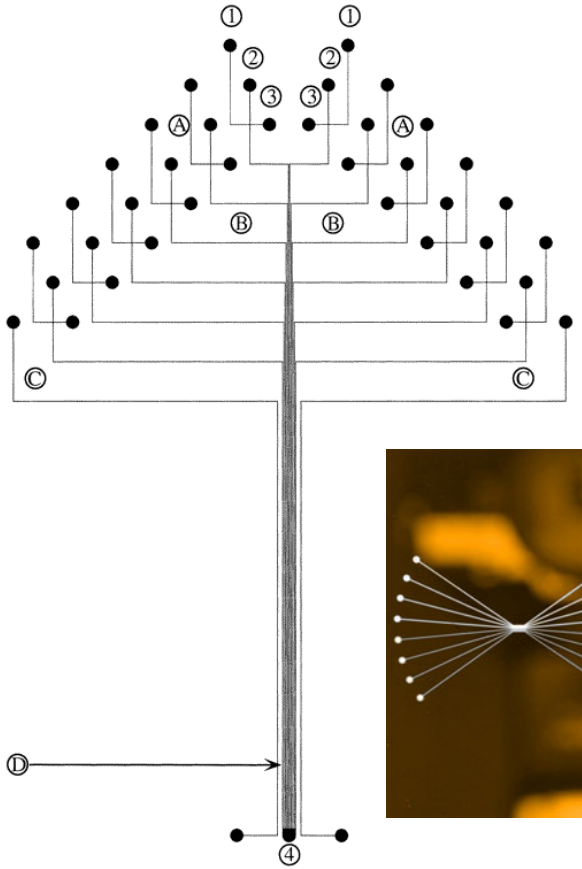
- Metering samples
- PCR reaction
- Gel electrophoresis
- Sensors and actuators

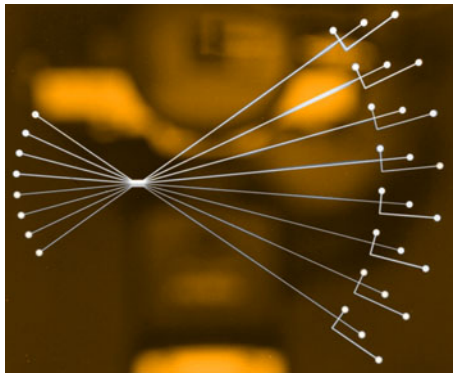


PCR chip (A. Manz, Imperial College)

- Etched glass
- Continuous
- Three T zones
- Thermal insulation

DNA electrophoresis II

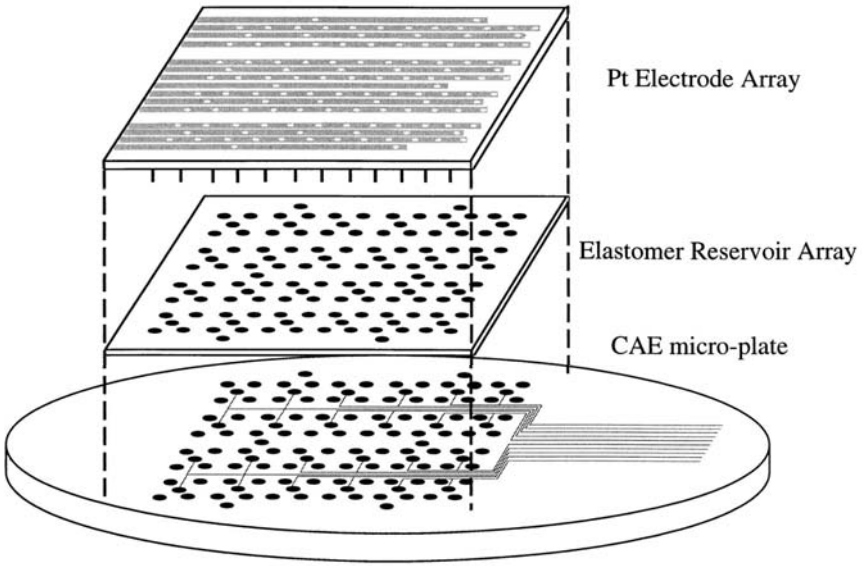


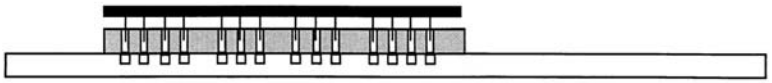


Mathies (Berkeley)

- High throughput
- Etched glass

- Electrode insertion scheme matching high throughput need

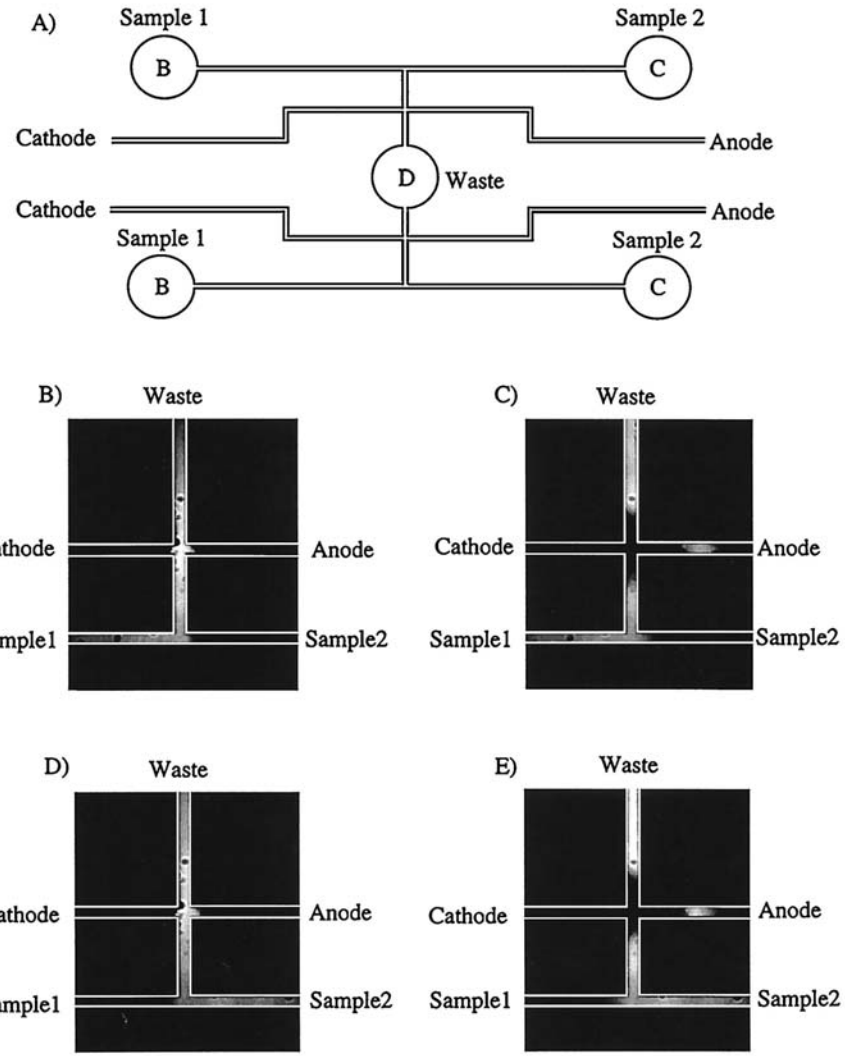


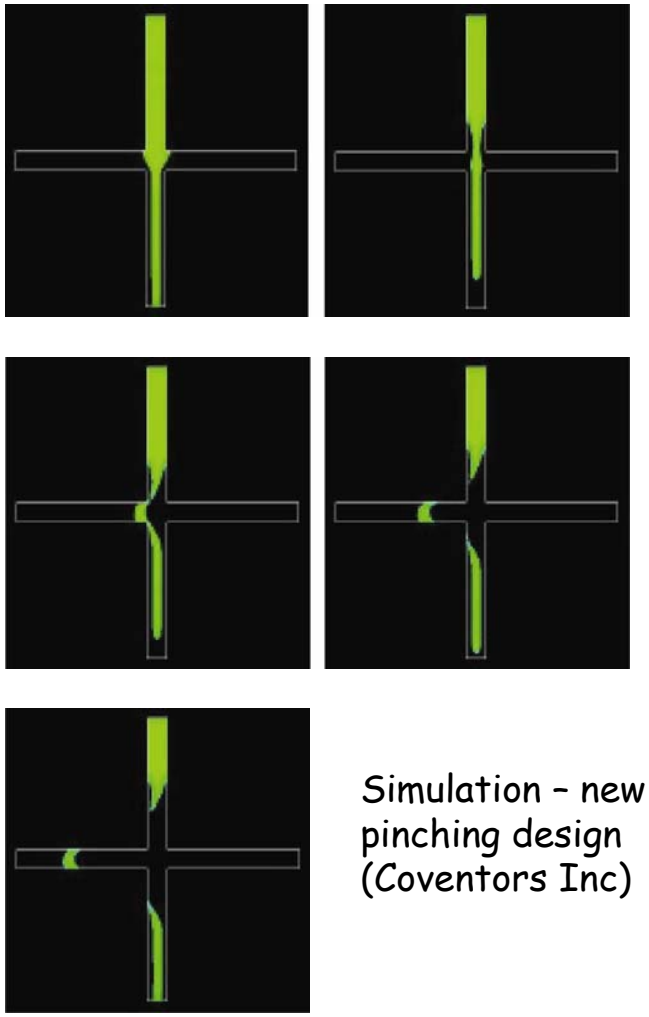


DNA electrophoresis III

Mathies (Berkeley)

- Sample injection

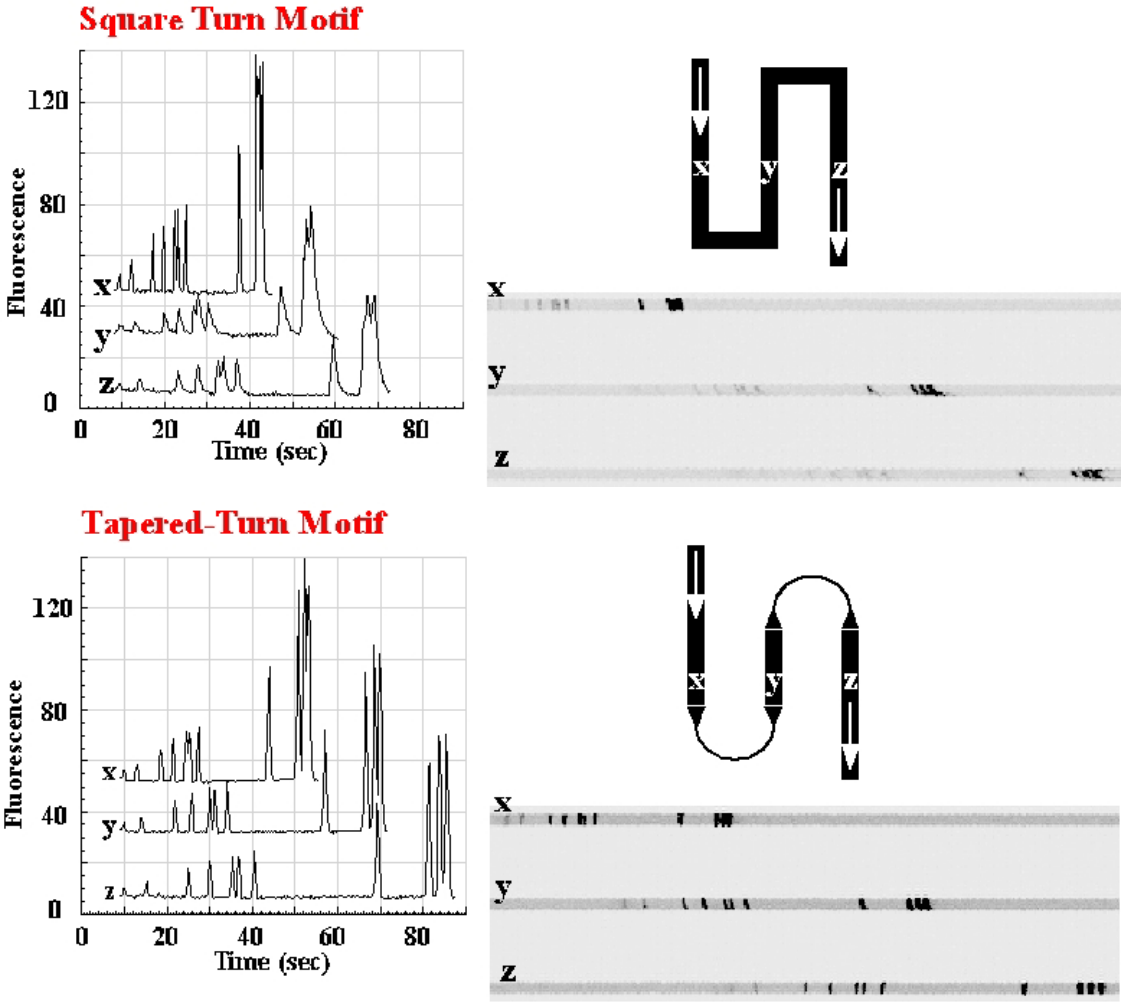




Simulation – new pinching design (Coventors Inc)

DNA electrophoresis IV

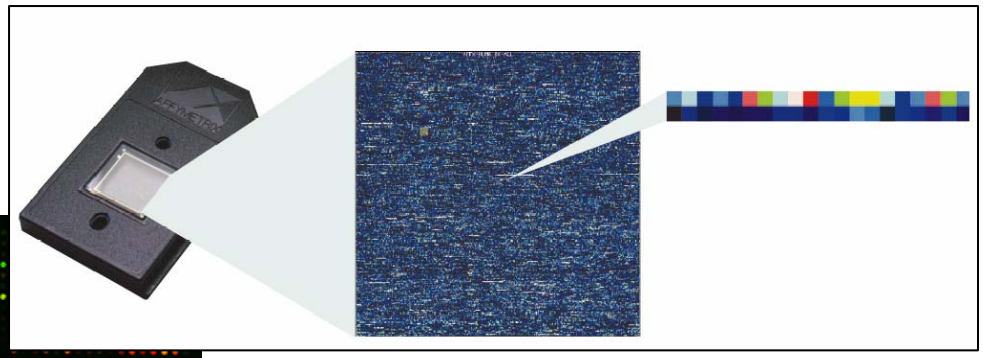
- Race track effect – optimizing the design



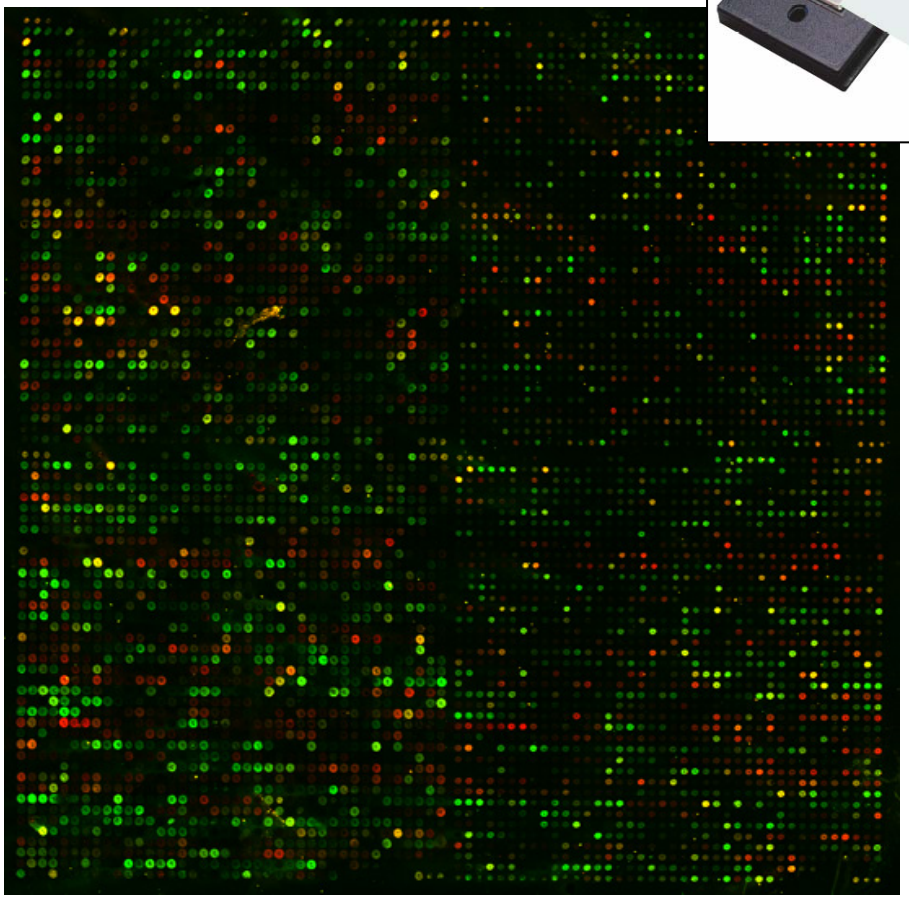
Mathies (Berkeley)

DNA microarrays

- Affymetrix

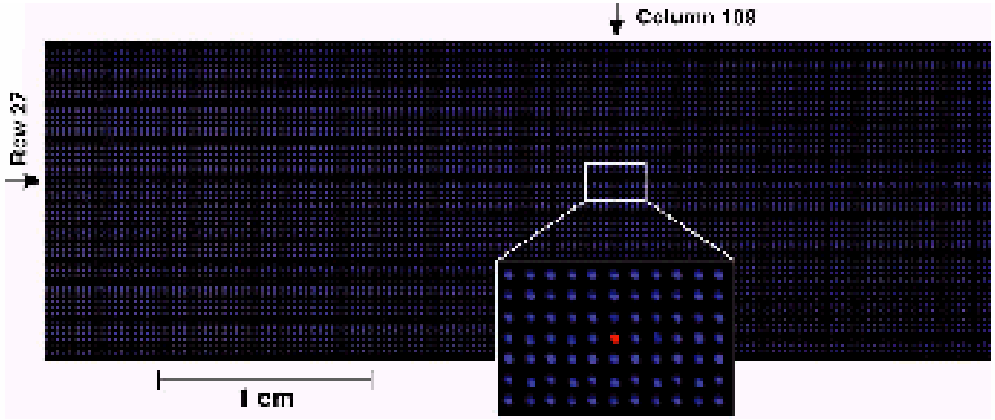


GeneChip (Affymetrix)



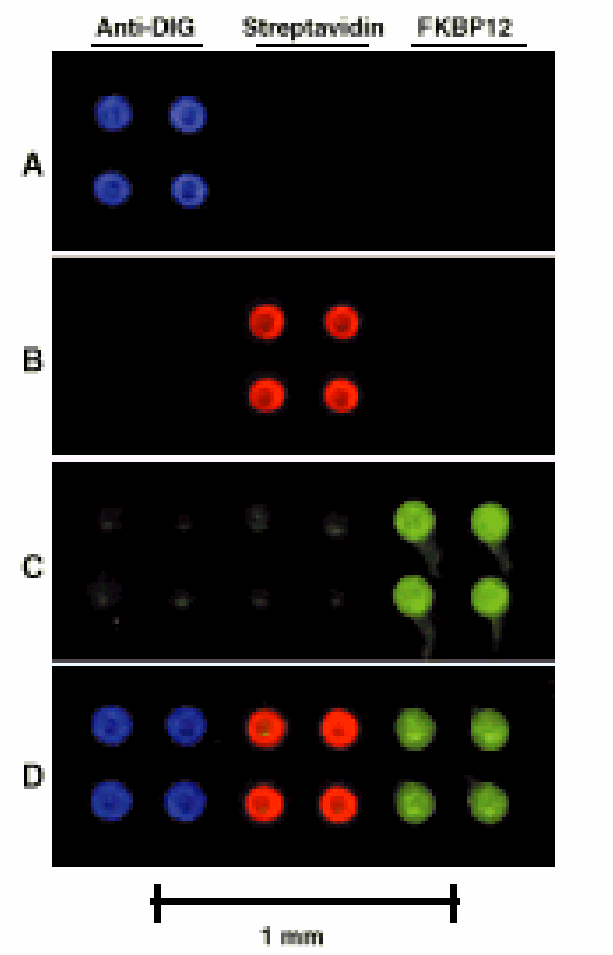
- cDNA arrays
- Genetic profiling
- Relative fluorescence measurement
- Fabricated with lithographic techniques

Protein microarrays



Schreiber (Harvard U.)

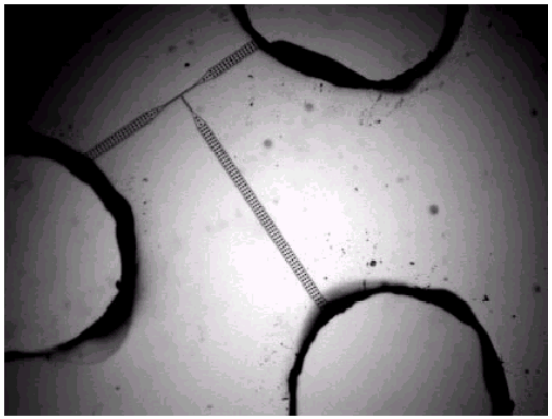
- Small molecule –protein interactions
- High throughput screening of compounds
- Printed glass slide



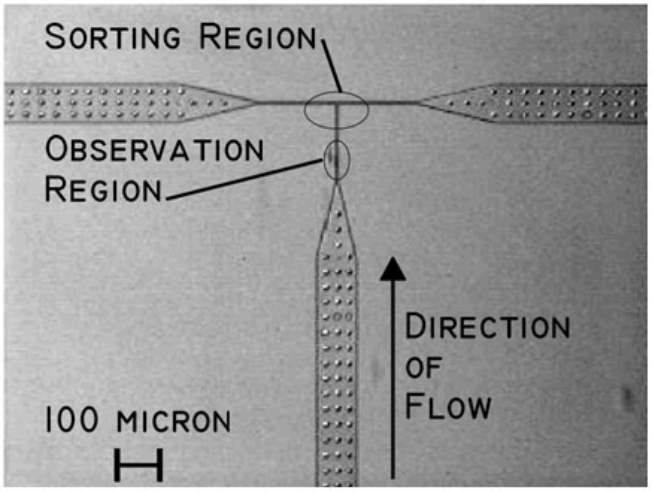
MacBeath (Harvard U.)

- Protein – protein interactions
- Protein profiling
- Derivatized glass slide

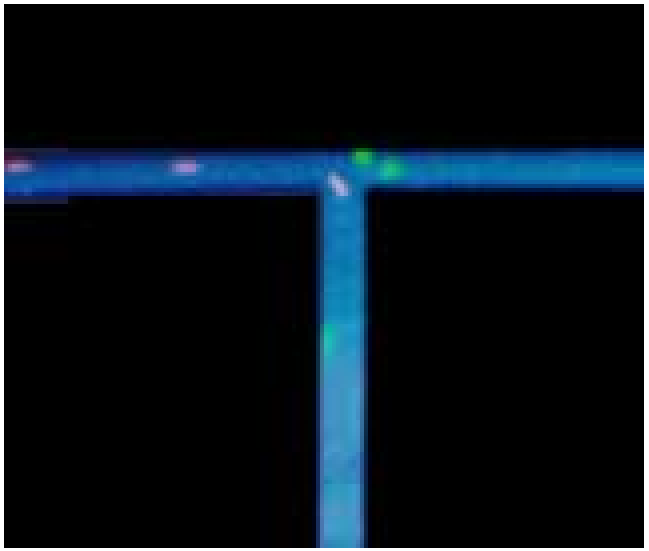
MicroFAC

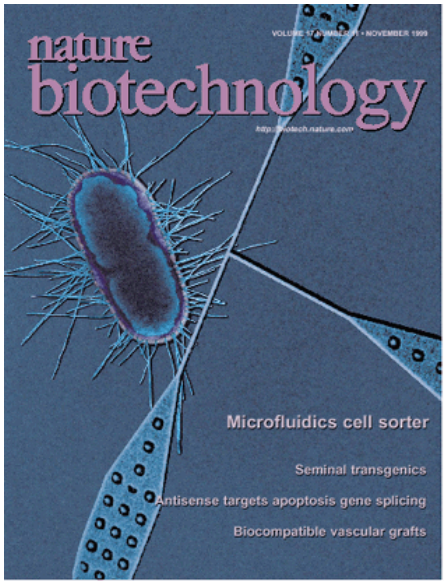


- Fluorescence based sorting
- PDMS molded from silicon master
- Feedback controlling fluid flow (electroOsmotic flow)



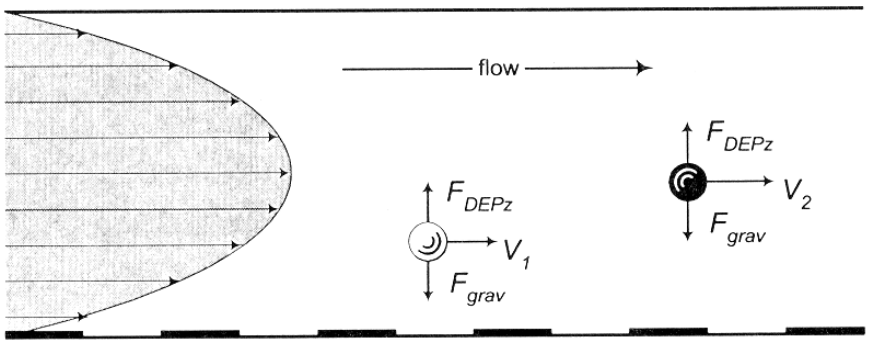
Quake (CalTech)

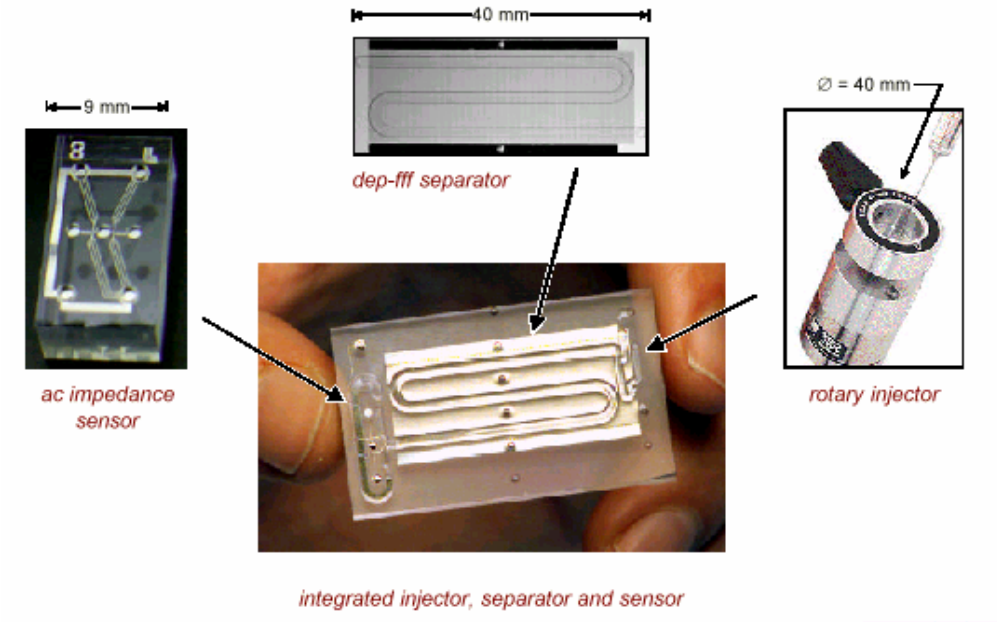


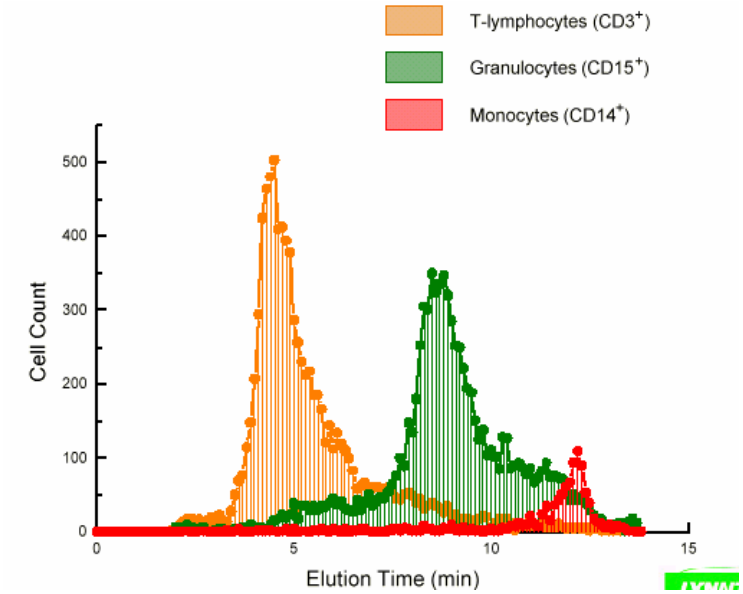


DEP Cell Sorter

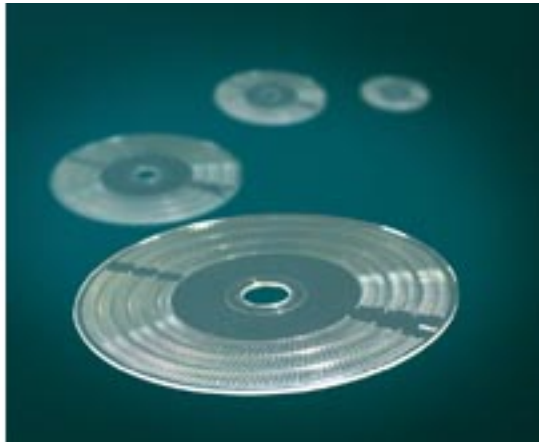
- U. Texas – Houston
- Rare cell detection
- Field flow fractionation using dielectrophoretic force



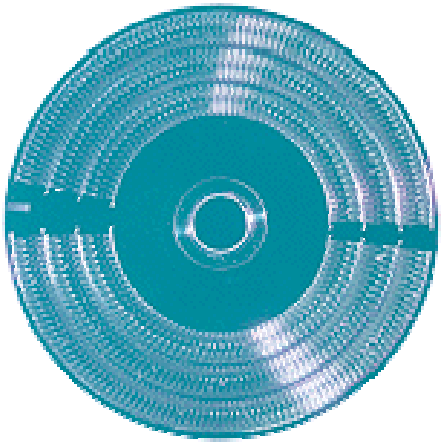




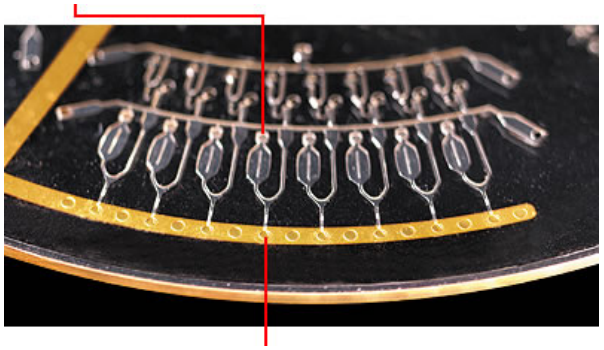
Microfluidics on a CD



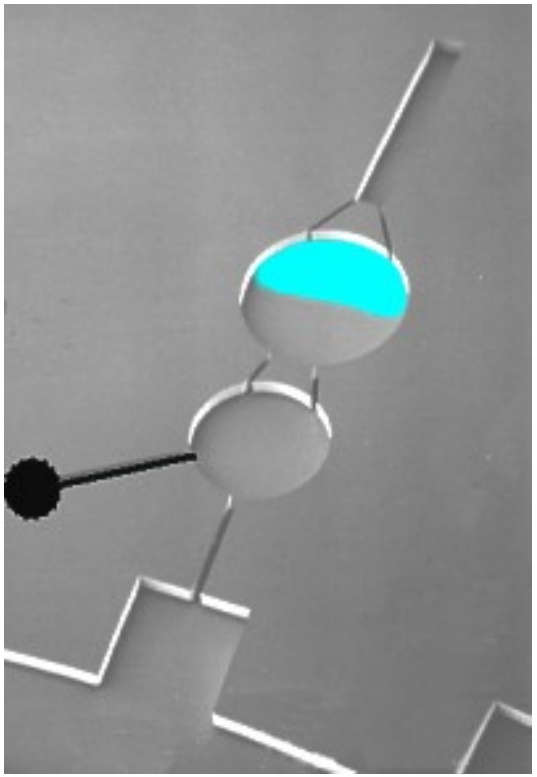
- Gyros Inc.
- Centrifugal forces
- Metering
- Fluid delivery
- Protein analysis
- Hematology

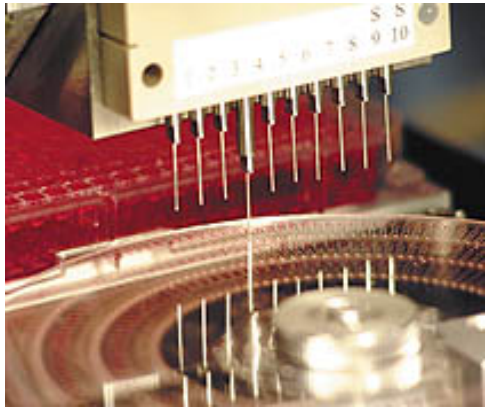


Sample well

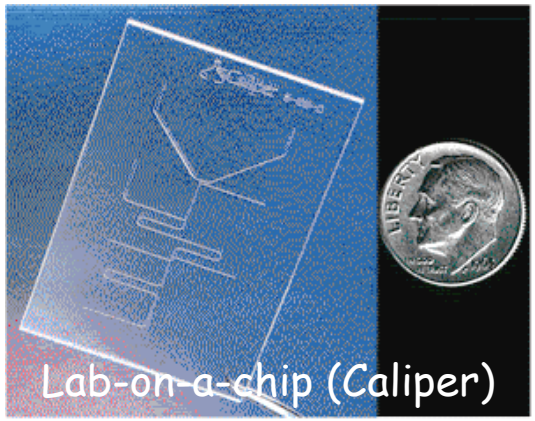


Reaction chamber



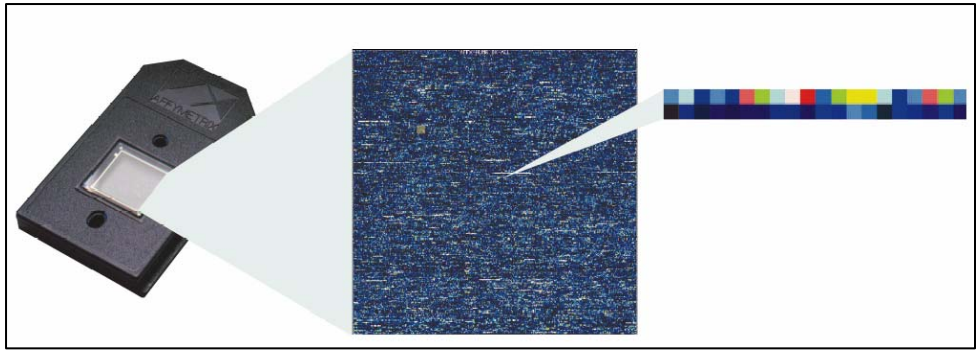


Examples of bioMEMS Systems



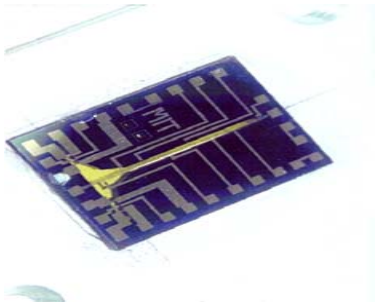
Lab-on-a-chip (Caliper)

- Detection and diagnosis
- Synthesis and analysis
- Interaction and interrogation
- Treatment

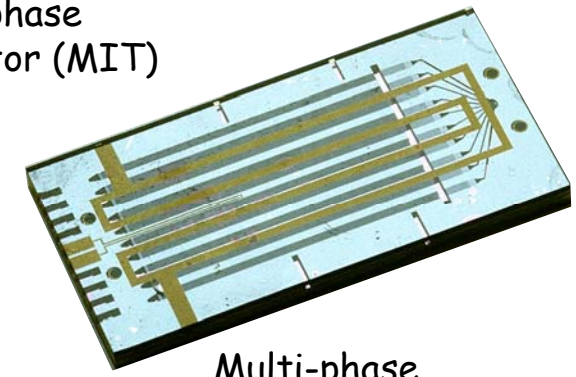

GeneChip (Affymetrix)


Immunochip (Aclara)

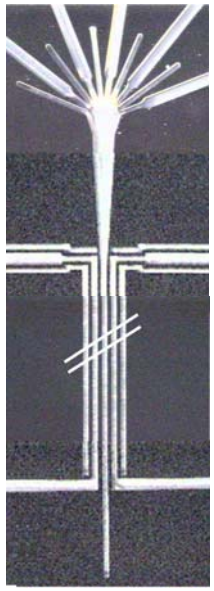
Synthesis with Microreactors



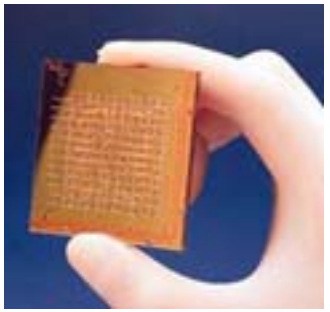
Gas phase reactor (MIT)



Multi-phase reactor (MIT)



Liquid phase reactor (MIT)

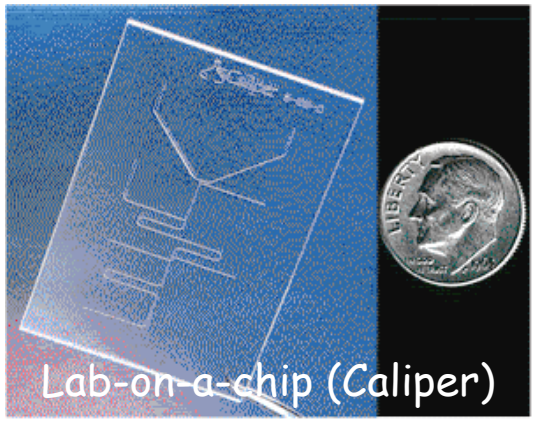


High throughput microreactor (Orchid BioSciences)

Micromixer (IMM)

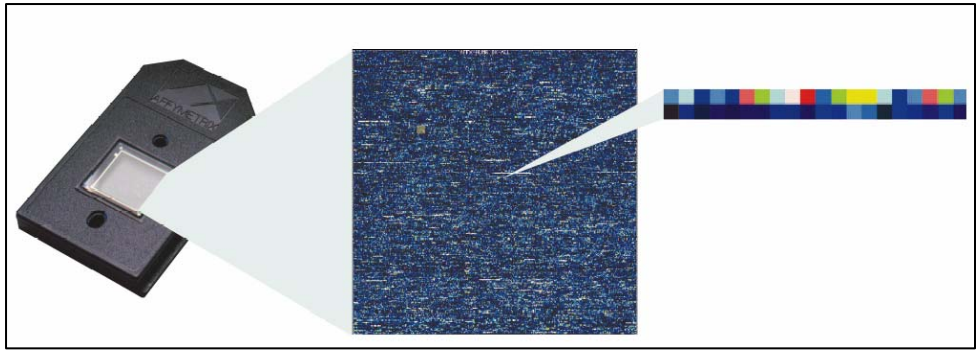
- Microreactors for synthesis and chemical researches
- Temperature and pressure sensors, heaters, heat exchangers, valves, separators…

Examples of bioMEMS Systems



Lab-on-a-chip (Caliper)

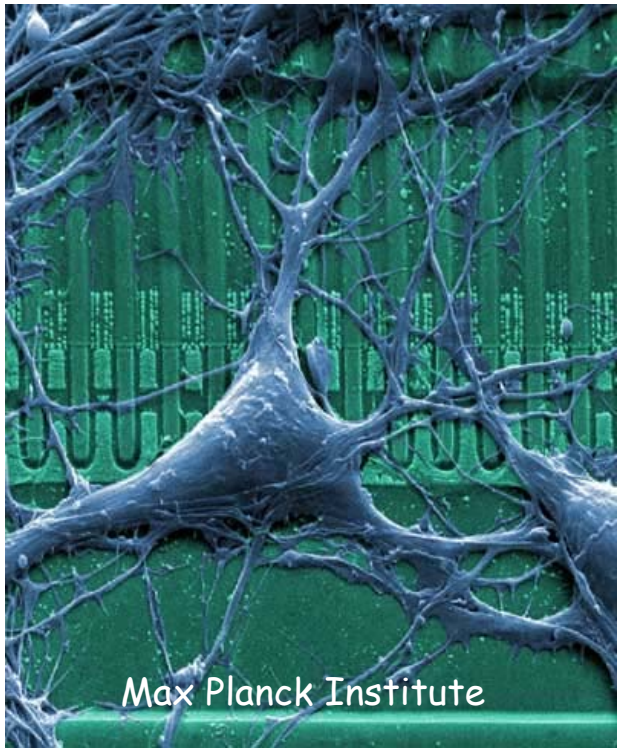
- Detection and diagnosis
- Synthesis and analysis
- Interaction and interrogation
- Treatment

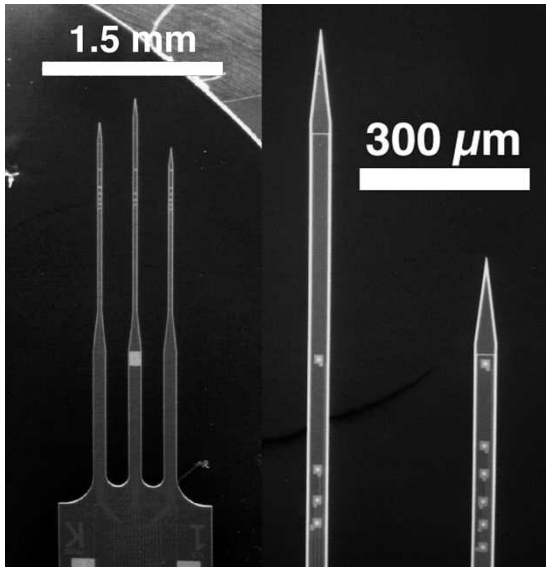

GeneChip (Affymetrix)


Immunochip (Aclara)

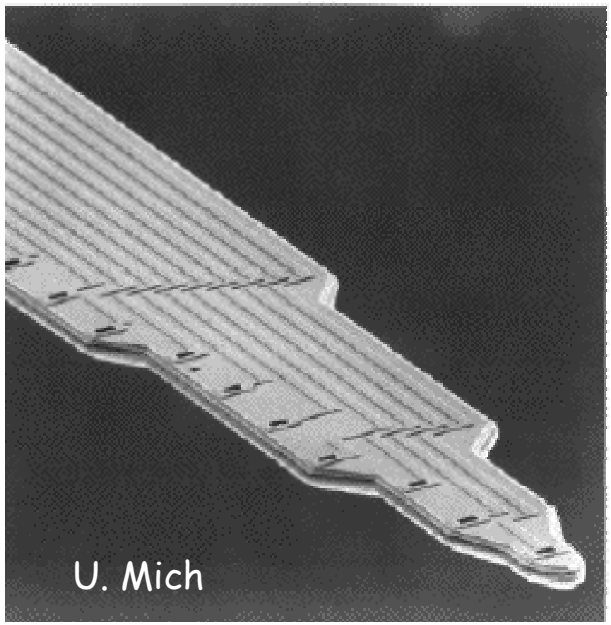
Neuro implant

- Neuro-circuit interaction – neuro recording
- Prosthesis research
- Chemical delivery – molecular probe
- Issues with long term implant – bio compatibility

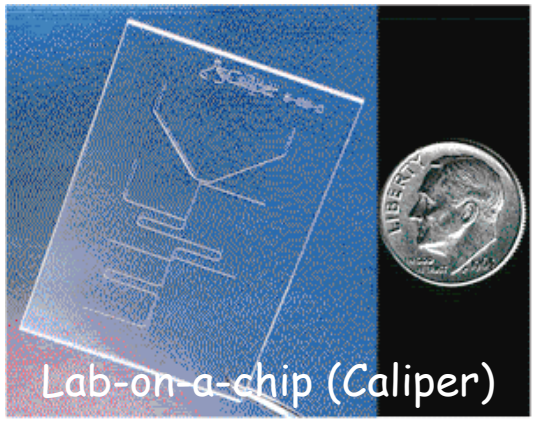




Stanford Neuro Probe

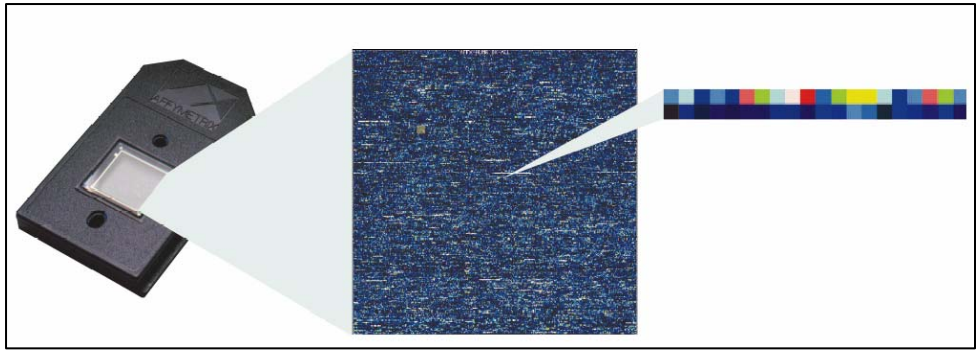


Examples of bioMEMS Systems



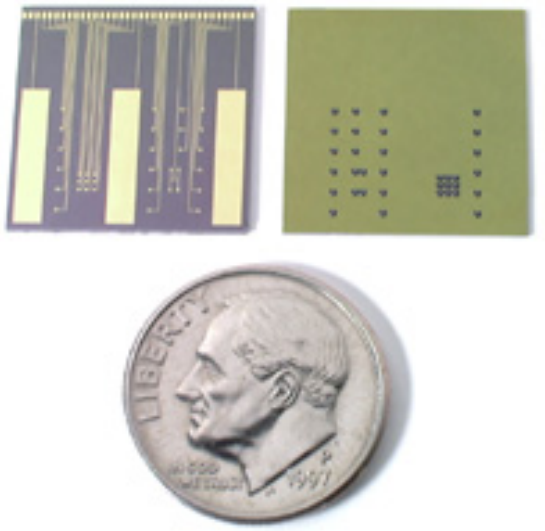
Lab-on-a-chip (Caliper)

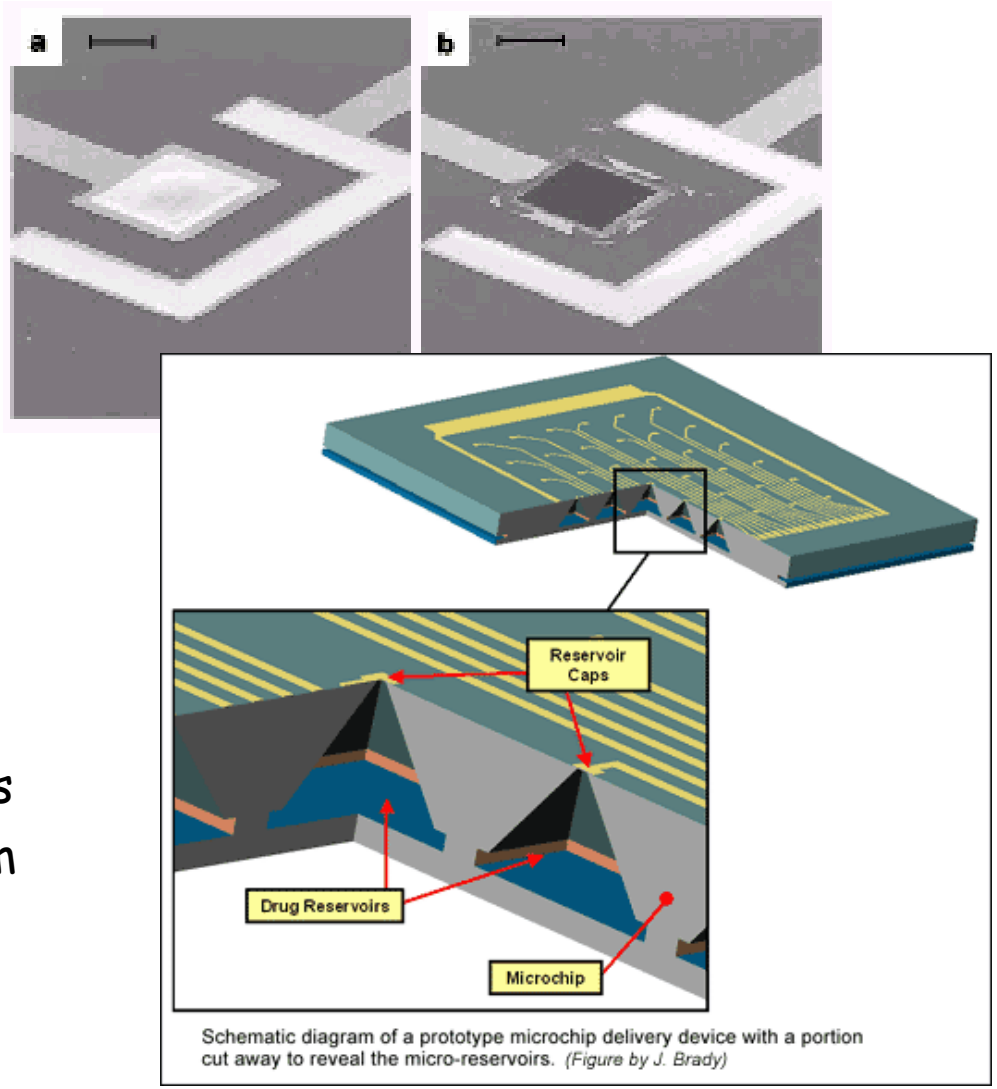
- Detection and diagnosis
- Synthesis and analysis
- Interaction and interrogation
- Treatment


GeneChip (Affymetrix)


Immunochip (Aclara)

Drug-delivery



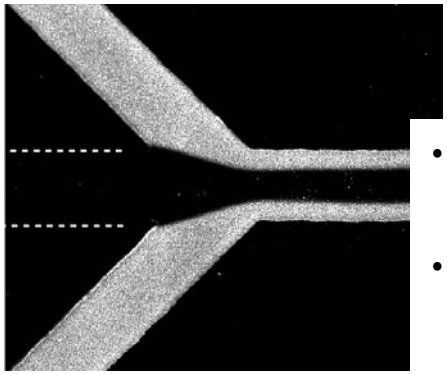


Schematic diagram of a prototype microchip delivery device with a portion cut away to reveal the micro-reservoirs. *(Figure by J. Brady)*

- Santini (Microchips)
- Controlled delivery
- Dry chemicals packed in wells
- Electrochemistry of gold film with body fluid (erosion)
- Quick response time

Tissue Engineering

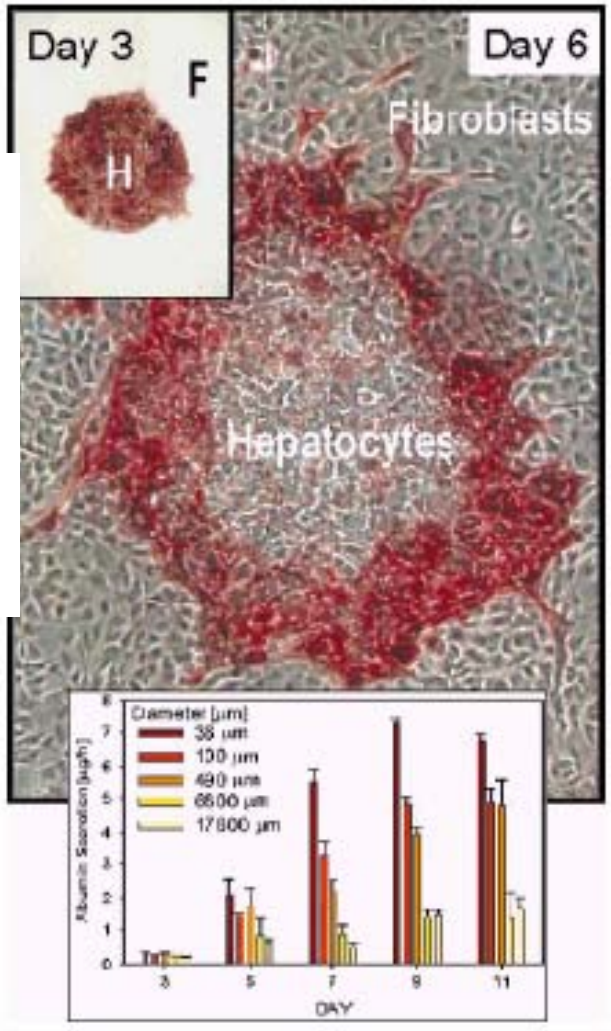
neoglyco-protein



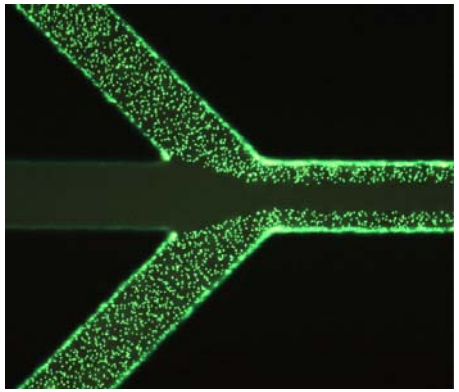
BSA

neoglyco-protein

- Patterning cells using microfluidics
- Patterning cells using micro contact printing
- Patterning protein
- Co-culture of cells (hepatocytes and fibroblasts)

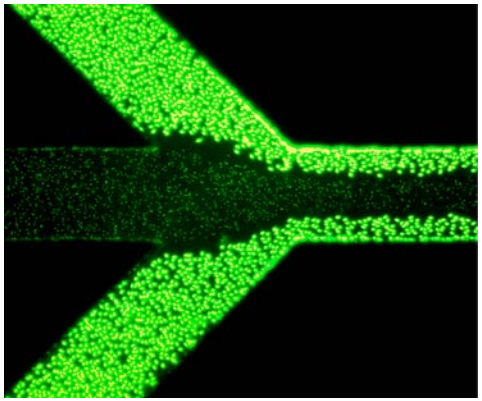


E coli



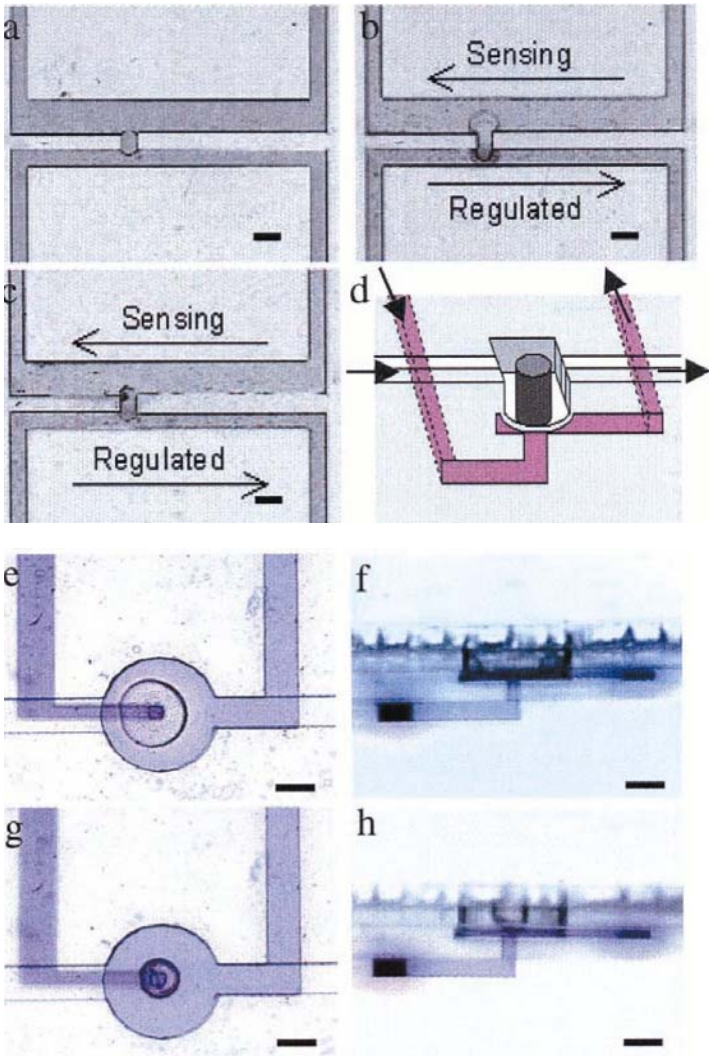
erythrocytes

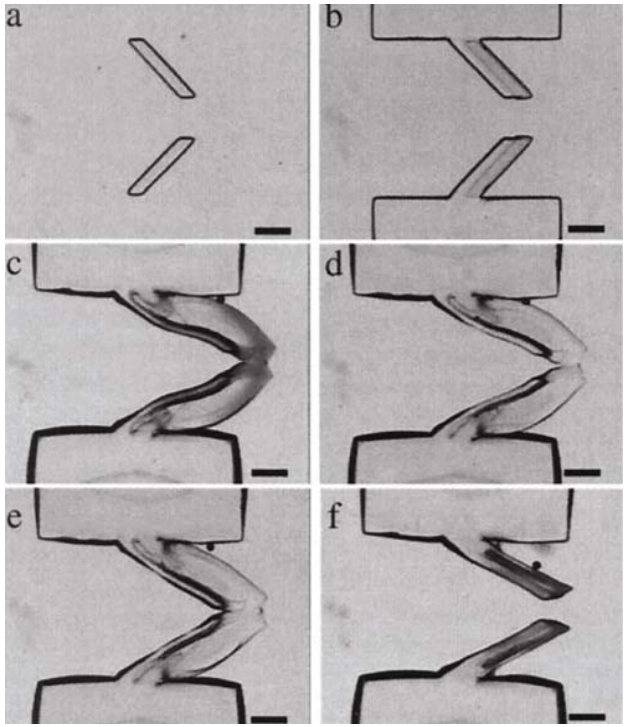
E. coli



erythrocytes

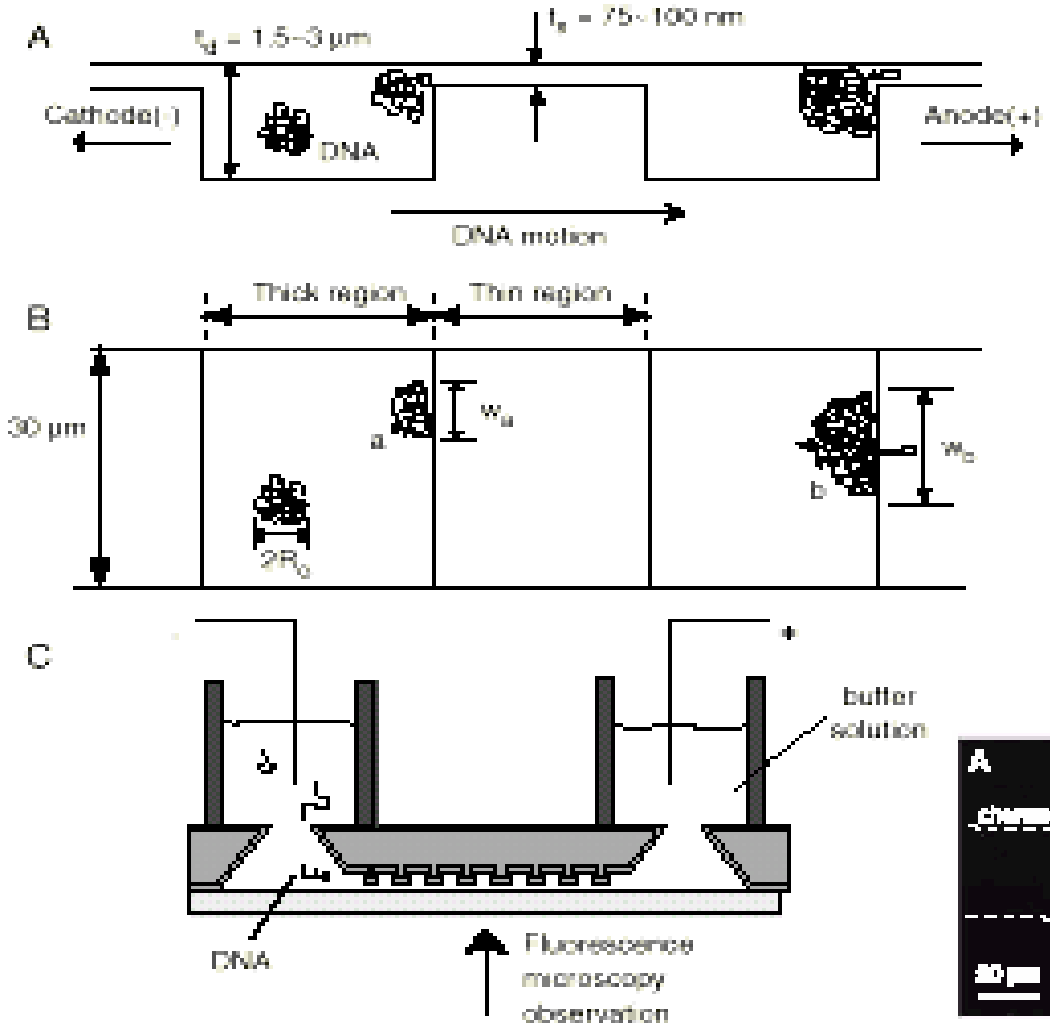
Small Materials – e.g. Hydrogel



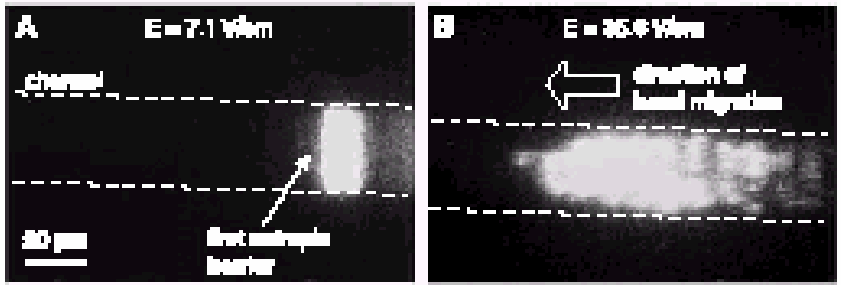


- Beebe (U Wisconsin)
- Hydrogel
- pH responsive
- Sensing and regulating
- In situ fabricated

NEMS/nanofluidics

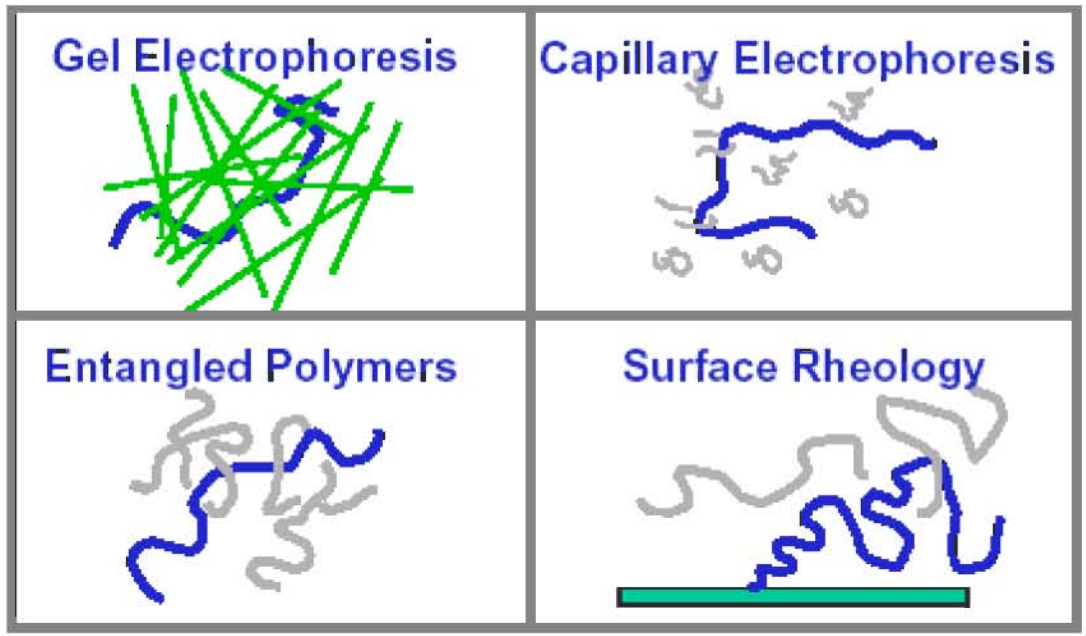


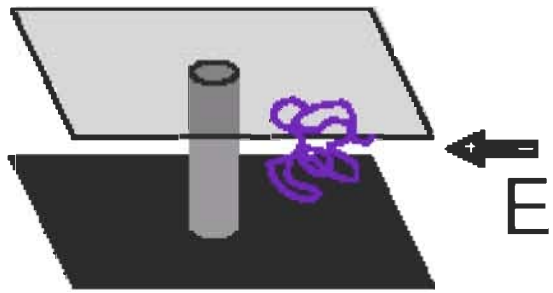
- Craighead (Cornell U.)
- Using entropic effect of large DNA molecules
- Near field fluorescence detection



Dynamics of DNA-Obstacle Collisions

Polymer collisions are important in complex fluids…





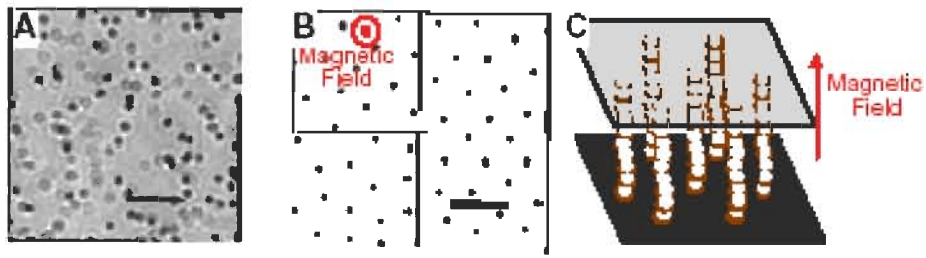
Greg Randall and Prof. Patrick Doyle

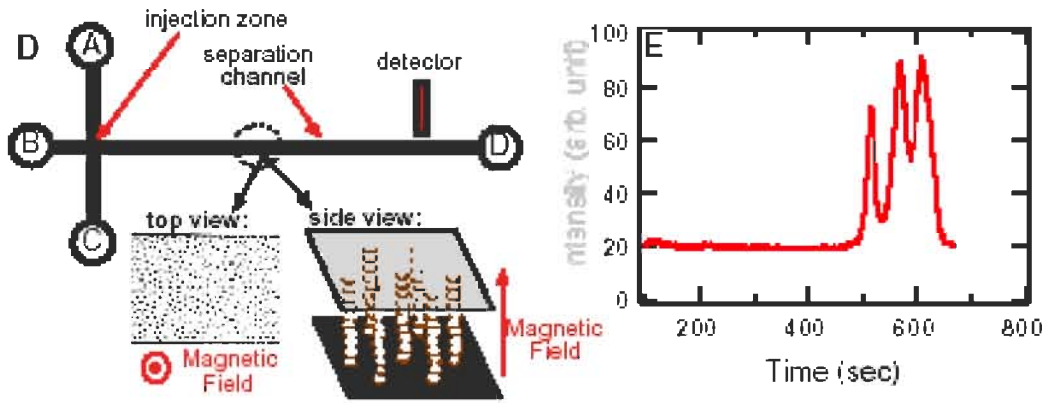
Motivation

DNA Electrophoresis in Magnetic Arrays

Doyle, Bibette, Bancaud and Viovy, Science 295, 2237 2002

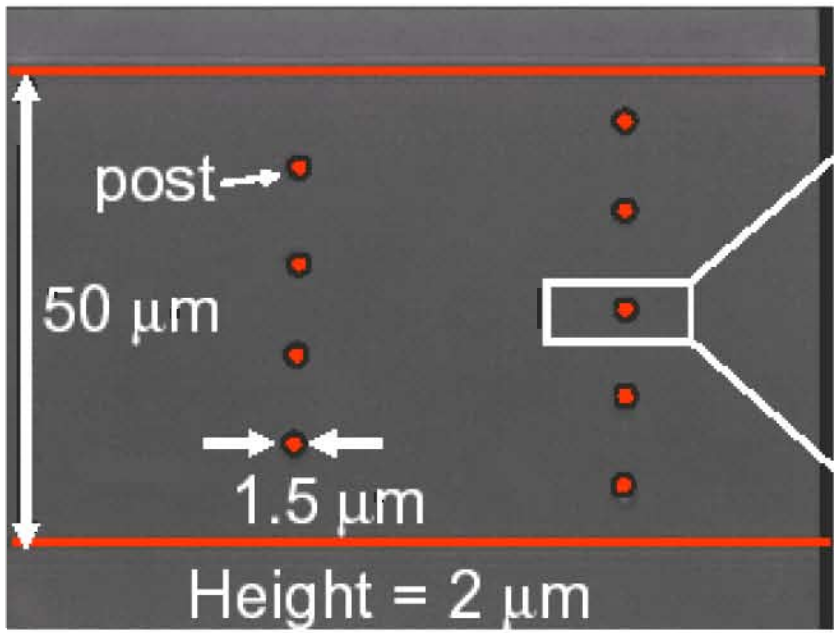
Separation occurs due to collisions with the posts

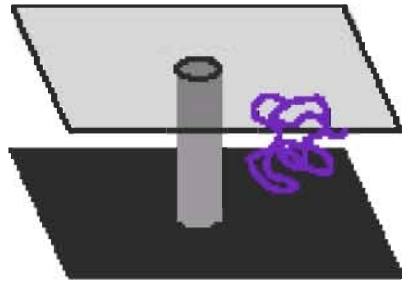




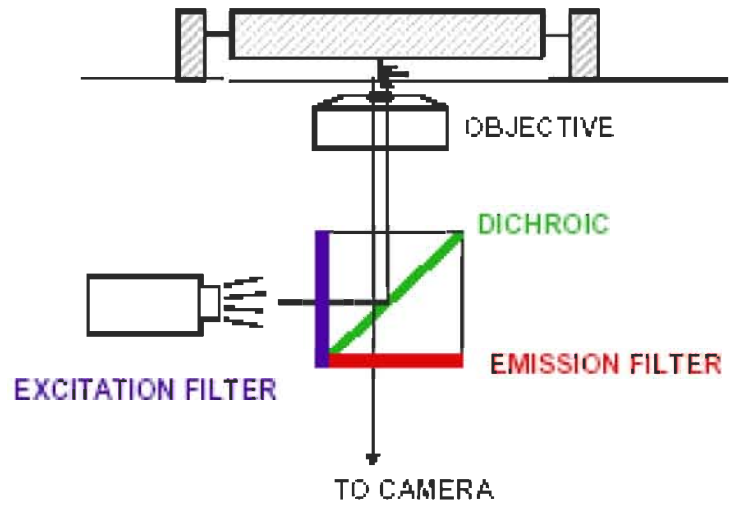
A Model System

Microfabricated posts: well defined, sparse





Electric field, E

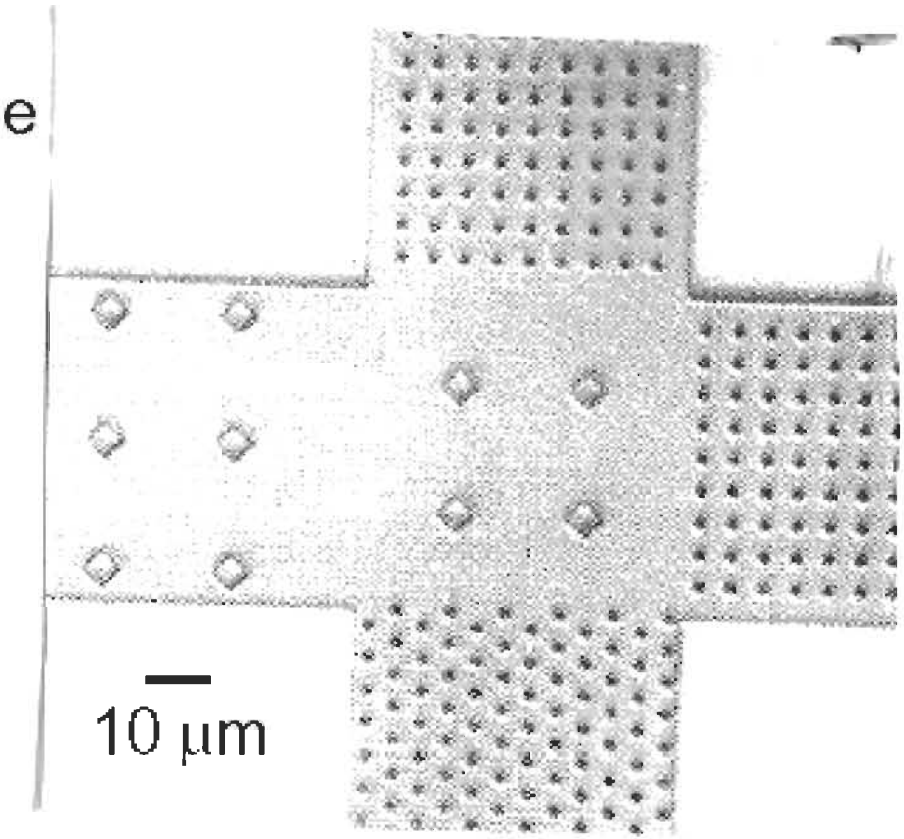


Molecule: λ-phage DNA
Fluorescent Dye: TOTO
Stain at 1 dye:5 bp

Image reversal resist

Used standard MTL Image Reversal procedure

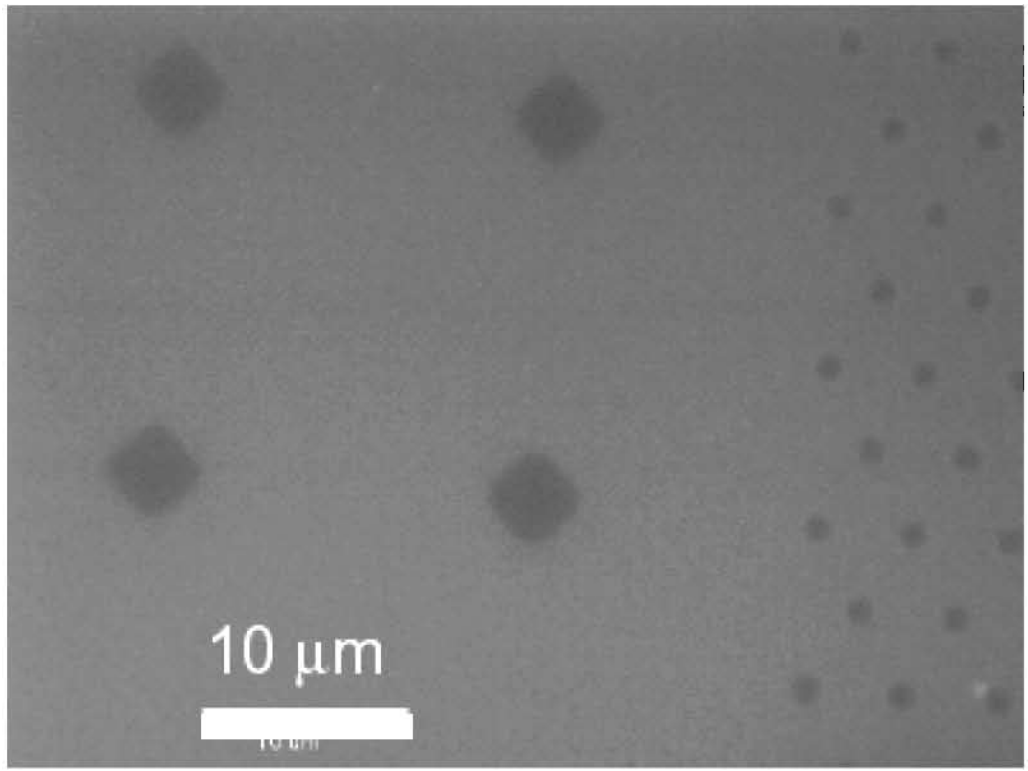
Great feature definition



2-μm thick AZ 5214

Image reversal resist

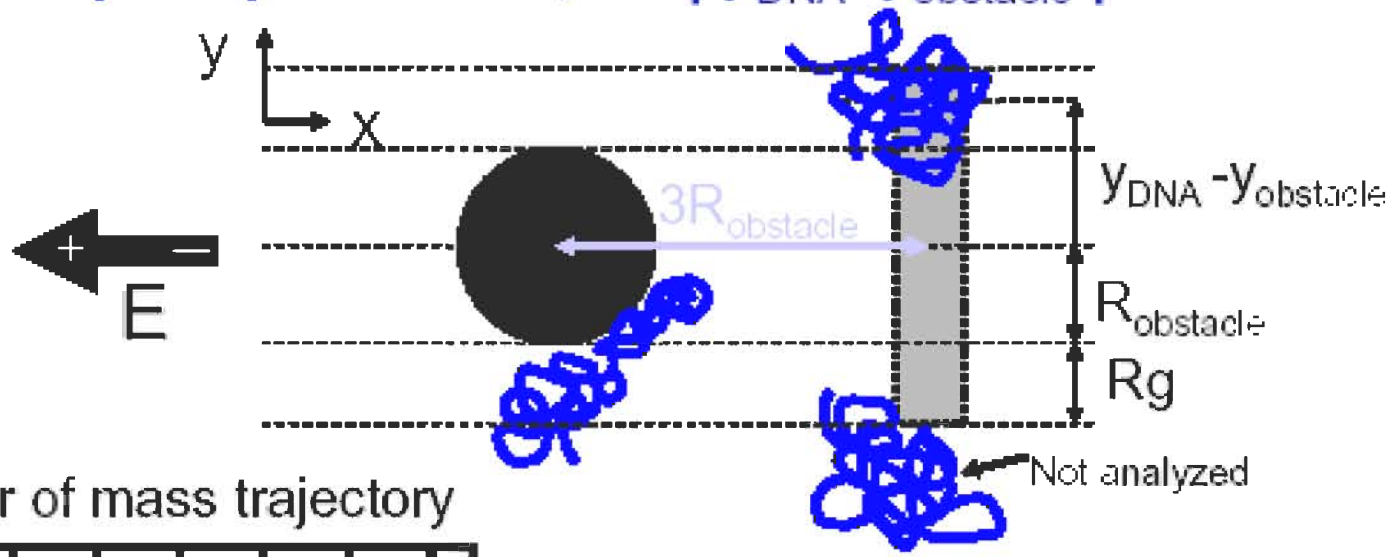
After molding PDMS



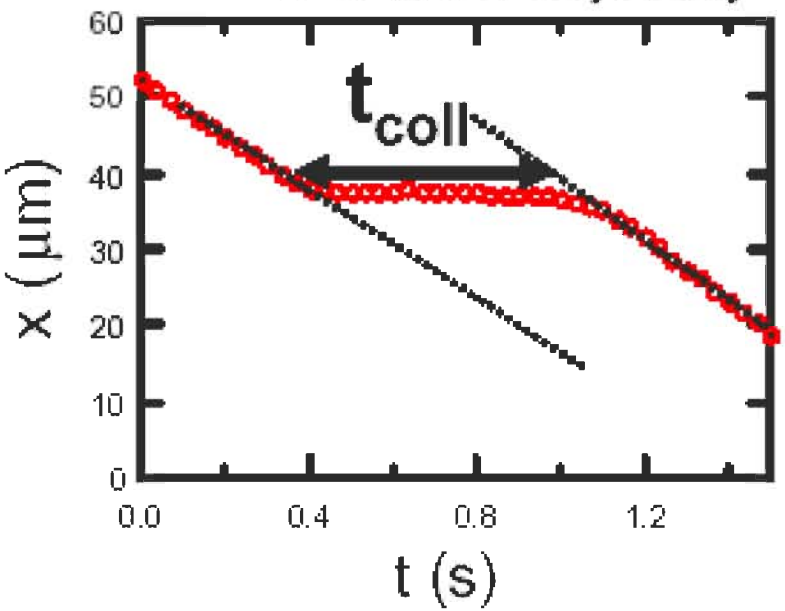
2-µm thick PDMS microchannel filled with fluoroscene

Collision analysis

Impact parameter, b= | $y_{DNA} - y_{obstacle}$ |



Center of mass trajectory

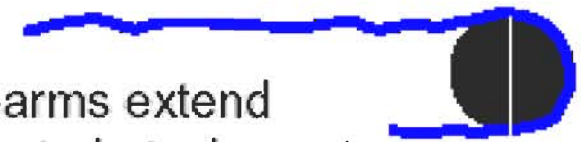


- Track DNA with $b < Rg + R_{obstacle}$
- Track center of mass position
- Determine collision time t_{coll} from linear offset

Types of Collisions: Hook or Roll-off

ROLL-OFF COLLISIONS

J-SHAPED COLLISIONS



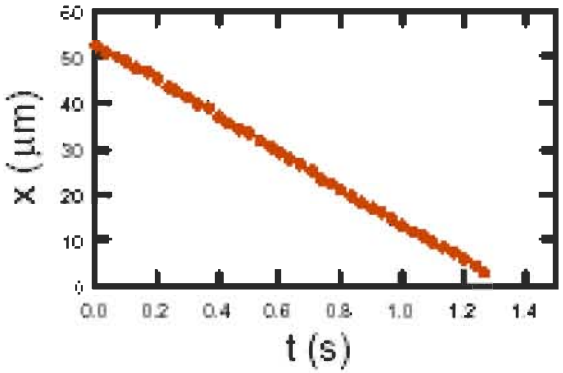
2-arms extend
past obstacle center
in x-direction

U-SHAPED COLLISIONS

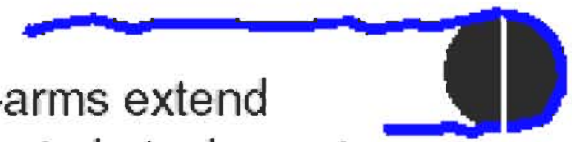
Movies!!

Analyzing Types of Collisions

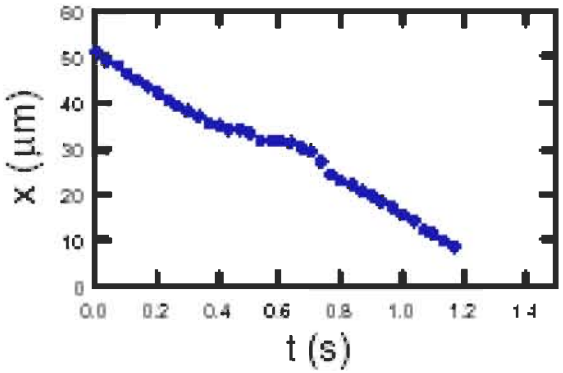
ROLL-OFF COLLISIONS



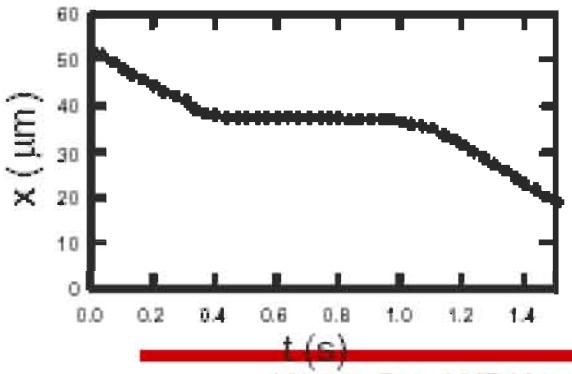
J-SHAPED COLLISIONS



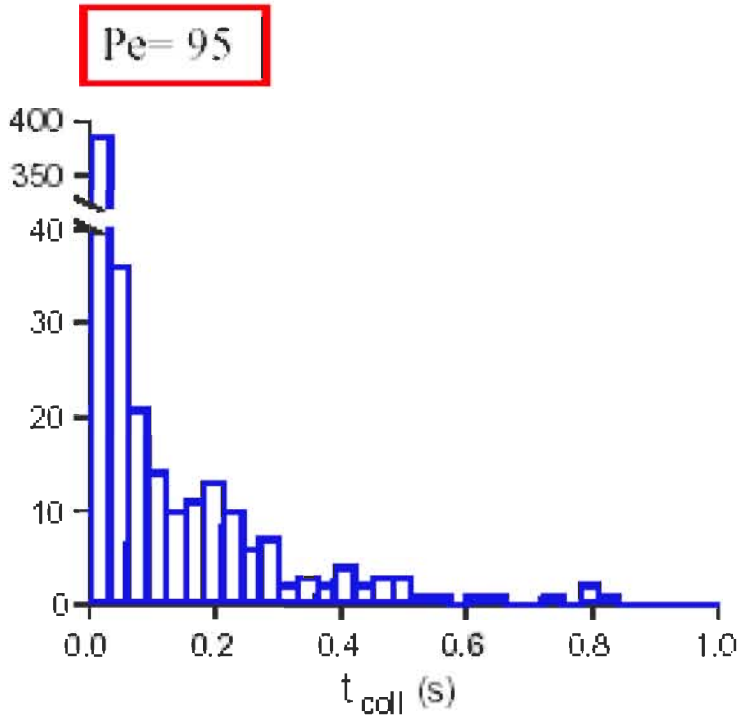
2-arms extend
past obstacle center
in x-direction

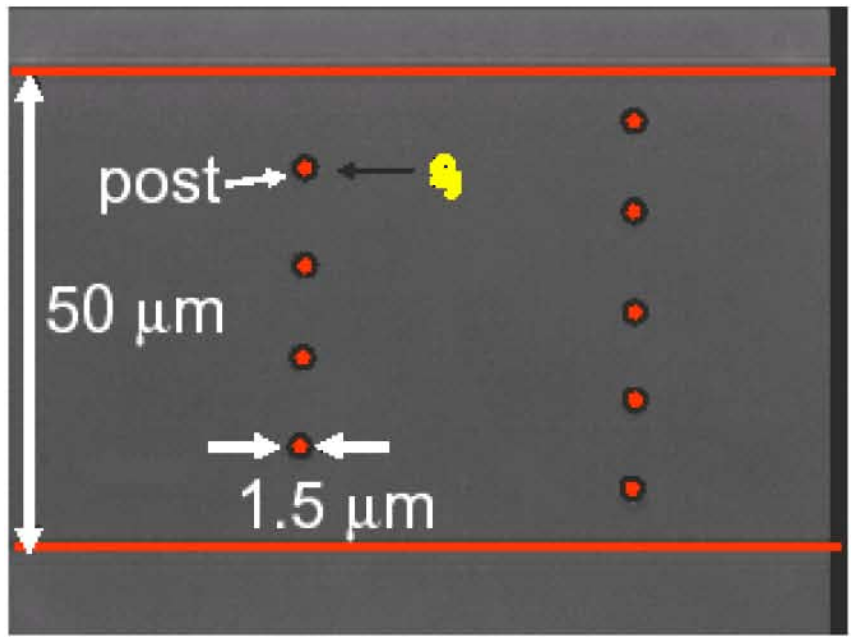


U-SHAPED COLLISIONS



Application to DNA Separations





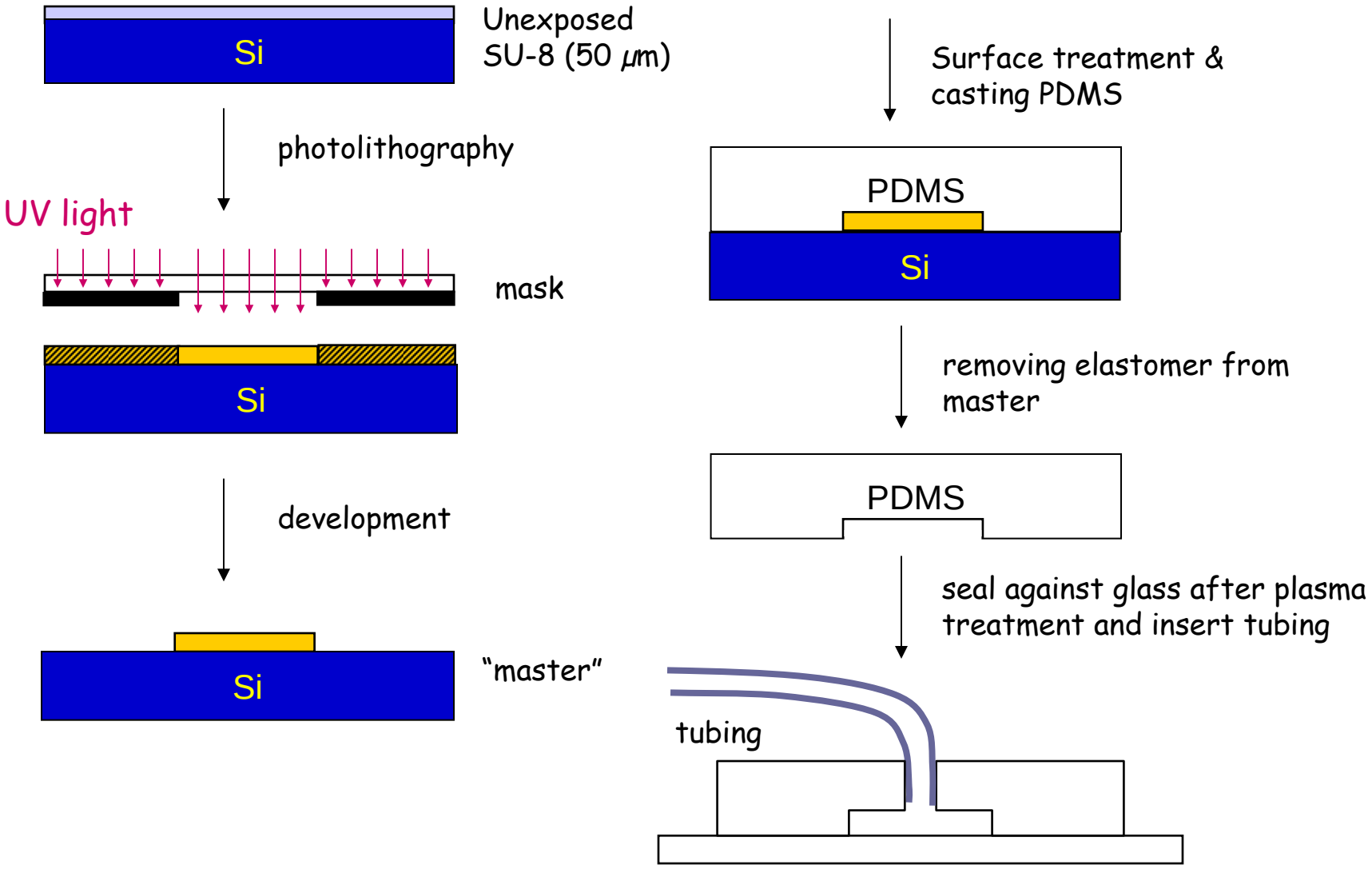
Collision time histogram can be applied to a "macrotransport" separation scheme

Reference: Brenner & Edwards (1993), Montroll & Weiss

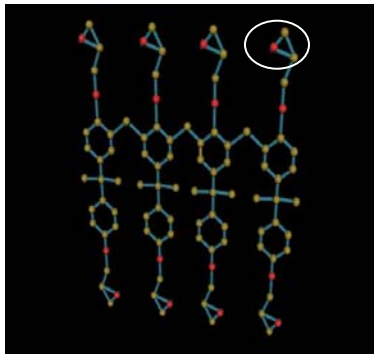
Related References: Dorfman & Brenner (2001)

Our Process

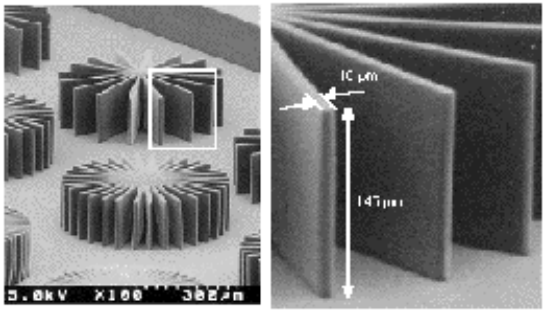
Process Flow - Overview



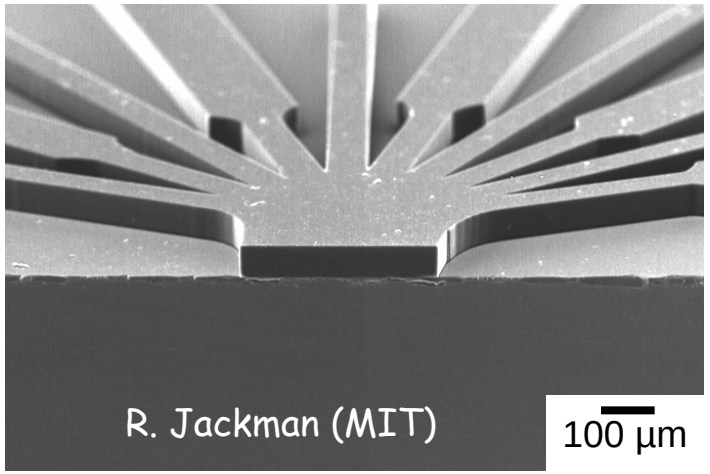
The Master Material - SU-8



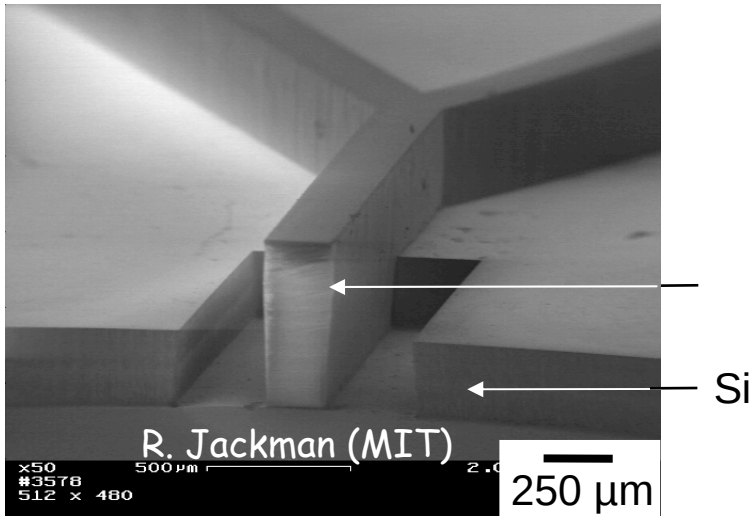
Structure of SU-8 molecule (SOTEC Inc)



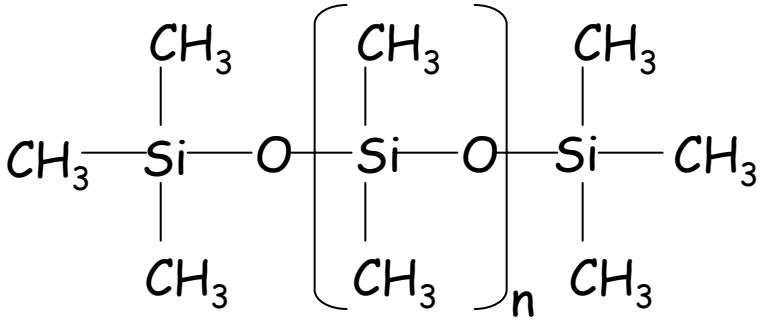
High aspect ratio structure (EPFL)



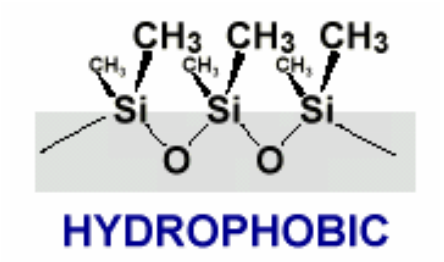
- Negative photodefinable epoxy
- Capable of forming high-aspect ratio (25:1) and thick (2mm) structures
- Used as electroplating template, in microfluidic applications, and as structure material for other microfabrication techniques



Replica Material - PDMS

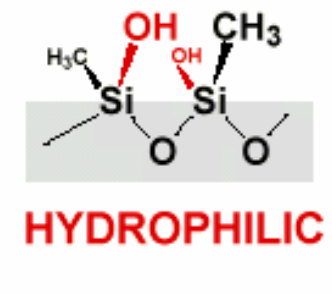


- Upon treatment in oxygen plasma, PDMS seals to itself, glass, silicon, silicon nitride, and some plastic materials.

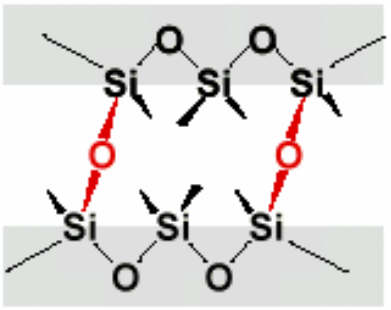


Plasma oxidation
(~ 1 min)

Air (~ 10 min)



contact PDMS surfaces



irreversible seal: formation of covalent bonds

Photolithography Steps

- 1. Define patterns on first layer

- 1.1 EML hotplate dehydrate wafer at 200C for 1 hr
- 1.2 EML hood spin coat SU-8
- 1.3 EML hotplate prebake 15 min at 105C (ramp up from room temp slowly and cool to < 60C)
- 1.4 EML photo expose through the mask
- 1.5 EML hotplate postbake 15-20 min at 105C
- 1.6 EML hood develop SU-8 in developer (PGMEA)
- 1.7 EML hood dry wafers with nitrogen

- 1.8 EML hood silanize wafers (1 hr)

Micromolding Steps

- 2. Molding SU-8 structures with PDMS

- 2.1 Mix prepolymer and initiator (10:1)
- 2.2 Degas the mixture
- 2.3 Cure PDMS at 65C for 2 hr

Packaging

- 3. Making PDMS-based devices

- 3.1 Carefully remove PDMS from wafer
- 3.2 Cut devices out using a razor blade
- 3.3 Punch holes in PDMS
- 3.4 Clean PDMS and glass substrates
- 3.5 Plasma ash PDMS and glass substrates
- 3.6 Bond
- 3.7 Insert tubing
- 3.8 Test

Our Mask