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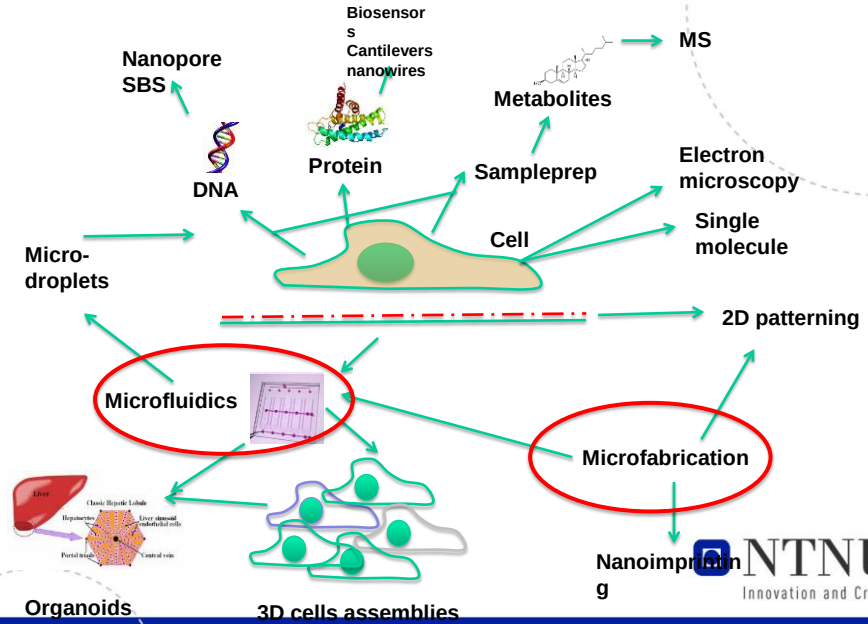
Norwegian University of Science and Technology

Microfluidics & Microfabrication

Øyvind Halaas, IKM,
Nanomedicine I Mol3014 - bioanalysis

Course outline : nanotechnology for biomedicine : analysis



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Learning goals

After the lecture, students should be able to

Describe uses of microfluidics in biomedicine

Describe basic conscept on microfluidics
- **laminar flow**
- **wettability**
- **surface effects on fluid flow**

Describe basic microfabrication processes
- **mask design**
- **photolithography**
- **soft lithography**

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The motivation for using a microfluidic system is analogous to the argument for using integrated circuits to replace the discrete component circuits.

Advantages:
- Miniaturization
- Integration
- Automation

=

Portability
Low Costs
Simplicity of operation

Limits
- some fluid reactions require a large volume and quantity

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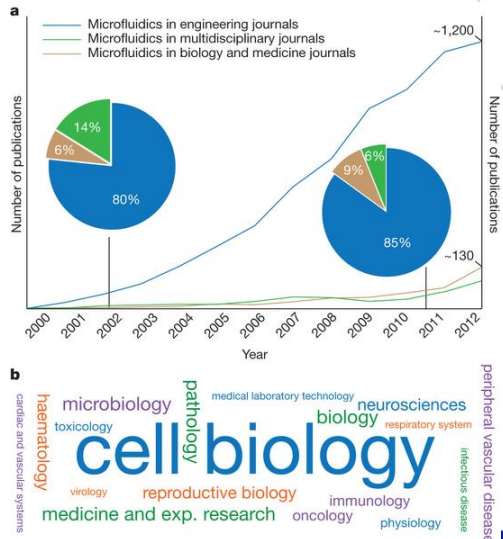

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Application Areas

- Life sciences research
- Medical diagnostics and analysis
- Drug discovery
- Drug delivery
- Environmental monitoring
- Process control e.g. oil industry and food industry
- Food analysis
- Security devices e.g. detection of explosives
- Energy technology including fuel cells


Photo: SINTEF/Stanford

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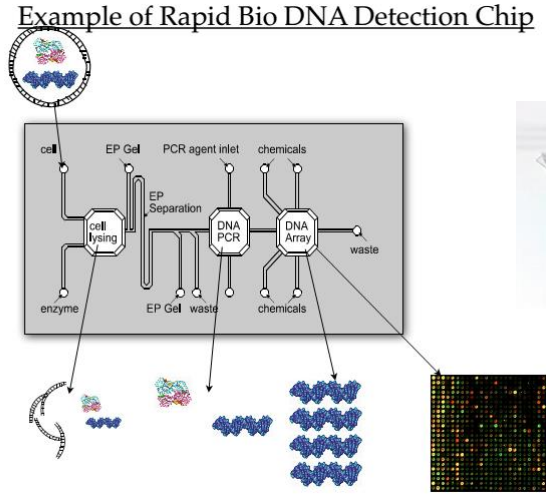
Example of Rapid Bio DNA Detection Chip



[Image from Chang Liu]

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Past and present

1990

244 *Sensors and Actuators, B1* (1990) 244–248

Miniaturized Total Chemical Analysis Systems: a Novel Concept for Chemical Sensing

A. MANZ, N. GRABER and H. M. WIDMER
Central Analytical Research, Ciba-Geigy AG, CH-4002 Basel (Switzerland)

2015

- **15th world Conference**
- **1200 participants**
- **700 posters**
- **30 countries**
- **many fields but focus on life sciences**

http://www.rsc.org/journals-books-databases/about-journals/lab-on-a-chip/utas-abstracts/

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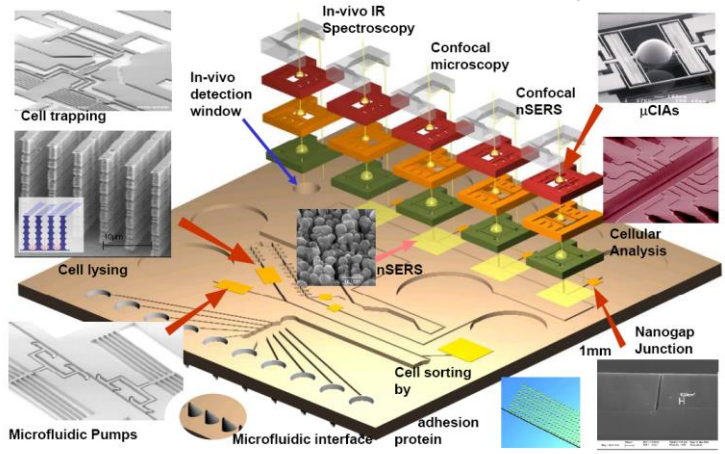
μTAS – wish list but how to make each component?



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μTAS are assemblies of Lab-on-a-chip (LOC) components

Advantages of LOCs

•low fluid volumes consumption (less waste, lower reagents costs and less required sample volumes for diagnostics)
•faster analysis and response times due to short diffusion distances, fast heating, high surface to volume ratios, small heat capacities.
•better process control because of a faster response of the system (e.g. thermal control for exothermic chemical reactions)
•compactness of the systems due to integration of much functionality and small volumes
•massive parallelization due to compactness, which allows high-throughput analysis
•lower fabrication costs, allowing cost-effective disposable chips, fabricated in mass production
•safer platform for chemical, radioactive or biological studies because of integration of functionality, smaller fluid volumes and stored energies

Disadvantages of LOCs

•novel technology and therefore not yet fully developed
•physical and chemical effects—like capillary forces, surface roughness, chemical interactions of construction materials on reaction processes—become more dominant on small-scale. This can sometimes make processes in LOCs more complex than in conventional lab equipment
•detection principles may not always scale down in a positive way, leading to low signal-to-noise ratios
•although the absolute geometric accuracies and precision in microfabrication are high, they are often rather poor in a relative way, compared to precision engineering for instance.

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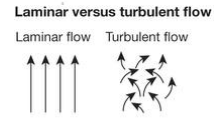
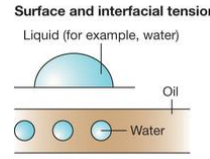
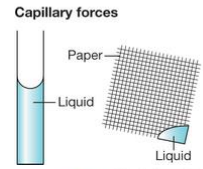
Microfluidics – some features

Laminar flow
Predictable, but difficult to mix
High surface-to-volume ratio
Surface effects dominate – ”new” physical behaviour
Excellent flow control possibilities
...if we can handle the small dimensions and precision level
Excellent particle manipulation possibilities
...if we can handle the flow







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Excellent lecture on microfluidics

https://www.youtube.com/watch?v=66Oc8fLKXlE

Excellent mathematics of microfludics
(not pensum but on its learning)

http://isites.harvard.edu/fs/docs/icb.topic507763.files/Basic%20Principles%20of%20Microfluidics%20-2%20.pdf

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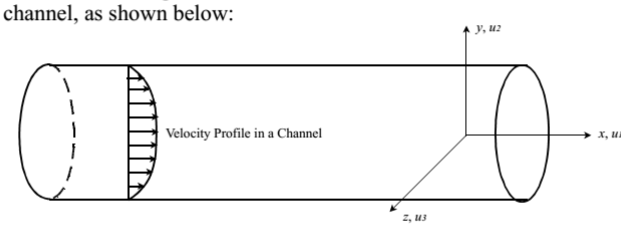
Pressure Driven Fluid Flow in Channels

- Consider the 'simple case' of a 'laminar' fluid flow in a circular channel, as shown below:

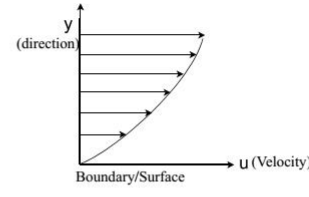


- Assume a 'zero slip' condition at the wall boundaries.
- Assume zero flow in the *y*-direction, and zero flow in the *z*-direction.

Basic Fluid Mechanics Concepts

- Density of fluid (ρ)

$$units\ of\ \rho \Rightarrow \left(\frac{kg}{m^3}\right)$$



- Dynamic Viscosity (μ),

(also simply called Viscosity)

$$units\ of\ \mu \Rightarrow \left(\frac{kg}{m \cdot s}\right) \Rightarrow (Pa \cdot s) \Rightarrow 10\ Poise$$

Eg: Viscosity of water: 0.01002 Poise, or 1.002 *cP* (centipoise)

- Kinematic Viscosity (ν)

$$units\ of\ \nu \Rightarrow \left(\frac{m^2}{s}\right)$$

$$where:\ 1\ stoke = 100 centistokes = 0.0001 \frac{m^2}{s}$$

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Basic Fluid Mechanics Concepts

- The Reynolds Number:

$$\mathrm{Re} = \frac{\rho V L}{\mu}$$

where: Re = Reynolds Number
V = Characteristic Velocity
L = Characteristic Length
ρ = Fluid Density
μ = Dynamic Viscosity

- Definition of the Characteristic Length (By Example):
  - Airplane:
    - distance between wing tips
  - A microfluid channel with circular cross-section:
    - diameter
  - A microfluid channel with rectangular cross-section:
    - the height of the channel
  - A cell moving in a fluid:
    - diameter of cell

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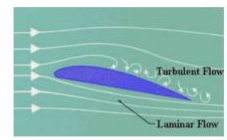
Laminar Flow and Turbulent Flow

- The Laminar flow:
  - fluid stream follows regular paths (i.e. streamlines)
- Turbulent flow:
  - unsteady flow stream (i.e. swirls and vortices)
- Laminar - Turbulent transition (i.e. critical Reynolds number):
  - *Depends on configuration*
  - for pipes, $Re_{critical}$: 2000-3000
- For microsystems, because of the small channel cross-section the Re is usually very small.



Laminar & Turbulent Flow
[http://www.daviddarling.info/encyclopedia]

Low Speed
Laminar
small Re

High Speed
Turbulent
high Re

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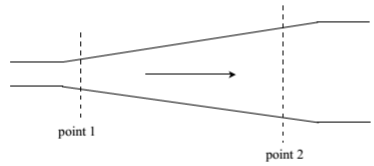
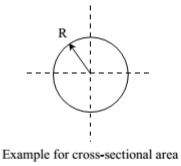
Basic Equations in Continuum Fluid Mechanics

- The mass-flow rate equation is:

$$\dot{m} = \rho_1 V_1 A_1 = \rho_2 V_2 A_2$$





Example for cross-sectional area

- If we assume an incompressible fluid, it becomes:

$$Q = V_1 A_1 = V_2 A_2$$

where:
- m = Mass
- $m(dot)$ = Mass flow rate
- ρ = Density
- V = Velocity
- A = Cross-sectional area
- Q = Volumetric flow rate in m^3/s

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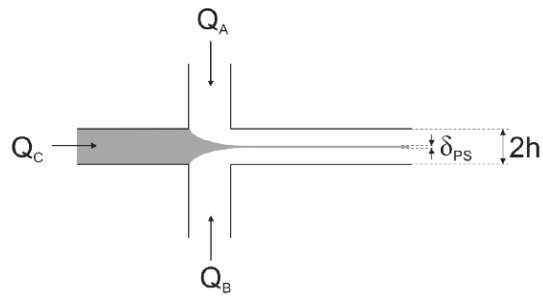
Case: flow manipulation by hydrodynamic focusing



- Q_A & Q_B: buffer streams
- Q_C: stream seeded with fluorescent particles
- Sheet thickness: $\delta_{PS}/2h \propto Q_C/(Q_A+Q_B)$
- Sheet position: $f(Q_A/Q_B)$
- Requirement: stable flow conditions at focusing intersection

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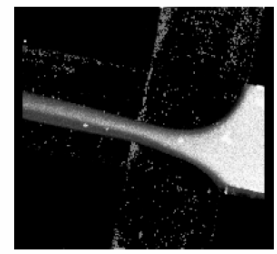
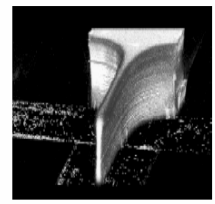
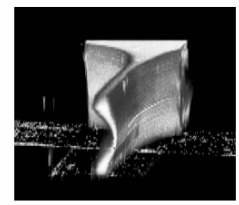
Case: flow manipulation by hydrodynamic focusing

- Flow adressing
- Rapid mixing
  - Decreased diffusion length
- Manipulation of particles
  - Stretching of DNA strands
- Selective coating of particles
- Polymer membrane generation
- Multiple buffer layers possible







http://www.youtube.com/watch?v=Q6VPMRfDooc

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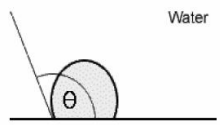
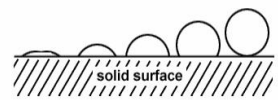
Wetting - hydrophilicity

- Wetting: the ability of a liquid to maintain contact with a solid surface
- High energy surfaces
  - Metals, ceramics, glass…
  - Hydrophilic
- Low energy surfaces
  - Polymers
  - Hydrophobic
- Wetting angle





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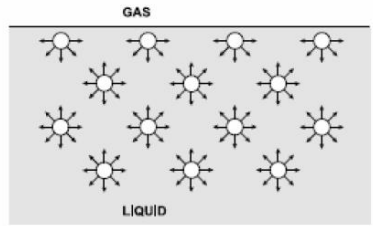
Surface tension

- What is surface tension?
  - Attractive intermolecular forces in a liquid (van der Waals)
  - Phase interface: assymmetry
  - Result: the surface ”pulls” itself together; membrane-like behaviour



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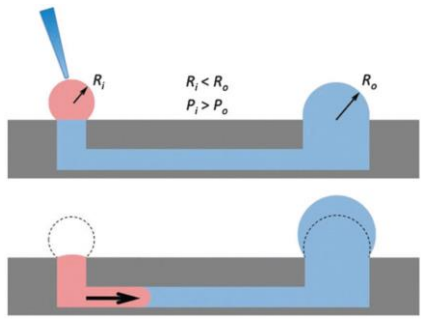
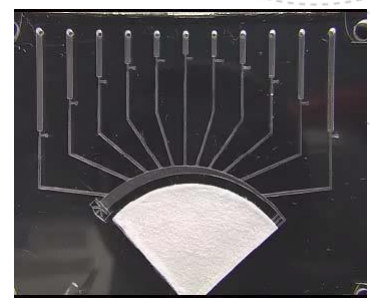
Surface tension drives capillary flow, good and bad

Bad in open systems



Good if part of design



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Summary microfluidic flow

Law of mass conservation ie total in = total out

Fluid flow laminar at low Reynolds number (<2000), turbulent at high Reynolds number (>3000)

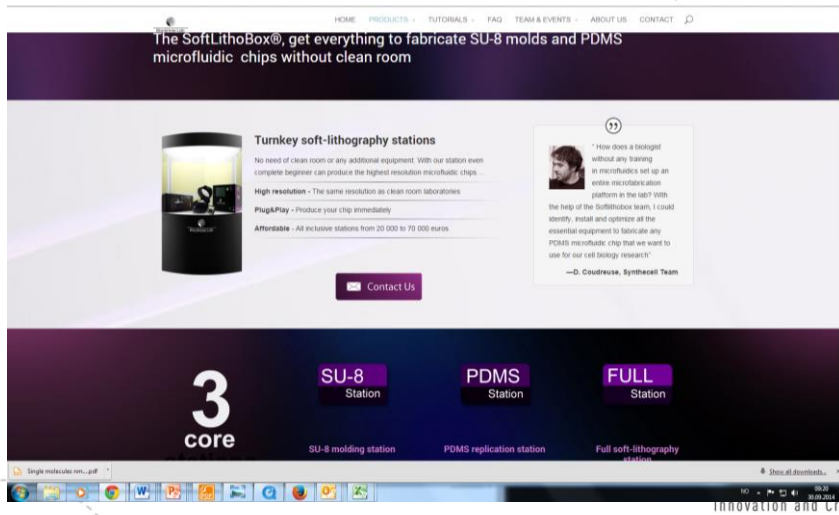
Laminarity: difficulties mixing

Laminarity: adressable fluid flows

Small scale: interaction with surface important

Small scale: surface tension is major determinant in open systems

How is it made?



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Microfabrication

- The process of fabricating structures micrometers and smaller
- Microsystems (EU), Microelectromechanical systems MEMS (US), Micromachines (Asia)
- Microfluidics, Lab-on-chip, BioMEMS, OpticalMEMS, RF-MEMS, PowerMEMS, nanosensors etc
- Developed by microelectronics industry
- Embraced by life scientists due to «life-relevant» scale

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Uses of microfabrication in life sciences

- Closed system: Microfluidics (and accessory features)
  - chemistry, biotechnology, cell biology, molecular biology, bioprocessing, drug-delivery fabrication
  - Special flow behaviour (see coming lecture)
- Open systems: Biopatterning (see earlier lecture)
- Combinations
- Integration with electronics and optics
  - e.g. sensing of cell by impedance
  - lenseless microscopes
  - Heaters, etc
  - Speak with tech-savvy experts

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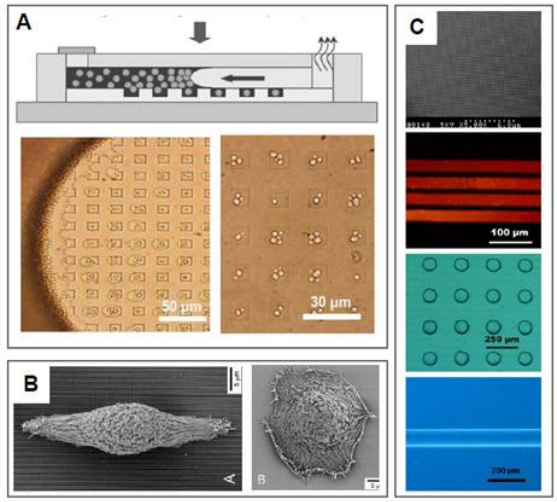
Examples from cell biology



Substrate physical patterning.

- (A) Top: Schematic of cell docking in microwells using capillary force. Down: Picture of SG3 yeast docking in microwells [83].
- (B) Cell guidance using physically modified substrate. Left: Picture of corneal epithelial cells on SiO2 substrate with 70nm wide ridges. Right: Cell on a smooth SiO2 substrate [91].
- (C) Example of pattern made by micromoldling technique. From top to bottom: 150nm diameter pillar, fluorescent image of 40µm stripe of quantum dot, 100µm hole in a 20µm thick PDMS layer, optical image of 100µm width and 20µm height wall of agar gel [84]

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Examples from cell biology

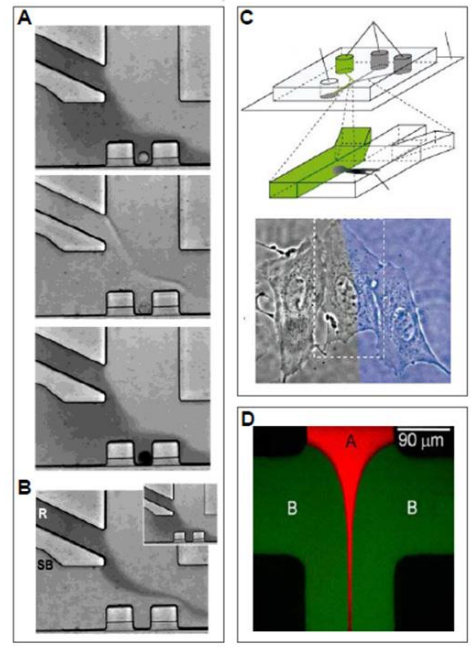
Spatiotemporal drug control.

(A) Picture from a 2 minute movie showing successive perfusion with Trypan blue dye on a live cell, and subsequent methanol and Trypan after cell's death.

(B) Picture showing the ability to change the stream in contact with a cell by changing inlet flow rate. This type of medium switching can be done in 130 ms [37].

(C) Schematic of PARTCELL principle [36]. Using laminar flow properties, partial treatment of a cell can be achieved. Picture shows treatment of a portion of a single cell with Latrunculin A and blue dye.

(D) Picture showing hydrodynamic focusing. Flows B (green) arriving from both sides of flow A (red) focused and maintained flow in a fine stream configuration [40].



The microfabrication process

- Substrates
- Deposition/growth
- Patterning

Not covered in Mol3014

- Etching
- 3D free form printing
- Micromachining

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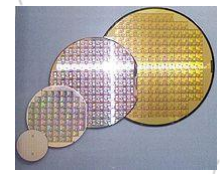
Substrates (the starting material)



- Silicon wafer (Si)
  - 3, 4, 6 inch standard
  - Not biocompatible, non-transparent
  - Serves as templates for further processing
  - Well known processing
- Glass (75% SiO_2, Other metal oxides)
  - For the final device, fully biocompatible, transparent
  - Can be microfabricated, but more difficult
- Polymers
  - Cyclic olefin polymers (COC), microinjection molding
  - PMMA (plexiglass)
  - Siloxanes (-Si-O-Si-), sisleqioxanes ($R_2SiO_{3/2}$)
  - Less defined techniques and larger features

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Deposition or growth

- **Layering the mask**
- **Layering the material to work with**

- **Metals**
- **Polymers**

- **Physical vapor deposition (sputtering)**
- **Chemical vapor deposition (chemical reaction)**
- **Coating**
  - **spin-coating**
  - **dip-coating**

Lithography

Definition: transfer of a pattern designed on a computer or template onto a novel material

Different kinds of lithography for different resolutions and different costs

Uses photons, electrons or ions to modify a material
- UV photolithography (Diffraction limit approx 200nm)
- Depends on the light source
- Type of mask (chromium on quartz, ink on transparent film)
- Cost is a major issue

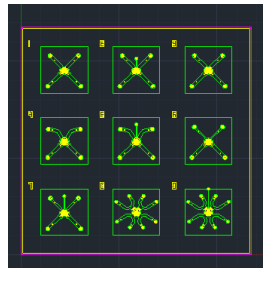
30cm

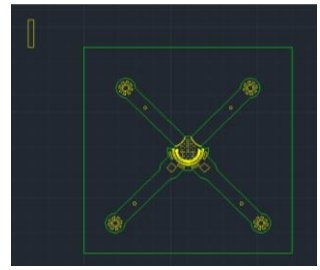
15µm

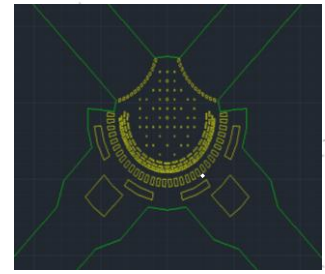
Patterning: Mask Fabrication

- Use AutoCAD or Clewin to design a mask.
- The mask designs are sent to an outside company either to be printed on film (for lower resolution) or to produce Cr masks.
- In a film mask: the ink blocks the passage of UV; the resolution is limited by the printer or photoplotter used and also by the ink used / film used
- In a Chromium mask: the chromium blocks the UV lights. A quartz (or soda lime) plate is covered with chromium then photoresist is spin coated. The desired design is used to guide the path of an electron beam or an excimer laser. The exposed areas are then etched out and the remaining photoresist is stripped.
- Chromium masks are more durable but significantly more expensive than film masks

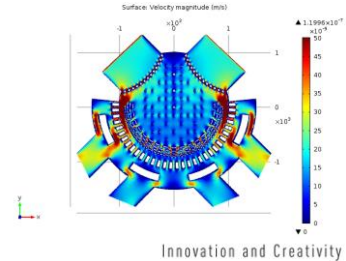
Mask design in my own project







Flow simulation



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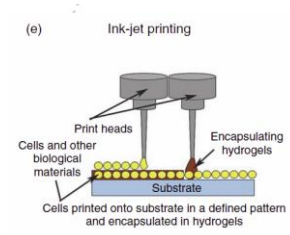
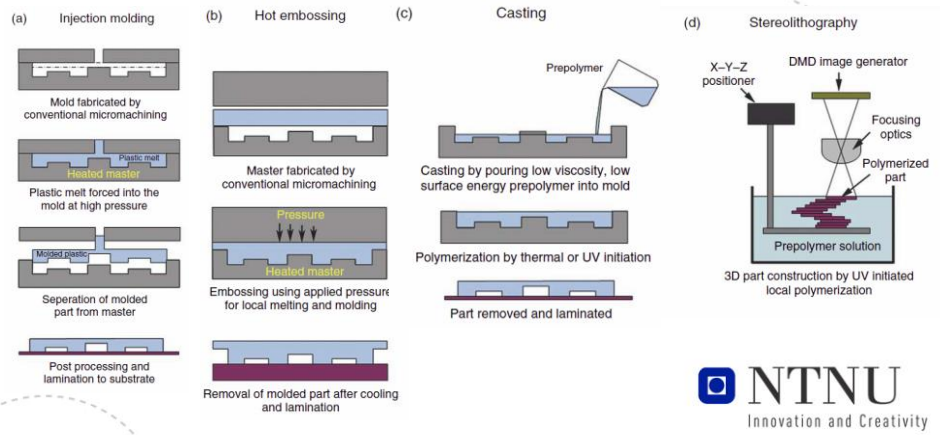
Direct polymer microfabrication

Different techniques for different purposes and polymers





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Two options for replica moulding

Hard masters (metals)
- **Difficult/expensive to make**
- **can be cleaned and reused many times**
- **transfer to biolaboratories**

Soft masters (polymers)
- **Easy/Cheap to make**
- **Must be remade every 10th cycle**

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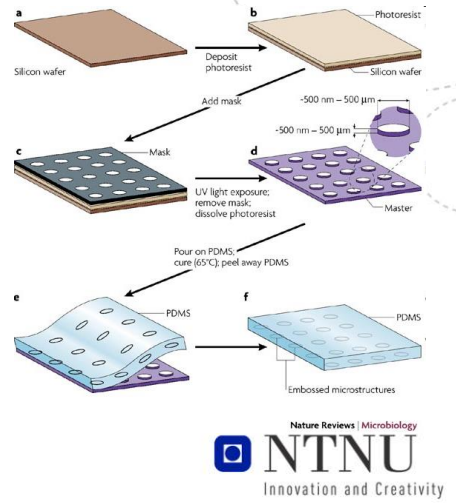
Photolithography

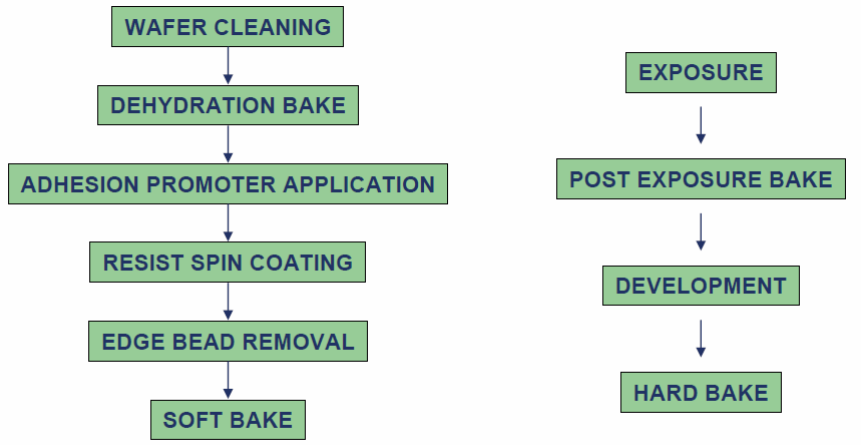
Use of UV light to reproduce a mask design on a substrate using a photoresist and a mask aligner.

After close to 50 years of development, it is still the central technology in the reduction of feature and pitch sizes for the semiconductor industry.



Nature Reviews | Microbiology

Process Flow for Photolithography



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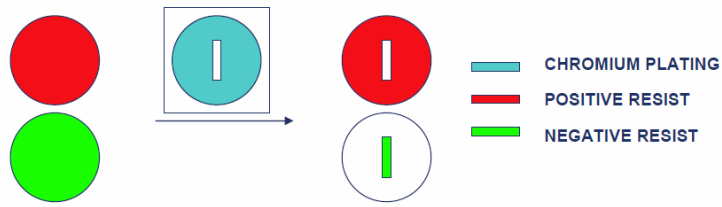
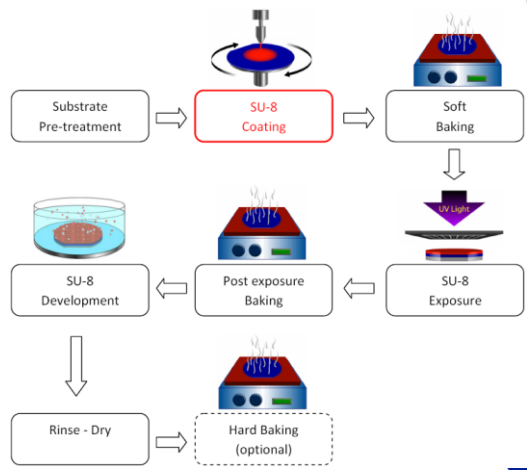
Different Photoresists

- Polarity: Positive vs Negative.
- In positive photoresists, UV light exposure makes the film more soluble in the developer solution.
- In negative photoresists, UV light exposure polymerizes the resist (thus it becomes less soluble in the developer solution).



40

Depositing photoresist by spin-coating



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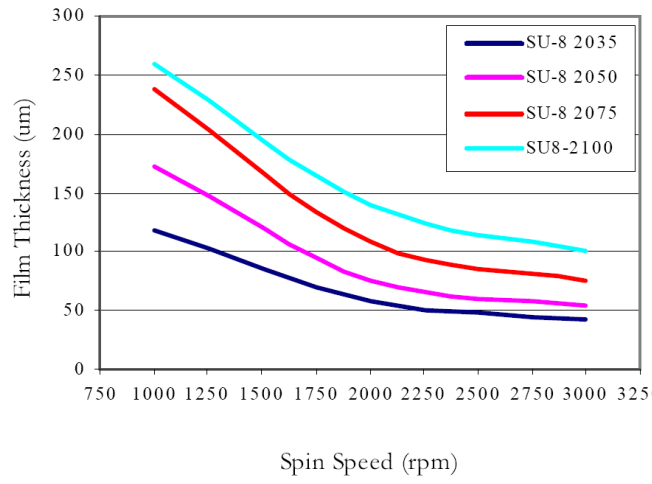
Your thickness can be tailored using different photoresists and spin speads



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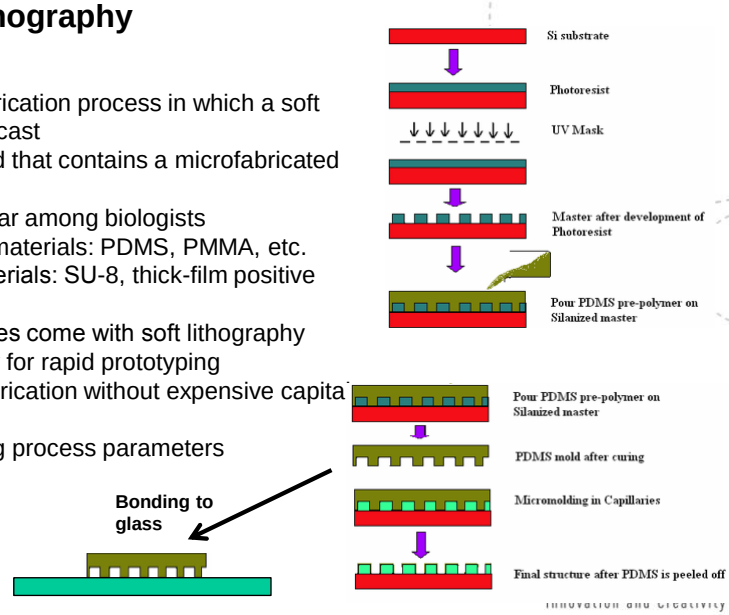
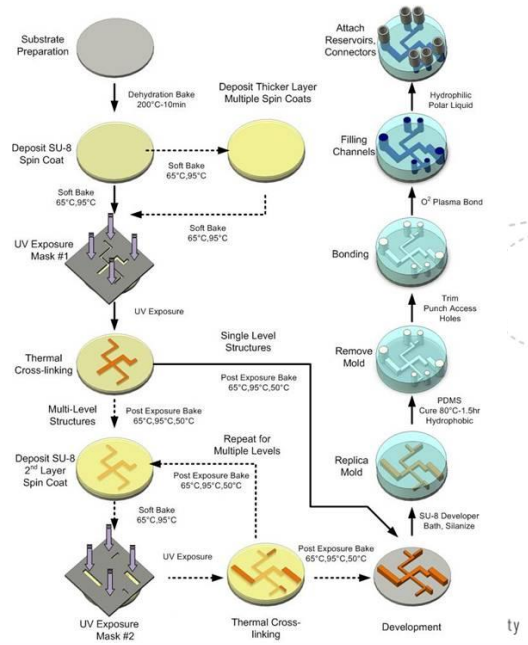
Soft lithography

A microfabrication process in which a soft polymer is cast
onto a mold that contains a microfabricated pattern.
Most popular among biologists
• Polymer materials: PDMS, PMMA, etc.
• Mold materials: SU-8, thick-film positive photoresist
• Advantages come with soft lithography
1. Capacity for rapid prototyping
2. Easy fabrication without expensive capita equipment
3. Forgiving process parameters

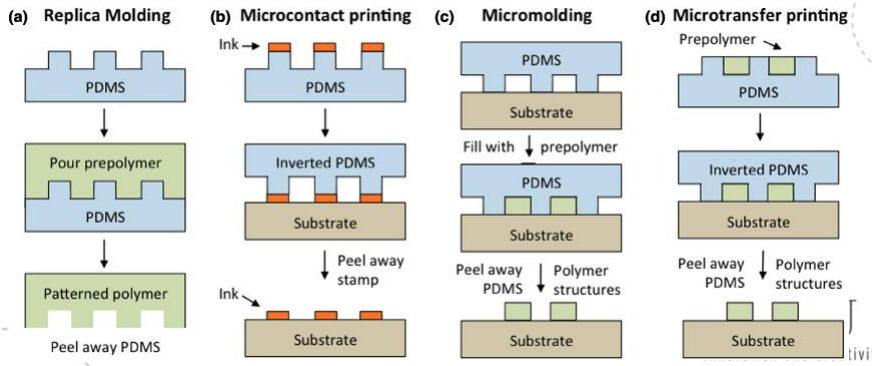


Multilayered microfluidic systems with photolithography



Uses of soft lithography

1. **Replica moulding**
2. **Microcontact printing**
3. **Micromoulding in capillaries**
4. **Microtransfer moulding**
5. **Microfluidics**

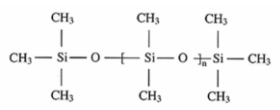


Soft Lithography Process

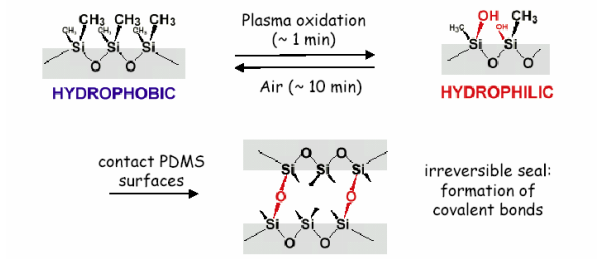
Advantages come with soft elastomeric polymer

1. **Excellent sealing between glass and PDMS**
2. **Easy for connecting a tubing adapter**
3. **Transparent material, great for microscopic observation**
4. **Permeable to gas but not to analytes or ions**
5. **Allow multi-layer process toward 3D networks**
6. **Biocompatible (?)**

Poly(dimethylsiloxane)



- **Deforms reversibly**
- **Can be molded with high fidelity**
- **Optically transparent down to ~300nm**
- **Durable and chemically inert**
- **Non-toxic**
- **Inexpensive**



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

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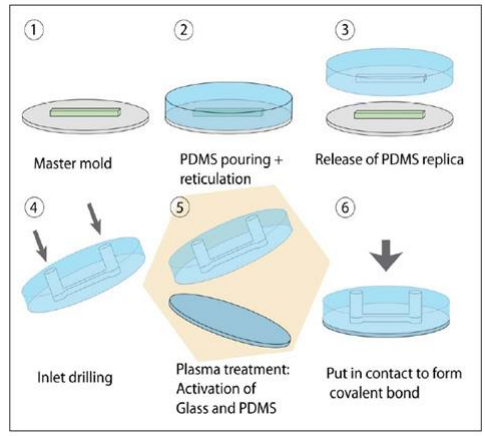
The process with inlets



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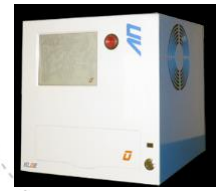
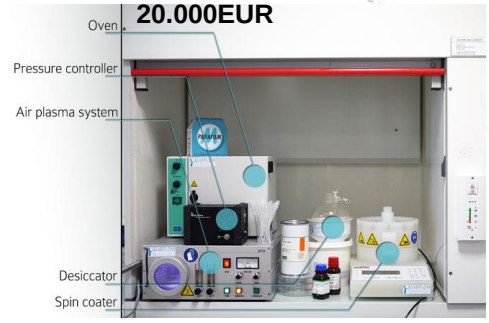


Equipment Required

Buy your own 20.000EUR

<u>Equipment</u>:
Spin coater
Hot plate
Mask aligner

<u>Consumables</u>:
Masks
Photoresists
Developers
Solvents



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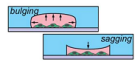
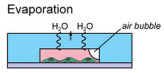
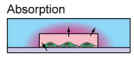
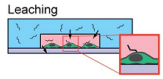
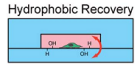
Drawbacks and limitations using PDMS

Table 1 Limitations of PDMS for microfluidic cell-based systems

Problem	Cause	Applications Affected	Solution	References
Deformation 	- High compliance (low stiffness) - Low aspect ratio	- Endothelial cell response to shear	- Modify curing parameters - Avoid low aspect ratios - Avoid high pressure flows	- Gervais *et al.* (2006)
Evaporation 	- Permeability to water vapor	- Static no-flow experiments - Osmolarity-sensitive experiments - Cell death from bubble propagation	- Coat with Parylene - Ensure environments humidified - Incorporate media baths or sacrificial liquid reservoirs	- Verneuil *et al.* (2004) - Heo *et al.* (2007) - Berthier *et al.* (2008) - Lecault *et al.* (2011)
Absorption 	- High permeability of material	- Soluble factor signaling studies involving small hydrophobic molecules	- Coat with Parylene - Coat with paraffin wax	- Toepke & Beebe (2006) - Regehr *et al.* (2009) - Ren *et al.* (2010)
Leaching 	- Uncrosslinked oligomers	- Protein trafficking across membrane - Signaling through membrane-bound receptor proteins	- Coat with Parylene - Soxhlet extraction	- Regehr *et al.* (2009)
Hydrophobic Recovery 	- Surface diffusion of low molecular weight chains	- Unstable surface treatment or functionalization	- Use surface-treated device as soon as possible after treatment - Use hybrid devices with non-PDMS culture surface	- Eddington *et al.* (2006)

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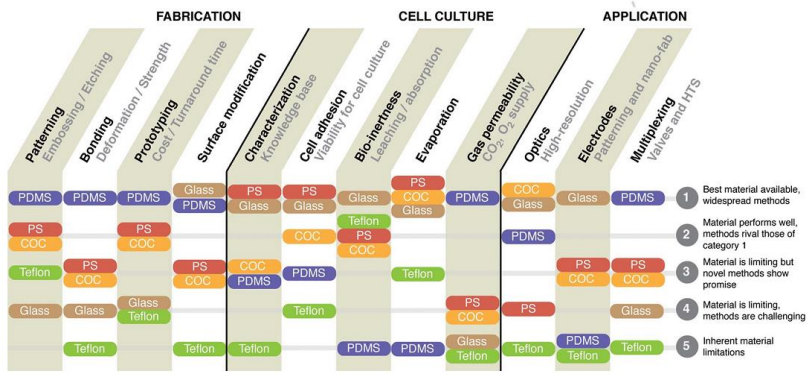

Fig. 4 Comparative strengths and weaknesses of materials used for microfluidic cell-based device fabrication. The materials are ranked for their abilities for various properties important in cell-based experiments, which are grouped under three general categories: The ability to fabricate the microsystems, the ability to perform controllable cell-based experiments, and the potential for integrated micro-engineering applications.

DOI: 10.1039/c2lc20982a

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How it is done in practice:

Stanford tutorial

http://www.youtube.com/watch?v=xWdRczefirs

http://www.youtube.com/watch?v=1bxf9QRVesQ

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Much on lithography out there

https://www.youtube.com/watch?v=PUDlFq8vaws

http://www.elveflow.com/

http://www.memsuniverse.com/

http://www.memsuniverse.com/microfabrication/makingdevices.html

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www.ntnu.no

Learning how to build bioanalytical microdevices

Advantages

lowering the reagent cost by using small volumes

processing many samples in parallel

integrating functionalities such as electronic detection or data processing into a single system

constructing portable systems – an ability that is important in point-of-care analysis devices and field forensics

taking advantage of new scale-dependent physical phenomena to improve the device performance.

Modules

Pumps

Valves

Filters

Mixers

Gradients

Meters

Cell traps

Separation

Heaters

Analysis

Integrations with electronic microsystems

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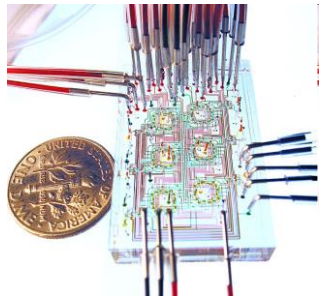
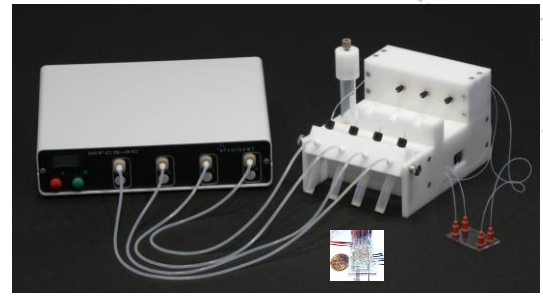
Microsolutions gives macrofrustrations

Fluid control (many companies. Here: Fluigent)





State of the art Pressure-pumps

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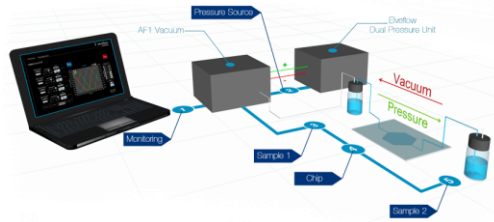
Getting fluids through the system

Syringe pump- a closed incompressable system

Easy to use
Cheap
Difficult to manipulate
2 at the time
Slow

Pressure pump - an open system



Difficult to use
Expensive
Easy to manipulate
Many channels
Fast

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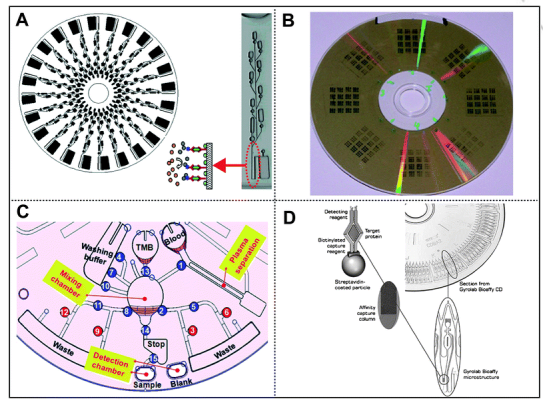
Centrifugal microfluidics

Instead of pumps, centrifugal force is used to move fluids around



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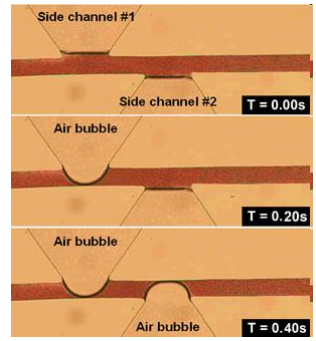
To avoid hassle with external macropumps, on-chip micropumps are being developed



http://www.rsc.org/Publishing/ChemTech/Volume/2009/06/Microfluidics_pumps_it_up.asp

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Valves - an absolute need for time-controlled reagent delivery

Pneumatic (air pressure)

-well established technology

-difficult design and implementation

Electrical (membrane deflection)

-easy design/implementation

-difficult actuation

Magnetic

Manual

-difficult regulation of flow-rates/pressures

Biological

-most promising/versatile

-difficult effectuation

-non proven

Mechanical

-difficult actuation

http://www.youtube.com/watch?v=Al4kZzg825g

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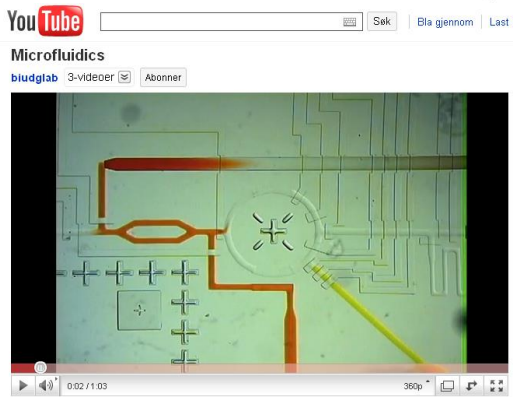

http://www.youtube.com/watch?v=VUxuTlbyylA&feature=related

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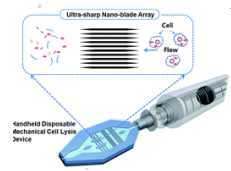
Other features such as cell lysis can be incorporated directly



Heat

-denatures protein

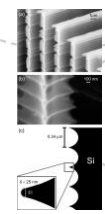
-easy to effectuate

Knives

-easy fabrication

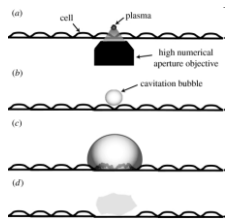
-high throughput

-problems with material deposition



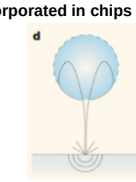
Fluid Jets

-focused laser beam cavitations



Acoustic (cavitation)

CMOS-ultrasound can be incorporated in chips



Chemical (next slide)

Reagentless mechanical cell lysis by nanoscale barbs in microchannels for sample preparation Dino Di Carlo, Ki-Hun Jeong and Luke P. Lee
Lab Chip, 2003, 3, 287-291 DOI: 10.1039/B305162E , Paper

Handheld mechanical cell lysis chip with ultra-sharp silicon nano-blade arrays for rapid intracellular protein extraction Sung-Sik Yun, Sang Youl Yoon, Min-Kyung Song, Sin-Hyeog Im, Sohee Kim, Jong-Hyun Lee and Sung Yang Lab Chip, 2010, 10, 1442-1446

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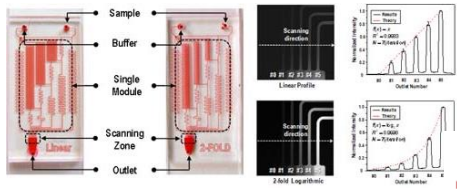
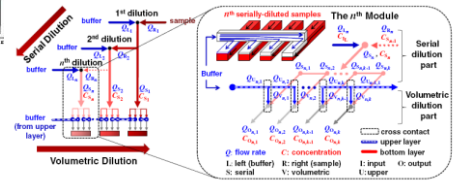
Dilutors

A need for serial dilutions

- **input: most biological activities are concentration-dependent**
- **output: improving performance over a wide range of concentrations (analysis)**





Kangsun Lee, Choong Kim, Byungwook Ahn, Rajagopal Panchapakesan, Anthony R. Full, Ledum Nordee, Ji Yoon Kang, and Kwang W. Oh, "Generalized serial dilution module for monotonic and arbitrary microfluidic gradient generators," Lab Chip, 9, 709 – 717, 2009 [Link].

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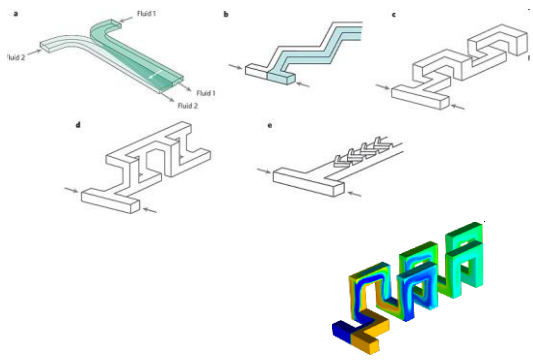
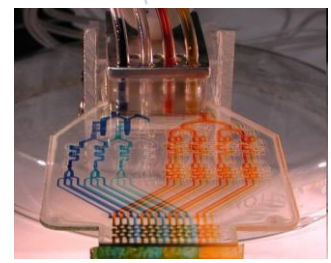
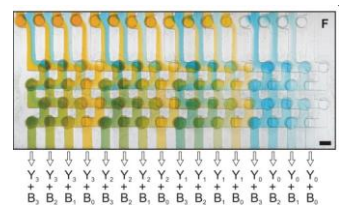
Mixers

Micro-flow is laminar (http://www.youtube.com/watch?v=5QVwljd04Kw) and mixing must therefore be enforced







Nature 442, 394-402 (27 July 2006) | doi:10.1038/nature05062; Published online 26 July 2006
Control and detection of chemical reactions in microfluidic systems

Andrew J. deMello1

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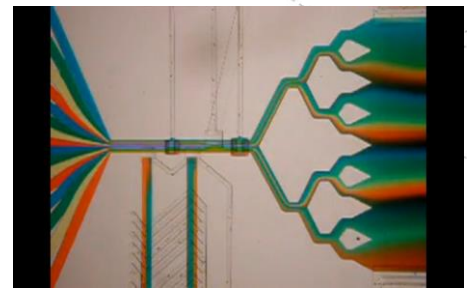
Gradients

Instead of controlled stepwise dilutions: gradients may be used



http://www.youtube.com/watch?v=8mW7TJPPcDs&feature=related

http://www.youtube.com/watch?v=BIXvgU1ud_c

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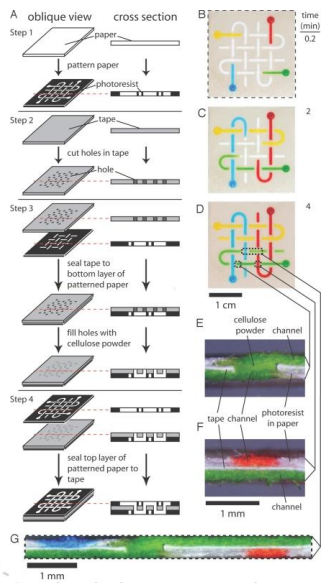
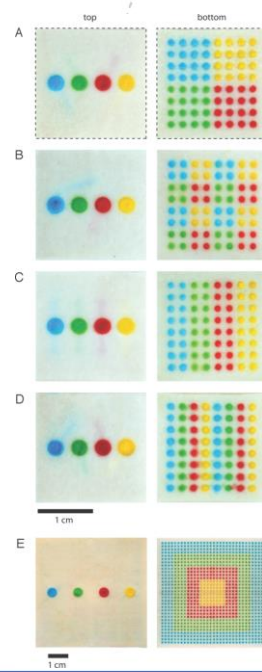
A second option: use paper as building material





Proc Natl Acad Sci U S A. 2008 December 16; 105(50): 19606–19611.

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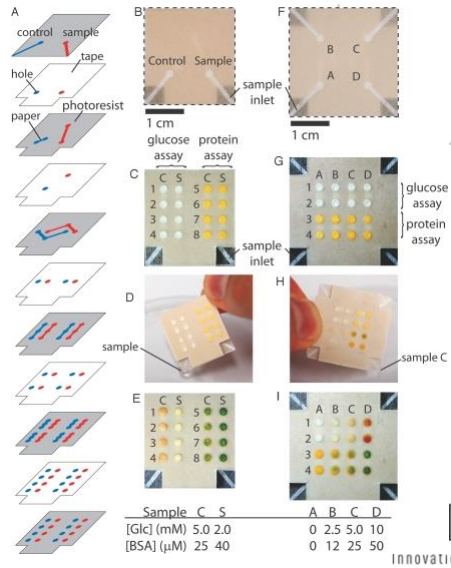
Innovation and Creativity

Analyzing urine /blood for glucose/protein



Proc Natl Acad Sci U S A. 2008
December 16; 105(50): 19606–19611.

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Innovation and Creativity

Paper-based microfluidics

3D Tissue constructs

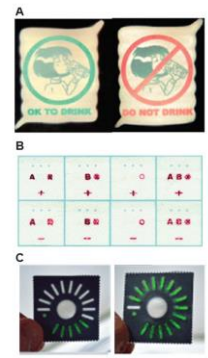
Cheap in vitro diagnostics

Chemical (toxins) analysis

Pathogen analysis

So cheap that it can be incorporated into everything

Needs very little external equipment



https://www.youtube.com/watch?v=WYi-C3jGwKA&list=PL6WN2uFxyyABQvBYe0MAmVjx-pW1p78Cd

Paper-based microfluidic point-of-care diagnostic devices
Ali Kemal Yetisen,
Muhammad Safwan Akrama and
Christopher R. Lowea
Lab Chip, 2013,13, 2210-2251

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Two important principles

KISS: Keep it simple stupid

Always keep your scientific question in mind

http://www.youtube.com/watch?v=66Oc8fLKXlE

Examples of LOC Applications

Real-time PCR: detect bacteria, viruses and cancers.
Biochemical assays
Immunoassay: detect bacteria, viruses and cancers based on antigen-antibody reactions.
Dielectrophoresis: detection of cancer cells and bacteria.
Blood sample preparation: can crack cells to extract DNA.
Cellular lab-on-a-chip for single-cell analysis.
Ion channel screening (patch clamp)
Testing the safety and efficacy of new drugs, as with lung on a chip

REVIEW

doi:10.1038/nature13118

The present and future role of microfluidics in biomedical research

Eric K. Sackmann[1], Anna L. Fulton[2] & David J. Beebe[3]