Microfluidics

Handling with microvolumes

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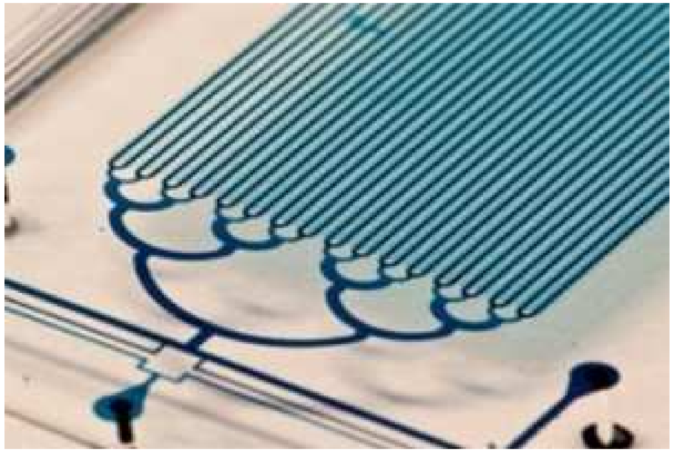
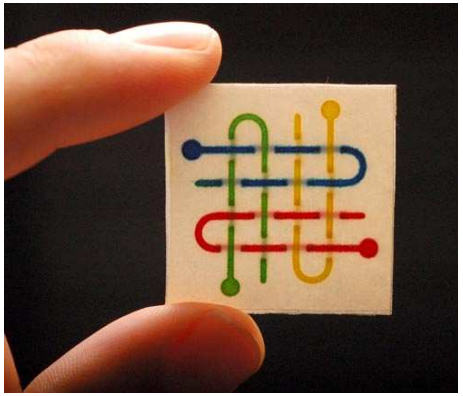
Microfluidics

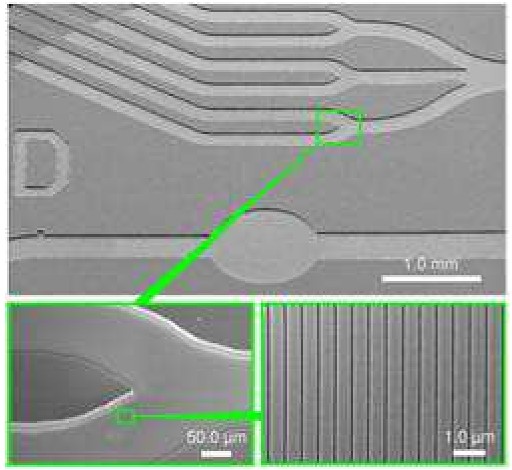
- Handling small volumes (µL, nL, pL)

- Interdisciplinary discipline
  - Engineering
  - Physics
  - (Bio)chemistry
  - Nanotechnology
  - Biotechnology



- Potential to influence subject areas from
  - Chemical synthesis
  - Biological analysis
- to
  - Optics
  - Information technology





Microfluidics

- Firstly used in analysis
  - Small volume of sample
  - Small reagent consumption
  - High resolution
  - Low cost
  - Miniaturisation

- New capabilities to control concentrations of molecules in space and time

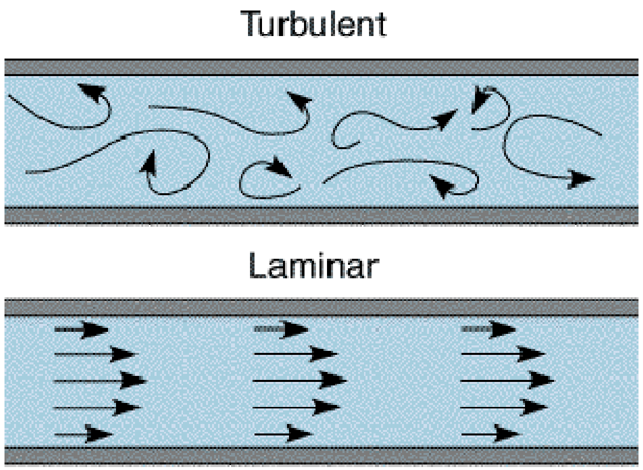
- Historical background
  - Defence purposes – NEED of miniaturaisation
  - Molecular biology – NEED of higher throughput, sensitivity and resolution
  - Microanalytical methods – ABILITIES of (HPLC, GC, CE)
  - Microelectronics – ABILITIES of

Microfluidics

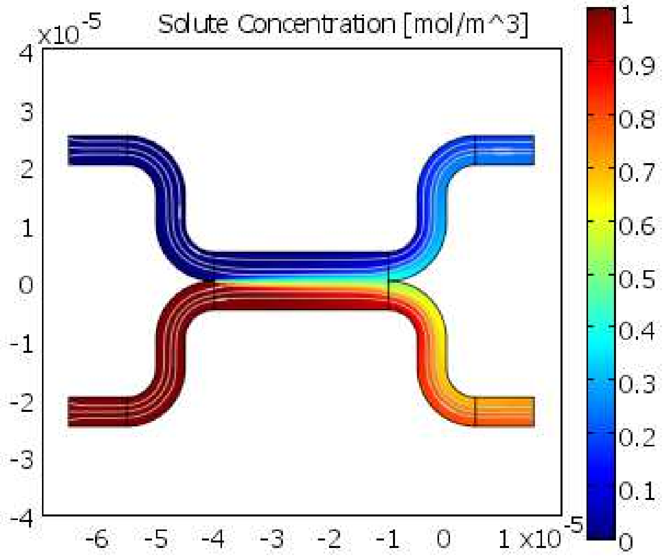
- At small length scales (dimensions):
  - Transport phenomena can be precisely controlled:
    - mixing
    - thermal transfers
    - concentration
    - flows
  - surface effects are important and confinement plays role

Microfluidics

- Liquid behaves differently at microscale (and lower dimensions)
  - No turbulence
  - Only laminar flow
  - Two separated liquids mix only through diffusion – parallel flow



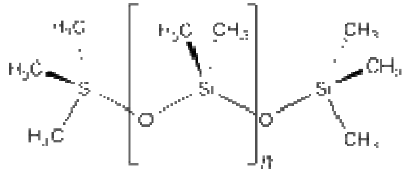
alevelnotes.com

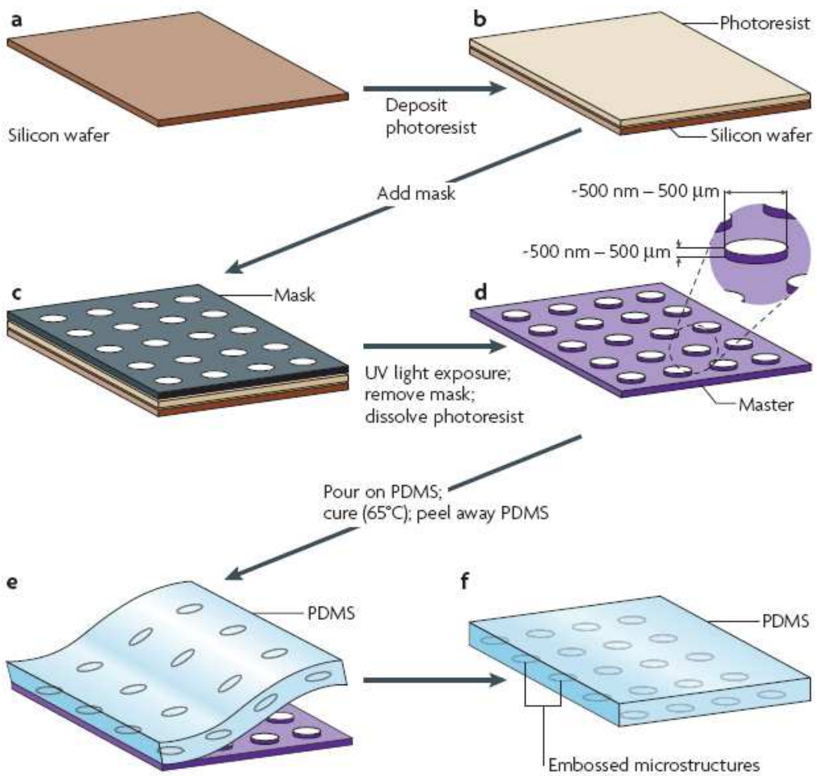


www.veryst.com

Soft (PDMS) lithography

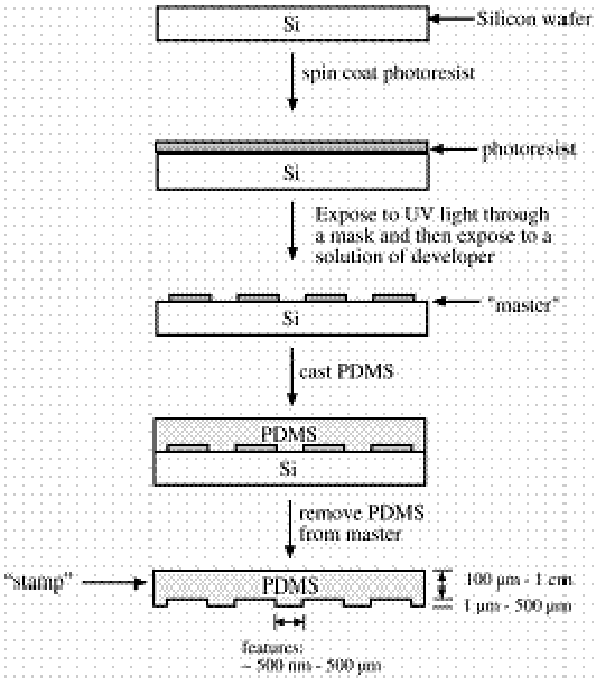
- Soft lithography using PDMS
  - polydimethylsiloxane



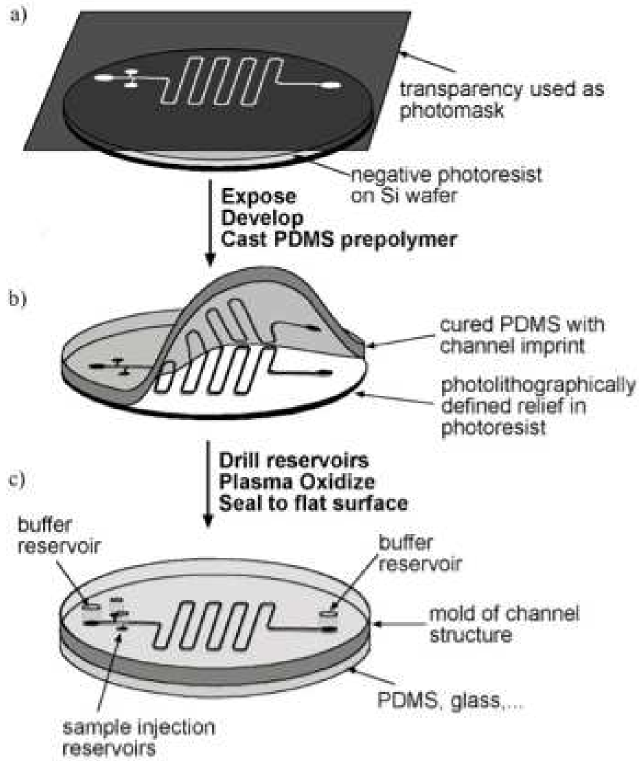


http://www.elveflow.com/microfluidic-tutorials

Soft (PDMS) lithography



http://www.bioc.rice.edu



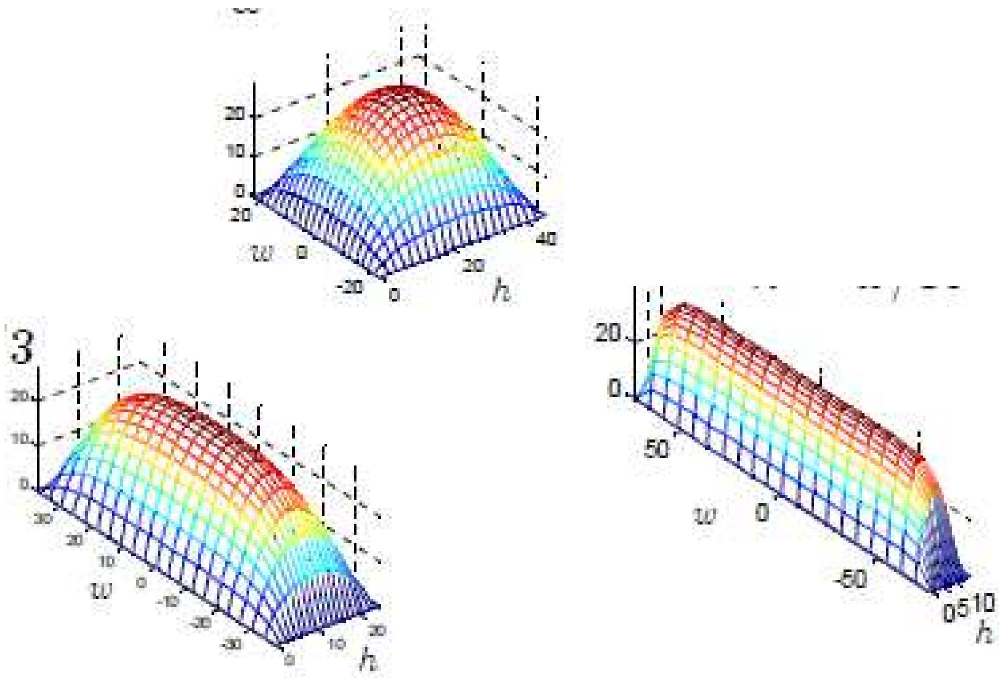
http://bdml.stanford.edu

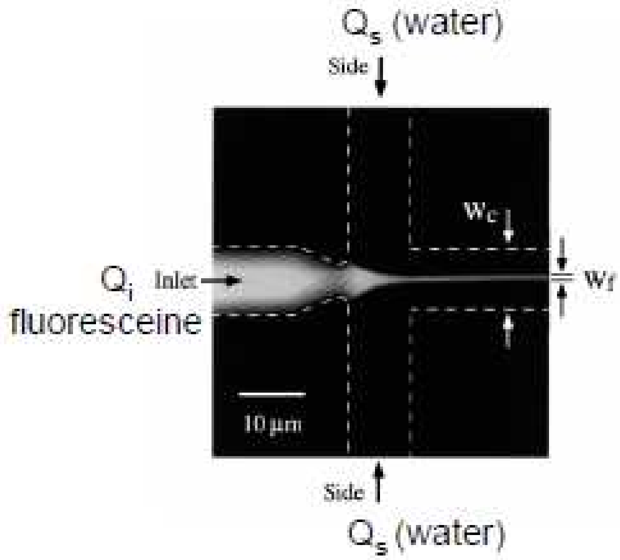
Types of microfluidic flows

- Pressure-driven flows
- Capillary-induced flow
- Droplet microfluidics
- Evaporation-induced flows
- Electroosmotic flow

Pressure-driven flows

- Physical computations
- Navier-Stokes equations
- Dimensionless characteristic parameters
  - Reynolds number, Re





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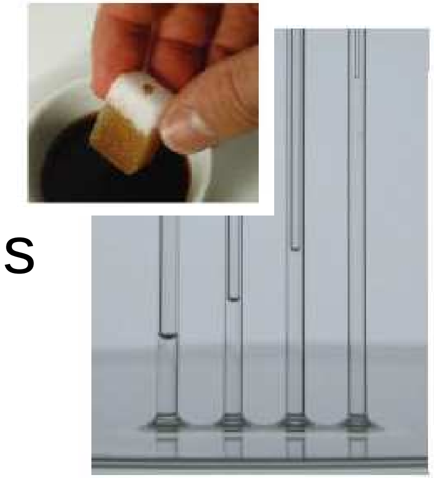
Microfluidics for lab-on-chips
www.lof.cnrs.fr

Capillary-induced flow

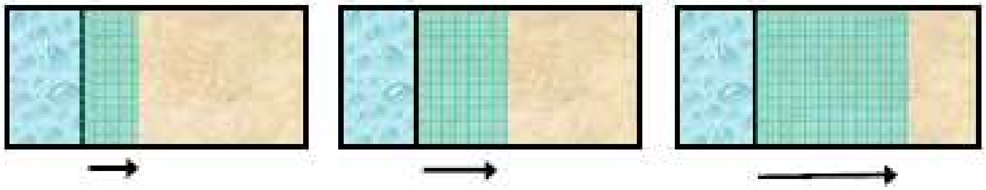
- Based on surface tension

- Capillary forces



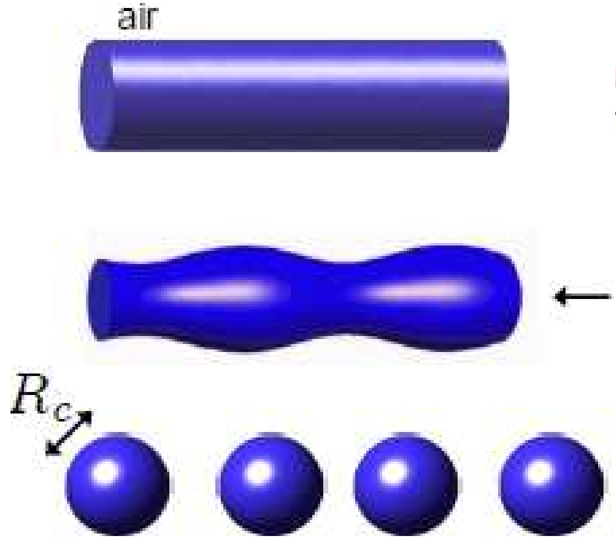
- Paper based microfluidics
- Diffusive spreading

http://www.technologyreview.com



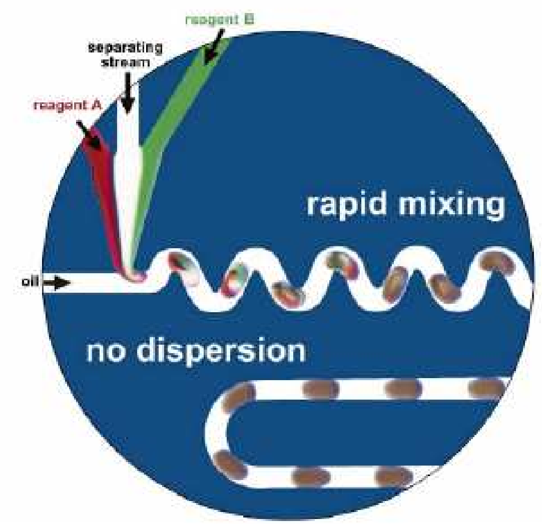
Droplets in microfluidics

- Generation of monodisperse droplets when two immiscible fluids flow in microchannels



- formation of droplets in microfluidics on the basis of surface tension

- Microreactors



http://www-microdroplets.ch.cam.ac.uk

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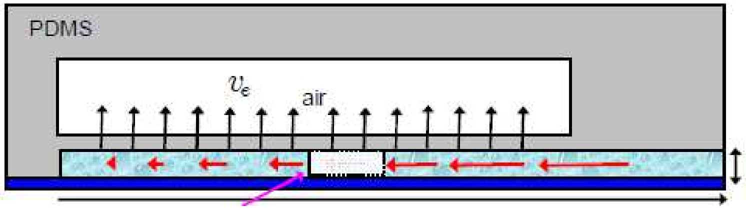
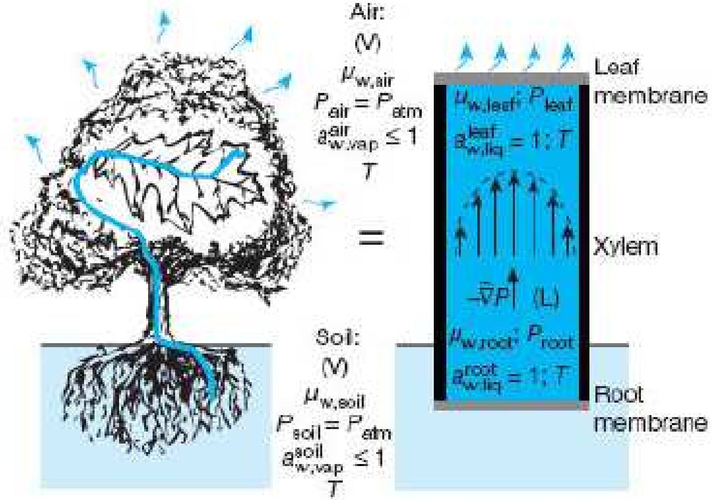
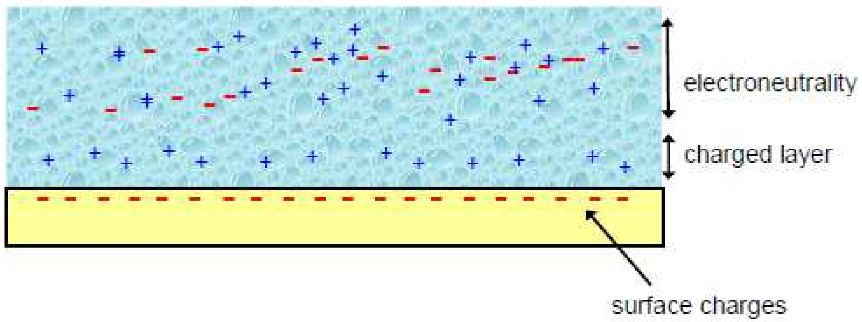
Evaporation-induced flows

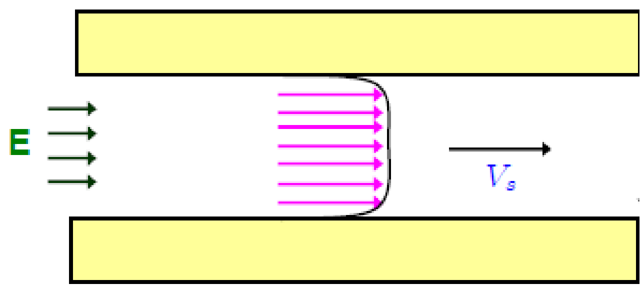




Wheeler and Stroock, Nature 2008

Electroosmotic flow





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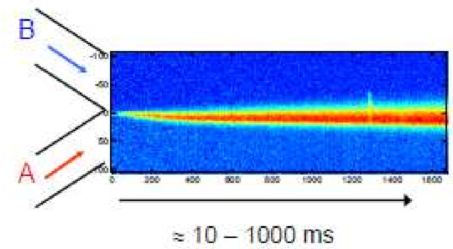
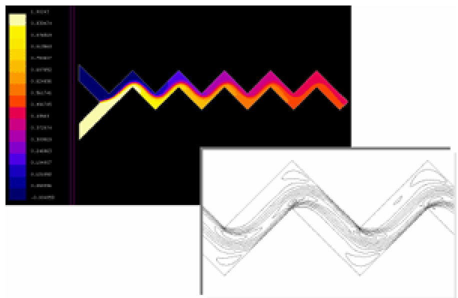
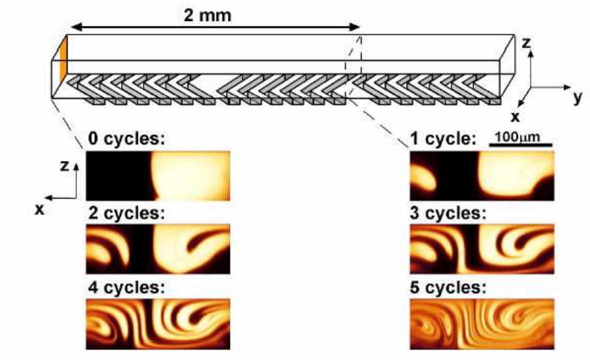
Transport phenomena in microfluidics

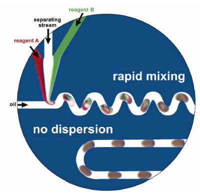


- Convection/diffusion in microfluidics
- Hydrodynamic dispersion
- Mixing strategies
  - diffusion is not sufficient





- Droplet vs. co-flow for chemistry



- Active concentration in µ-evaporators
  - crystallisation

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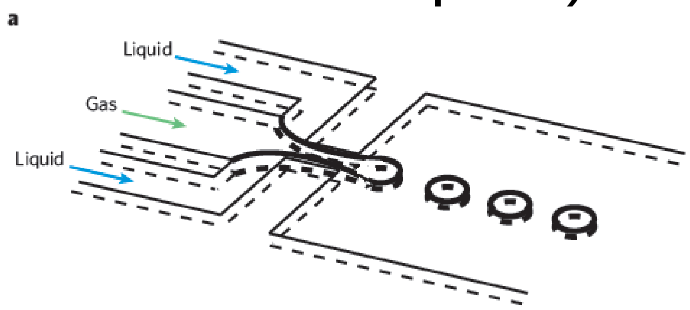
Microfluidics applications

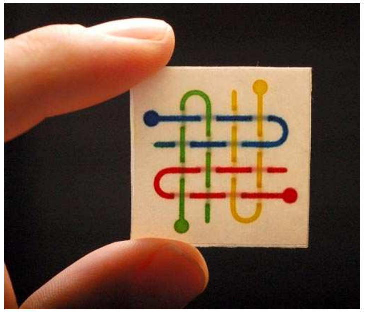
- Screening for optimal protein crystallisation conditions
  - Screening of large number of conditions
- Separation - coupled with MS
- Screening in drug development – high throughput
- Bioanalysis
- Manipulation of samples consisting single cell or molecule
- Organic synthesis of derivatives for emission tomography
- Manipulation of multiphase flow (bubbles and droplets)
- Combinatorial chemistry

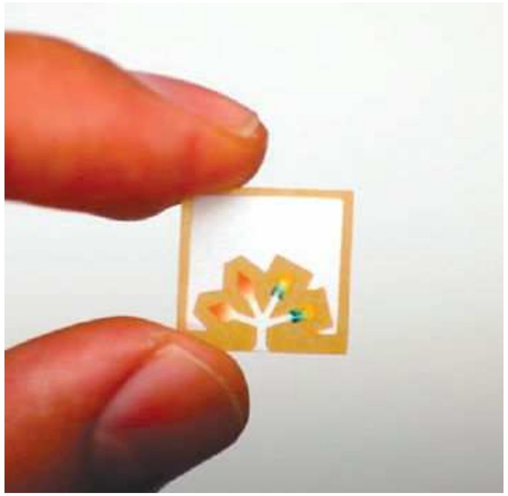


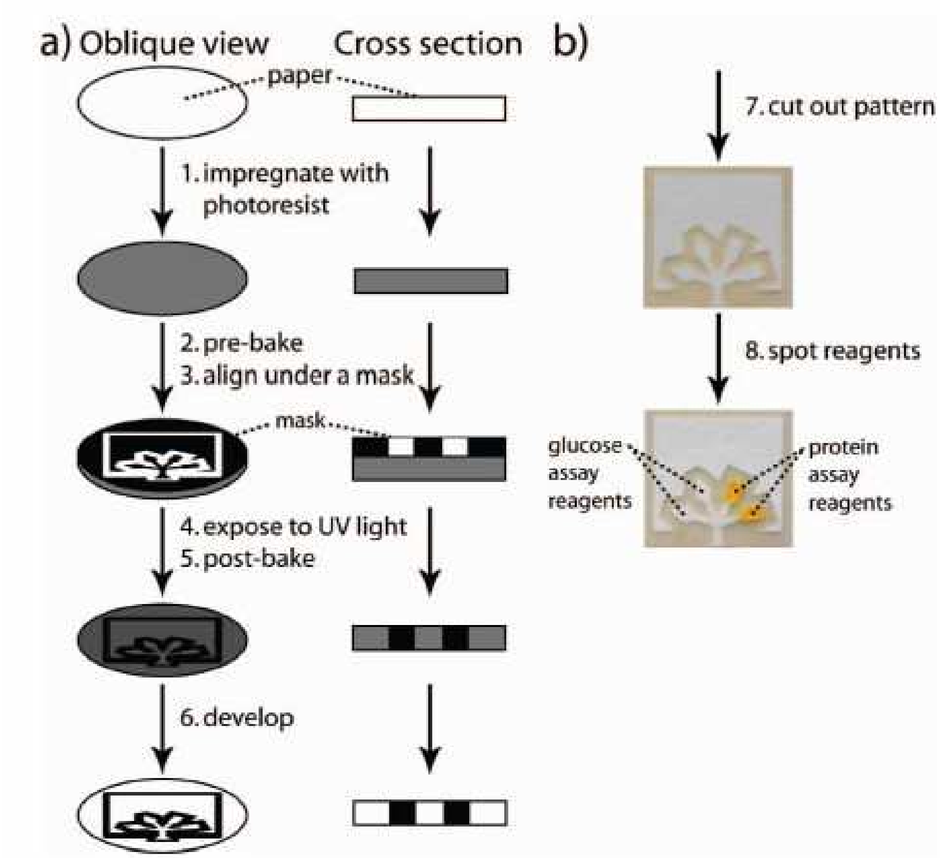
Whitesides, Nature 442 (2006) 368

Paper microfluidics

- Photolithography or wax printing to define hydrophilic & hydrophobic zones in paper
  - channels
- Capillary wicking of fluids
- Low cost







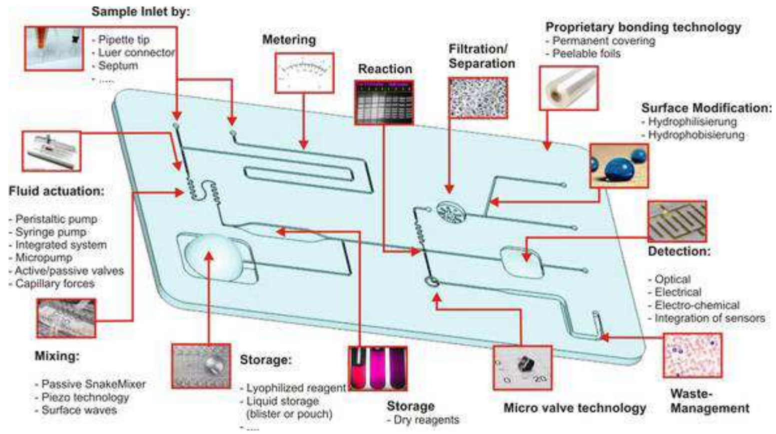
Martinez and Whitesides, Anal. Chem, 2008, PNAS 2009

Mcrofluidics enabling LoC

- Microfabrication techniques enable
  - Microchannels = pipes
  - Valves
  - Mixers
  - Pumps
- Enabling real Lab-on-Chip – *factories on a chip*

Lab-on-Chip

- Popular topic



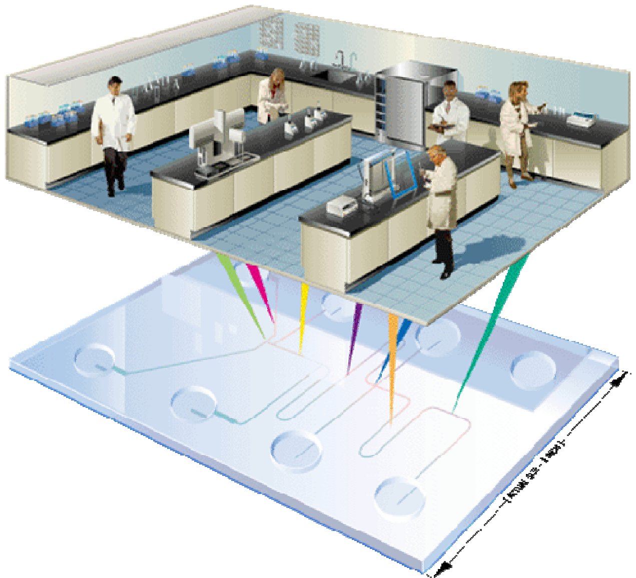
- Scientific journal

“Miniaturisation for chemistry, physics, biology, materials science and bioengineering”

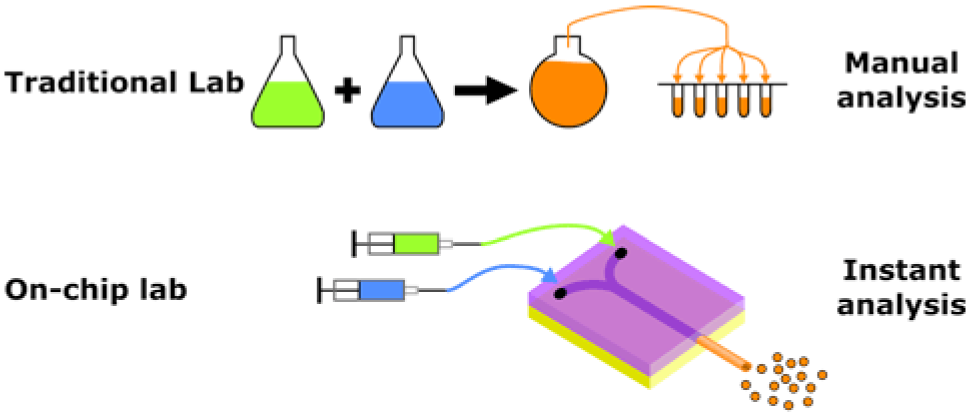
- Point-of-care

Lab-on-Chip (LoC)

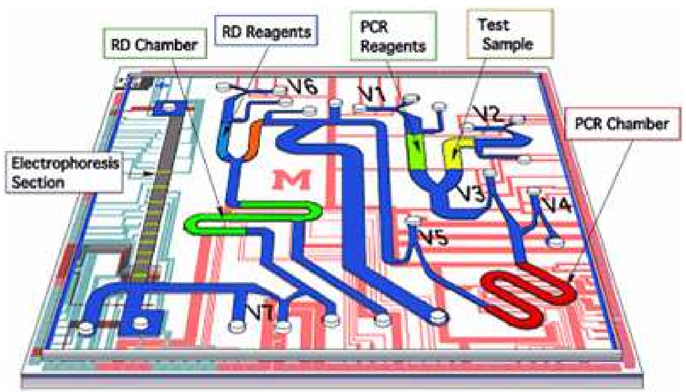
- Originated due to the microfluidics
- Whole "laboratory" on single chip
  - All necessary procedures integrated on one single element



http://lab-on-chip.gene-quantification.info/



Redrawn from: Brivio, M., Verboom, W., & Reinhoudt, D. N. (2006). Miniaturized continuous flow reaction vessels: influence on chemical reactions. *Lab on a Chip*, 6, p. 329.



http://www.azonano.com

Lab-on-Chip (LoC)

- Low volume of sample (droplet)
- Faster analysis
- Robustness of the system
- Safe platform for handling with dangerous samples
  - Infectious or (bio)hazardous samples
- Bringing down cost for one analysis – mass production

- Not always ↑↑
  - still only proof-of-concept stage

- LoC for HIV diagnosis

Point-of-care (PoC)

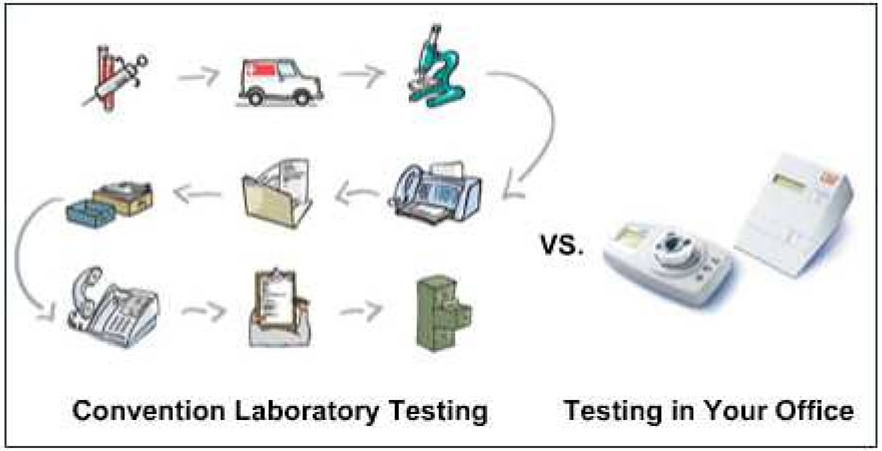
- Generally
  – Delivery of healthcare products and services to patient at time of care

- **PoC testing**
  – Transfer of analytical event to location of sample collection (location of patient)
    - Treatment can be adjusted before the patient leaves
  – Field applications, bed site

  (environmental analysis, blood test)

Point of care testing (PoCT)

- Simple
  - Experiment performance
  - Interpretation of results
  - Operation
- Portable – small dimensions
- Robust
- Fast



http://www.whitmiremedical.com

- Electronic/remote communication (data collection)

- **To ensure reliability of results!**
  - Different, unskilled operators

Point-of-care testing (PoCT)

- Sensing part (sample introduction)
- Signal processing (electronics, microcomputer)
- Evaluation (algorithms and programs)
- Output (display)

- Paper-based indicators – pH, urine test strips
- Sophisticated instruments – small bench instruments

Analytes performed by PoCT and devices

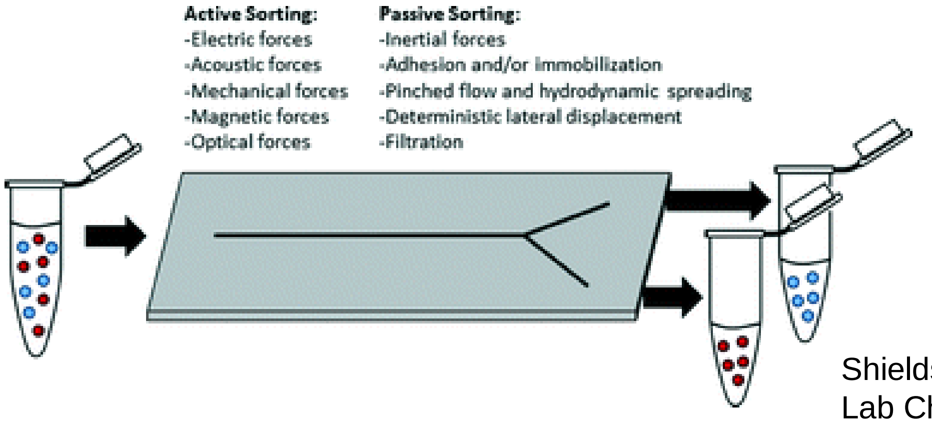
- Glucose
- Blood gases
- Lactate
- Co-oximetry
- Hemoglobin A1c

- Abbott Precision Xceed Pro Glucose Meter

- IL Gem Blood Gas analyser

- Siemens DCA 2000 Haemoglobin A1C Analyser

Cell sorting



Shields IV, Reyes, Lopez, Lab Chip 5 (2015) 1230

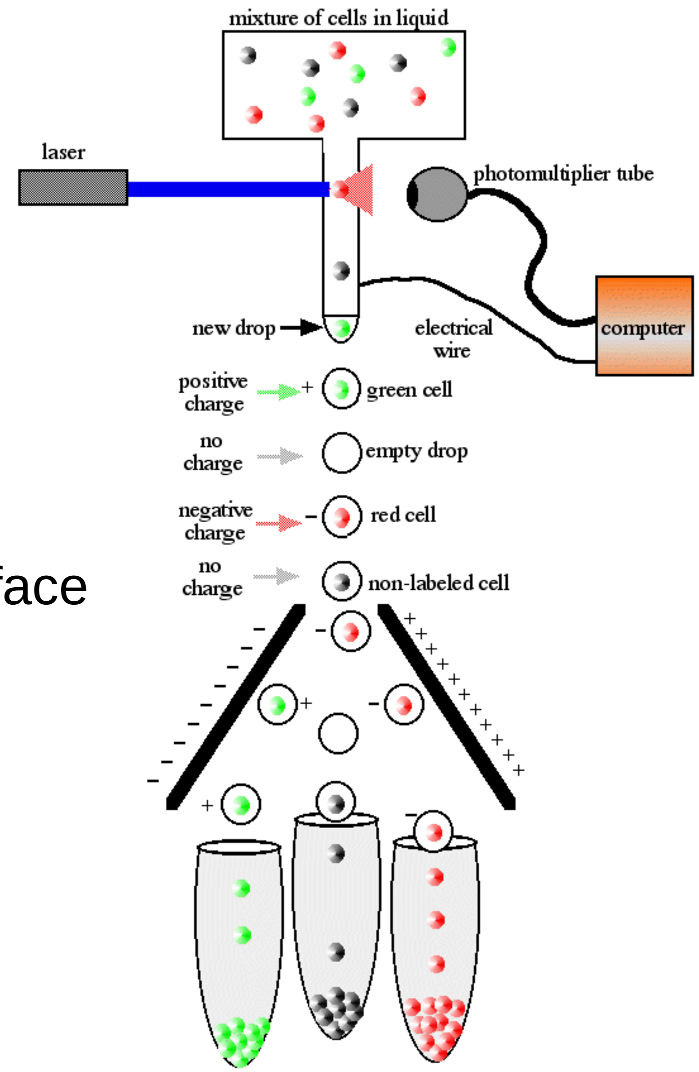
- Sorting of cells on the basis of their properties
- Physical principles (mainly)
- Chemical properties

- Preconcentration purposes for
  - Diagnosis – circulating tumour cells
  - Therapeutics – stem cells

- Theranostics and personalised medicine
  - Treatments are tailored to the prognoses of patients

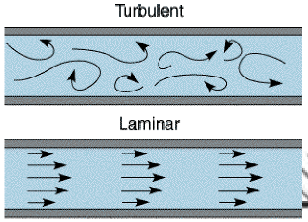
Cell sorting

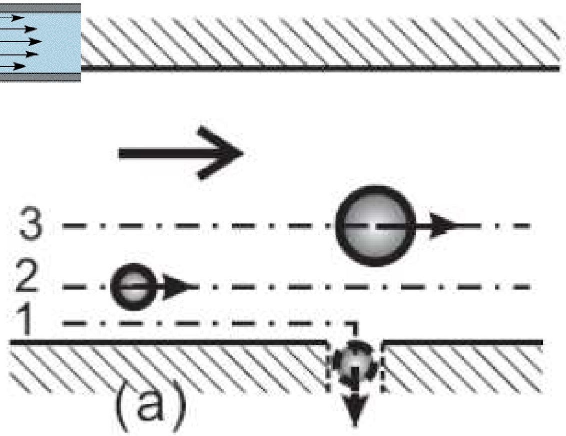
- Introduced in 1969 by Herzenberg et al.
- Fluorescence-activated cell sorting (FACS)
- Current instruments based on FACS
  - Up to 50 000 cells/s
  - automated, robust, and capable of exceptional specificity
  - using multiple morphological and fluorescent cell signatures (e.g. cell surface labels, cell size, and granularity)
- Magnetic-activated cell sorting devices
  - Separating cells with magnetic labels by permanent magnet



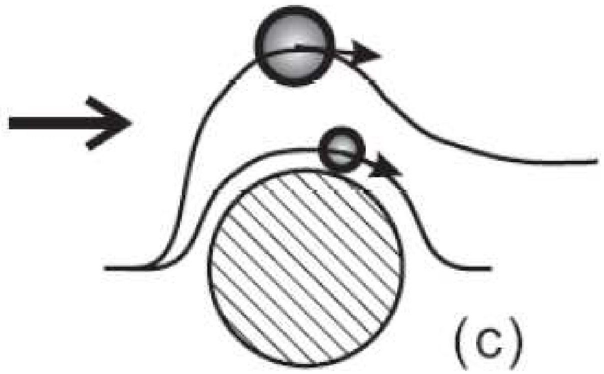
http://www.bio.davidson.edu

Physical principles of cell sorting

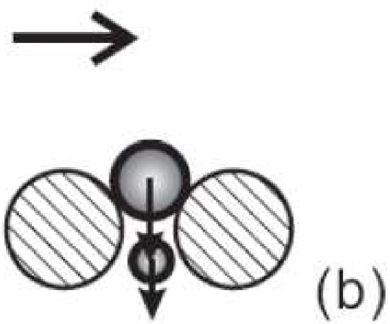




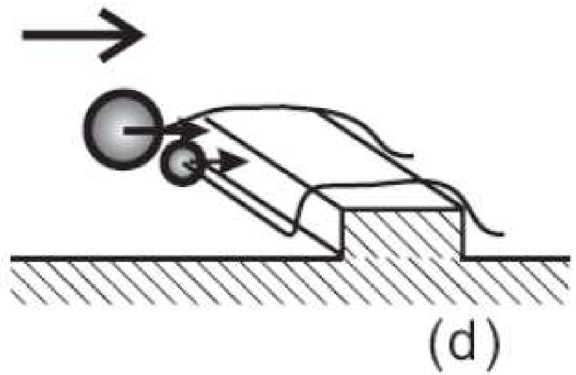
Size determined distribution



Size determined displacement



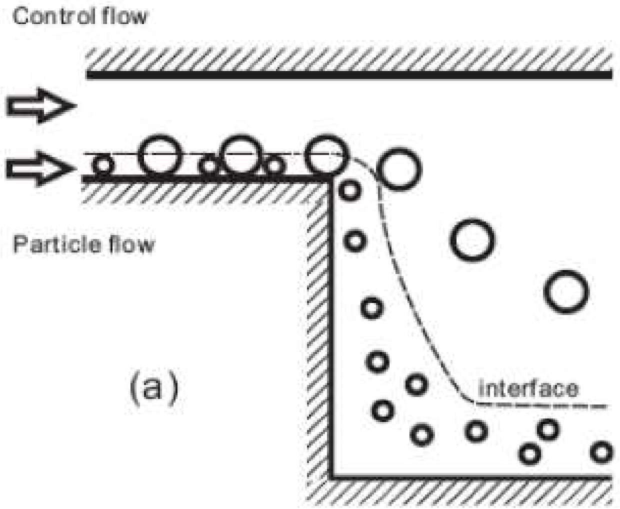
Size determined filtering



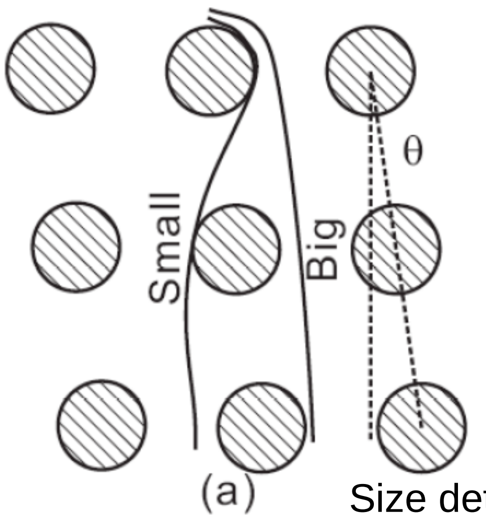
Size determined guiding

Wu, Hjort, Micro Nanosyst 1 (2009) 181

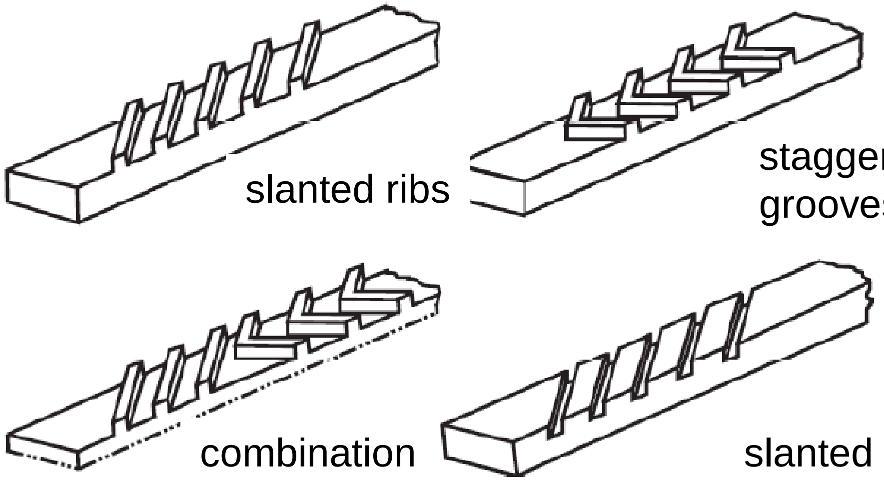
Physical principles of cell sorting

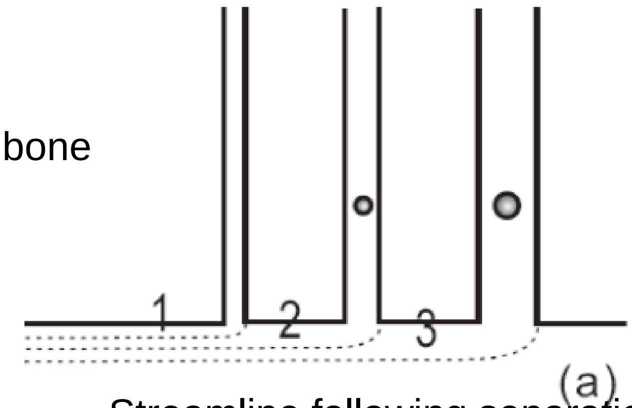


Continuous wall based hydrodynamic separation



Size determined displacement particle separation

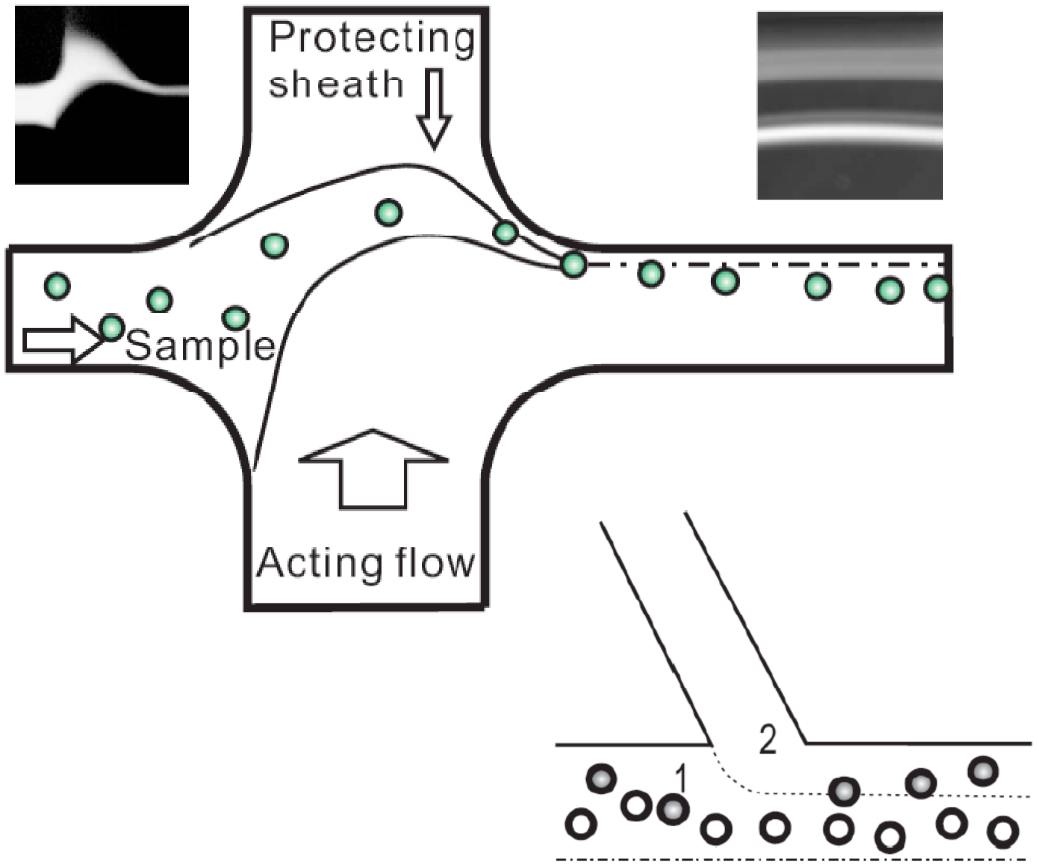


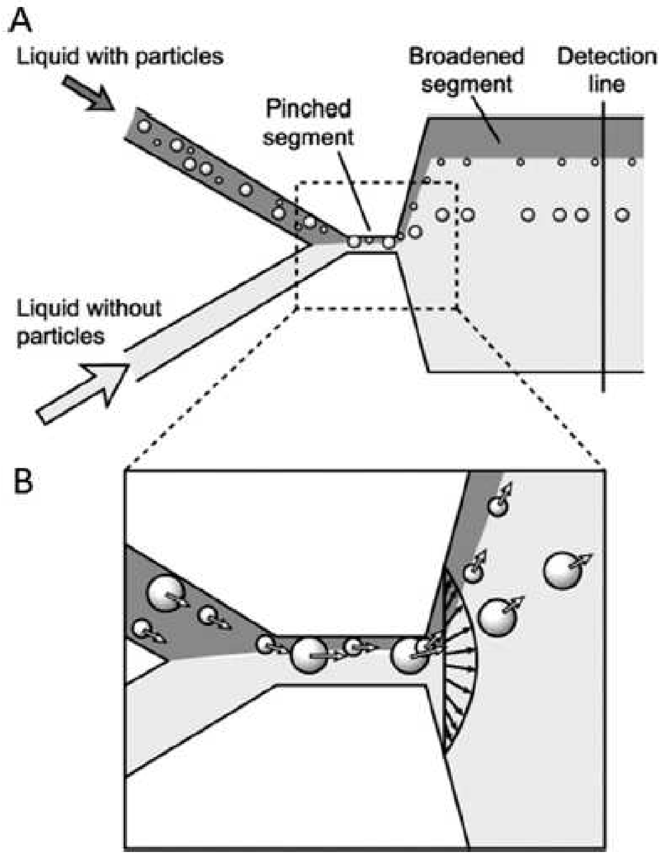


Streamline following separation

Wu, Hjort, Micro Nanosyst 1 (2009) 181

Physical principles of cell sorting
Soft inertial separation





Wu, Hjort, Micro Nanosyst 1 (2009) 181

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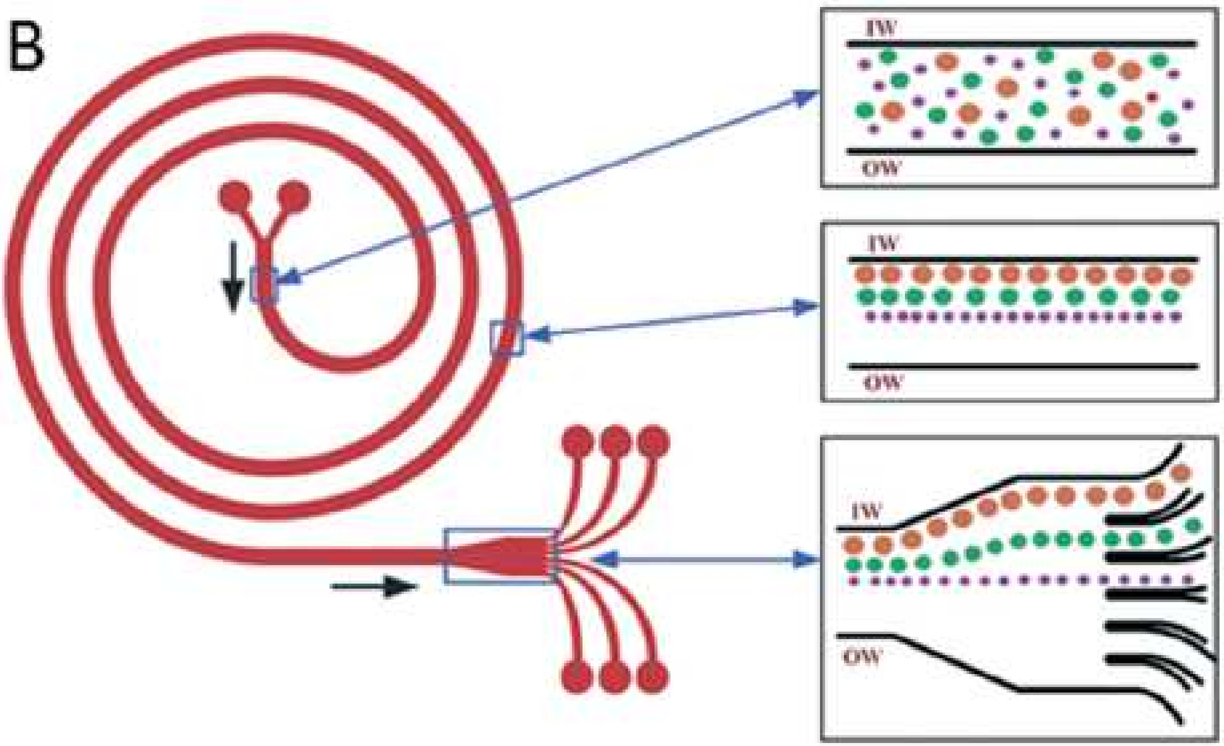
Physical principles of cell sorting

- Centrifugal forces



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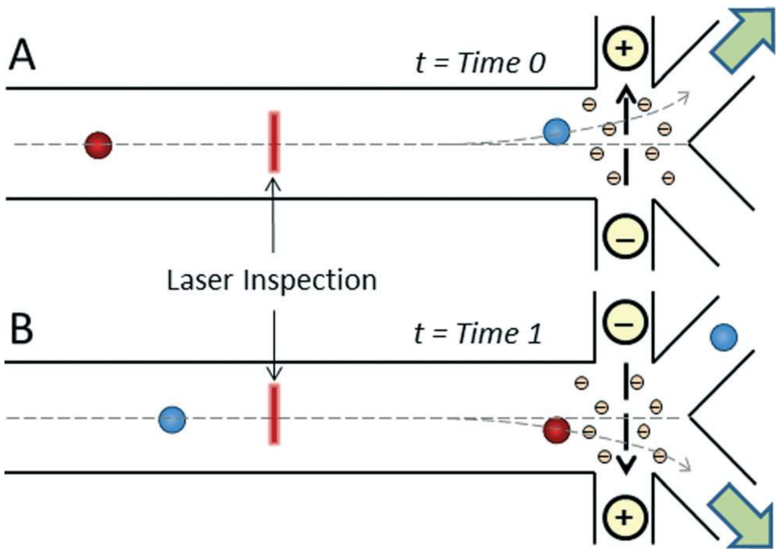
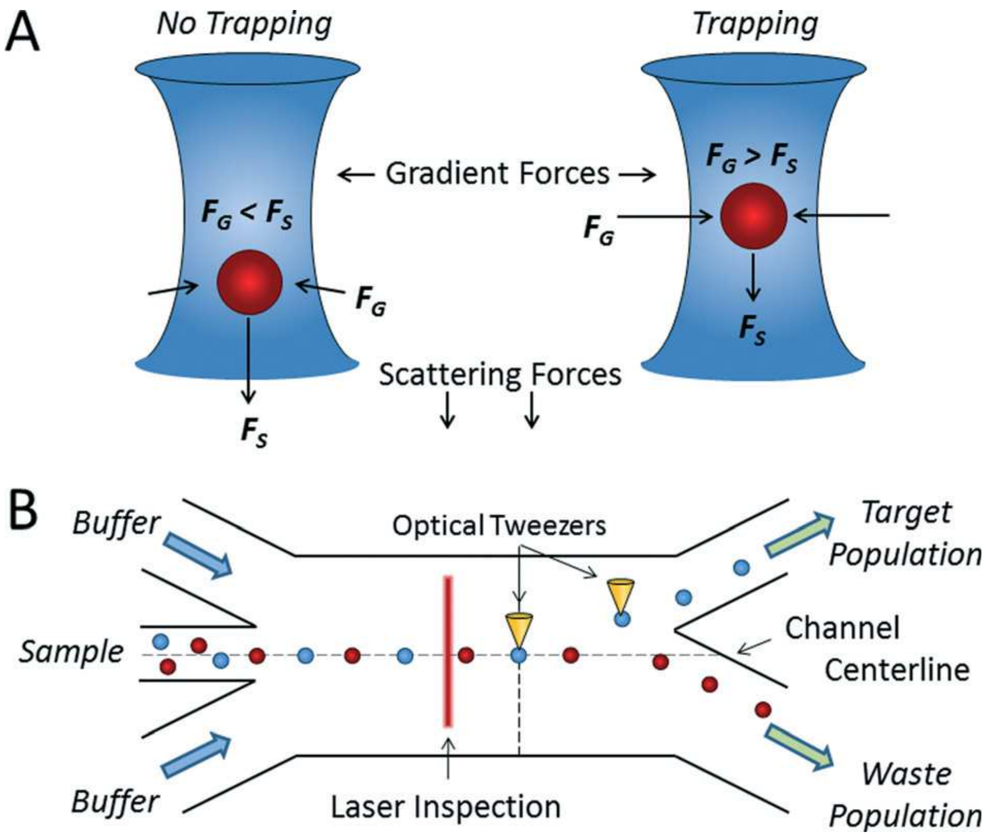
“Active” cell sorting

- After inspection cells are sorted by external operator



Electromagnetic field



Optical tweezers

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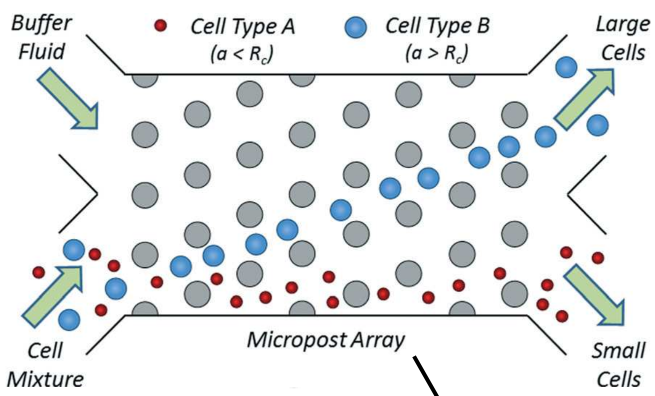
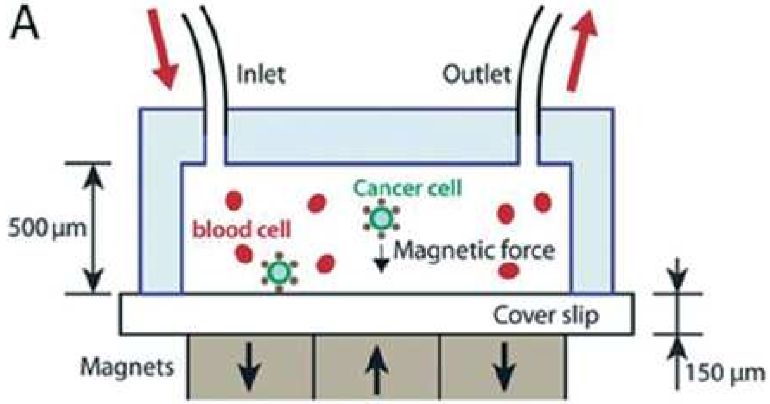
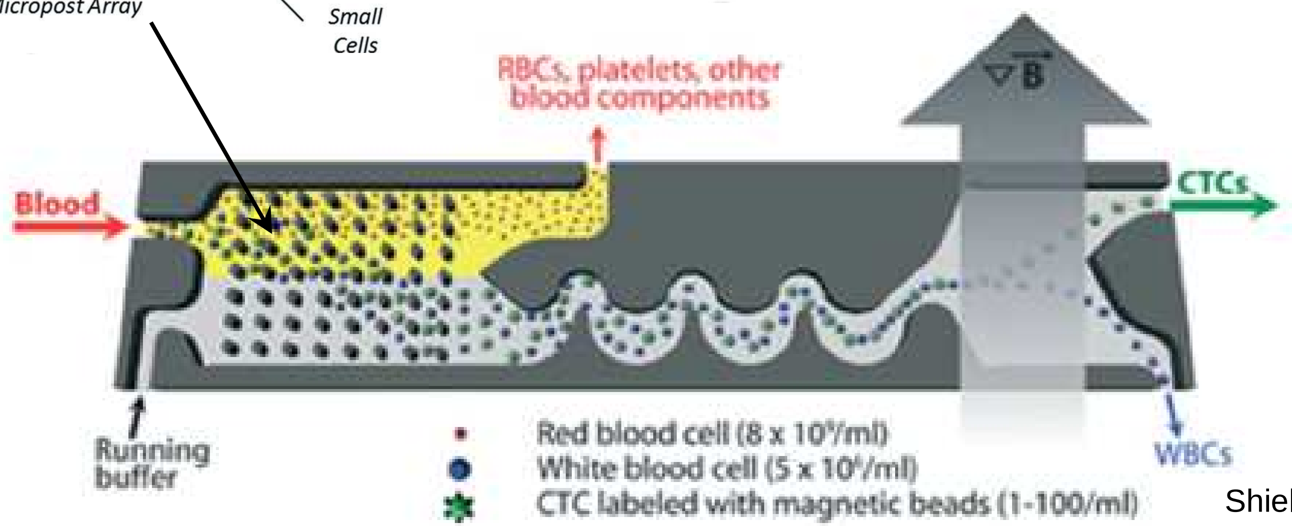
Chemical properties based cell sorting

- Specific antibodies magnetically labelled
- Magnetic labelling of cells







Shields IV, Reyes, Lopez,
Lab Chip 5 (2015) 1230

Cell sorting overall

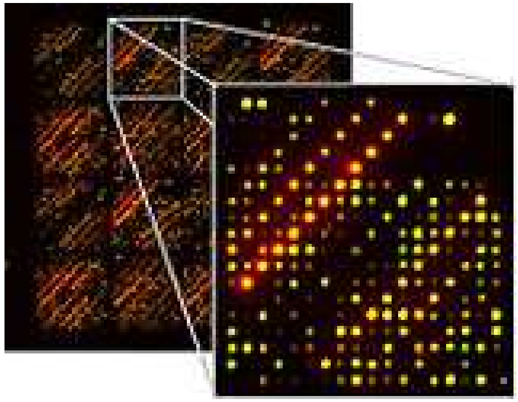
- Promising cell sorting using microfluidics
  - Accessible fabrication
  - Low reagent consumption
  - Small footprints
  - Improved safety over traditional cell sorting
    (eliminating potentially biohazardous aerosols)

- Problems
  - Many technologies in proof-of-concept stage
  - Low throughput due to single-channel design
  - Blocking or clogging of the microchannels
  - Sample preparation still necessary

Biochips and sensing arrays

- “Miniaturised laboratory”

- Collection of miniaturised sensors arranged in array on solid substrate

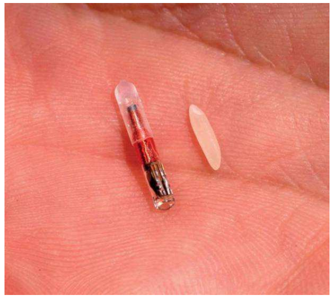


http://www.igb.fraunhofer.de

- Many tests performed simultaneously
  - Hundreds or thousands of (bio)chemical reactions

- Small dimensions

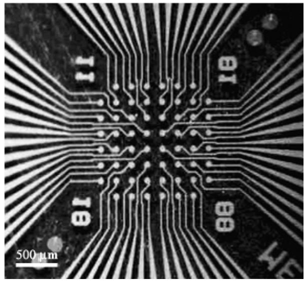
- Term overlapping with implanted carriers of information
  - Replacing drivers licence, ID card, medical records…



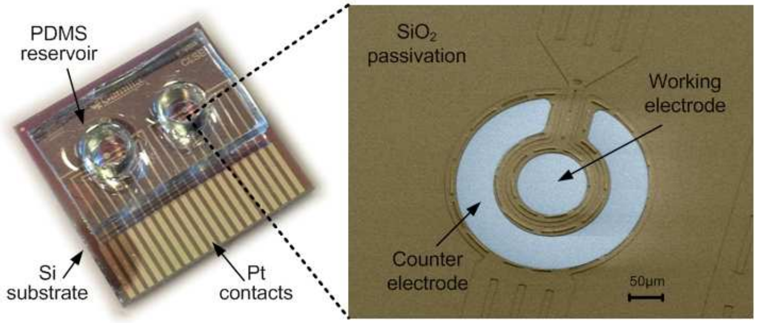
https://gdvmahesh.wordpress.com

Biochip & microarray design

- Transduction
  - Electrochemical

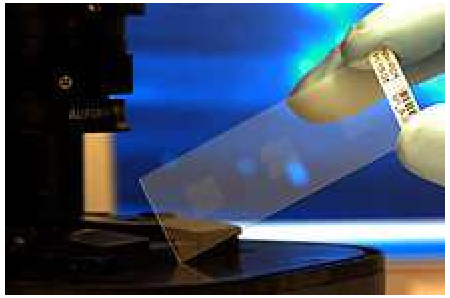


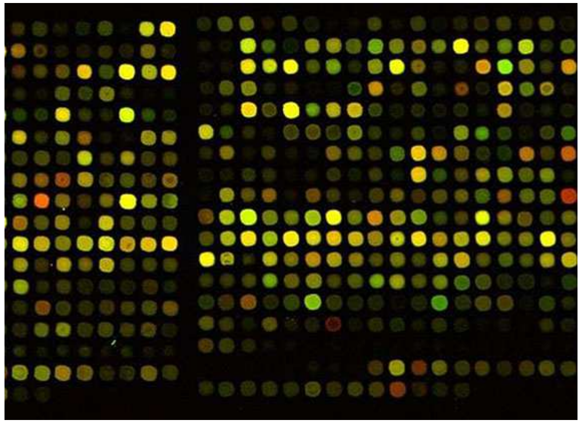
http://www.gersteltec.ch



http://clse.epfl.ch/

  - Optical

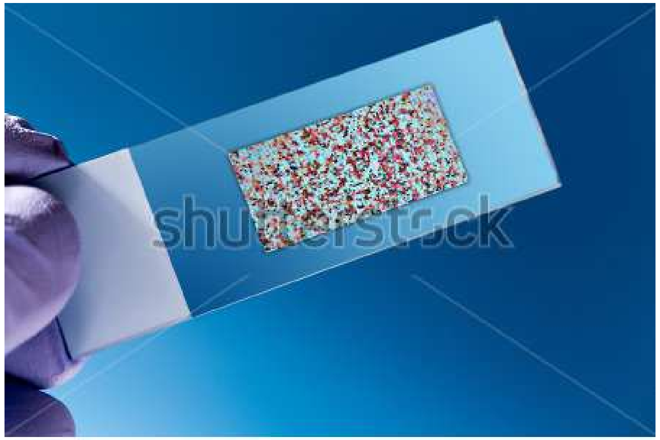


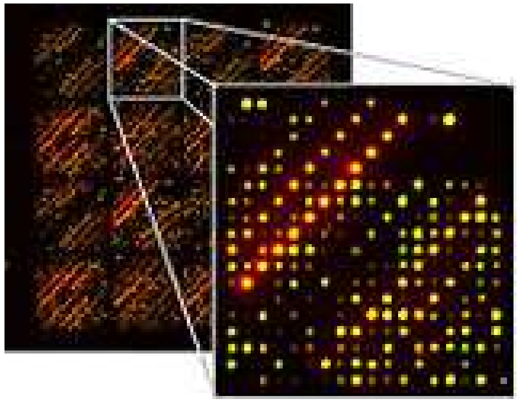


http://www.scienion.com

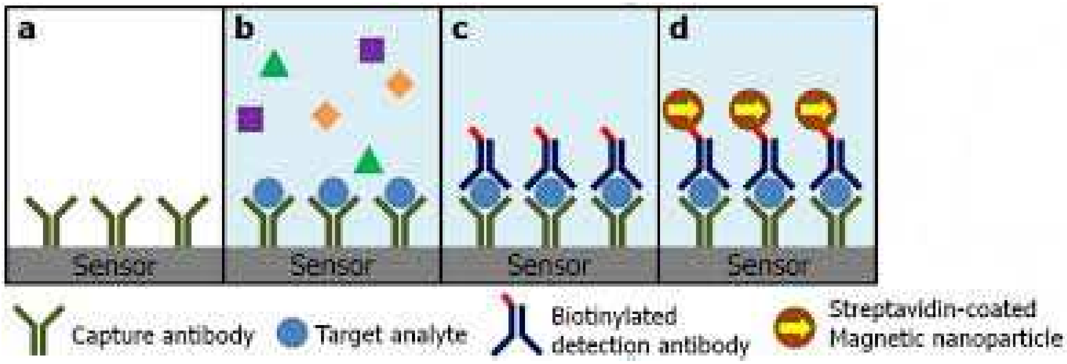
Microarrays

- DNA and protein microarray
- Each spot is modified with specific protein marker/DNA/antibody etc.
- Localisation related information
- Evaluation of photography
- Valid for electrochemical transducer
  – Localisation of microelectrode



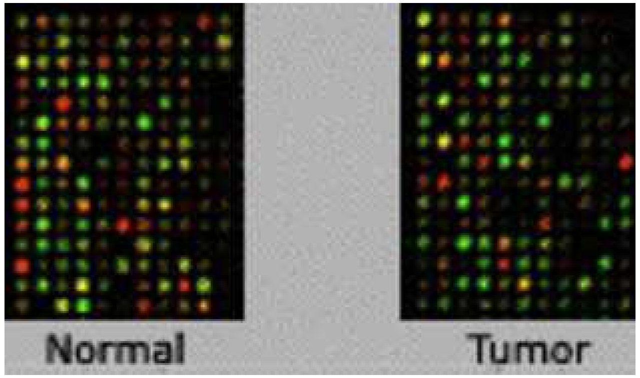


http://www.igb.fraunhofer.de



Microarrays

- Necessary digital evaluation of results



http://prohardver.hu

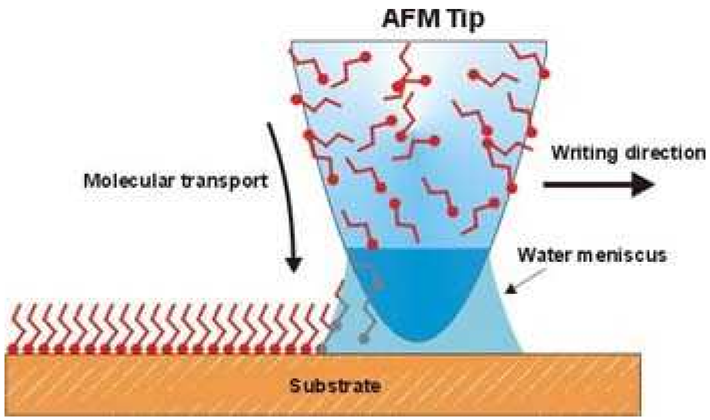
- Crucial – fabrication of sensor array

Deposition of biomolecules at nanoscale

- High resolution modification of sensing array
- Several methodical approaches
  - Nanolithography (SPM)
  - Nanofabrication
  - Nanodeposition
- Activation of the surface (chemical, physical)

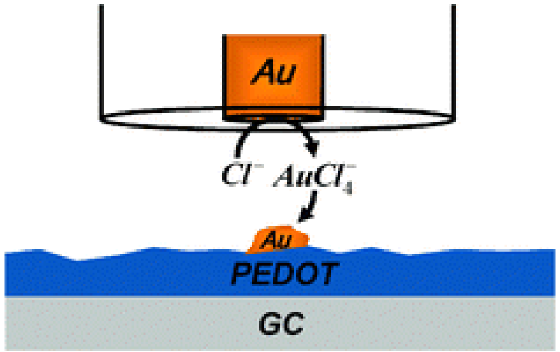
Nanolithography

- AFM, (SECM)
- Dip-pen nanolithography

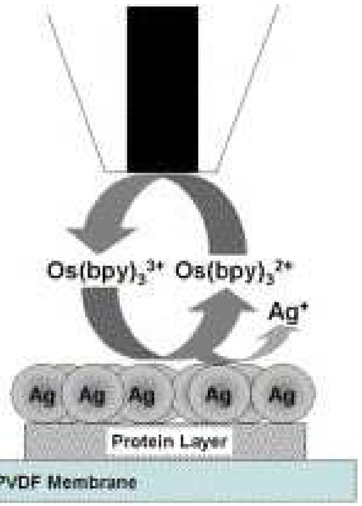


http://www.npl.co.uk

- Local electrochemical modification (removal, deposition)



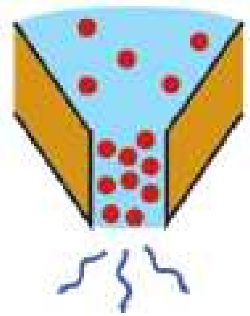
Danieli, Colleran, Mandler,
PhysChemChemPhys 13 (2011) 20345

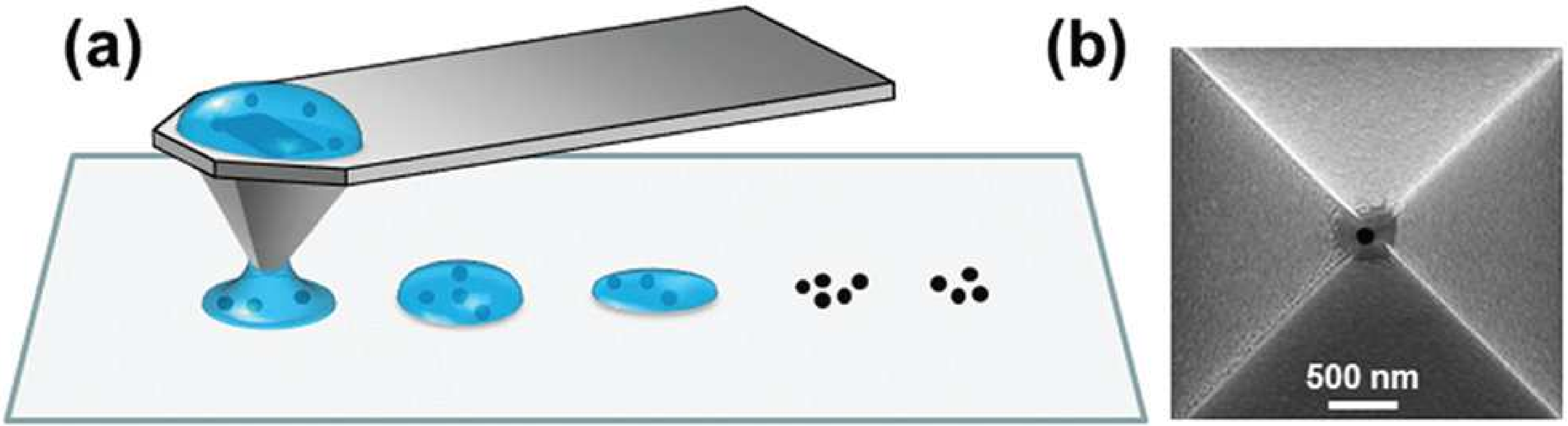


Carano, Lion, Abid, Girault,
Electrochem Commun 6 (2004) 1217

Liquid nanodispersing

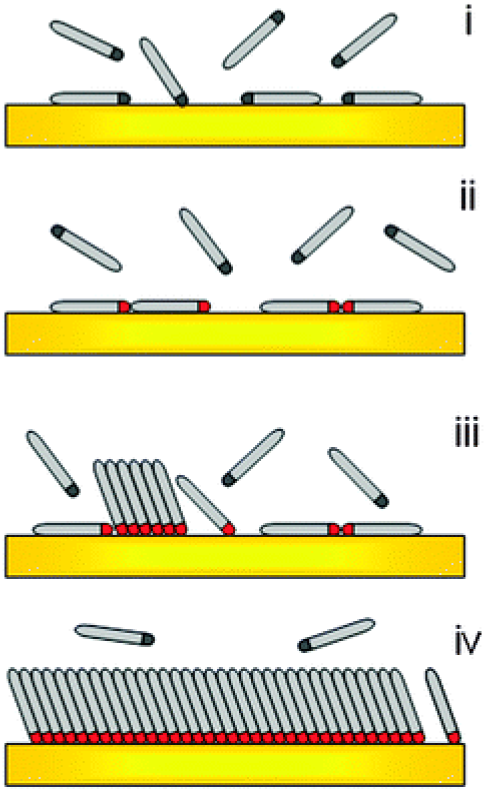
- Deposition of droplets through nanochannel drilled in AFM tip



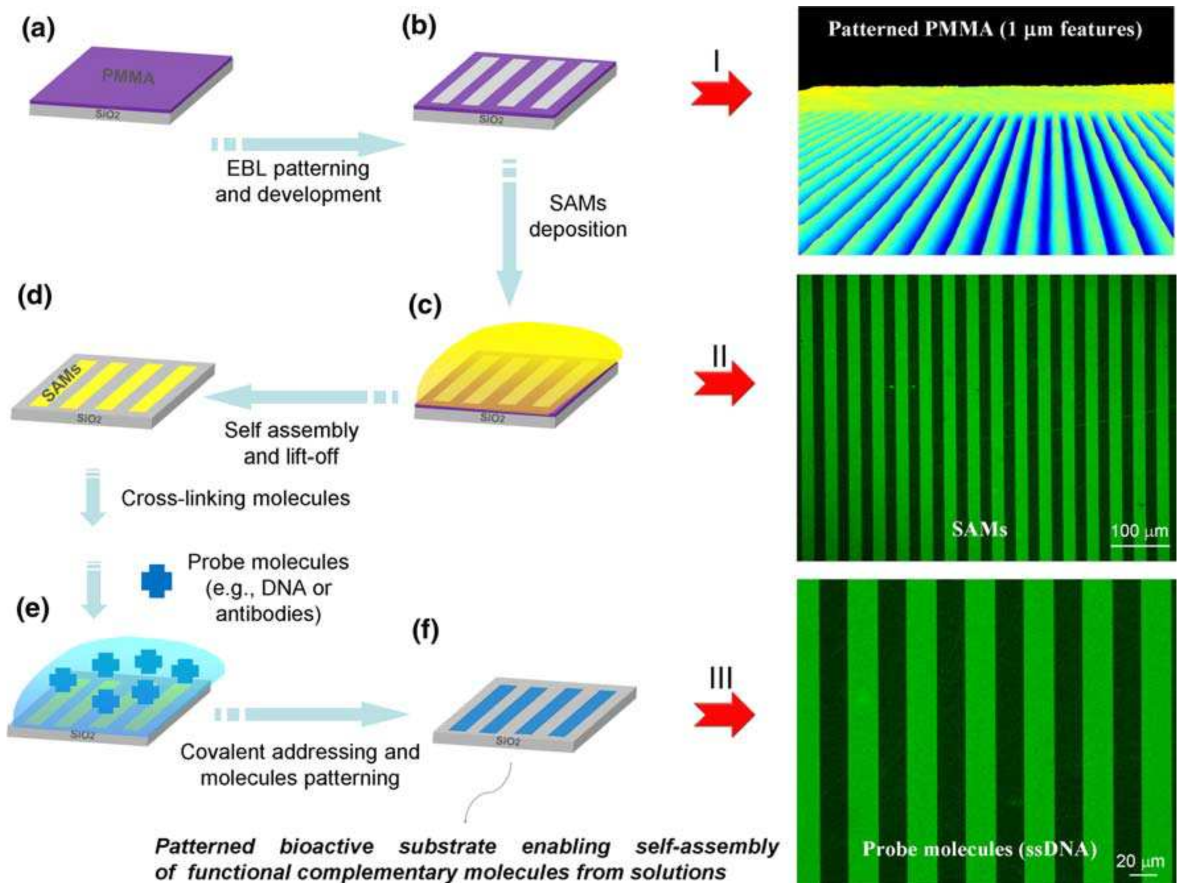


Fabié, Agostini, Stopel, Blum, Lassagne, Subramaniam, Ondarçuhu, Nanoscale 7 (2015) 4497

Nanofabrication
Self assembled monolayers



Self-assembly



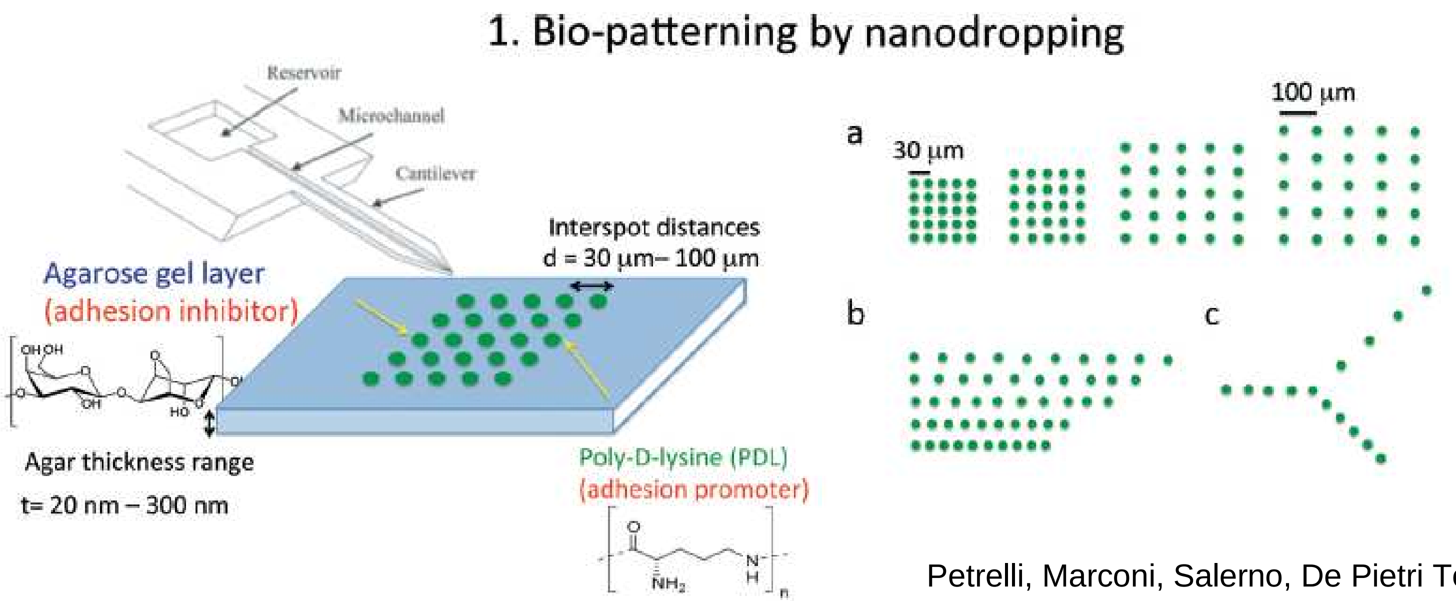
Vericat, Vela, Benitez, Carro, Salvarezza, Chem Soc Rev 39 (2010) 1805

Sabella, Brunetti, Vecchio, Della Torre, Rinaldi, Cingolani, Pompa, Nanoscale Res Lett 4 (2009) 1222

Deposition of biomolecules at nanoscale

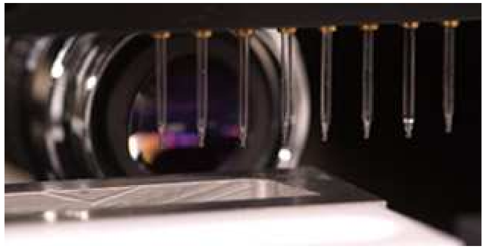
- Deposition of nanodrops
- System for generation of micro- or nanodrops

- Highly suitable for “array sensing”
- Activation of surface (surface chemistry)



Petrelli, Marconi, Salerno, De Pietri Tonelli, Berdondini, Dante, Lab Chip 13 (2013) 4419

Nanodrop



- Scienion
- http://www.scienion.com/support/movies/

- For high throughput array production
- Piezo-dispensing technology