CHEM-E8135 Microfluidics and BioMEMS

Types of Microfluidics and BioMEMS

17.2.2021

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Learning outcomes:

ILO 3: The student understands the basics of advantages and disadvantages of polymers, glass, silicon and paper as materials for microfluidic chips.

ILO 4: The student can design microfluidic components: channels, mixer, reactors, droplet generators. **The student recognizes many different types of microfluidics (channels, droplets, paper etc.).**

Overview:

We have already seen:

”Standard” channel based microfluidics

Capillary filling microfluidics

In this lecture overviews of:

Inertial microfluidics

Acoustofluidics

Droplet microfluidics

Paper microfluidics

Digital microfluidics

Centrifugal/CD microfluidics

+

BioMEMS

Part 1: Types of microfluidics

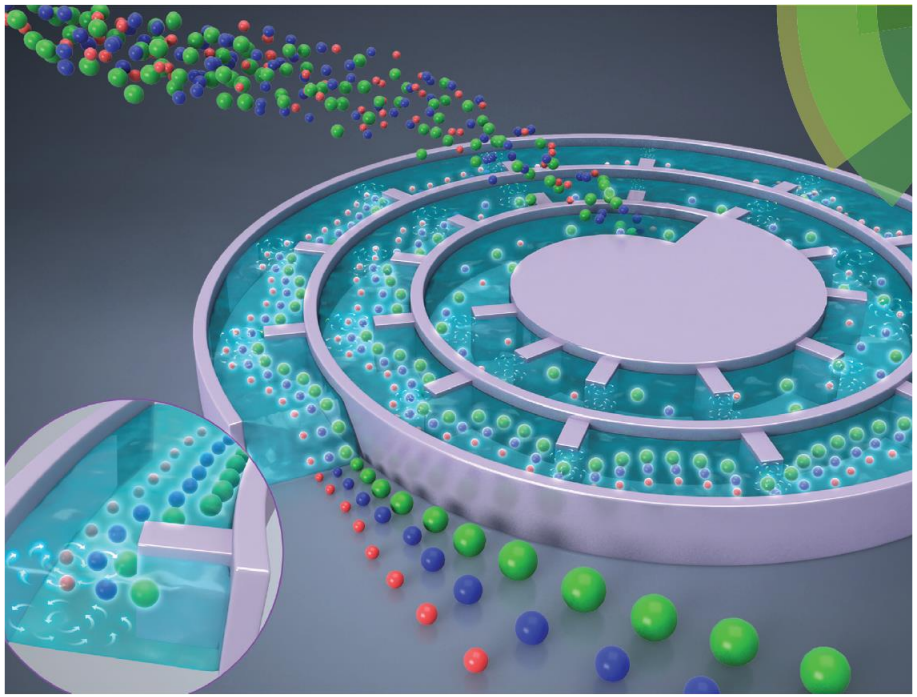
Inertial microfluidics

Keywords: channel, pump, high flowrate, inertial effects for separation

Inertial microfluidics utilizes very high flow rates (ml/min) in a channel to achieve significant inertial forces on e.g. particles or cells.

Inertial microfluidics is for **high-throughput label free separation of particles/cells based on size dependent inertial effects.**

Inertial microfluidics is NOT turbulent. Reynolds number typically <2000 but can typically be >100.
(pressures are high, interconnections need extra work so as not to leak)



Inertial microfluidics

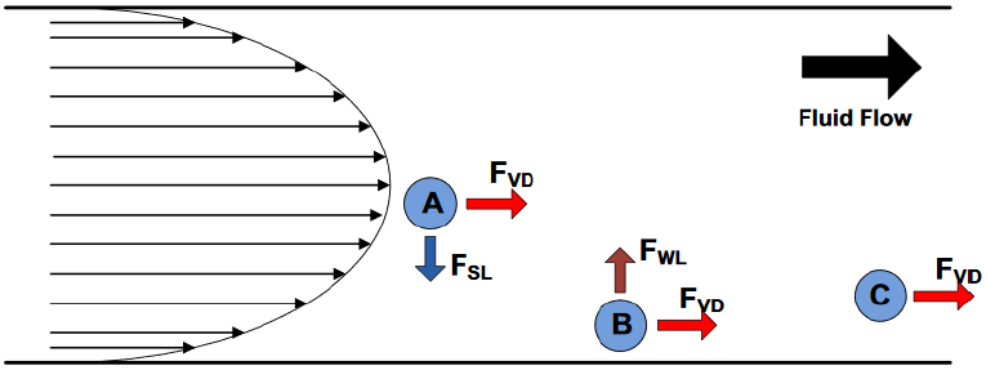
Pressure driven flow has a parabolic velocity profile.

Shear induced force: parabolic flow profile pushes particles toward the edge of channel.

Wall lift force: the walls push particles toward the center of the channel.

The equilibrium position depends on the size of the particle/cell

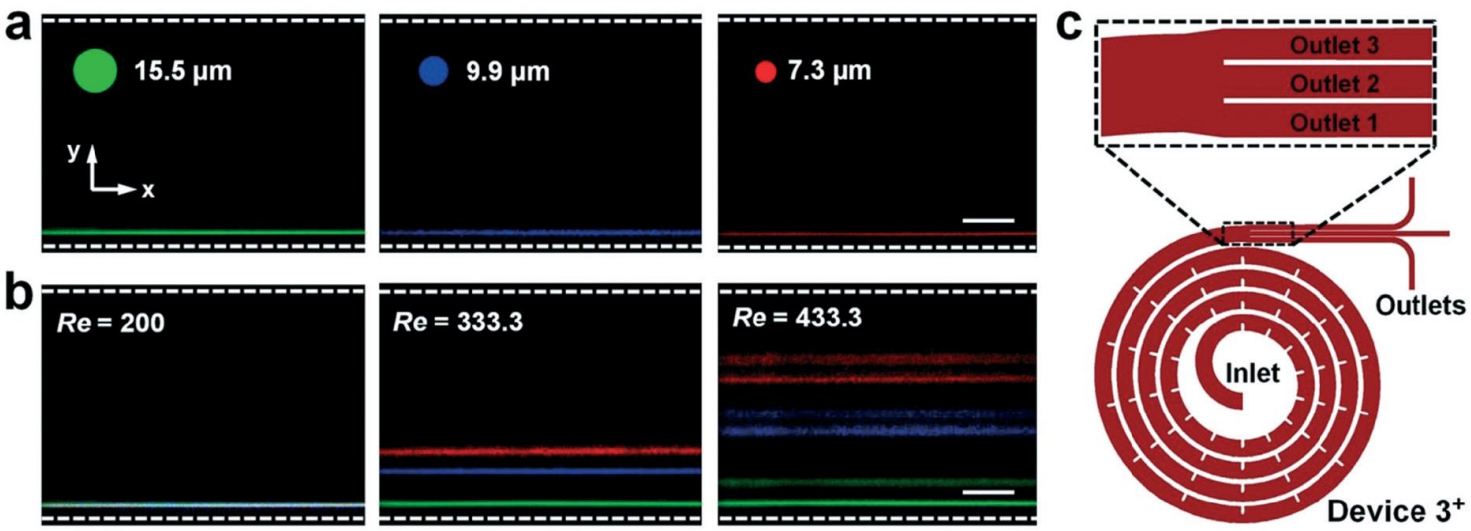
Channel geometry (curvature, sudden turns etc.) also creates forces on particles/cells in the channel and can be used to fine tune / enhance.



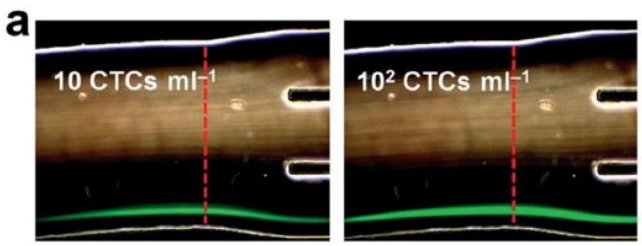
F_{VD} viscous drag force, F_{SL} shear induced force, F_{WL} wall lift force

Kuva: Tiia Tervamäki, masters thesis, 2019

Cell separation by inertial microfluidics



Different sized particles focus to different lateral locations of the channel.
These can be separated to different inlets due to laminar flow.



CTC enrichment from blood

Circulating tumor cells (stained green) are rare cells that typically larger than other cells in blood.

They can be enriched for diagnostics by inertial microfluidics

Acoustofluidics

Keywords: channel, pump, medium flowrate, piezoelectric acoustic transducer

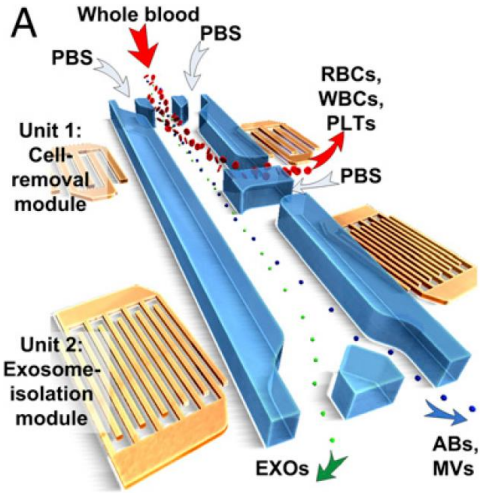
Acoustofluidics combines channel based microfluidics to ultrasound to separate particles/cells based on their physical properties.

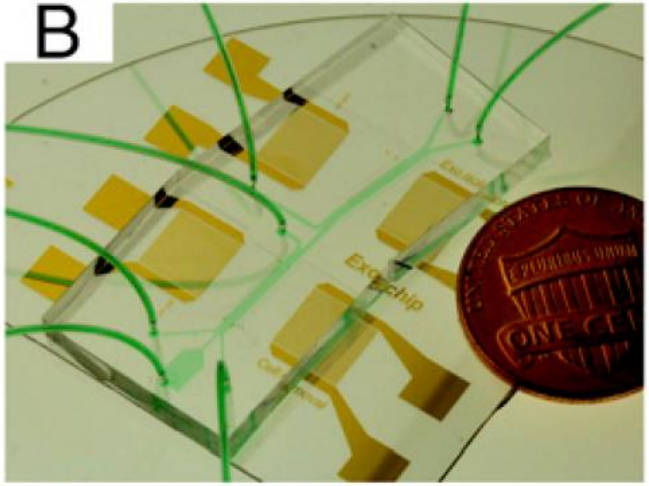
Separation based on: size, density, compressibility

Label-free separation

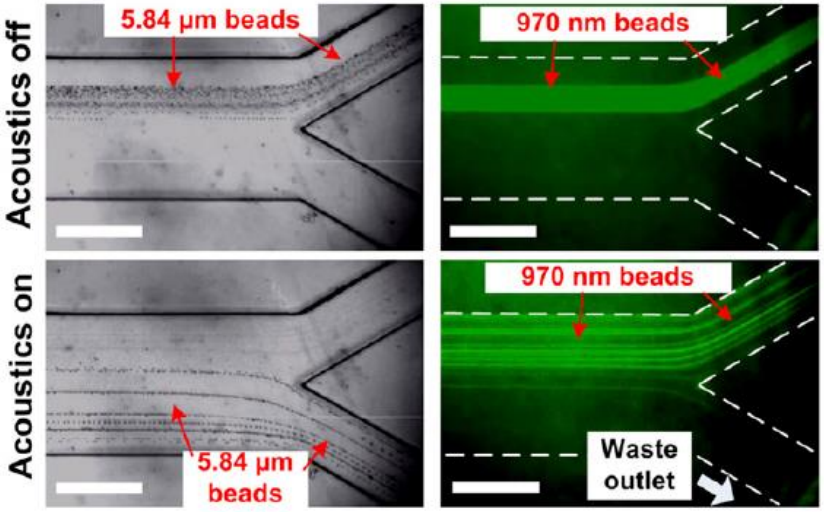
Good throughput (commonly µl/min),

Channels usually simple and large -> no clogging or pressure problems.

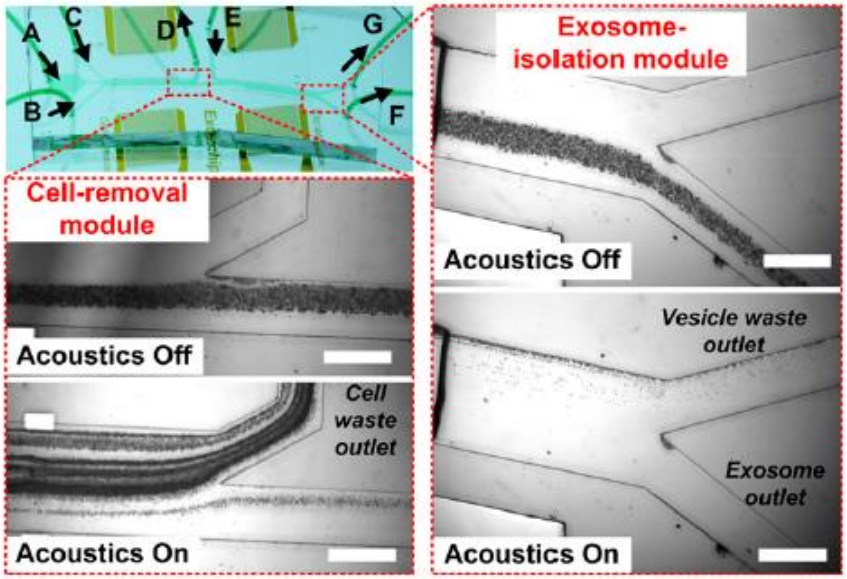




Acoustofluidic exosome separation



Acoustofluidic size based separation of 6 µm beads from 1 µm beads



Acoustofluidic exosome separation from whole blood.

Two acoustofluidic components:

-First to remove cells

-Second to isolate exosomes from other vesicles.

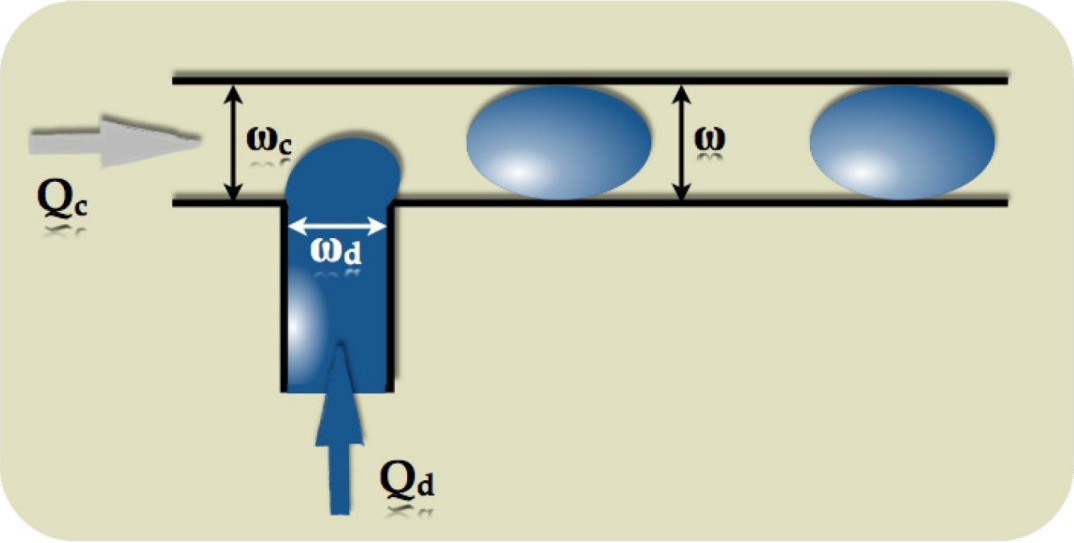
Droplet microfluidics

Keywords: channel, pump, medium flowrate, two immiscible phases

Droplet microfluidics means two-phase microfluidics where (typically) water droplets surrounded by oil are generated in channels.

Instead of one continuous flowing phase, the water droplets are discrete: Each droplet can be viewed as a single experiment. **Applications in high-throughput screening.**

Massive compartmentalization and parallelization of experiments -> Very high throughput of experiments (can be 1000s of droplets analysed per second)



Capillary number

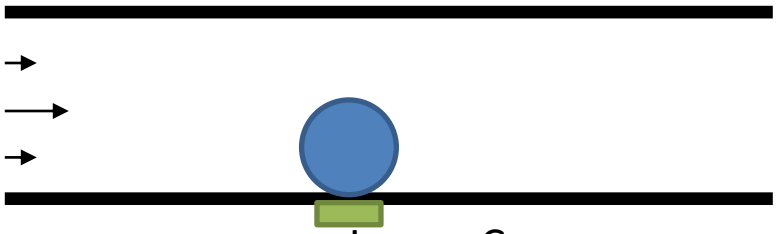
Dimensionless number that characterizes the ratio of viscous forces to surface forces
Viscous shear pressure = μv/L, Capillary pressure= γ /L

μ = dynamic viscosity (in multiphase systems, opt for the higher viscosity)
γ = surface tension
v = velocity

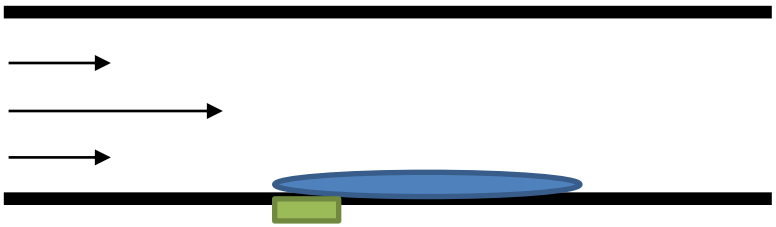
$$Ca = \frac{\mu v}{\gamma}$$

Viscous forces and surface forces are both significant at microscale.
Capillary numbers in microfluidics can be high or low. (Note that the characteristic dimension does not appear in Ca.)

Illustration: a droplet of liquid is immobilized in a channel where an immiscible liquid flows. Will it stay as a sphere held together by surface tension or be elongated due to shear forces?



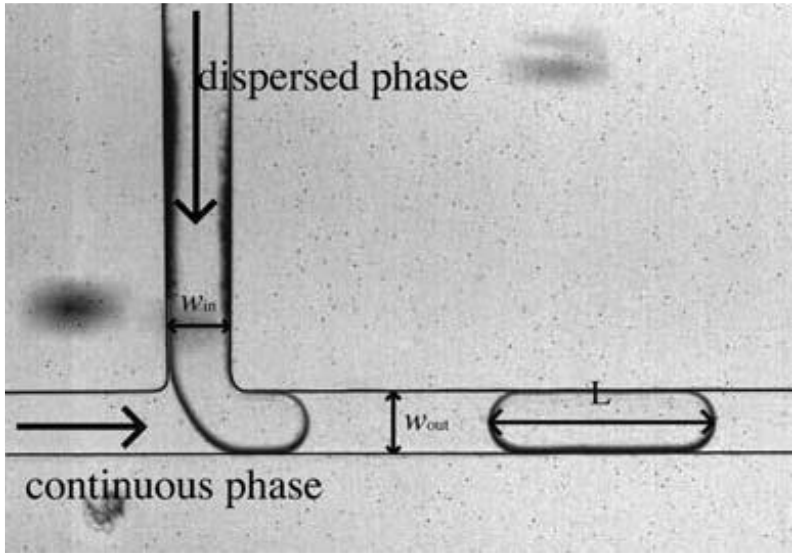
Lower Ca
(more influence of surface tension)



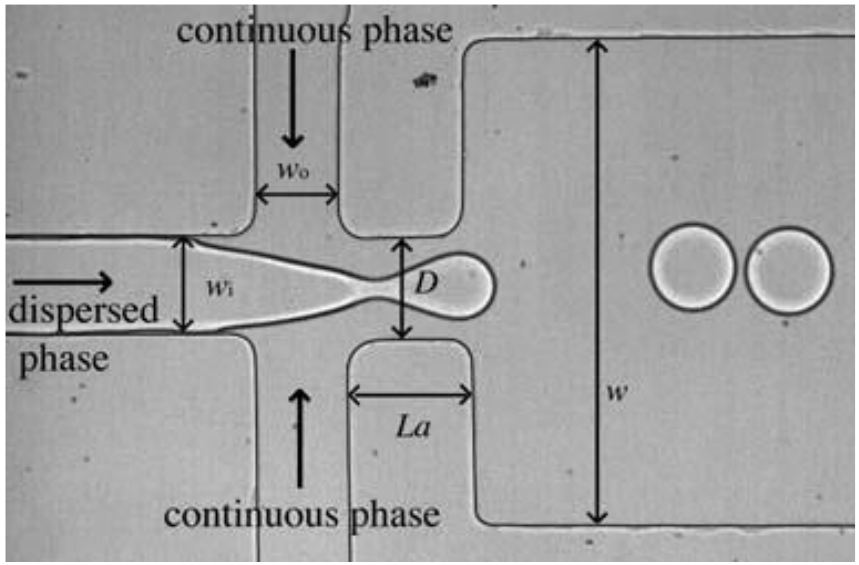
Higher Ca
(less influence of surface tension)

Droplet generation

- Two immiscible phases, typically water and oil/fluorinated oil.
- The walls of the system are wetting toward the continuous phase and anti-wetting toward the dispersed phase
- Droplet production is dependent on: capillary number, geometry, and ratio of the flows of the dispersed and the continuous phases.
- Shear forces attempt to divide the dispersed phase while surface tension tries to keep the dispersed phase together. Ca typically 0.001-10
- Droplet generation rate can be in the range of **10kHz**



T junction

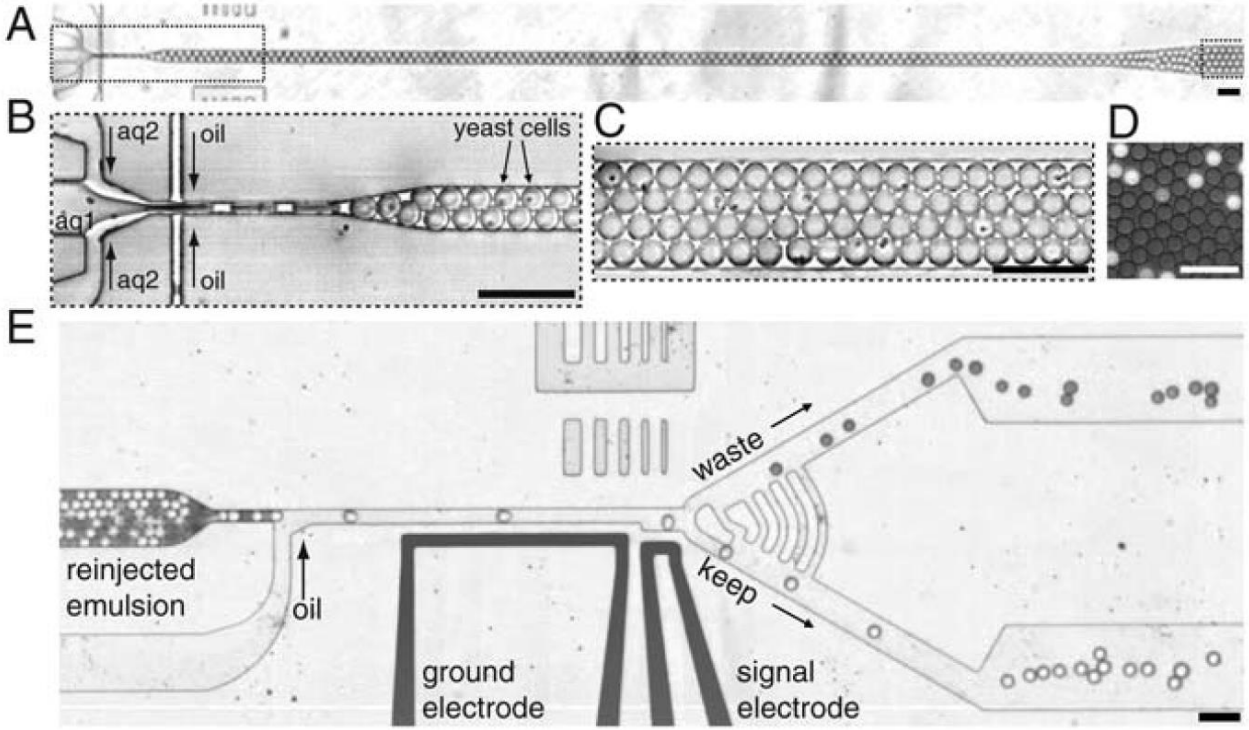


Flow focusing

Lab Chip, 2010, 10, 2032–2045

Droplet fluidic directed evolution of yeast

A, B: A population of yeast cells is loaded into droplets.
C, D: The yeast population is incubated. Droplets with suitable mutants have higher activity of the desired enzyme and thus give out higher fluorescent signal.
E: The incubated population is run through a device that utilized automatic fluorescent detection combined to dielectrophoretic picking of the high fluorescent yeast cells.



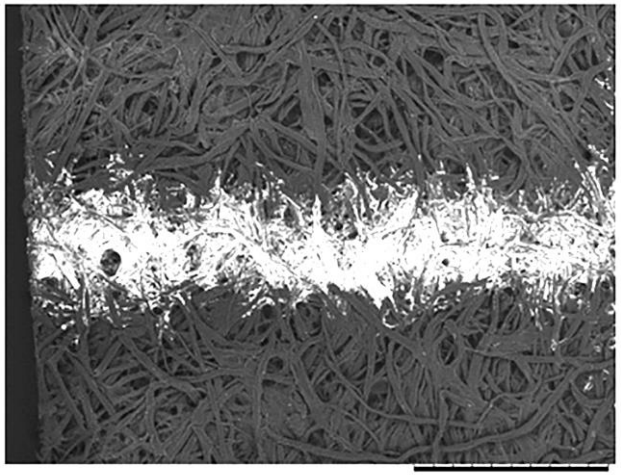
Paper microfluidics

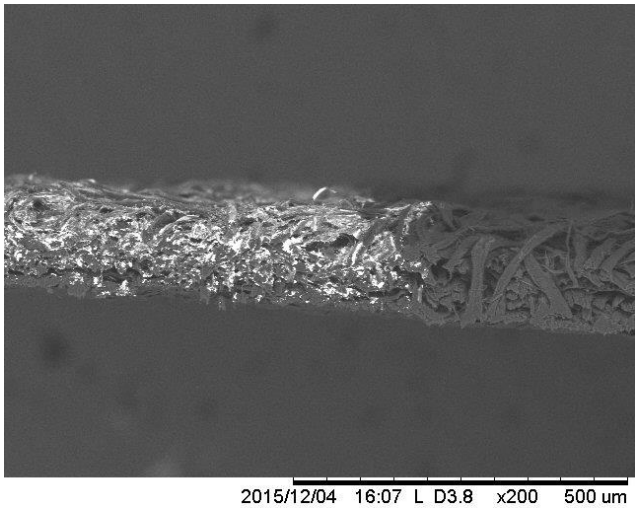
Keywords: no channel, no pump, low flow rate, cheap, simple

Paper microfluidics utilizes porous paper as both the channel and the capillary pump.

Paper microfluidics is ultra-cheap way to realize simple microfluidic operations without interconnections. Paper fluidic chip can cost a few cents.

Untreated paper is a hydrophilic porous matrix. Hydrophobic barriers can be used to control the capillary filling.





Whatman no. 1 chromatography paper.

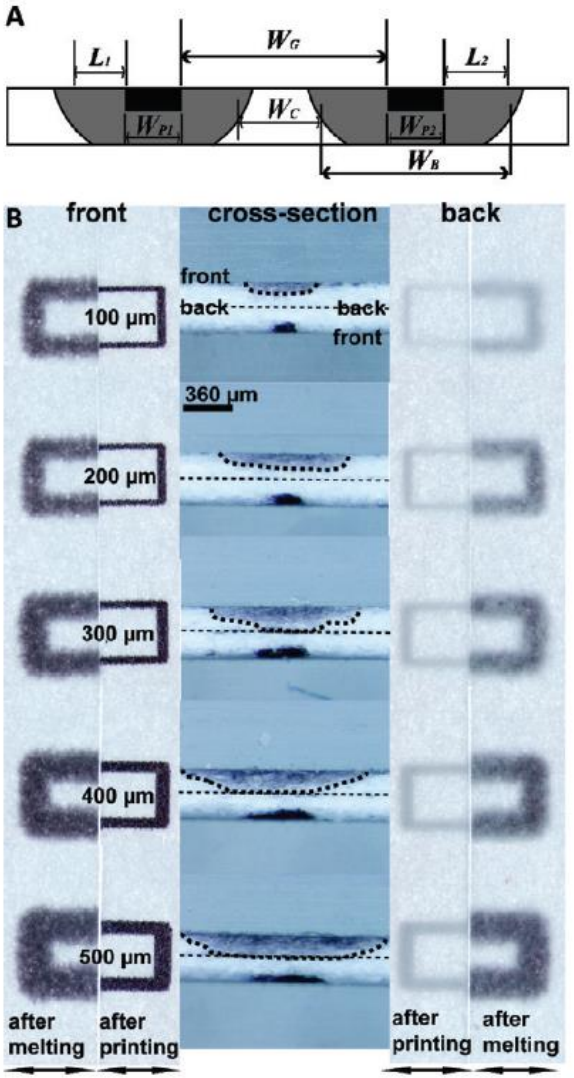
(the silvery areas are printed silver electrodes, the gray areas area the fibers and pores of this paper)

Biomicrofluidics 10, 064120 (2016)

Wax printing

The most common method to define channels on paper: Printing a hydrophobic wax to act as a barrier.

Wax needs to be baked in order for it to penetrate the entire depth. Isotropic process so leads to limitations in resolution. Smallest lines ≈ 500 – 1000 µm.

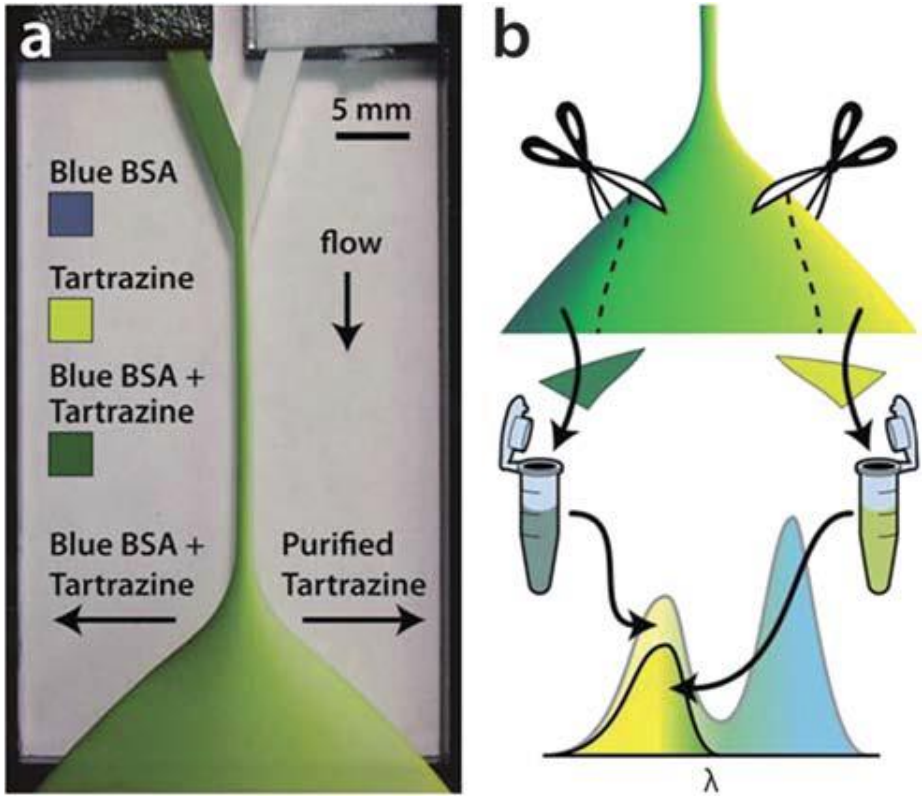


Analytical Chemistry, Vol. 81, No. 16, August 15, 2009

H filter in paper

Paper fluidics is typically simple.

However: many of the common microfluidic phenomena have been replicated in paper, such as mixing, gradient generation, hydrodynamic flow focusing and H filter.

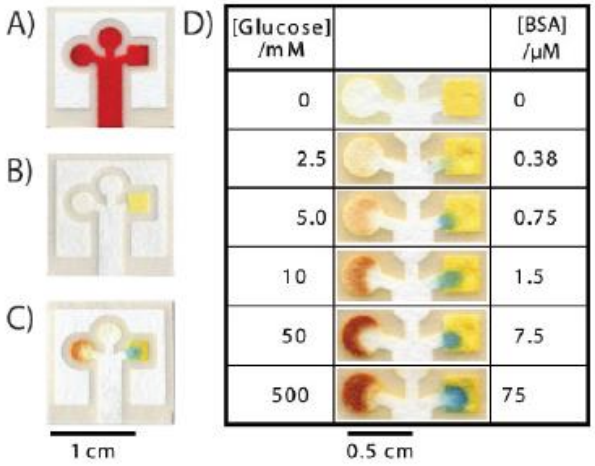


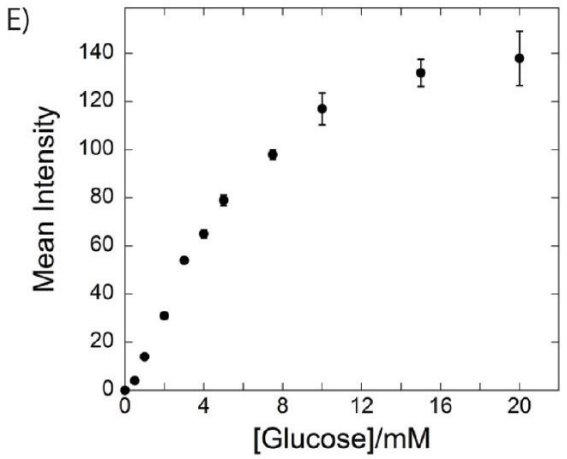
Paper fluidic colorimetric detection of glucose and proteins from urine

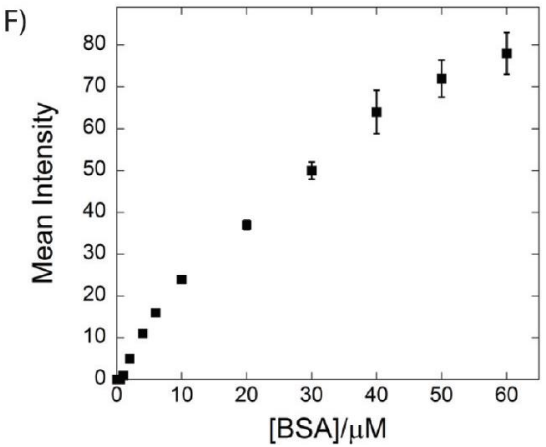
Paper fluidic device exposed to a urine sample containing glucose and a protein (BSA)

Glucose assay: enzymatic oxidation of iodide (clear) to iodine (brown) in the presence of glucose.

Protein assay: tetrabromophenol blue goes from yellow to blue as it ionizes and binds a protein.







Martinez, A. W.; Phillips, S. T.; Butte, M. J.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1318–1320.

Analytical Chemistry, Vol. 82, No. 1, January 1, 2010, 3-10

Paper as material

Paper advantages:

Capillary filling

Ultra cheap material, cheap fabrication techniques

Disposable (by burning)

White colour gives good background to colorimetric assays

Biocompatible and can be modified chemically to covalently bind e.g. proteins, DNA

Disadvantages:

Simple operations only

Usually limited to colorimetric detection

Adsorption problems.

Digital microfluidics

Keywords: no channel, no pump, droplets, electrical actuation

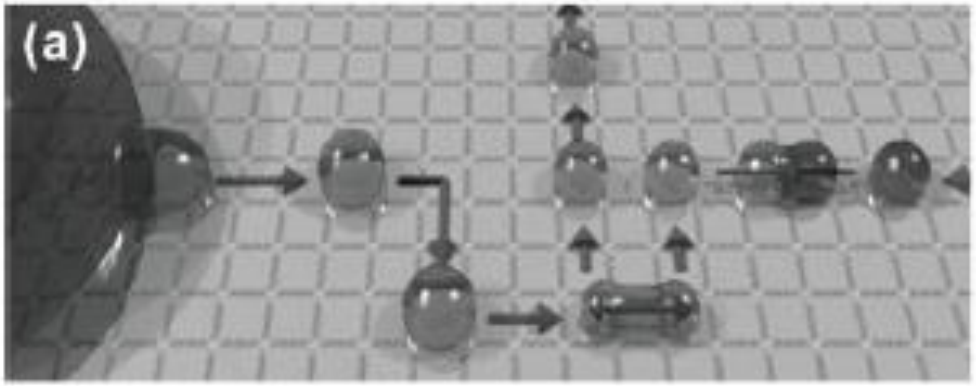
Digital microfluidics utilizes droplets on top of electrodes to perform programmable operations suitable for e.g. diagnostic assays.

The main advantage is programmability: there is no pre-determined channel network, so there is no pre-determined task the chip performs.

Instead: computer program can be coded to give instructions of where to move which droplet and when to merge, split, mix.

A single chip + battery + mobile phone software -> to perform all microfluidic tasks?

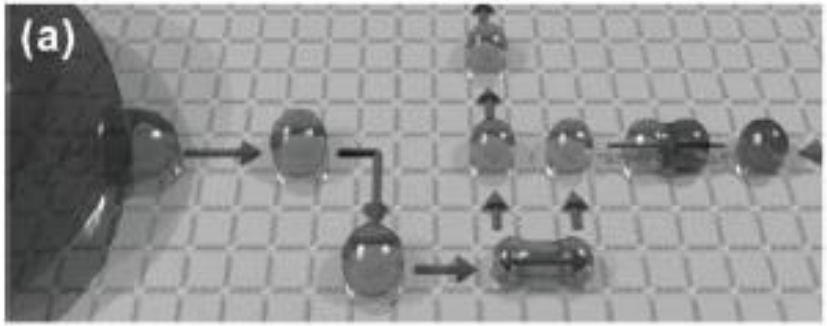
Most potential for point-of-care applications, especially in developing countries.

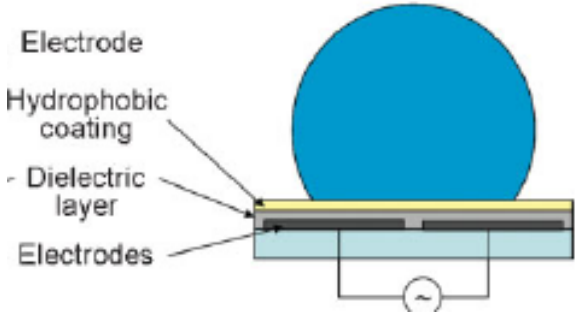


Digital microfluidics: Electrowetting

Droplets on hydrophobic surfaces, surface tension holds the droplets together
Either open surface or more commonly between 2 hydrophobic plates.

Electrowetting: electrical field used to modify the contact angle of the front edge into more hydrophilic -> Droplet movement on an electrode array

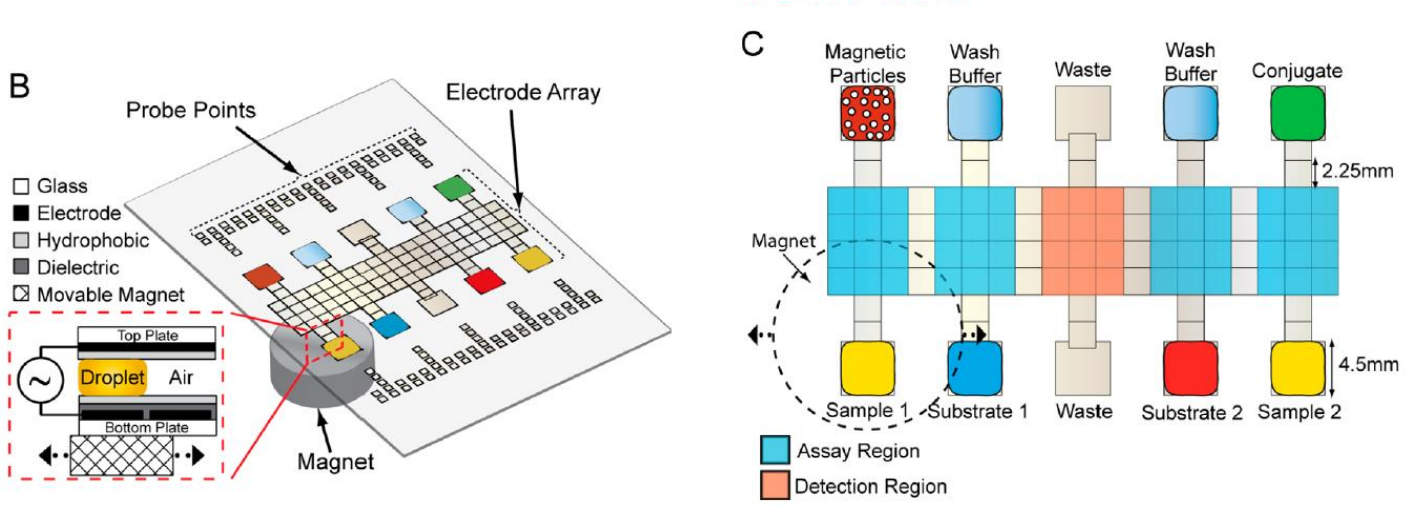




$$\cos\theta = \left(\frac{\gamma_s - \gamma_{ws}^0 + \frac{CV^2}{2}}{\gamma_w} \right)$$

V = applied voltage
C = capacitance
γ_s =solid surface energy
γ_w = water surface energy
γ^0_{ws} = water solid interfacial energy with no electric field.

Digital microfluidic immunoassay



Digital microfluidics used to perform all steps of a standard immunoassay (dose, mix, time etc.) dx.doi.org/10.1021/ac3020627 | *Anal. Chem.* 2012, 84, 8805–8812

Video example of DNA preparation using digital microfluidics

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

CD microfluidics

Keywords: channel, no pump, centrifugal actuation, geometric and hydrophobic valves

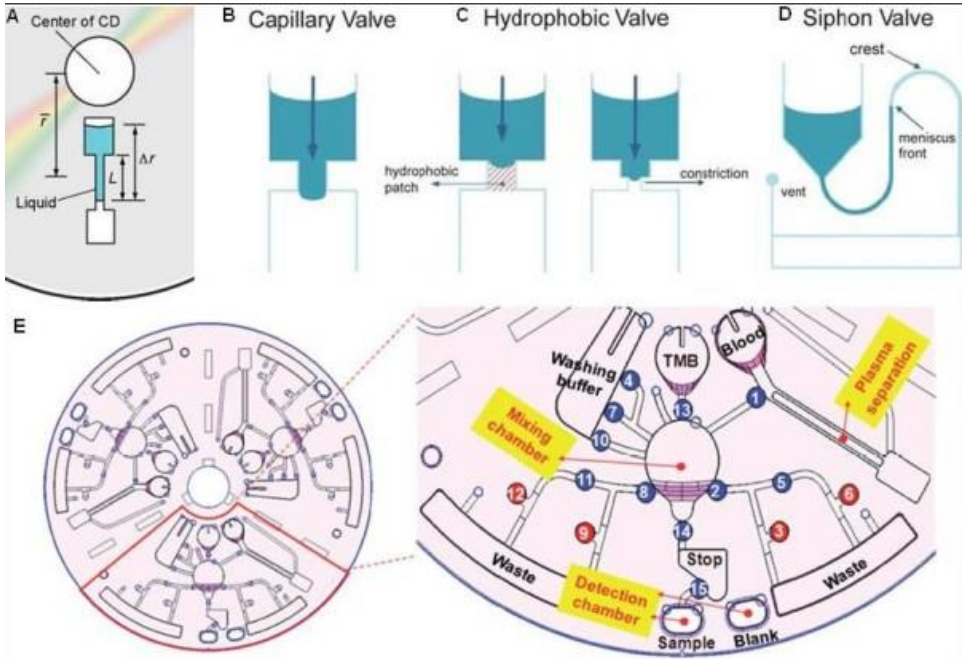
CD microfluidics utilizes centrifugal force to create the pressure to operate a microfluidic chip.

Flow is controlled by controlling the spinning rate (rpm) and capillary and hydrophobic valves.

Main advantage is “plug and play”. Sample is inserted onto the chip, the chip is inserted into a cd-player like machine and then the program is a series of rpm:s and times.

Capillary valve: an enlarging channel, which would force more liquid/air interface

Hydrophobic valve: a hydrophobic patch in a (preferably small) channel.



Shortest summaries:

	Main advantage	Throughput
Inertial	Label-free separation	HIGH (in Q)
Acoustic	Label-free separation	HIGH/MEDIUM
Droplet	Many discrete tests	HIGH (in experiments)
Paper	Extremely cheap	LOW
Digital	Programmable, flexible	LOW
CD	Convenient?	LOW/MEDIUM

Part 2: BioMEMS

Microfluidics
= the science of manipulating small amounts of liquids. (whether in channels or as droplets)

BioMEMS, Bio micro electromechanical systems
=A system for studying biological entities containing either a miniaturized electrical or mechanical component?

Microfluidics = the science of manipulating small amounts of liquids. (whether in channels or as droplets)

BioMEMS, =A system for studying biological entities containing either a miniaturized electrical or mechanical component?

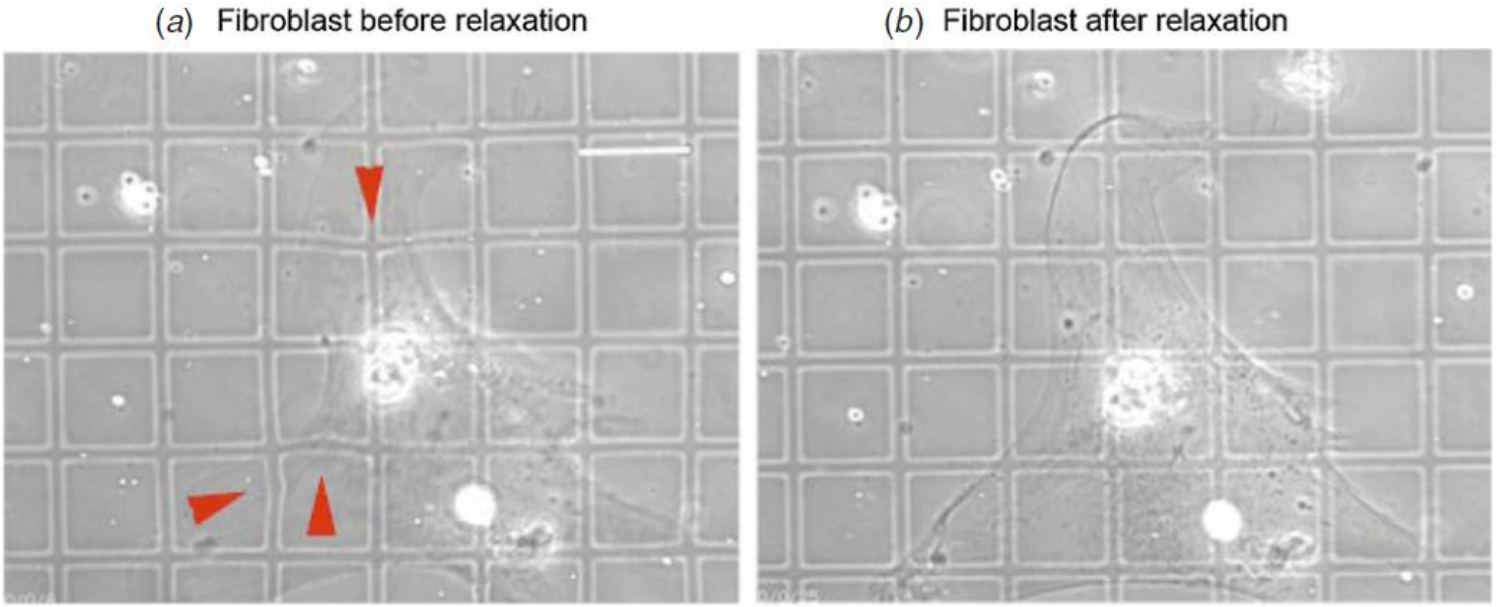
There is considerable overlap, and **the distinction is not very useful.**

Microfluidics but not BioMEMS	**Both**	**BioMEMS but not microfluidics**
Fluidic devices with no electrodes or moving parts e.g.	acoustofluidics digital microfluidics organ-on-chips	cantilevers microneedles microelectrode arrays
inertial microfluidics droplet microfluidics paper microfluidics	Any microfluidic chip with: -mechanical valve? -electrical detection?	Implantable chips

Mechanobiology 1

An easily deformable structure is used to detect forces applied by cells. This force is typically in the nN range.

Typically either a thin film cantilever (e.g. silicon nitride) or an elastomer polymer structure such as pillars or a grid.



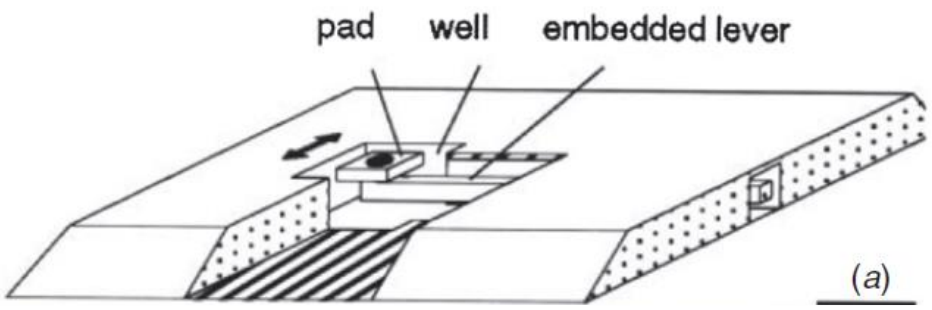
A thin PDMS sheet with grid markers. Contraction/relaxation of the cells warps the grid and allows force to be measured.

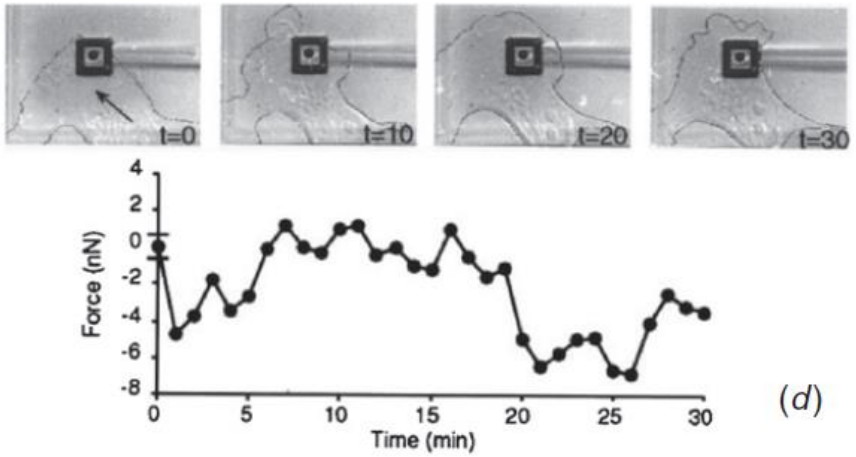
Balaban N Q *et al* 2001 Force and focal adhesion assembly: a close relationship studied using elastic micropatterned substrates *Nat. Cell Biol.* **3** 466–72

Mechanobiology 2: Cantilevers

Cantilever is a very typical MEMS component.

1. It deflects with a characteristic force (allowing forces to be measured)
2. It resonates with a characteristic frequency (allowing mass changes e.g. adsorption to be measured.



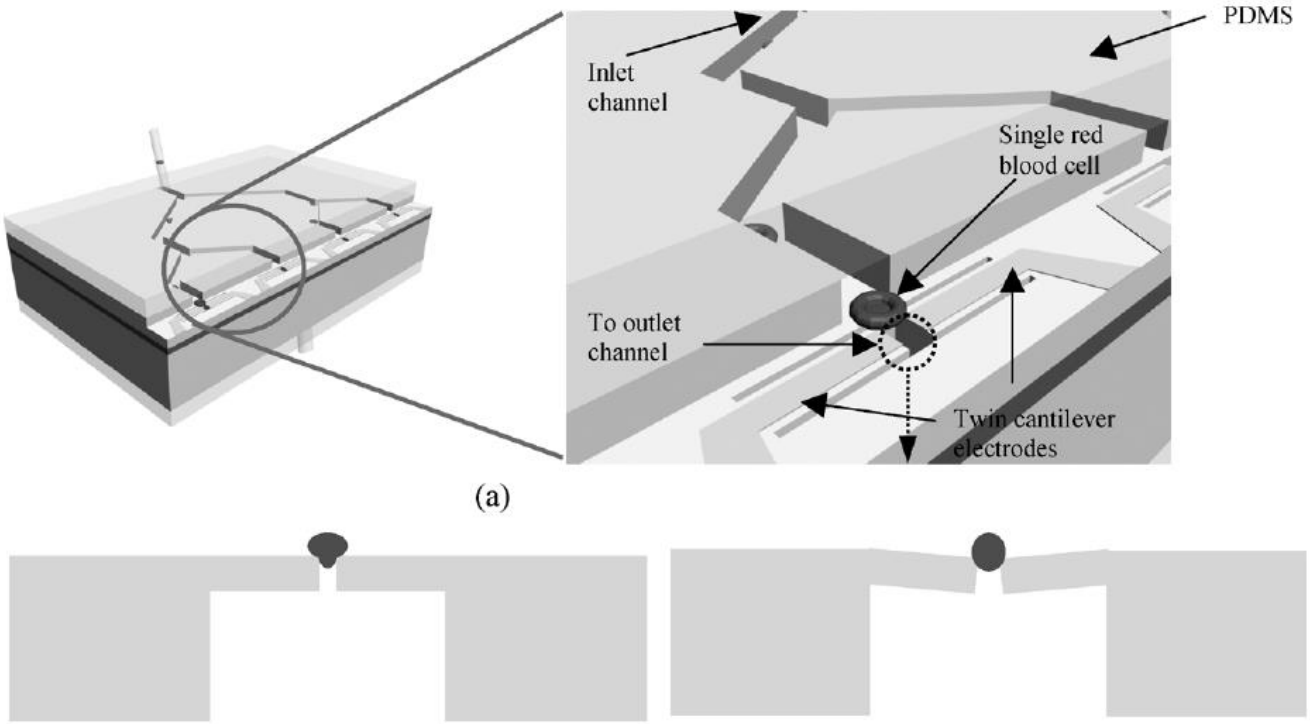


A fibroblast cell travels across a cantilever and the force the cell causes on the cantilever is measured from the deflection

Galbraith C G and Sheetz M P 1997 A micromachined device provides a new bend on fibroblast traction forces *Proc. Natl Acad. Sci. USA* **94** 9114–8

BioMEMS cantilever that is also microfluidics

A microfluidic chip brings blood cells through two cantilevers. If the cells are deformable (=healthy), they pass without causing the cantilevers to bend. If they are more rigid, the cantilevers bend more, which is detected.

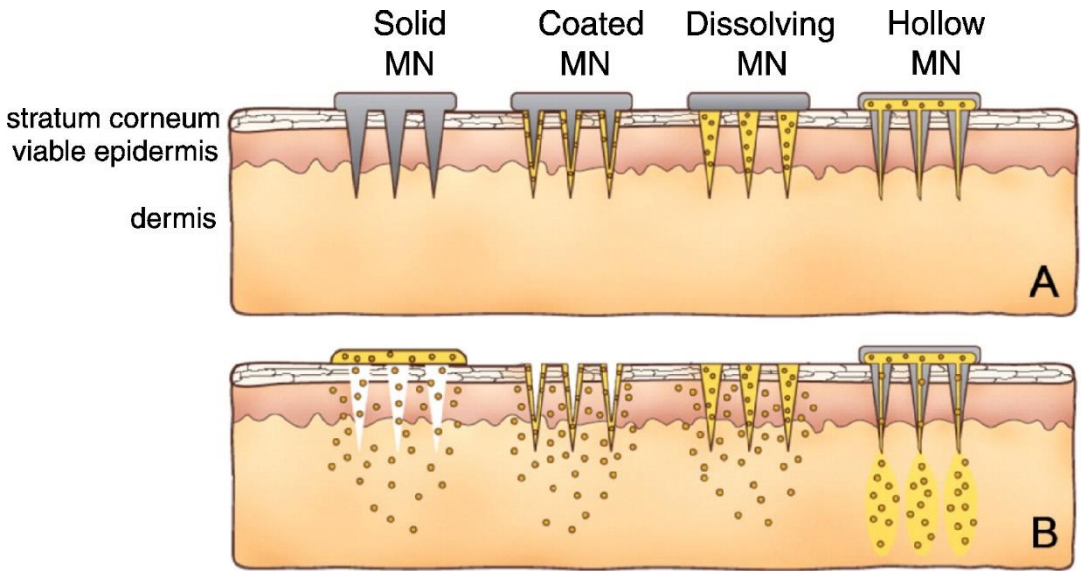


JOURNAL OF MICROELECTROMECHANICAL SYSTEMS, VOL. 15, NO. 2, APRIL 2006

Microneedles

"Macro" needles are needlessly large for delivering drugs. The skin layer that is impermeable to drugs is only few tens of microns thick.

Microneedles are in many cases sufficient and cause less pain and less tissue damage.

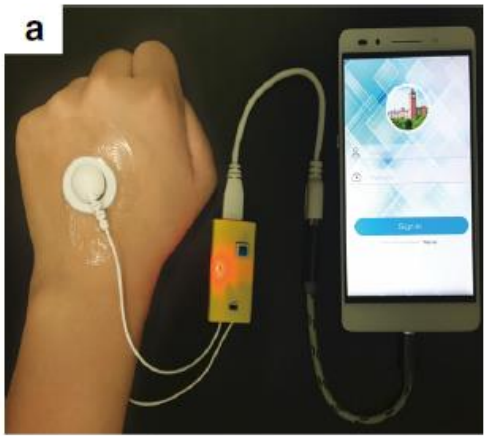


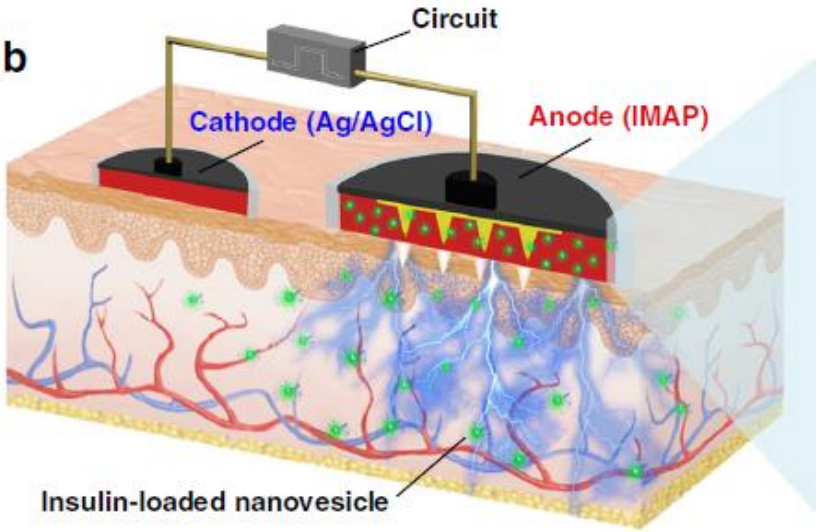
Advanced Drug Delivery Reviews
Volume 64, Issue 14, November 2012, Pages 1547-1568

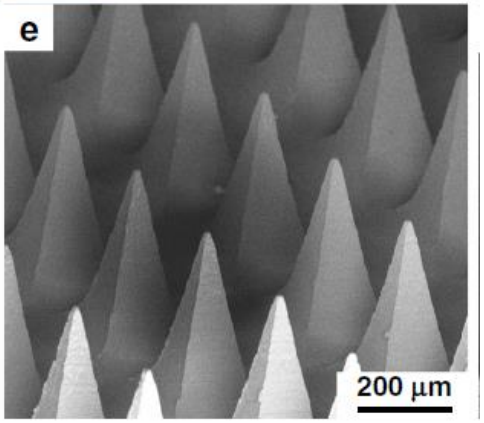
Microneedles 2

Microneedle array with added electrical dosing.

Drug is loaded into porous material (red in figure b).
PMMA microneedles (yellow in figure b) penetrate skin.
Electrical force causes charged drug vesicles to move into bloodstream







Yang et al. *Microsystems & Nanoengineering* (2020)6:112
https://doi.org/10.1038/s41378-020-00224-z

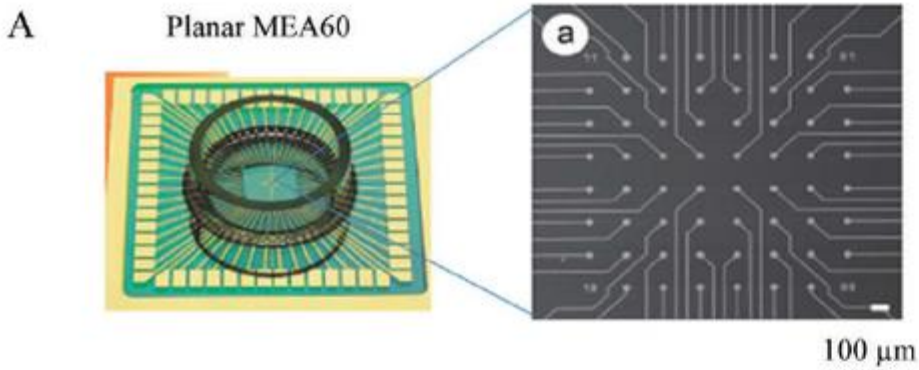
Microelectrode arrays

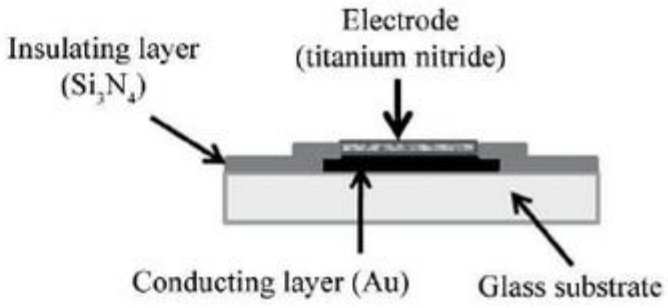
Microelectrode arrays (MEA:s) mean an array of spatially separated and individually addressable small electrode pads. Sizes and separations typically in 10s of microns.

Made from many (conductive) materials. Metals, carbon materials, transparent conductive oxides.

Electrodes can be flat or e.g. spikes to penetrate inside cells/tissue

Typical applications are electrical measurement and stimulation of cell cultures or tissue.





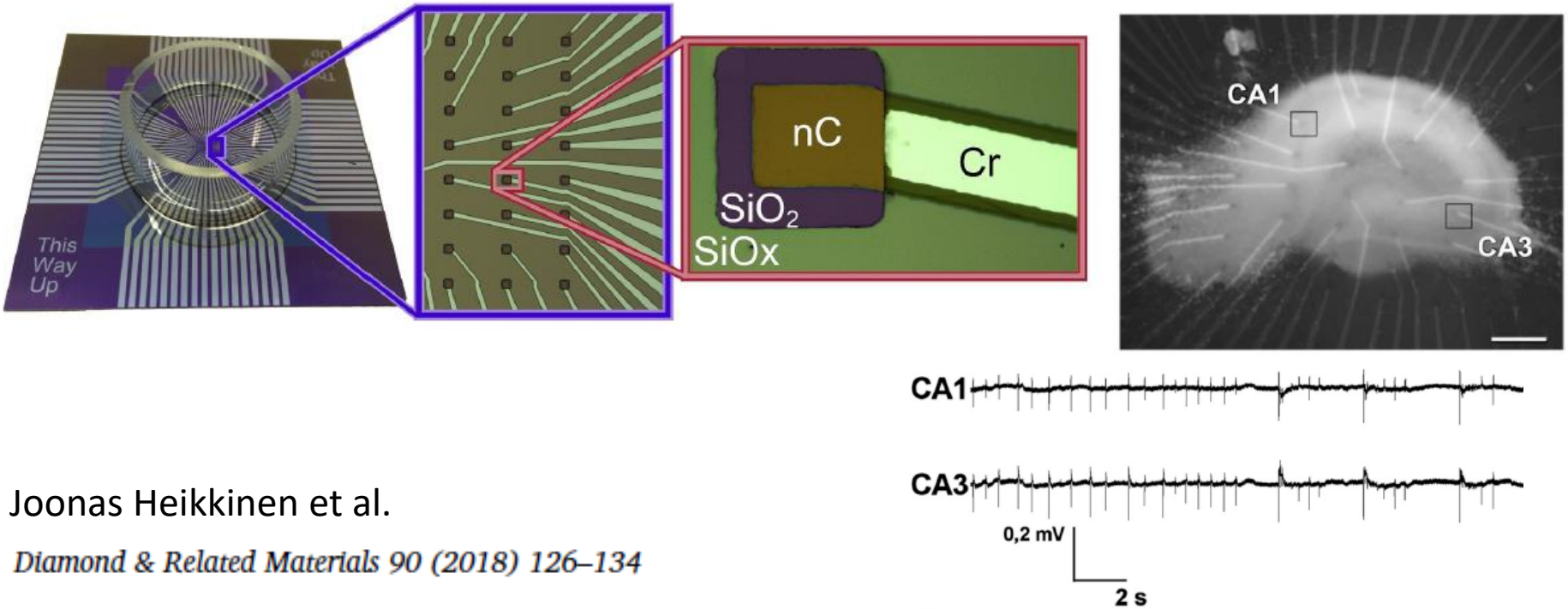
Egert et al. , Brain Res Brain Res Protoc, 1998

MEA for electrophysiology

Chromium wires with nanocrystalline carbon electrode pads.

A rat hippocampal brain slice is placed on top of the MEA.

Action potentials can be measured from any of the 32 electrode sites.



Joonas Heikkinen et al.

Diamond & Related Materials 90 (2018) 126–134

2nd half of course

Theme of the course in period IV: applications in chemistry, biochemistry, biology

No teaching during exam week (next week)

Design task 4 DL 3.3.2021 10:00

For design task 4, there is an opportunity to receive ≈15 minutes of tutoring either today 15:00-16:00 or Friday 9:00-10:00. Zoom link in lectures tab.

Poster project starts also 3.3.2021, we try to assign topics and pairs in the classroom session or during the week after.