Lab on a Chip and Microfluidics

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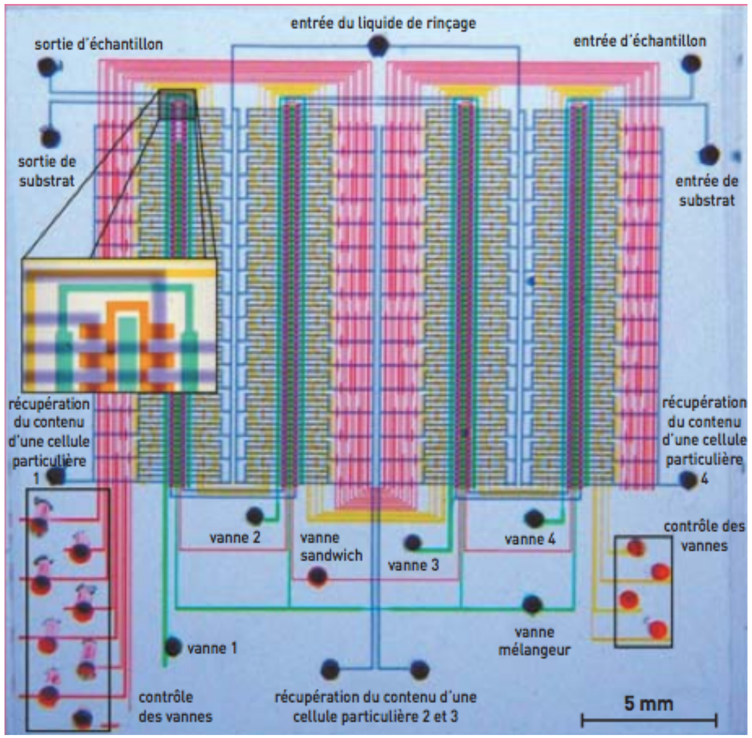
Part II. Lab On Chip technologies

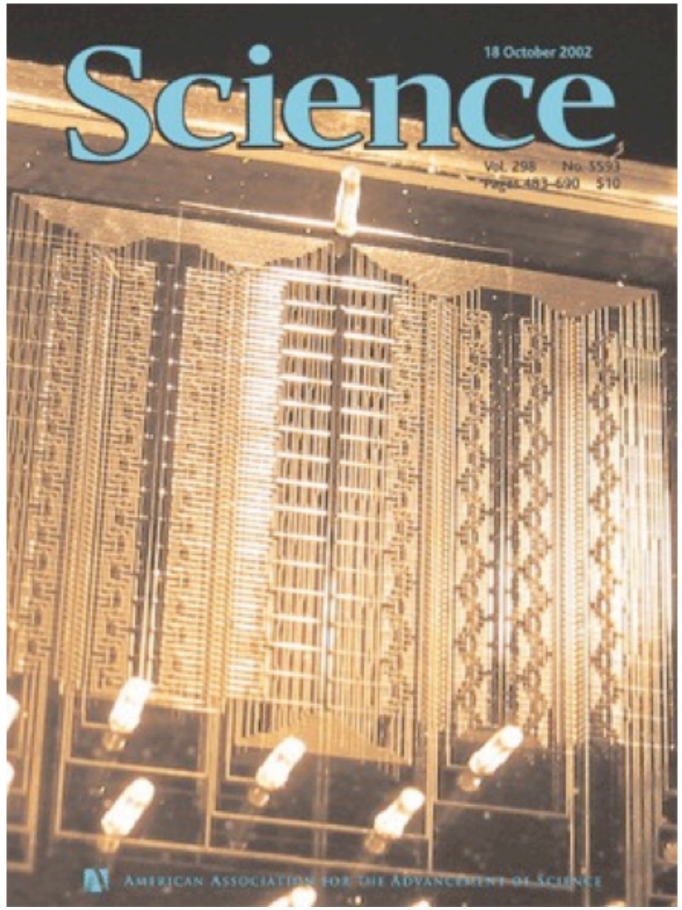
Lab On Chip

BioMEMS and microfluidics have started in 2000's

The idea is to use what has mad the success of microelectronics and MEMS to biochemical engineering and cellular biology.

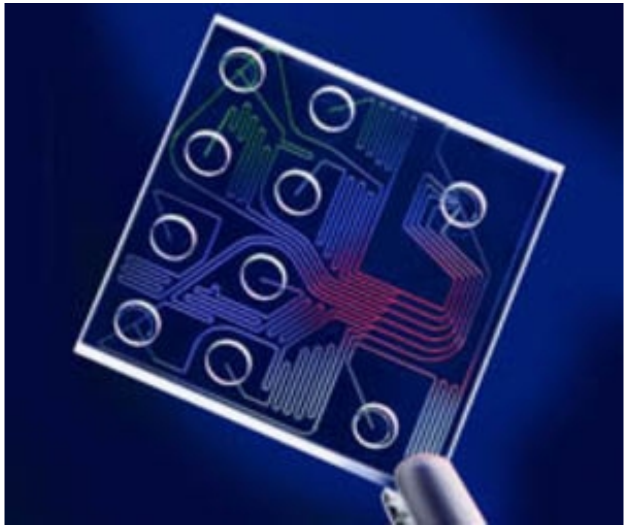
Miniaturisation
Integration
Parallelism
Batch Fabrication





Lab On Chip

Lab on chip (laboratories on chip)
µTAS (micro Total Analysis System)
Point of Care

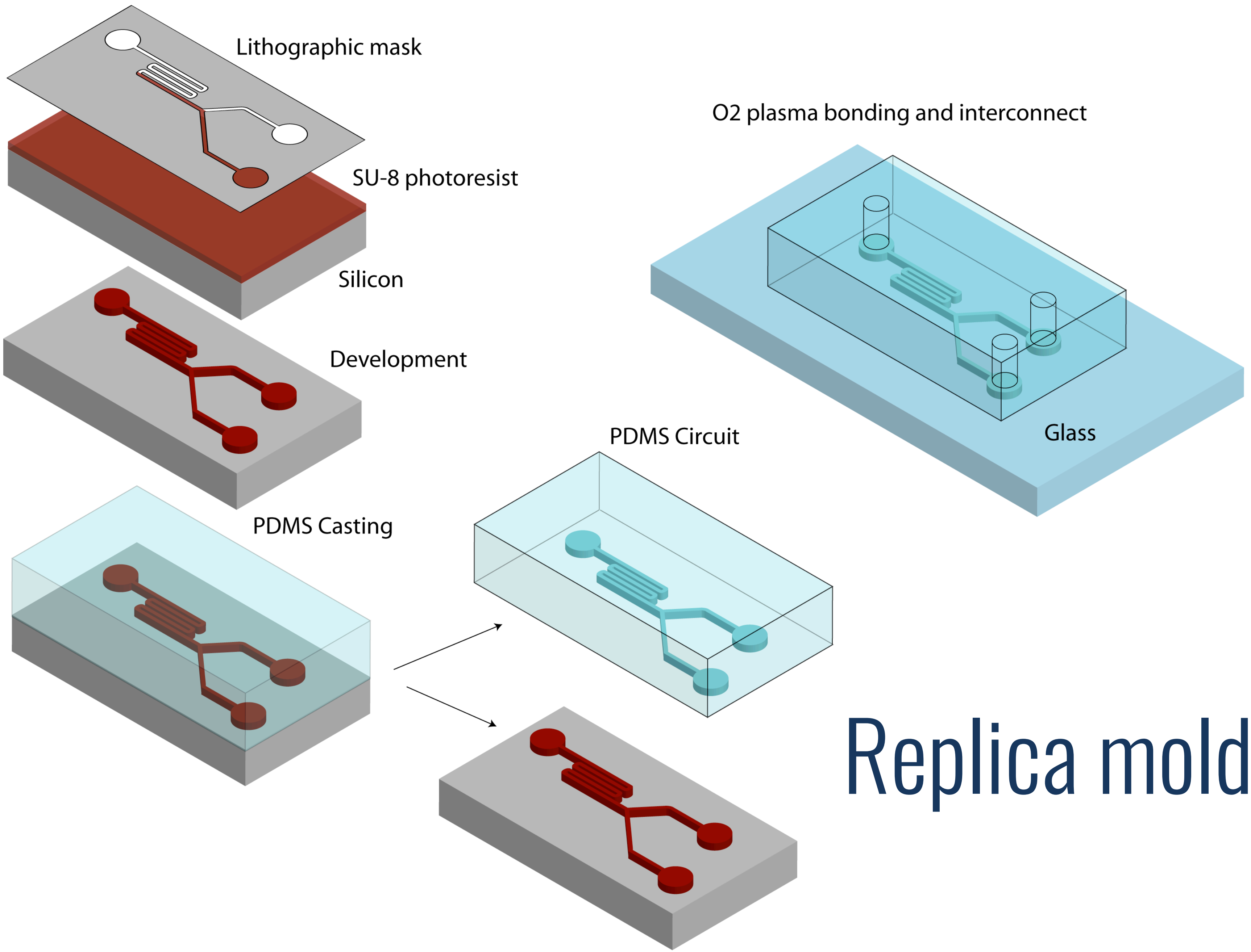


Functions operated on a Lab On Chip

Fluid transport (Electro-osmosis, Electro-phoresis, Hydrostatic pressure)
Preparation (Heating, Filtration, Extraction)
Separation (diffusion, electrophoresis, isoelectric focusing)
Mixing (diffusion, forced mixing)
Reaction (culture chambers, markers)
Detection (Chemiluminescence, electrochemiluminescence, fluorescence, Electrochemical detection, mass spectroscopy, Surface Plasmon Resonance)

How these devices are made?

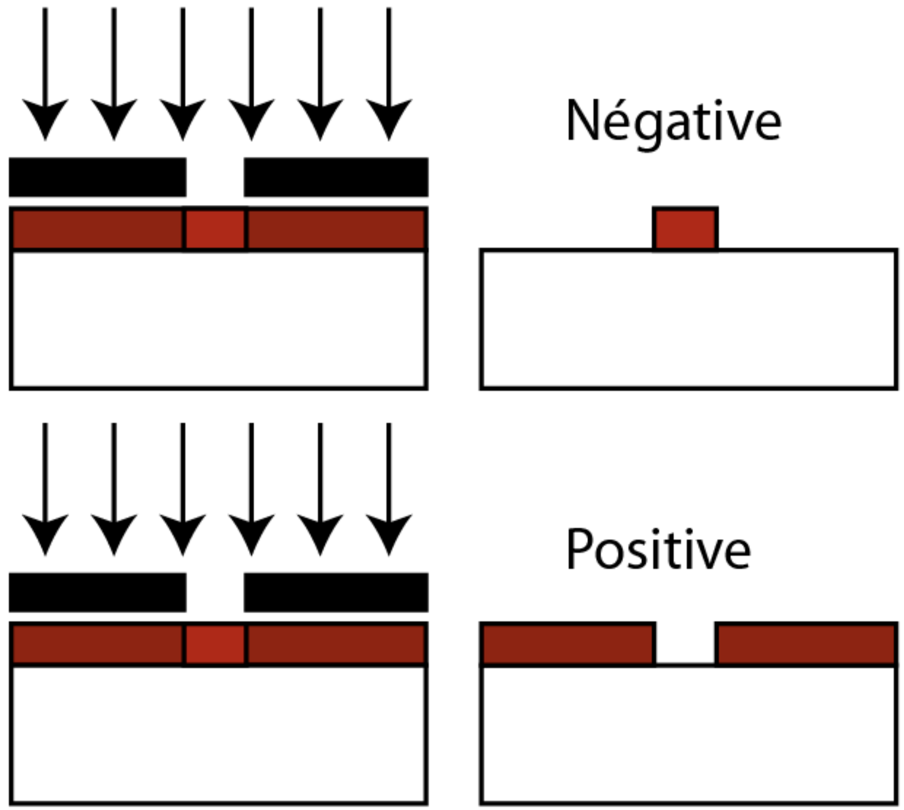
Microfluidic Technologies PDMS on glass



Replica molding

SU-8 photoresist

SU-8 photoresist is a negative photoresist that has the particularity to produce structures with high aspect



Microelectronic PR : 100nm to 2µm thick
S1818, S1805, AZ2020, ZPN 1150

SU-8 : from 2µm up to 200µm

900 Euro/500ml

SU-8 photoresist

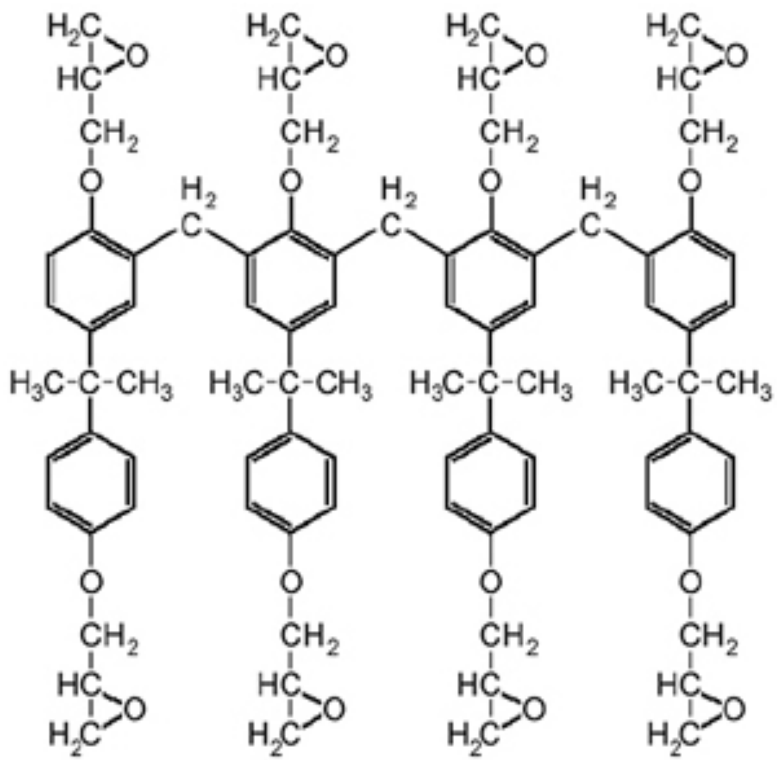
Composition :

Resist : epoxy (8 epoxy groups)

Solvant : Gamma butyrolactone

Photo initiator

Developator : 1-Methoxy-2-propanol acetate

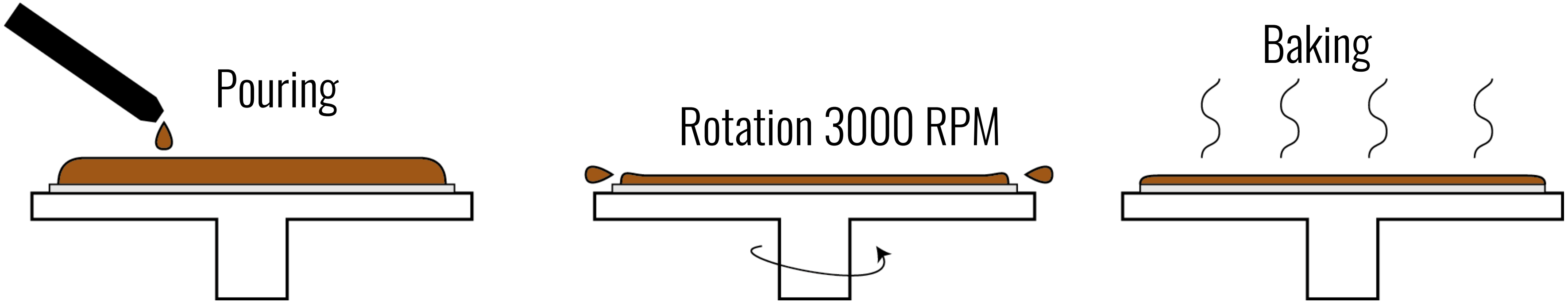


Photosensitivity with triarylsulfonium/hexafluroantimonate (CYRACURE UVI)

- High thermal stability (Tg > 200 °C).
- Low UV absorbance (high thicknesses)

SU-8 photoresist

Spin Coating



Baking, with slow temperature ramps, skin effect

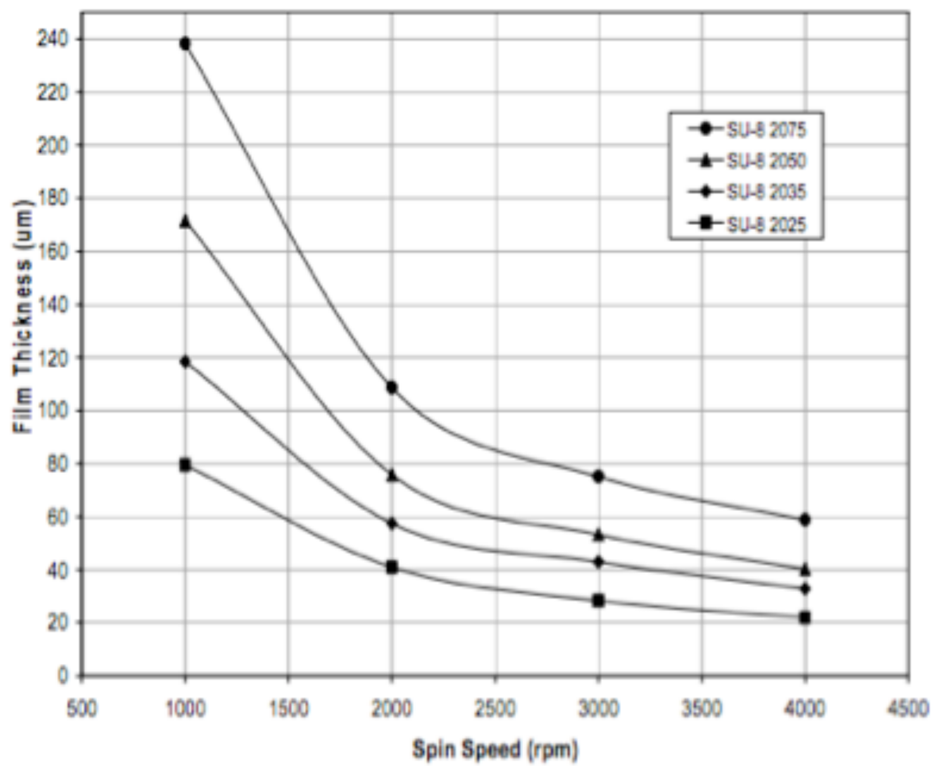
UV exposure (365 – 435nm) + Filter

Photolyse $Ar^{+}Sb^{-}F_{6}$ -> $H^{+}Sb^{-}F_{6}$ (strong acid)

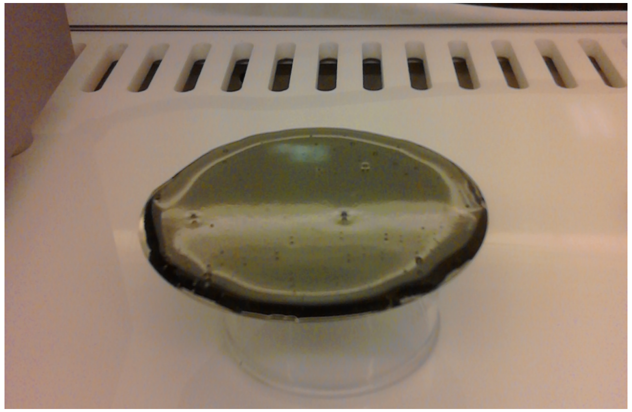
Pots exposure bake: catalysis of the cationic polymerisation and cross linking

Developpement : PGMEA

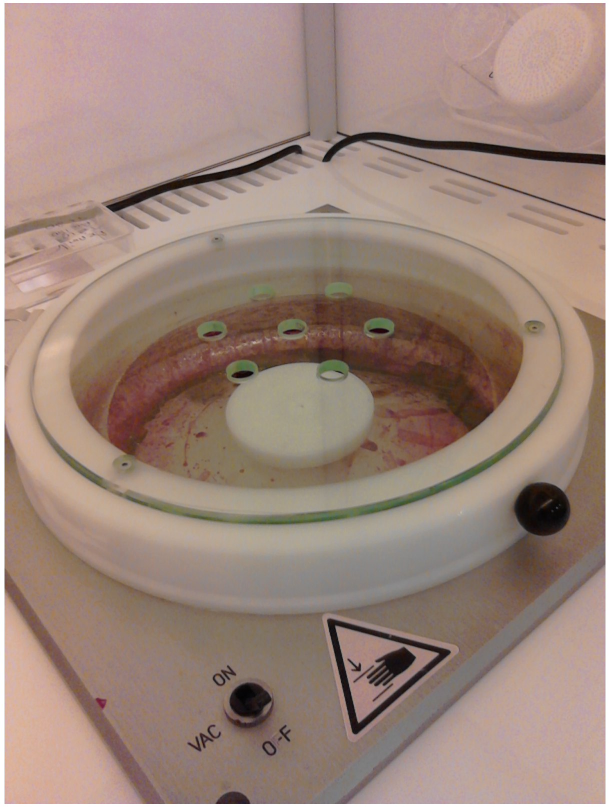
Rinse IPA



SU-8 photoresist



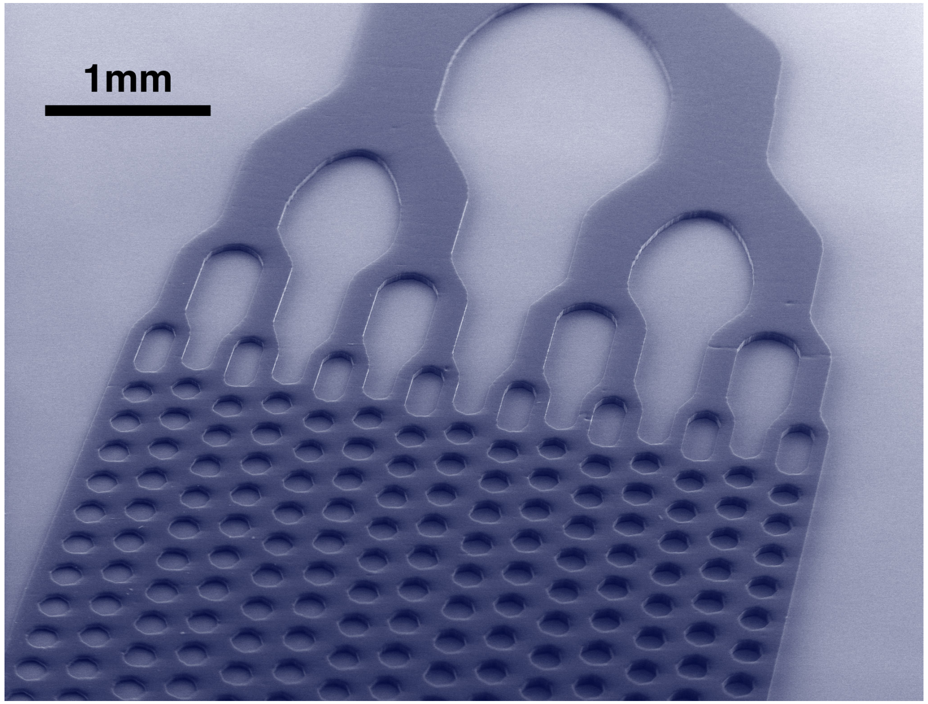
SU8 on 3 inches wafer

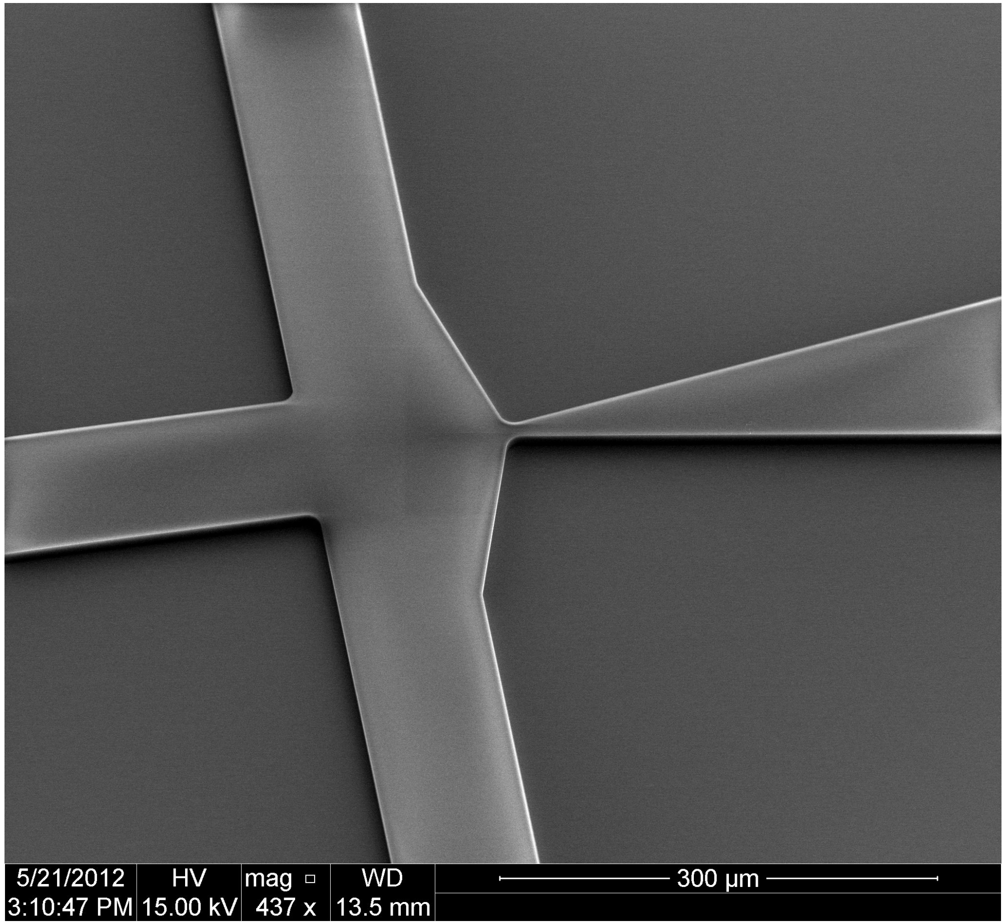


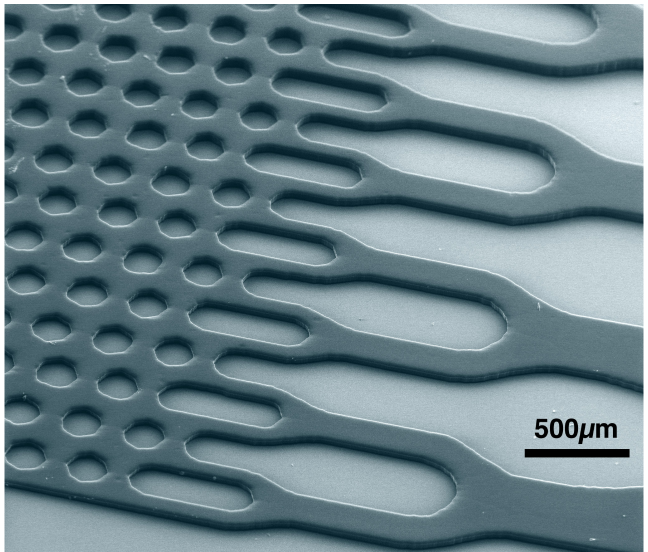
Spin coater

Hot plate

SU-8 photoresist

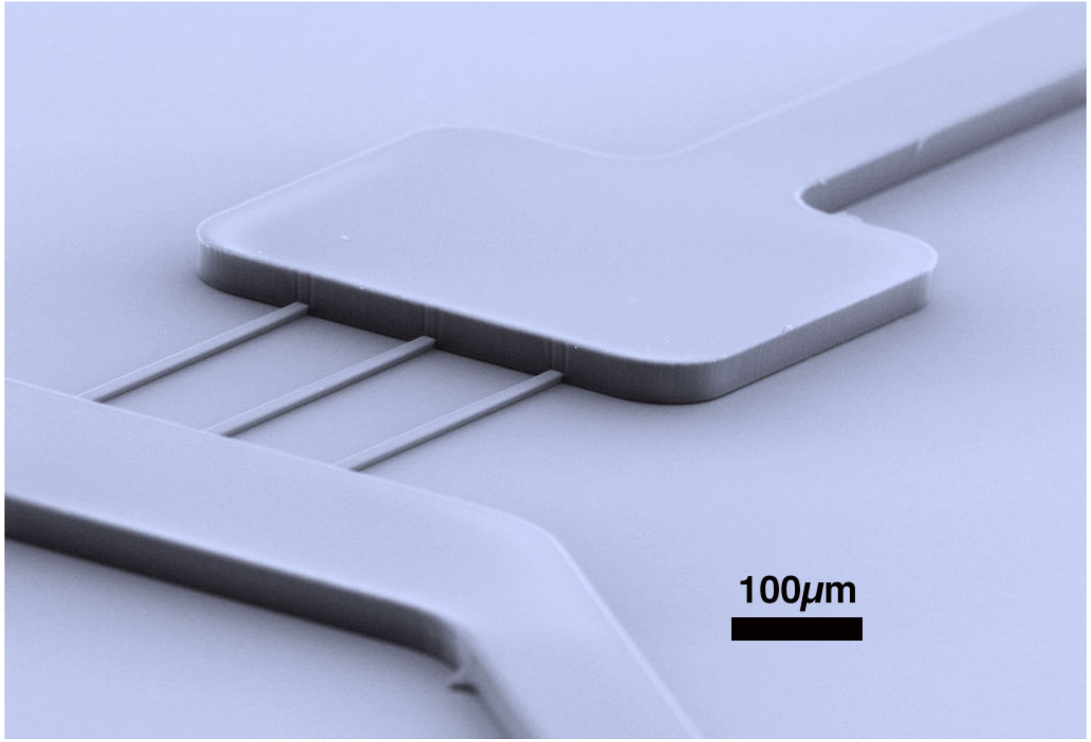


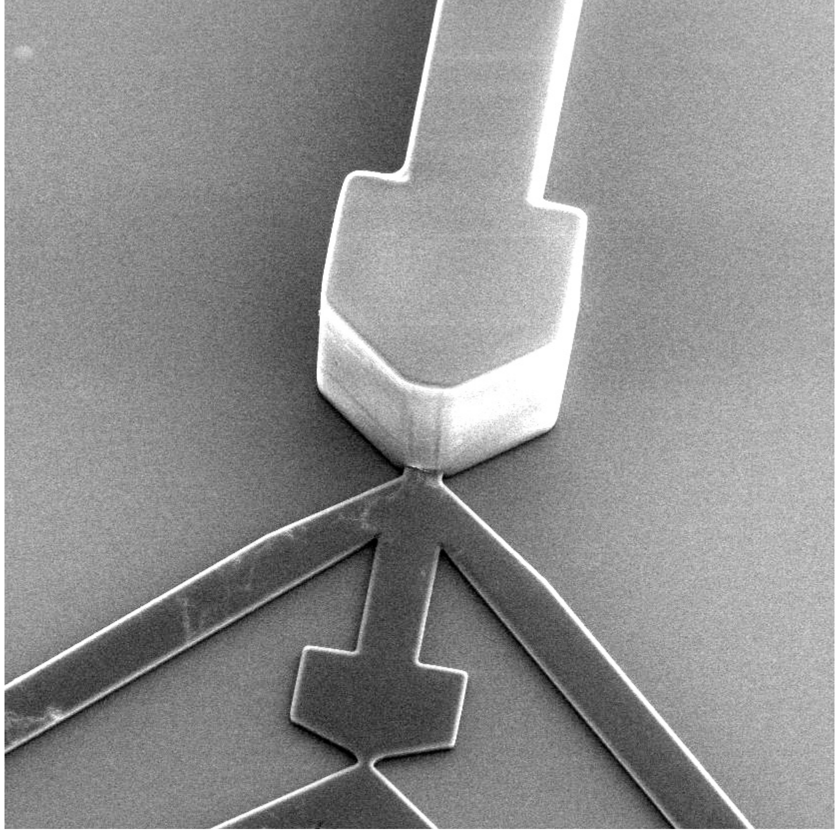


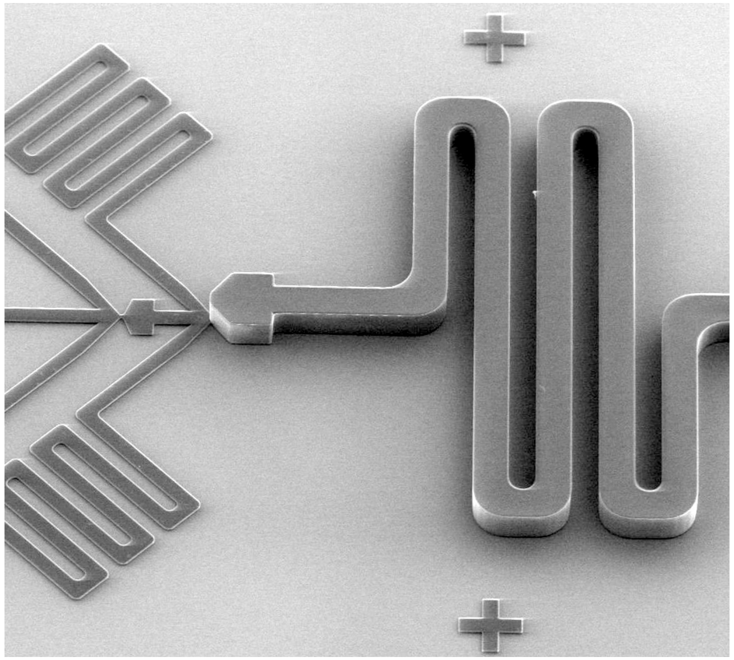


SU-8 photoresist

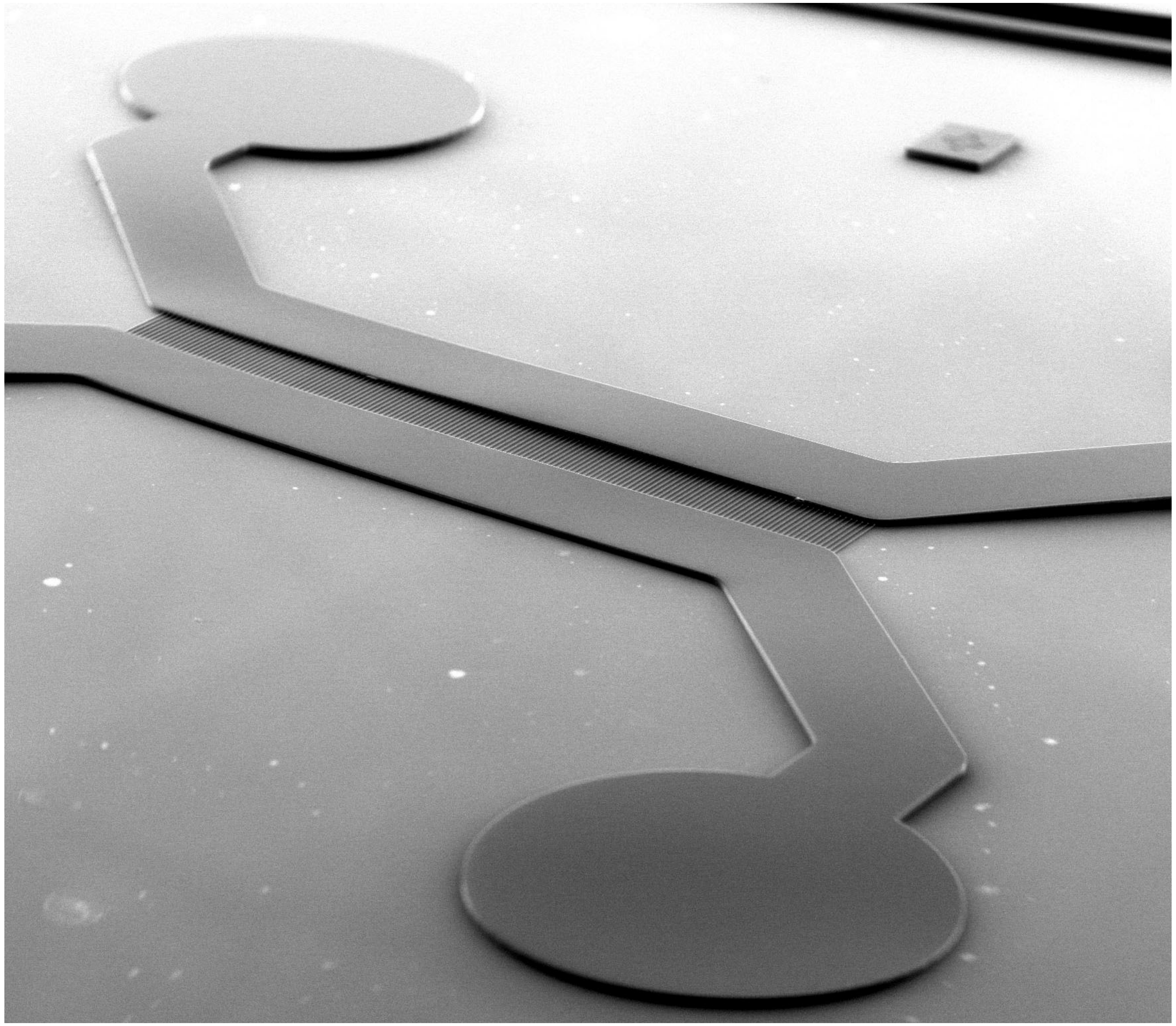
Dual thickness





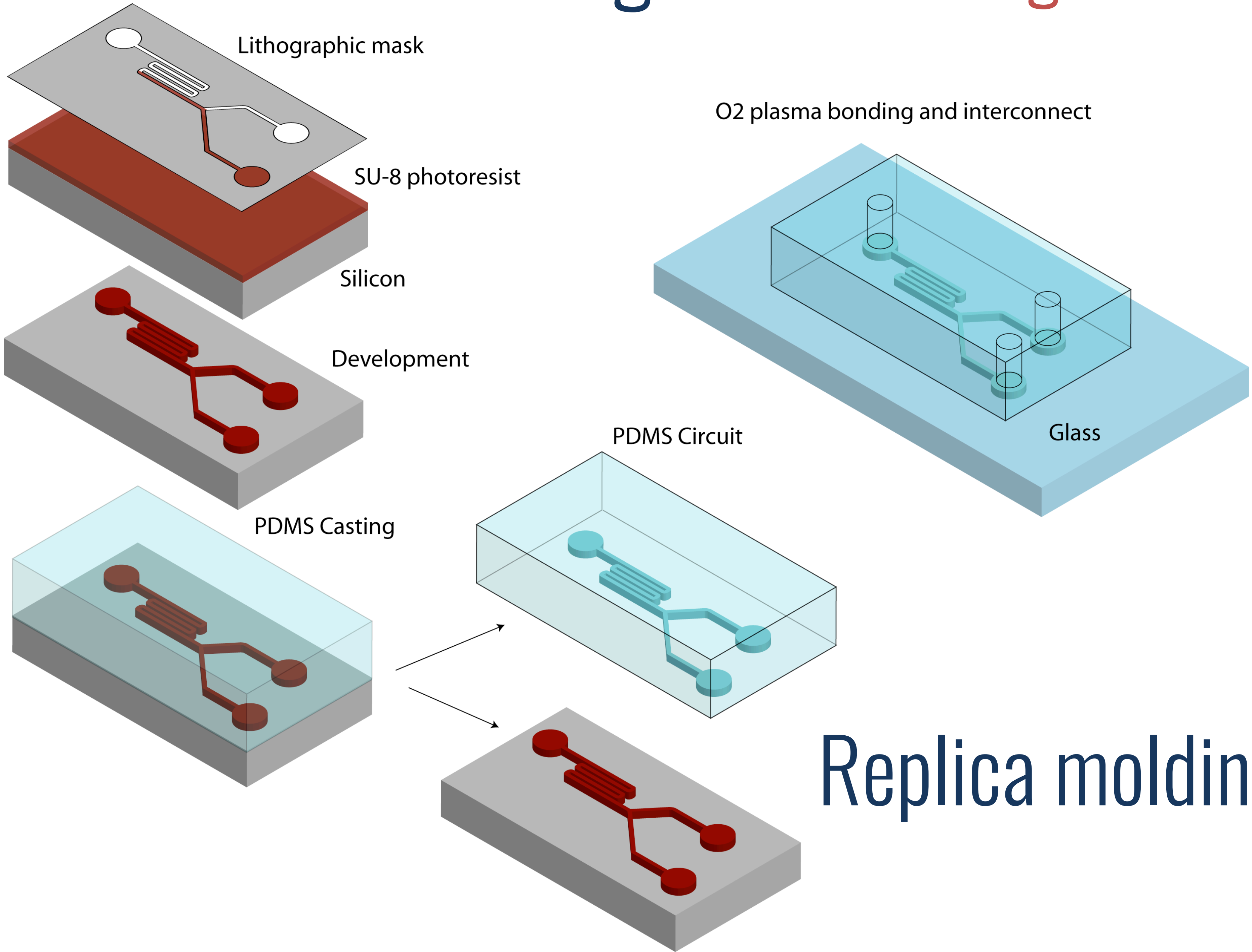


SU-8 photoresist



Microfluidic circuit for cell culture

Microfluidic Technologies PDMS on glass

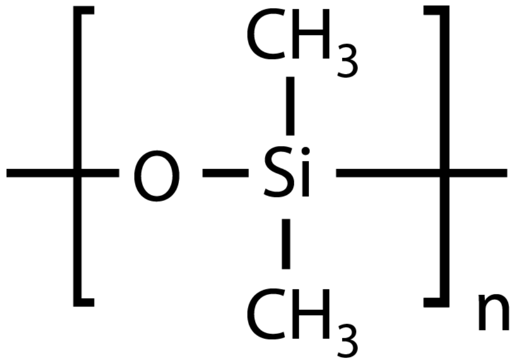


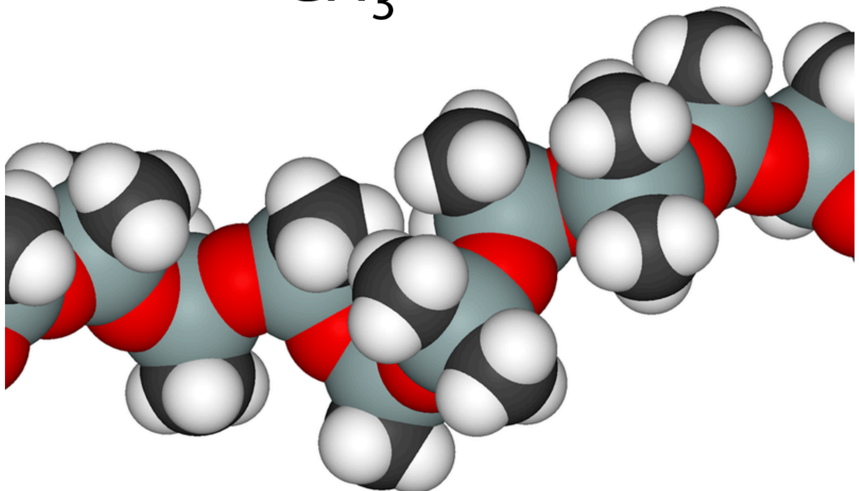
Replica molding

PDMS Polydimethylsiloxane

Can be found in Coca cola and shampoos

PDMS is a silicone polymere





Properties

- Hydrophobic
- Transparent
- Soft (E=1Mpa)
- Diffusion (of gazes)
- Bonding

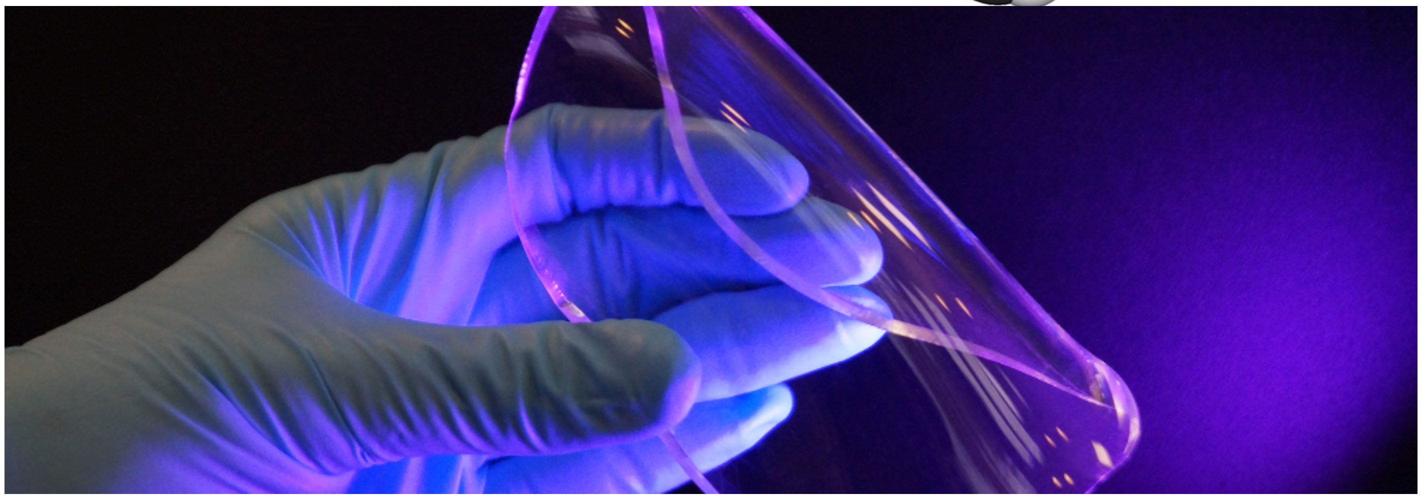
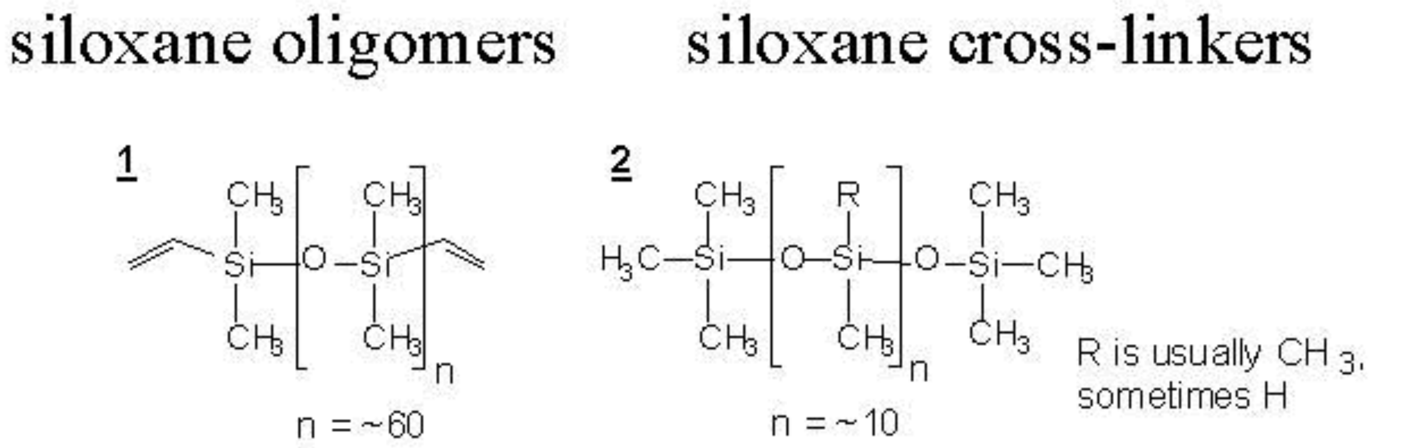
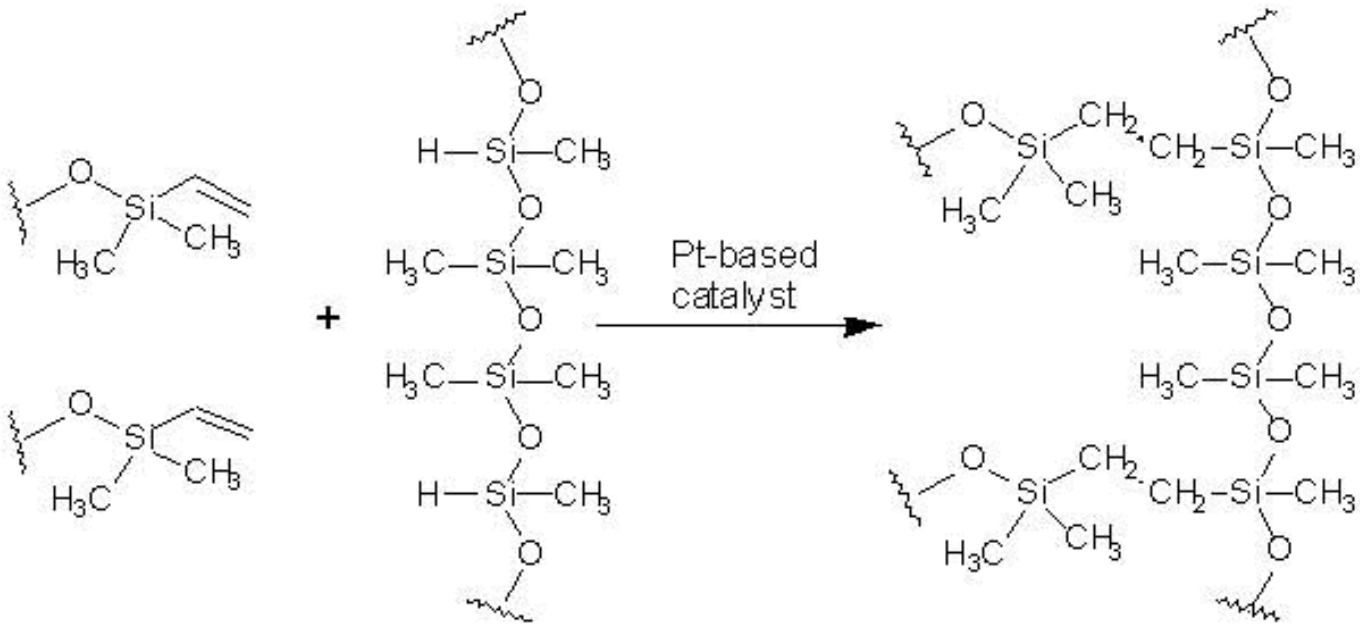


Image : Elveflow

PDMS

PDMS is a viscous liquid
That becomes solid by
reticulation

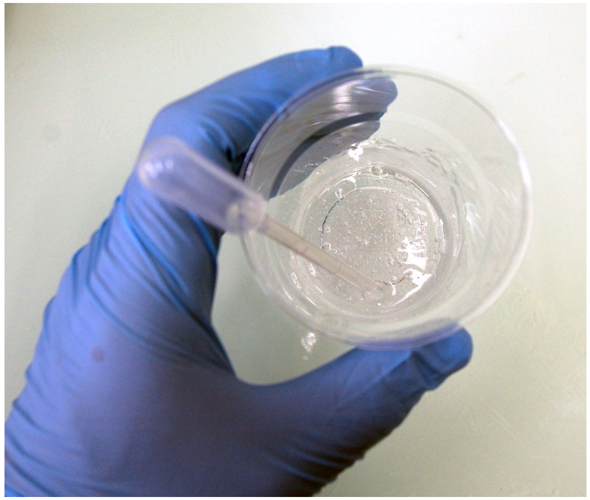


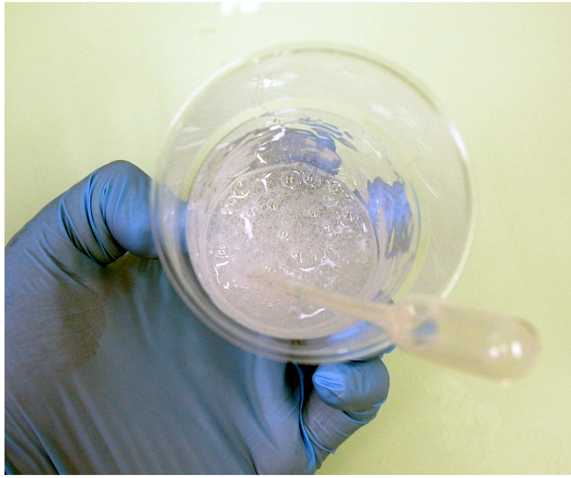


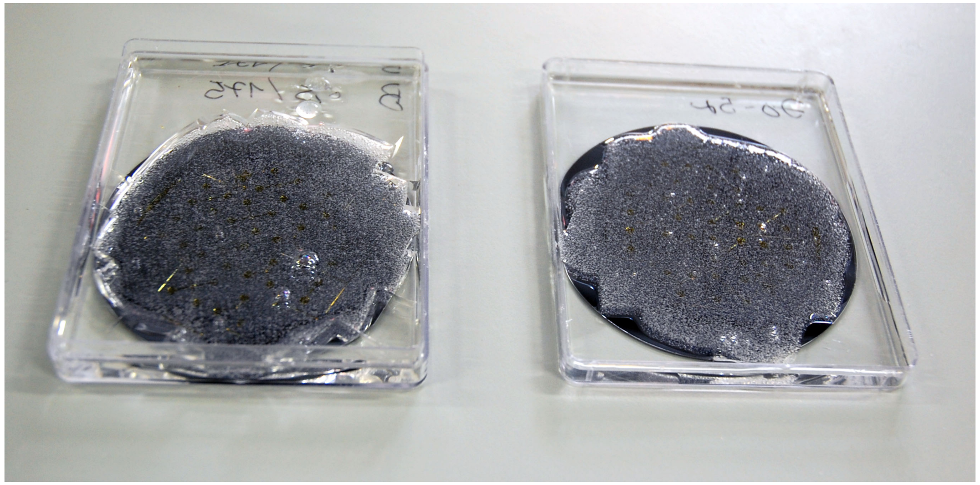
PDMS process

Mixing PDMS + hardener 9:1

Molding on wafer

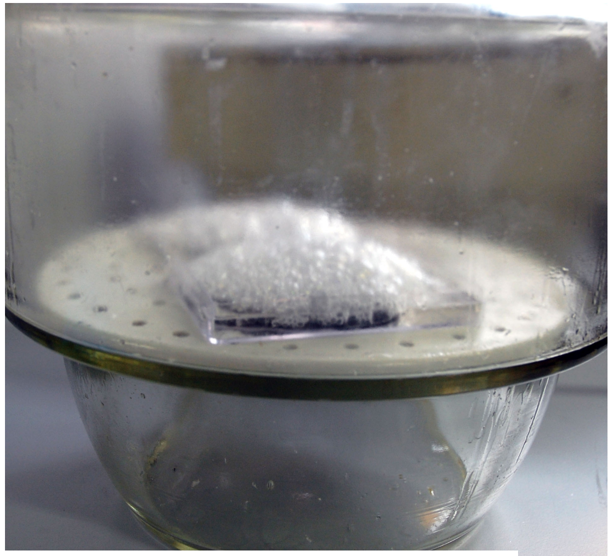


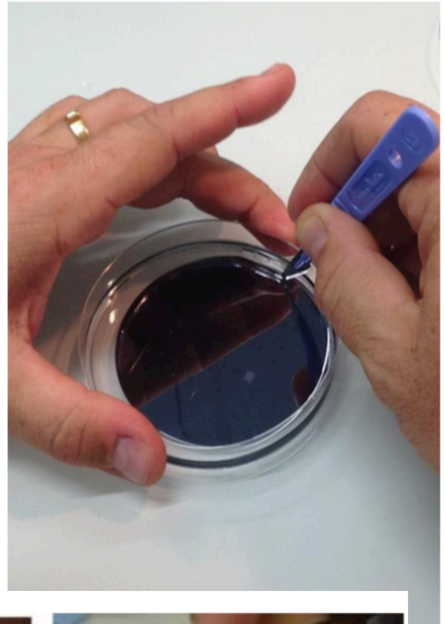


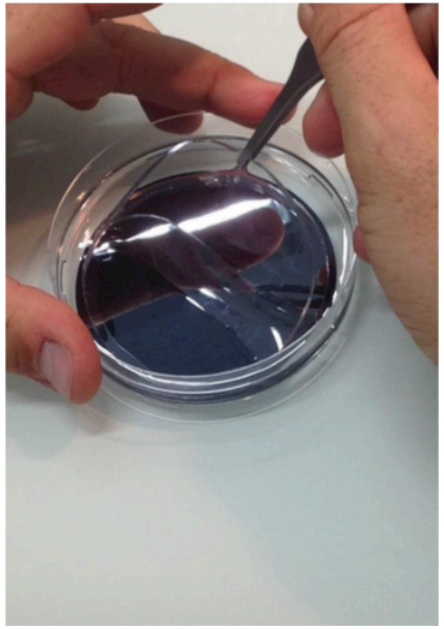


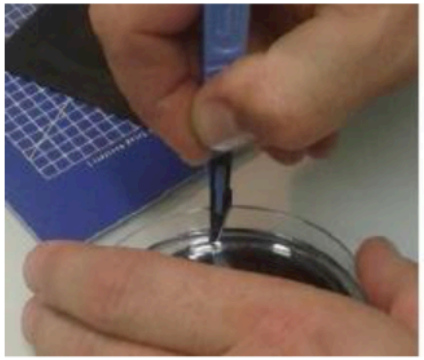
PDMS process

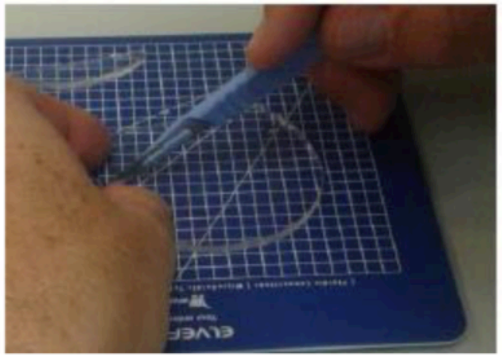
Degaz (vacum or centrifuge)
Baking (70°C for 2 hours)
Extraction
Punching
Bonding







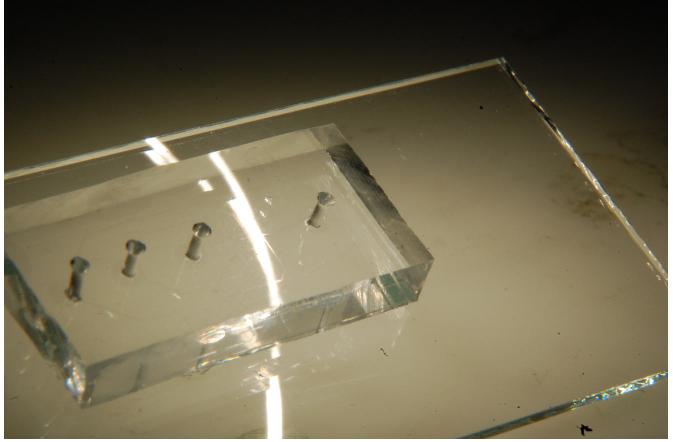




PDMS Bonding

PDMS surface is hydrophobic, composed of Si-$(CH_3)_3$

Plasma treatment replaces it with Si –OH (silanol group)



When two surfaces are plasma activated and enter in contact :

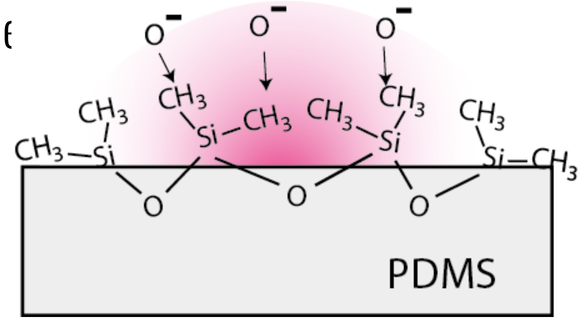
Silicone – Si-OH + Glass–Si-OH -> Glass–Si-O-Si-Silicone +H_2O

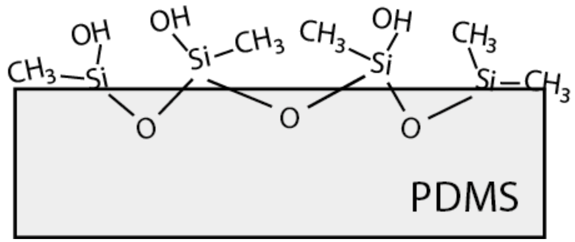
It works with every material containing Si (Glass, PDMS, SIO_2, Si_3N_4, ...)

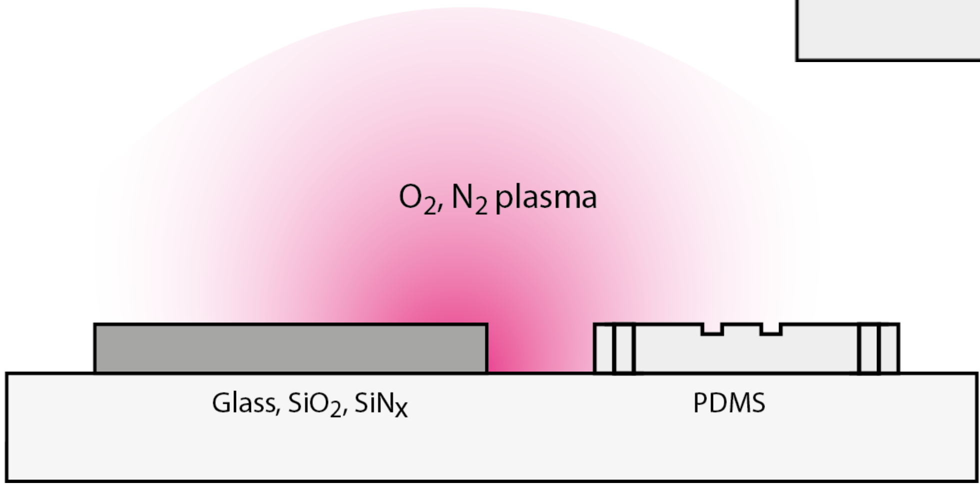
Note : Plasma activation fades in about 20 to 30mn (diffusion non crosslinked chains)

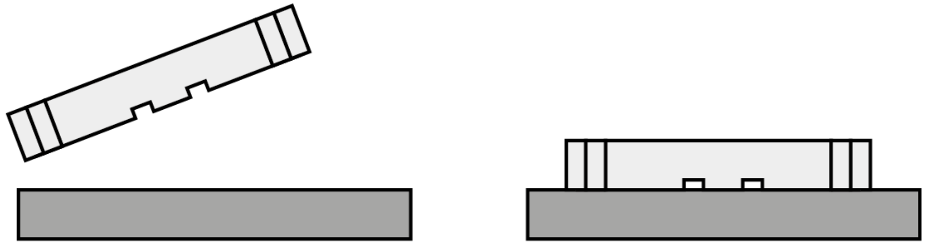
Requires a perfect contact (flatness, dust, particle

Moisture can be a problem





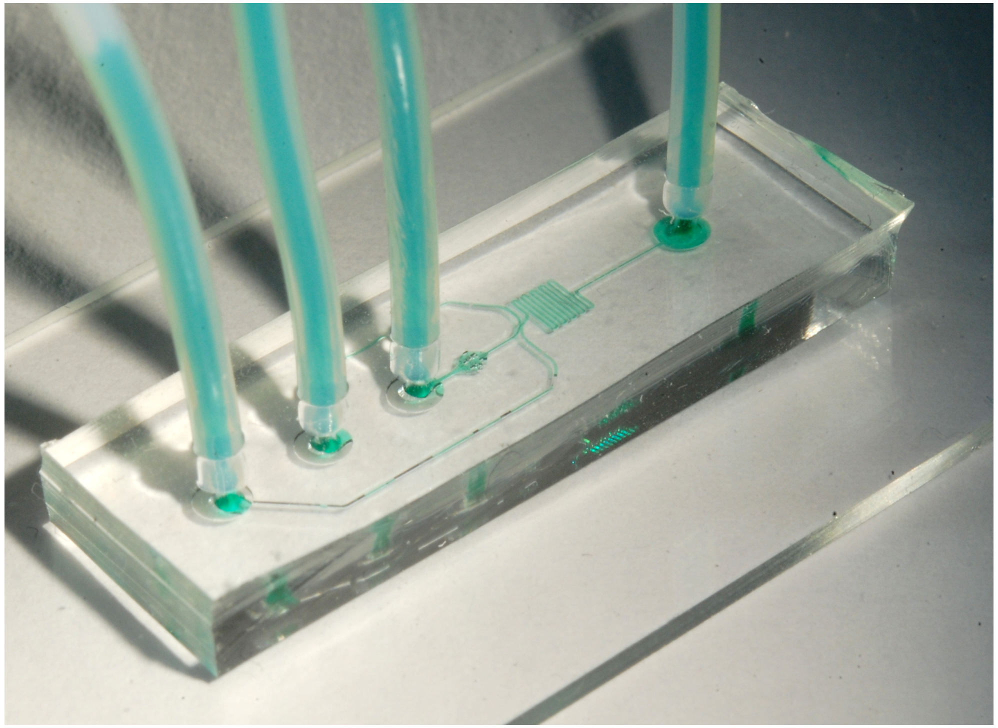


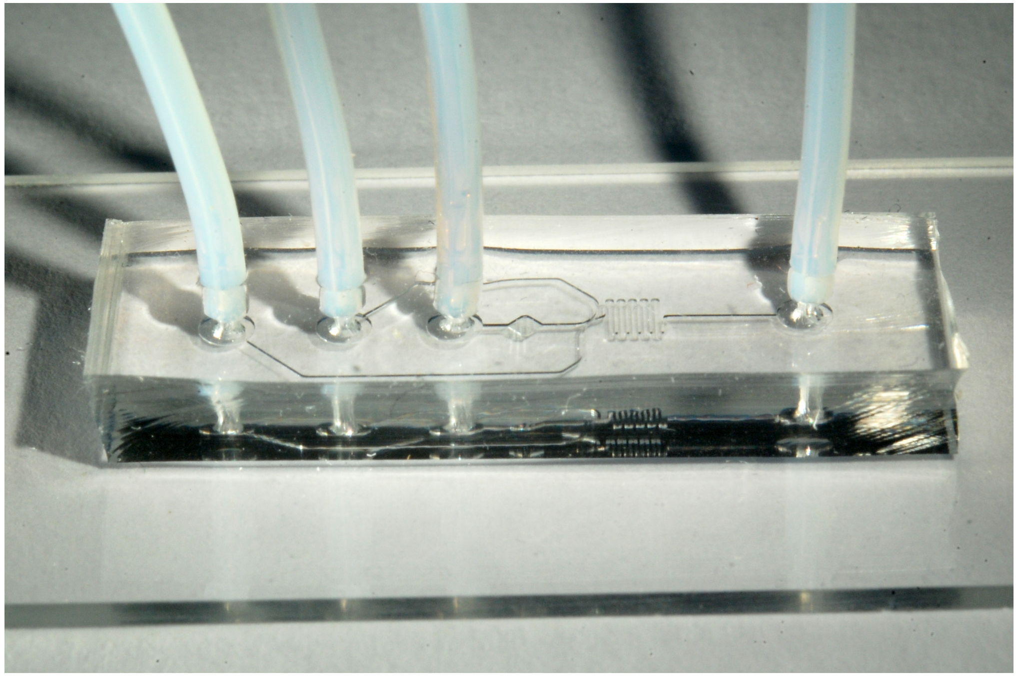


PDMS plasma bonding is strong and irreversible

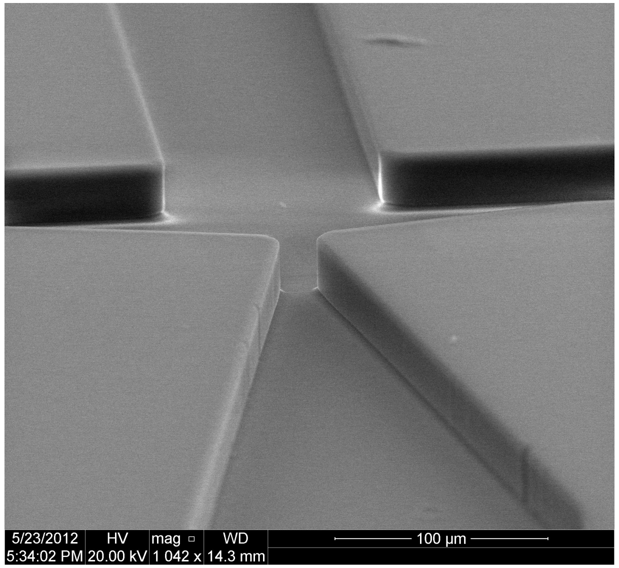
PDMS

Input Outputs

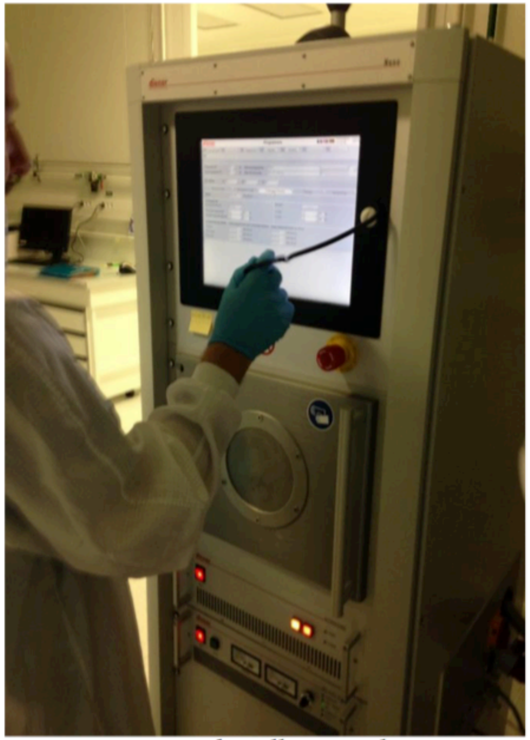


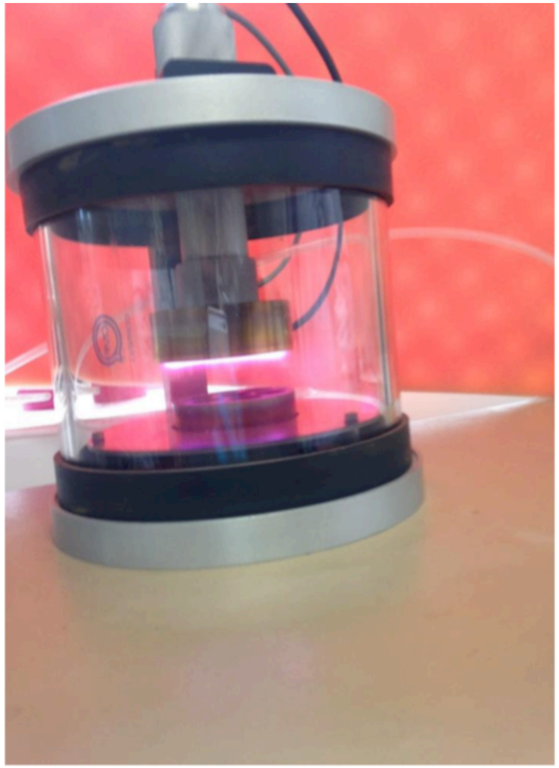


PDMS Bonding

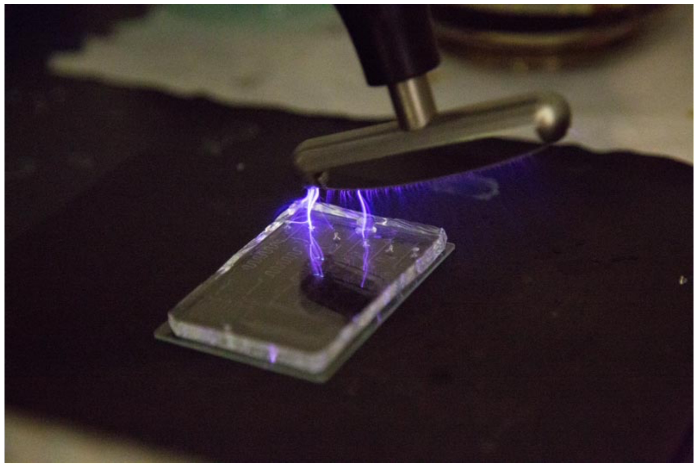


SEM of PDMS circuit

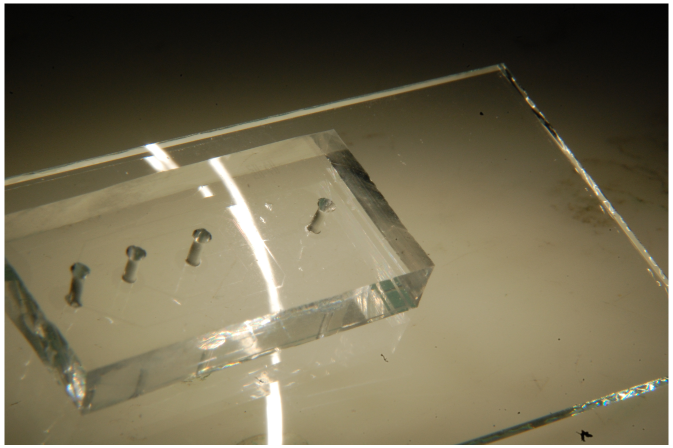




Plasma reactors



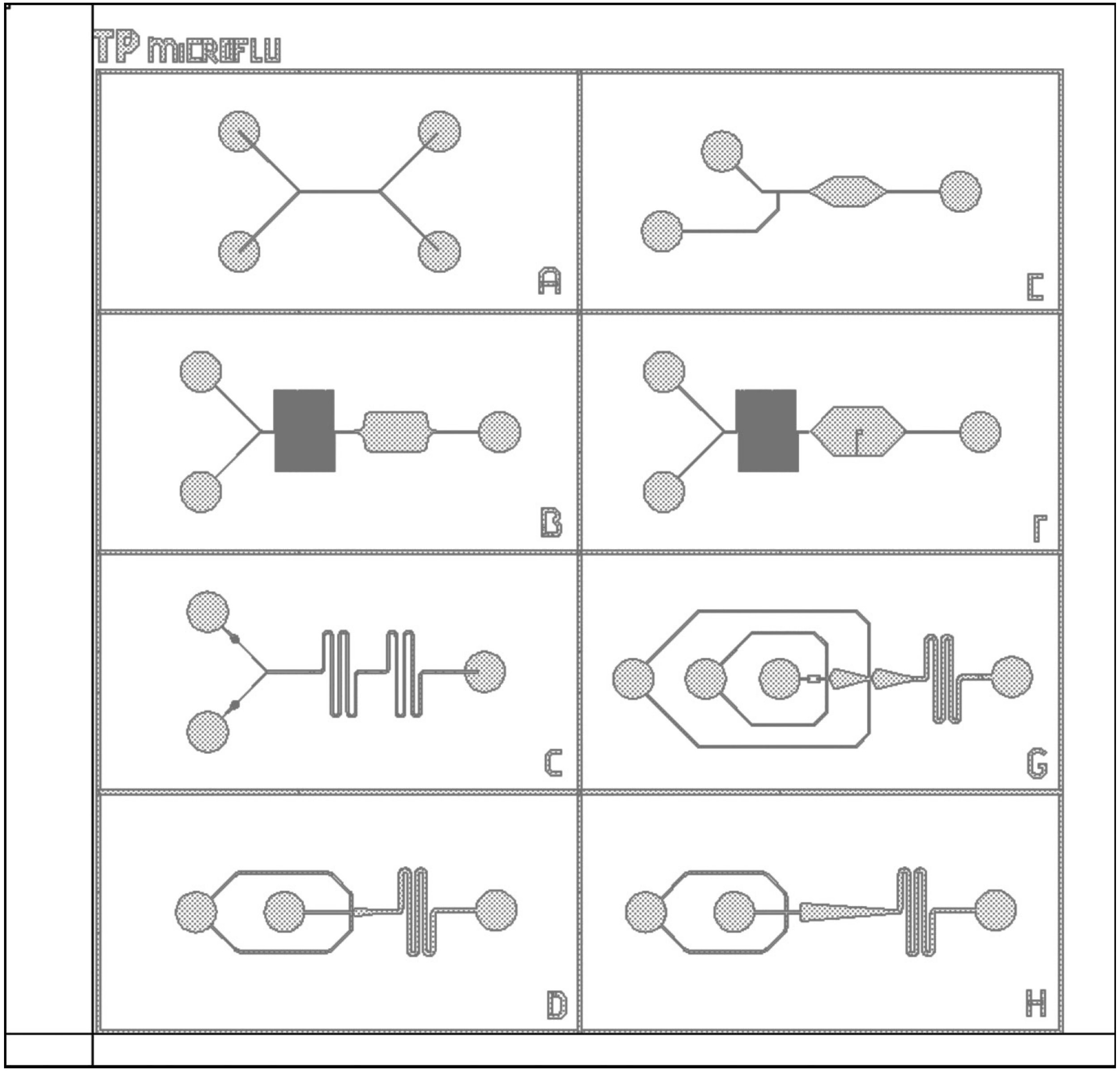
Alternative : Corona discharge



PDMS bonded on glass

PDMS

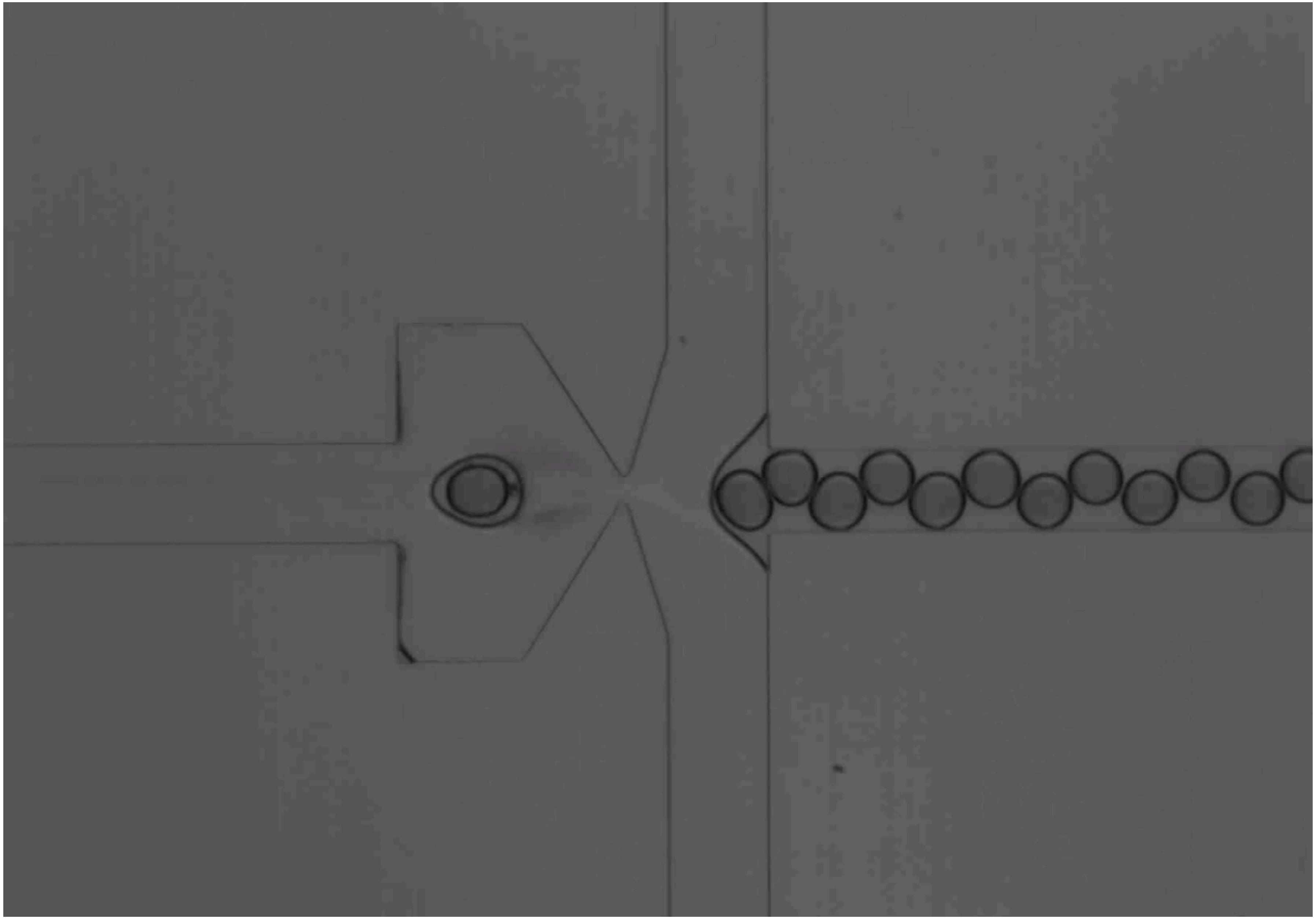
It is then possible to create different structures with PDMS on glass



Lithography mask for the practical work in cleanroom

PDMS

Example of diphasic microfluidic circuit



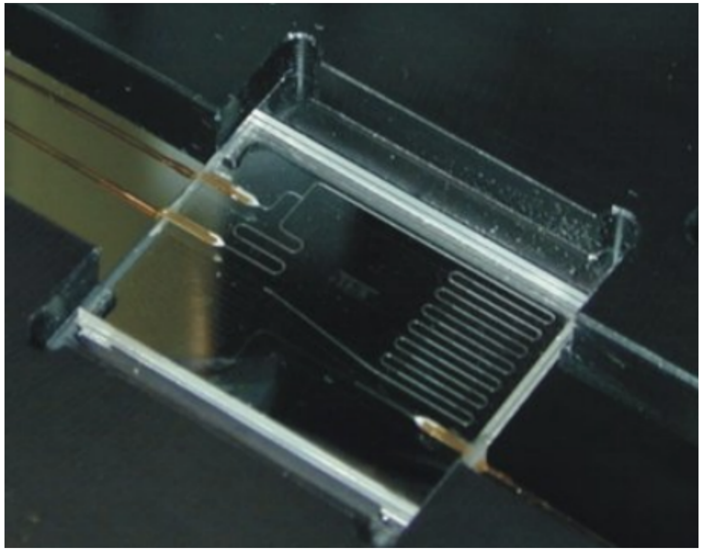
Microfluidics on Glass

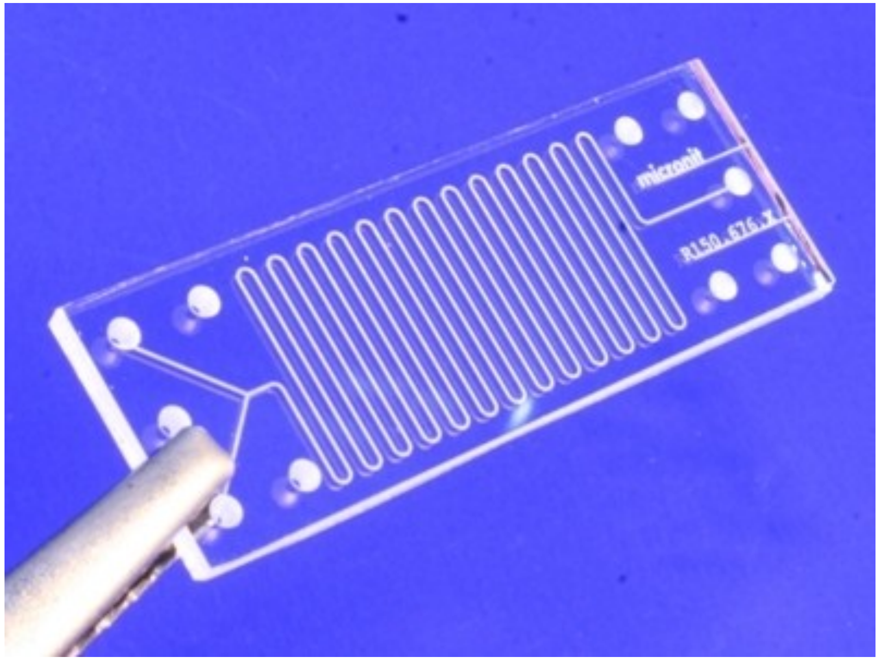
PDMS fits most microfluidics applications but is niot adapted for particular applications such as
High pressure, harsch conditions...

Glass has some advantages :

- Hydrophilic
- Chemically inert
- Transparence, no autofluorescence
- hardness
- Electric insulation
- Relative biocompatibility
- Not so expensive

Different types of glass are used
Quartz (cristalline SiO_2)
Soda Lime
Borofloat (Glass and boron oxide)





Microfluidics on Glass

Glass etching : channel formation in the substrate

- Wet etching : Isotropic + wall roughness (+ultrasound) : low etch rates

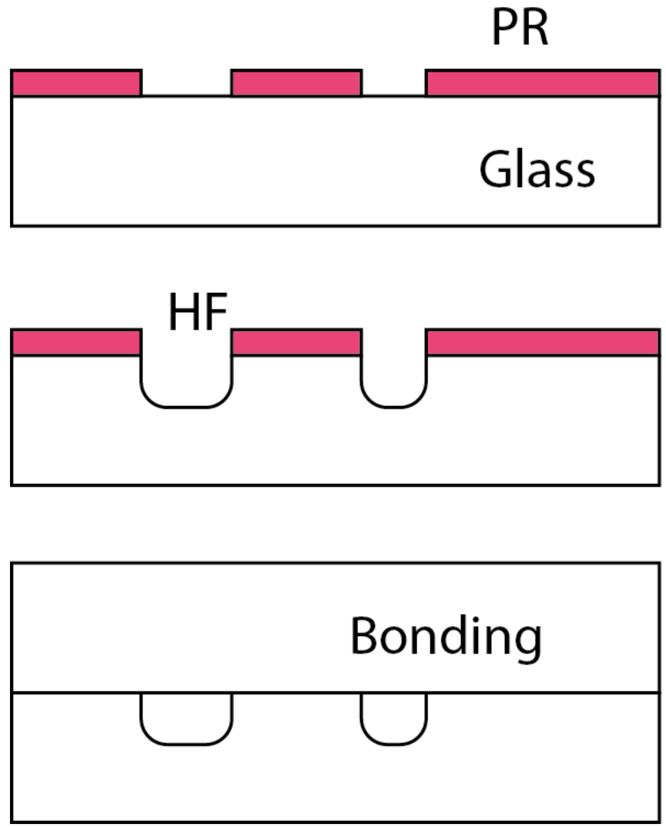
$$SiO_2 + 4HF \rightarrow SiF_4 + 2H_2O$$

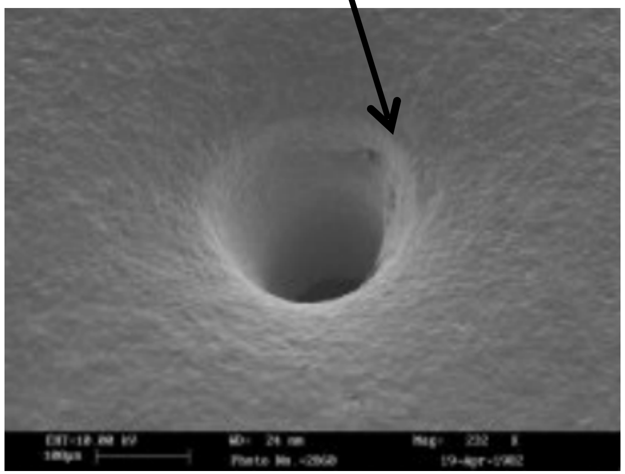
40% HF : 3,4 µm/min, 5% HF : 0.04 µm/min

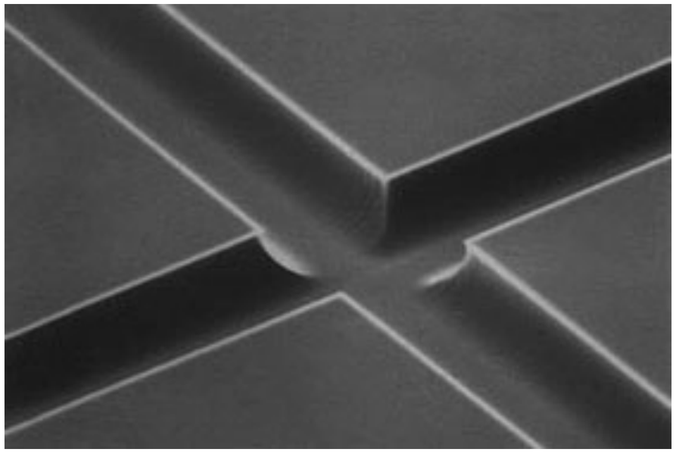
- Dry etching Fluor gazes plasma etching CHF_3, SF_6, CF_4 / O_2
  200 nm/min

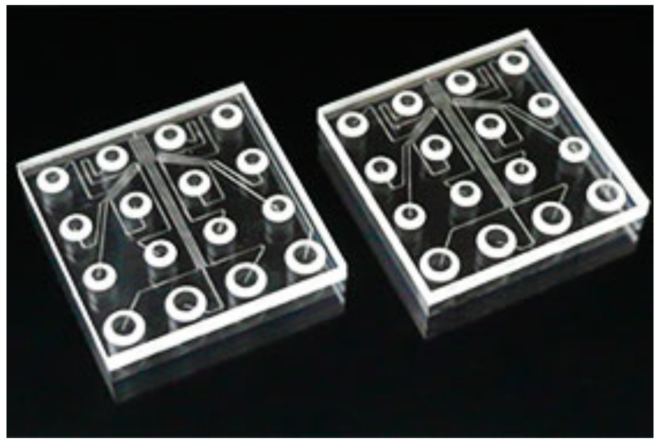
- Laser micromachining

- Powder blasting (Inputs and outputs)









Images : http://www.imtag.ch/

Microfluidics on Glass

Glass bonding :

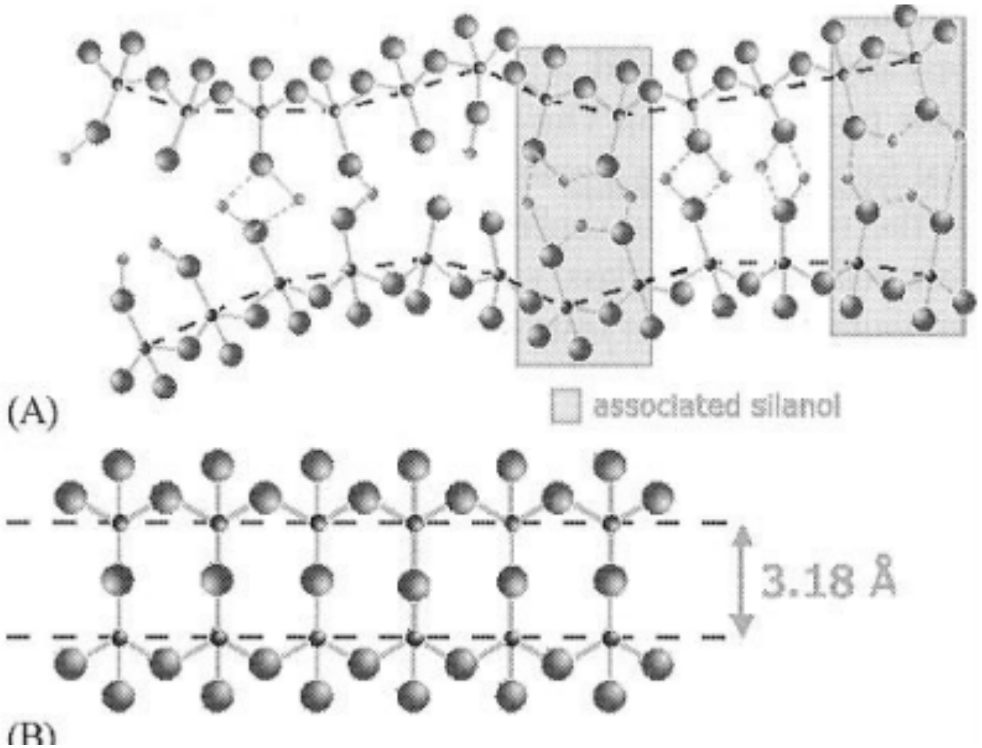
$$Si\text{-}OH + OH\text{-}Si \rightarrow Si\text{-}O\text{-}Si + H_2O$$

Fusion of of glass/glass interface

Requires a perfect interface : clean, flat, and smooth,

Pressure + T> Tg (550°C - 600°C) for several hours

Glass deformation : aspect ratio of channels



Microfluidics on Glass

Anodic Bonding

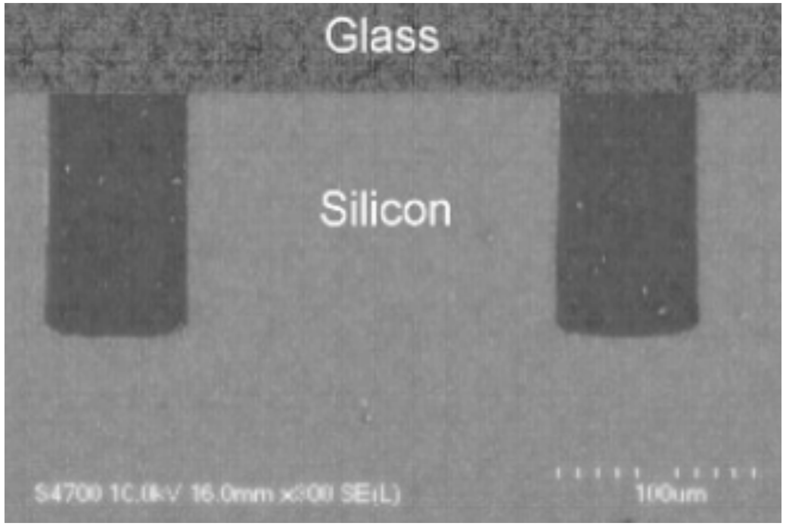
(Pyrex 77400)

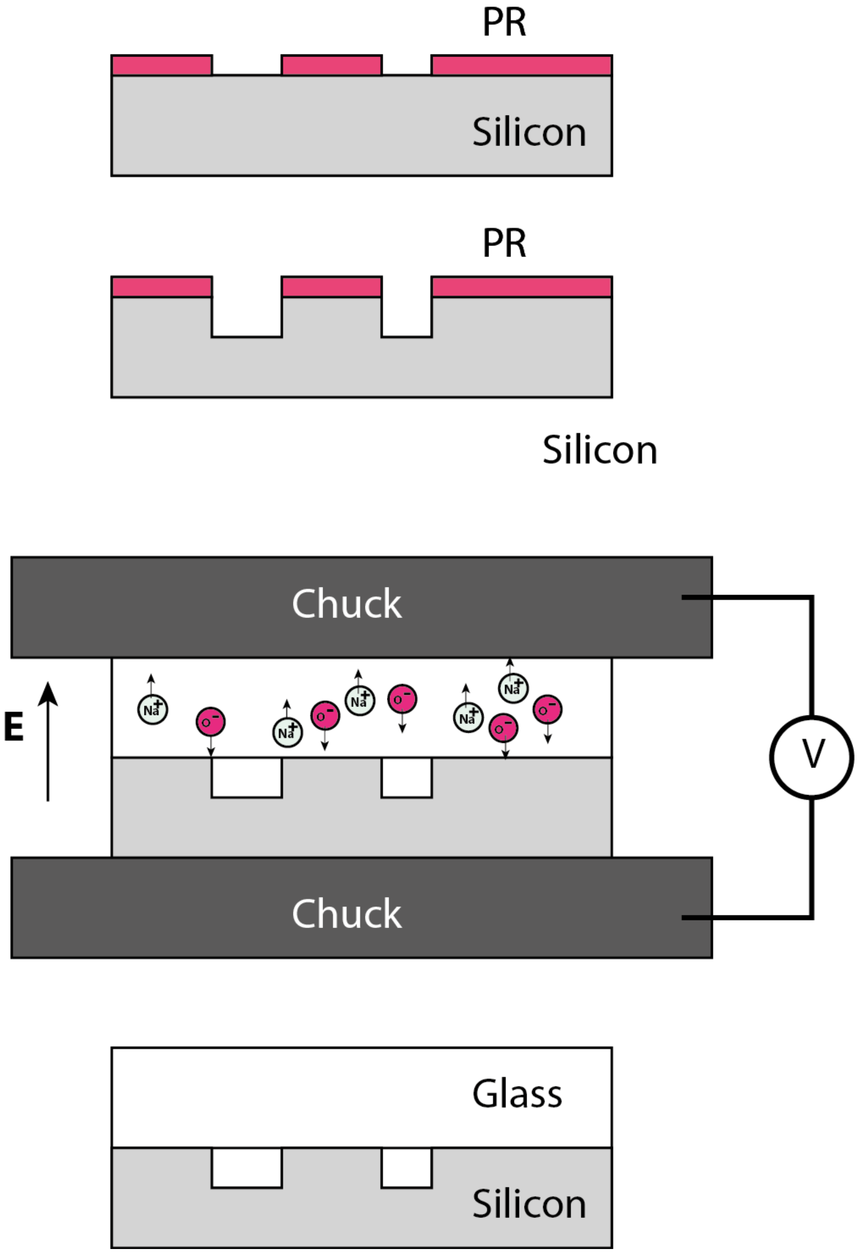
200 to 300°c.

Pressure + Electric field

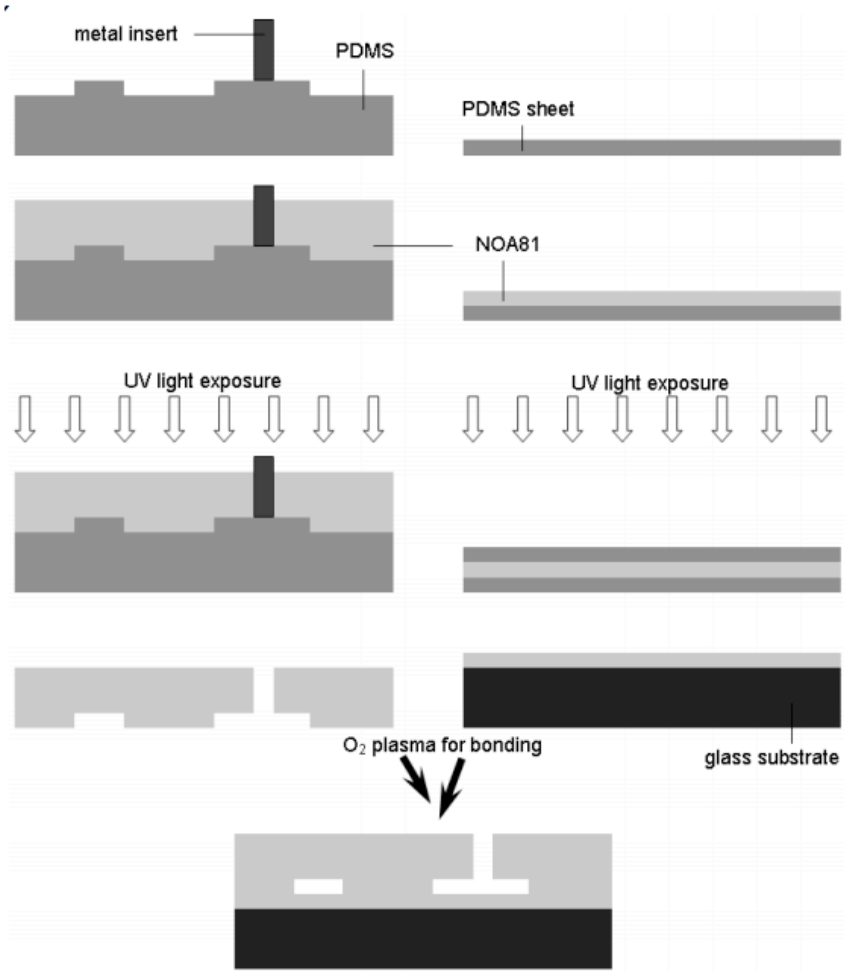
Ion migration

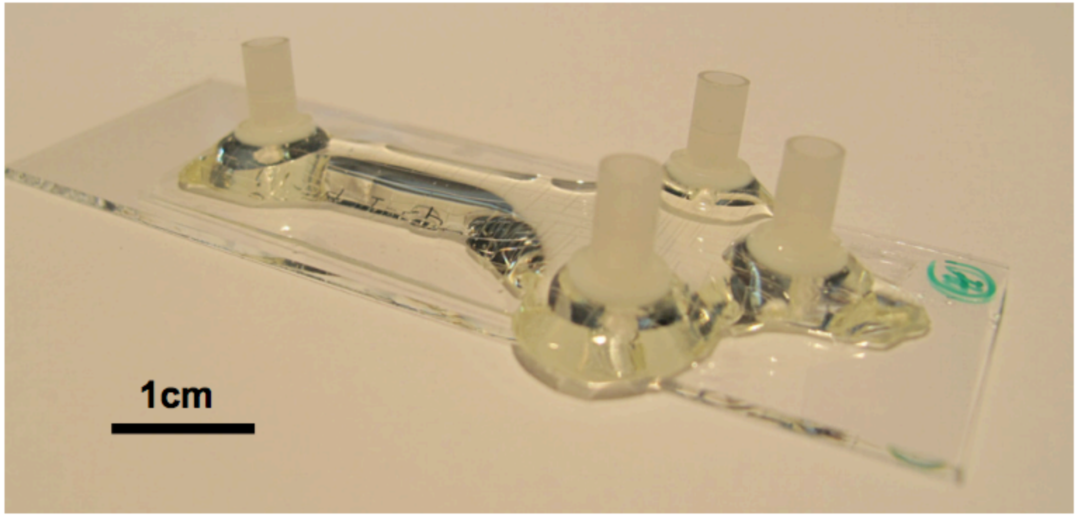
At the interface : Si oxidation and formation of a SiO_2 layer





Microfluidics on UV resist

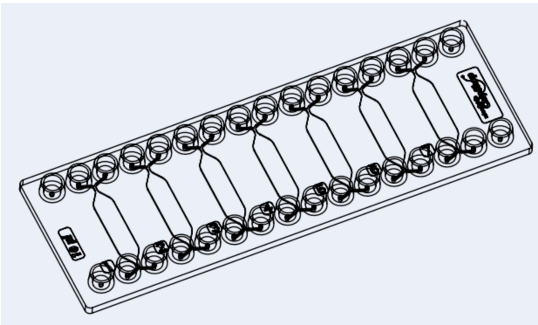


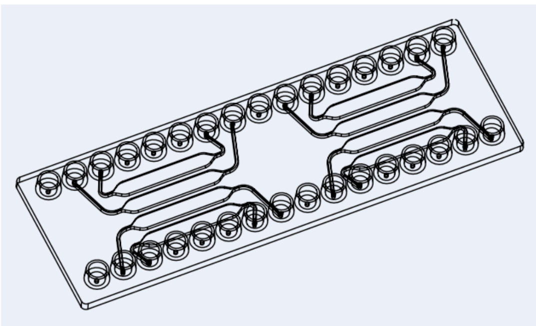


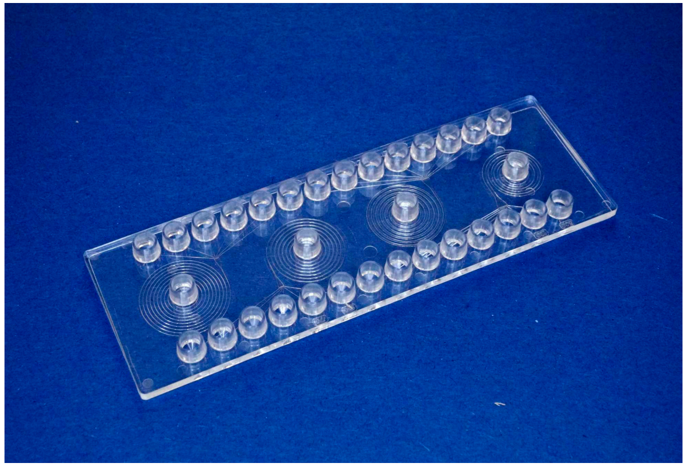
Simple process
Les deformable than PDMS
Requires a positive in PDMS

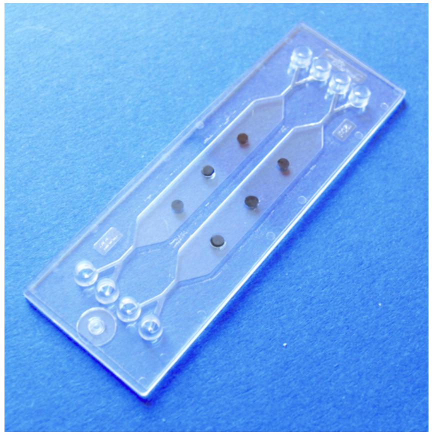
Thermoplastic microfluidics

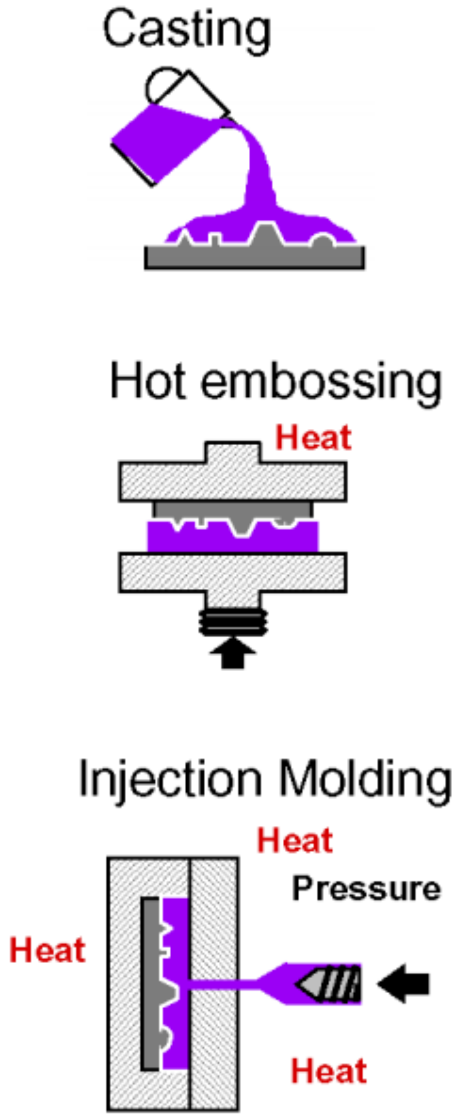
microfluidic ChipShop











Generic circuits catalog
Hot embossing on metalic substrate

Micro contact printing

PDMS can be used for deposition by contact prining

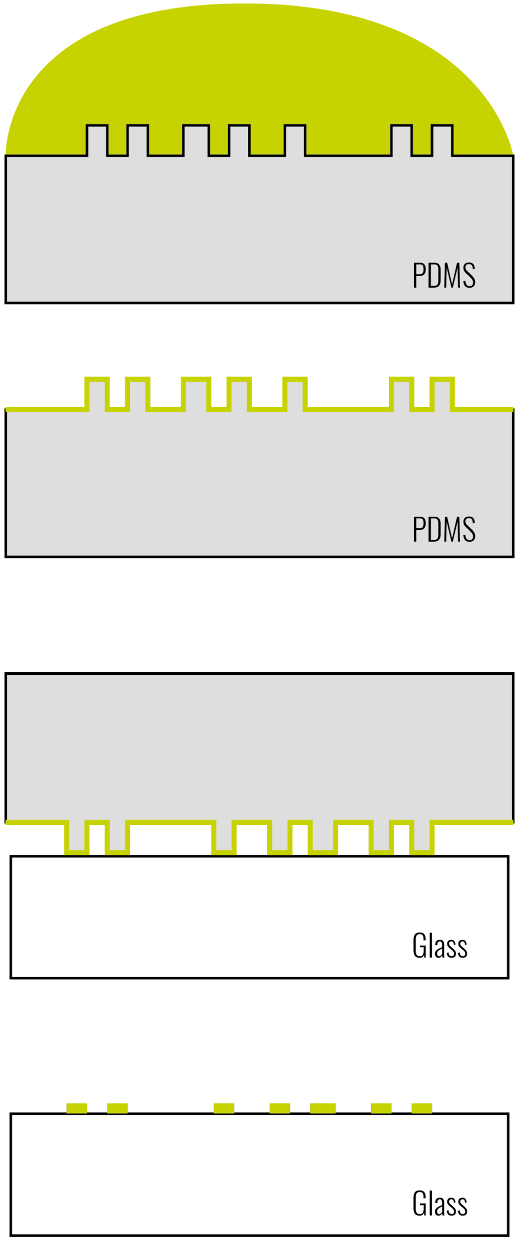
Surface activation O_2 Plasma

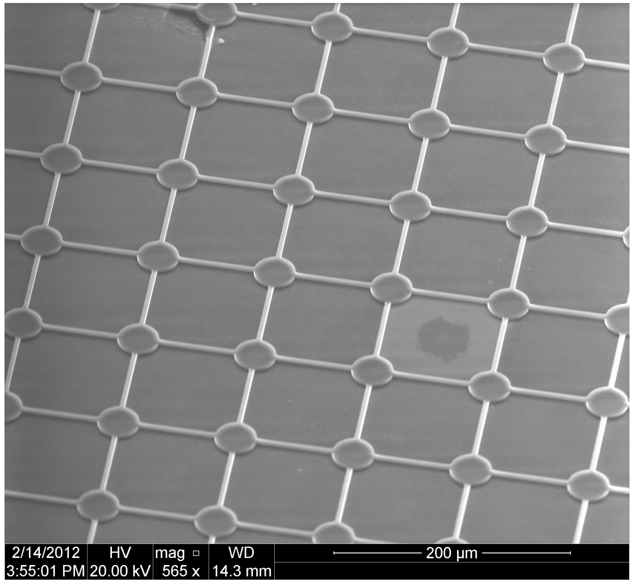
Wetting on PDMS 20mn

Rinse, blow drying N_2

Stamping

Passivation (PLL-PEG)

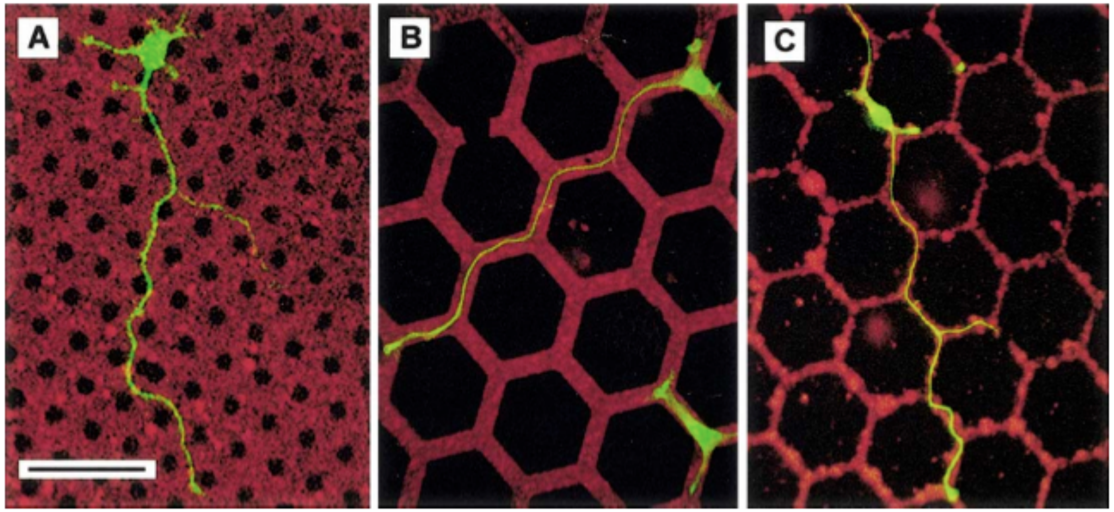


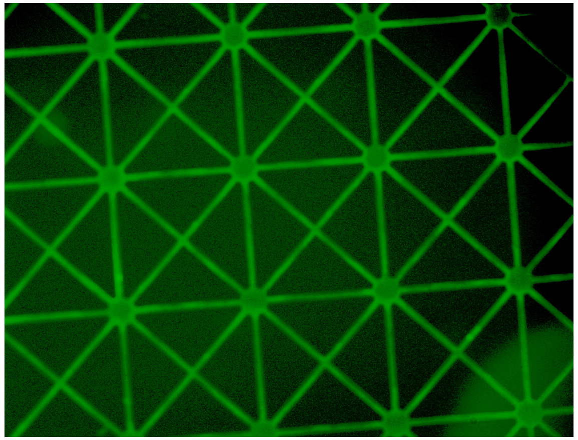


Micro contact printing

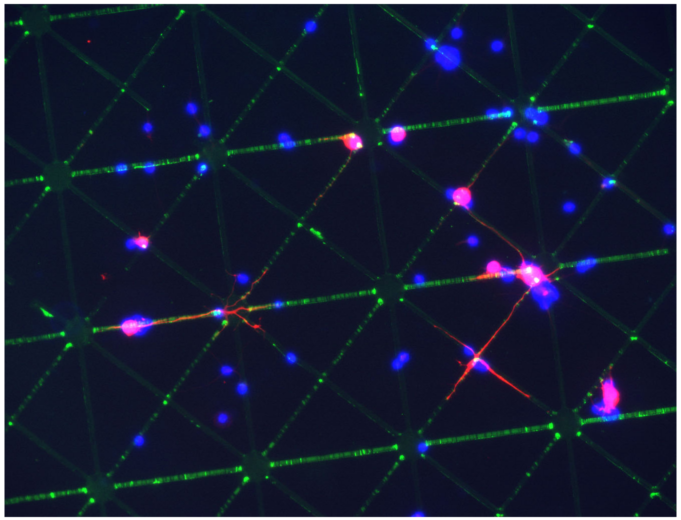
Proteins used for cellular culture

- Poly-L-Lysine
- Polyornithine
- Laminine
- Fibronectine





PLL-FITC



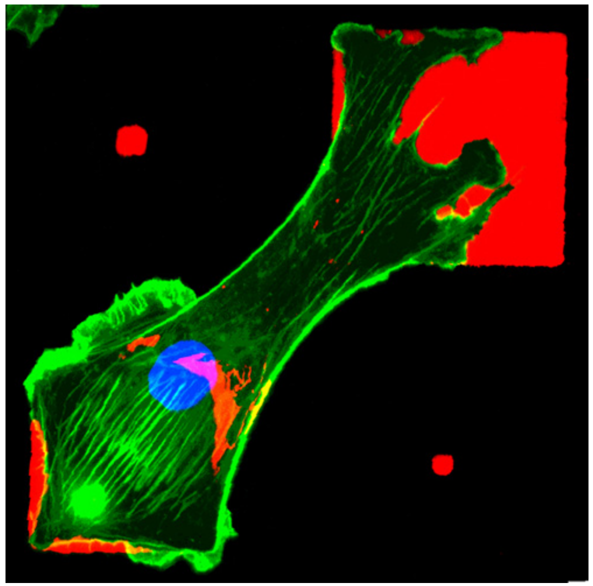


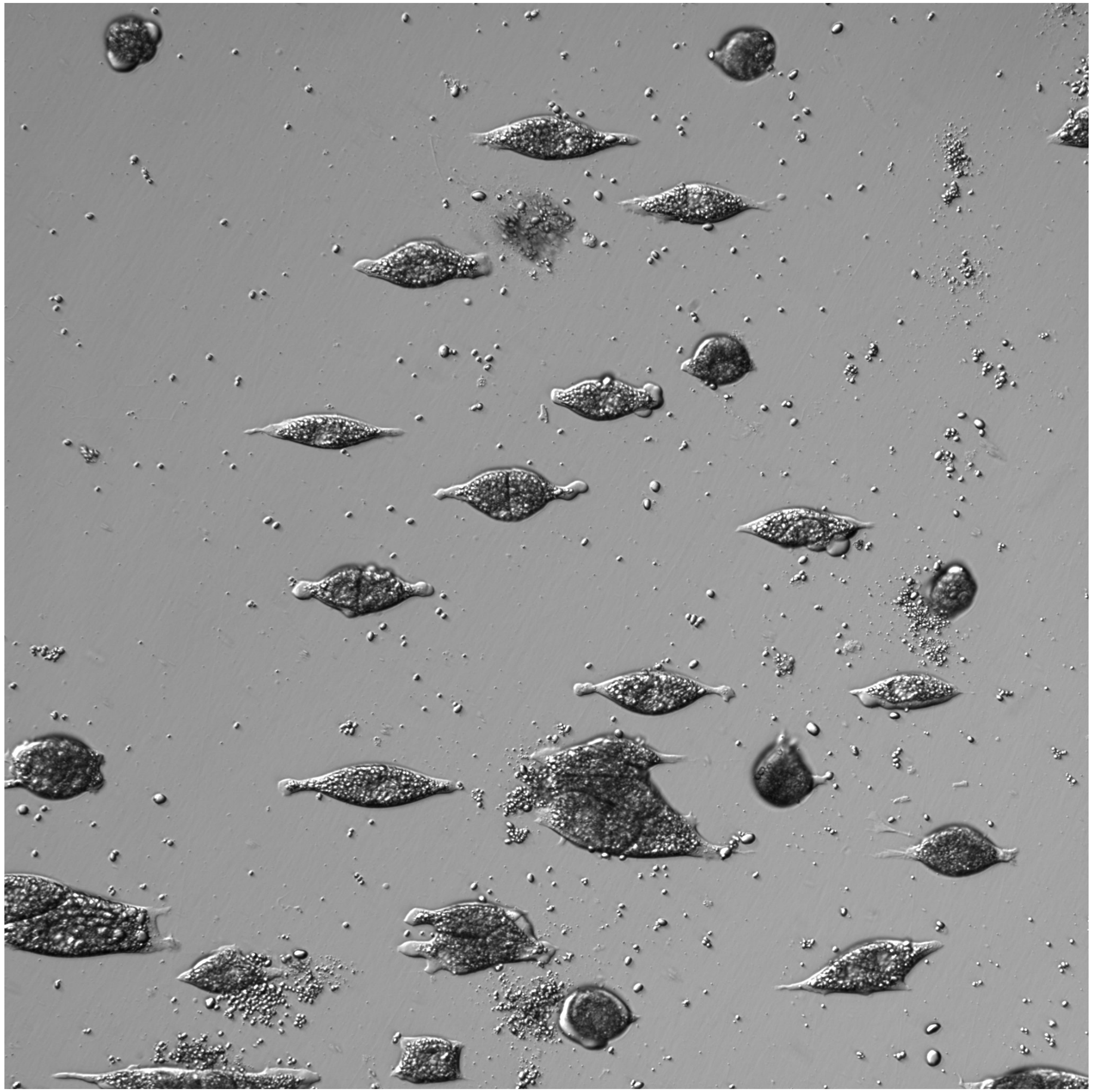
Image : (actin cytoskeleton shown in green; nucleus in blue) initially was plated on a single square (50 x 50 µm) extracellular matrix adhesive island (red) that was created with a microcontact printing technique.

Cliff Brangwynne in the Ingber Lab

Micro contact printing

Experiments with cells adhesion patterns

D.Rozema, Fagotto team, CRBM, Montpellier



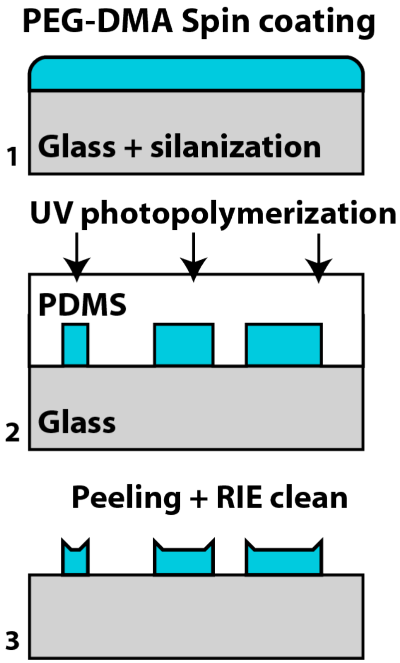
Micro contact printing PEG-DMA

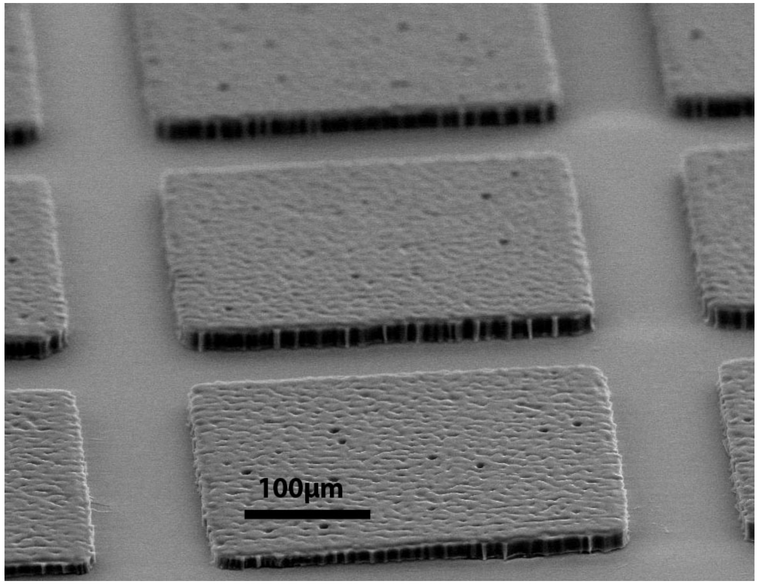
Non-immunogenicity
Non-antigenicity
Protein rejection

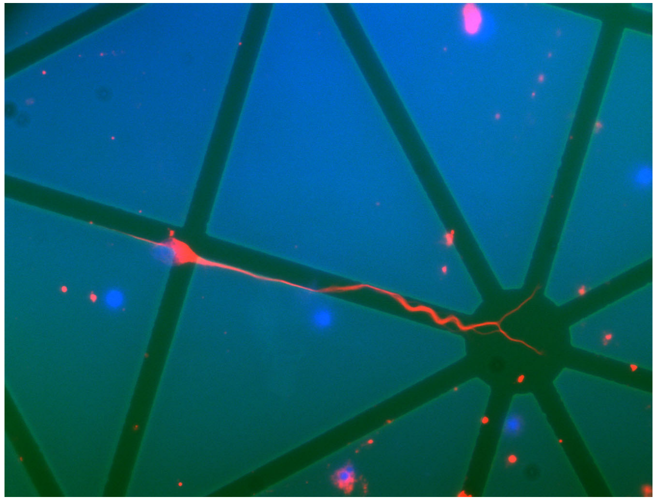
2,5 D cell culture pattern

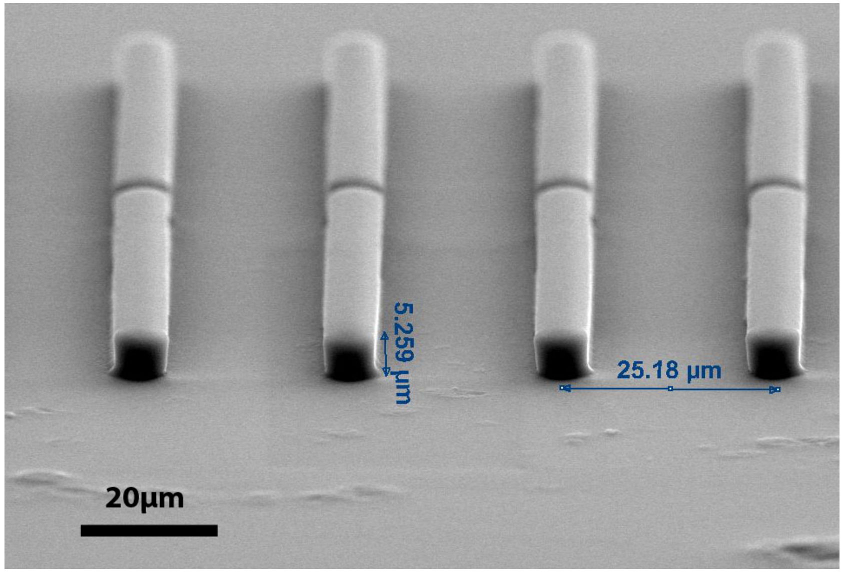
Confinement

Cell adhesion selectivity









Lab on a Chip and Microfluidics

Benoît CHARLOT

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l'institut d'électronique