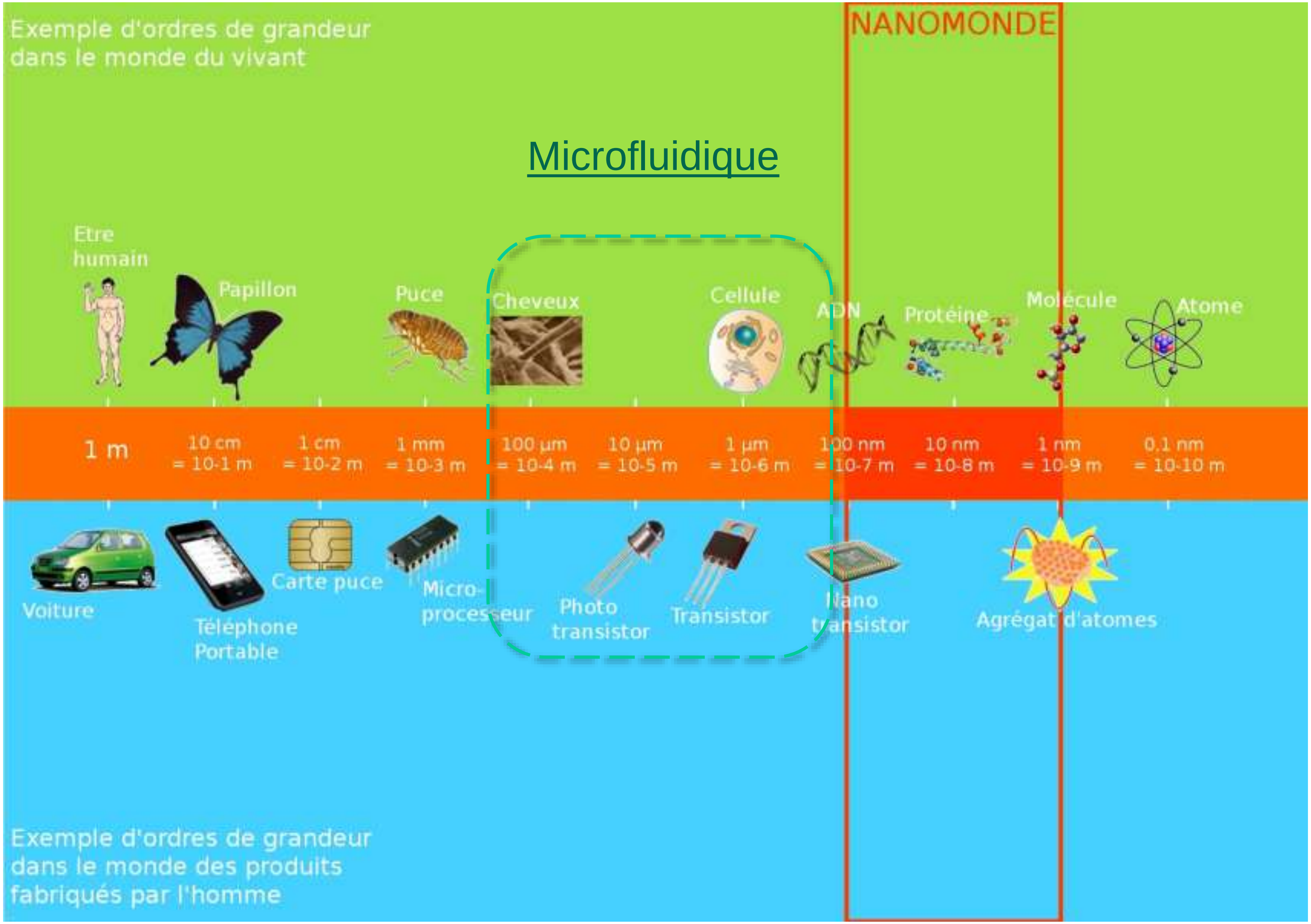
Technologies to make a Microfluidic chip

Pierre Joseph
LAAS-CNRS, Toulouse

14/10/2019, Sète, Microfluidics19

Microfluidics : scale matters …



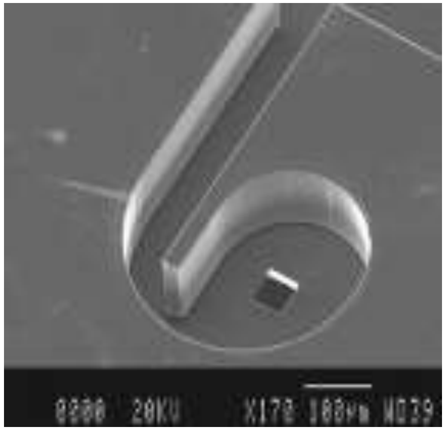
Intro: Fabrication technologies

➢ History : from microelectronics

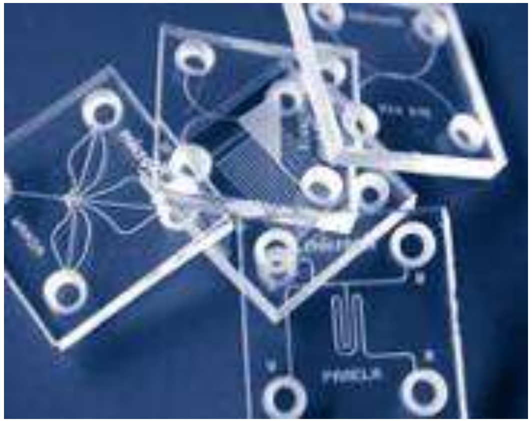
Photolithography,
Dry/wet etching
Evaporation/ sputtering
…

Silicon Technology

- ✓ Microelectronics know-how
- ✗ expensive
- ✗ Requires special means



Microdiode vortex,
DRIE in silicon [LAAS]



Commercial glass chips
[Micronit]

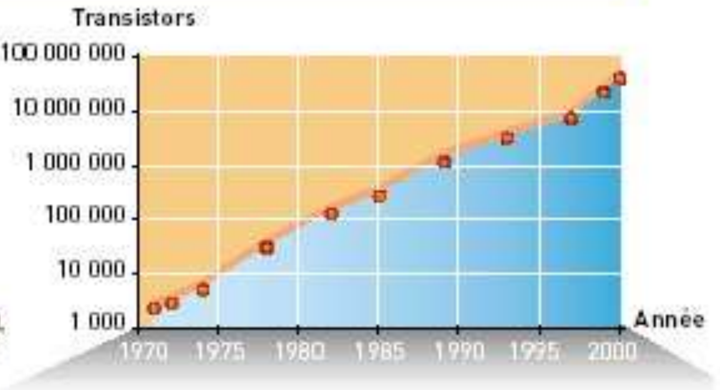
Glass technology

- ✓ transparency
- ✗ low aspect ratio,
- ✗ system integration challenging

Microfluidics : scale matters …

When Microfluidics benefits from Microelectronics

Moore’s law:
each 18 month, the number of transistors on the chip surface is doubled, which corresponds to a gate size reduction by a factor of 1.3.

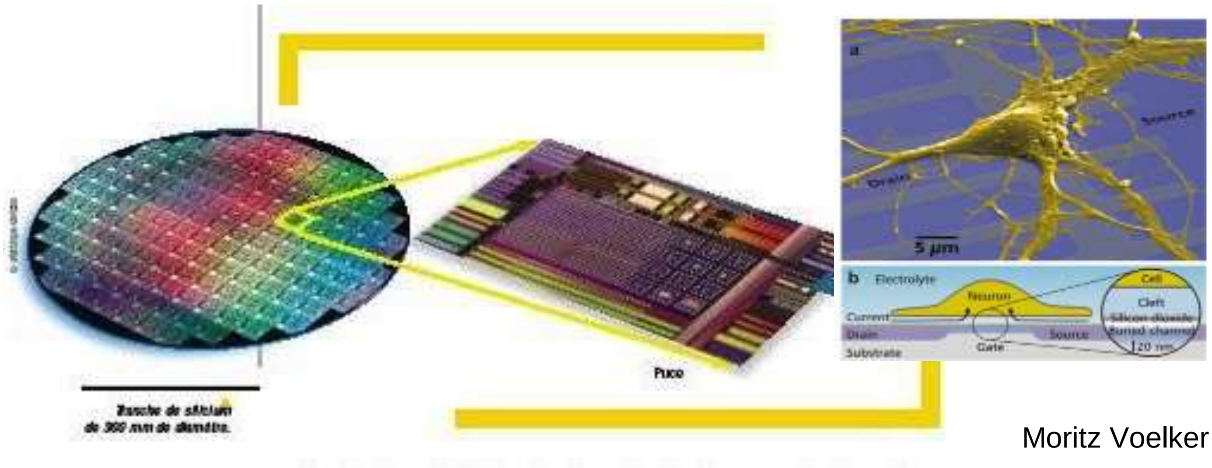


An enormous progress during the last 30 years due to a large enhancement in lithography resolution

Today: 50 billions of transistors on 1 cm^2

Microfluidics : scale matters … not only !

When Microfluidics benefits from Microelectronics …

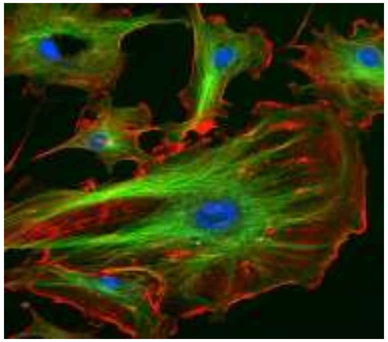


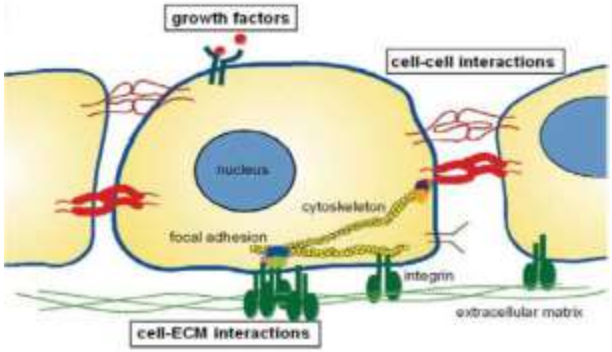
Moritz Voelker, Small 2005

- Building high resolution structures (micro, nano …)
- Building complex networks
- Massive integration
- Electrode integrations
- …

… but microfluidics requires specific developments !

- Expensive
- Not flexible
- Not transparent
- Process compatibility ??
- Biocompatibility ??
- …





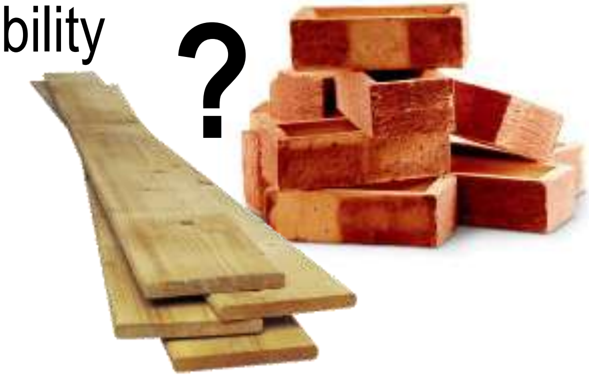
Motivation

Choosing the right *Material – Technology* combination

Material

- Physical properties
- Chemical properties
- Availability
- Price
- ...

?



Manufacturing process

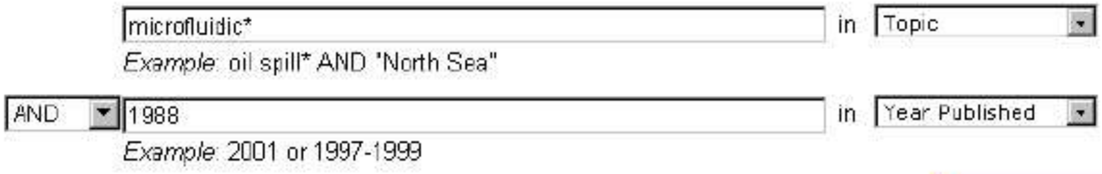
- Volume production
- Price
- Resolution
- Throughput
- Reliability
- Complexity
- …

?

Environmental context

- **Means / Resources**
- **Existing facilities**
- **Know How / Time**
- Collaborations …. **Training**

Intro: Impact of polymer microfabrication

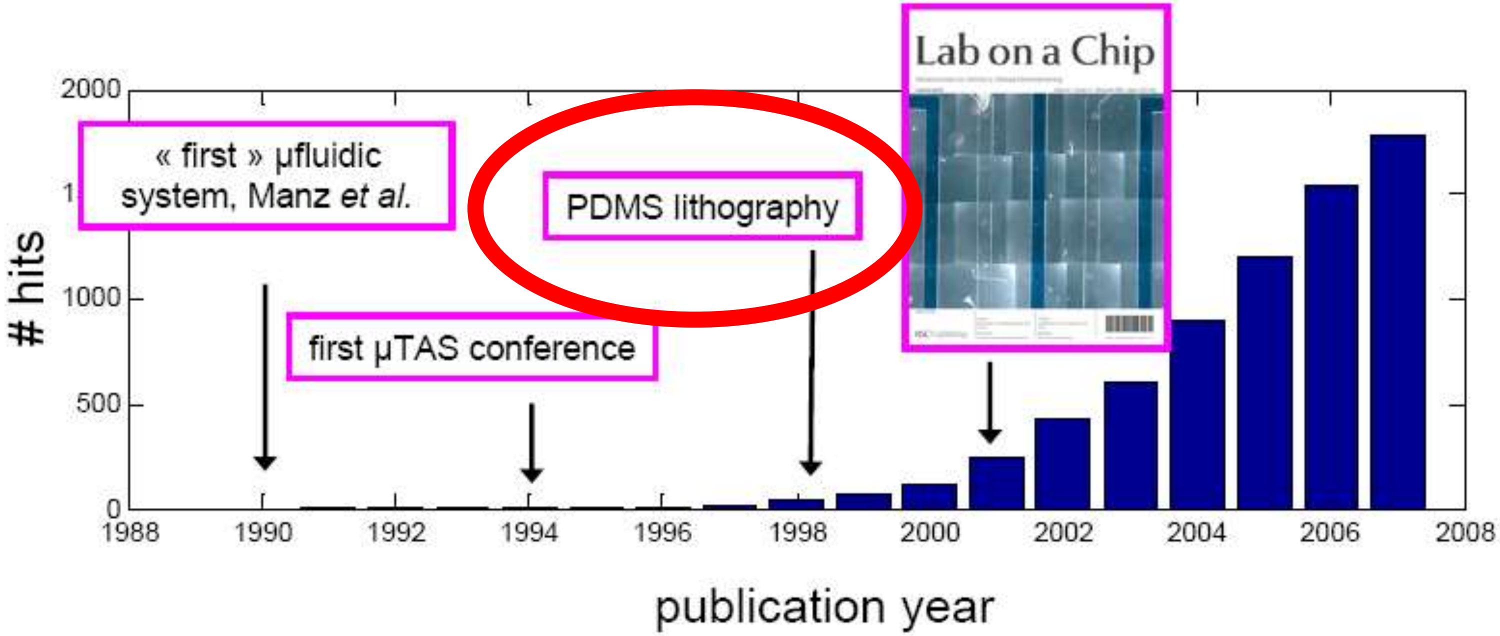


microfluidic* in Topic

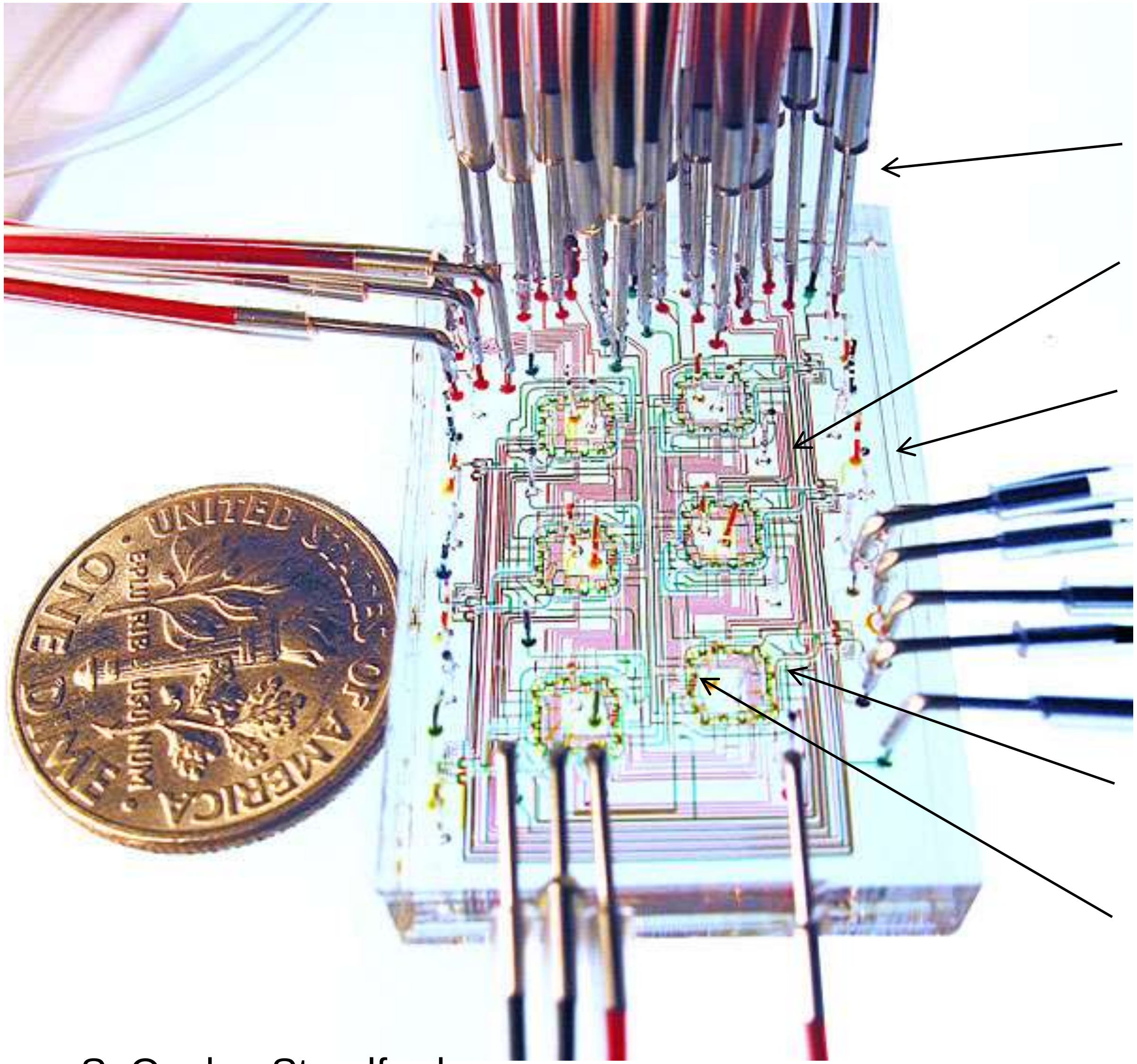
Example: oil spill* AND "North Sea"

AND 1988 in Year Published

Example: 2001 or 1997-1999



Motivation : from academic research …



World to chip connection

Channels (nm – mm range)

Material

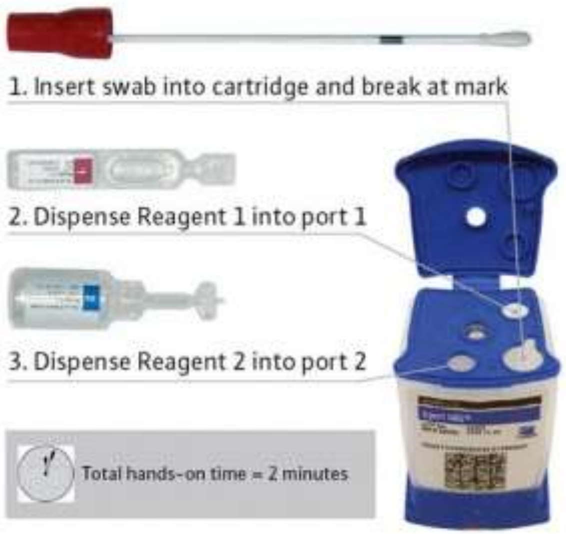
Valves

Pumps

S. Quake Standford

… to diagnosis Lab on chips

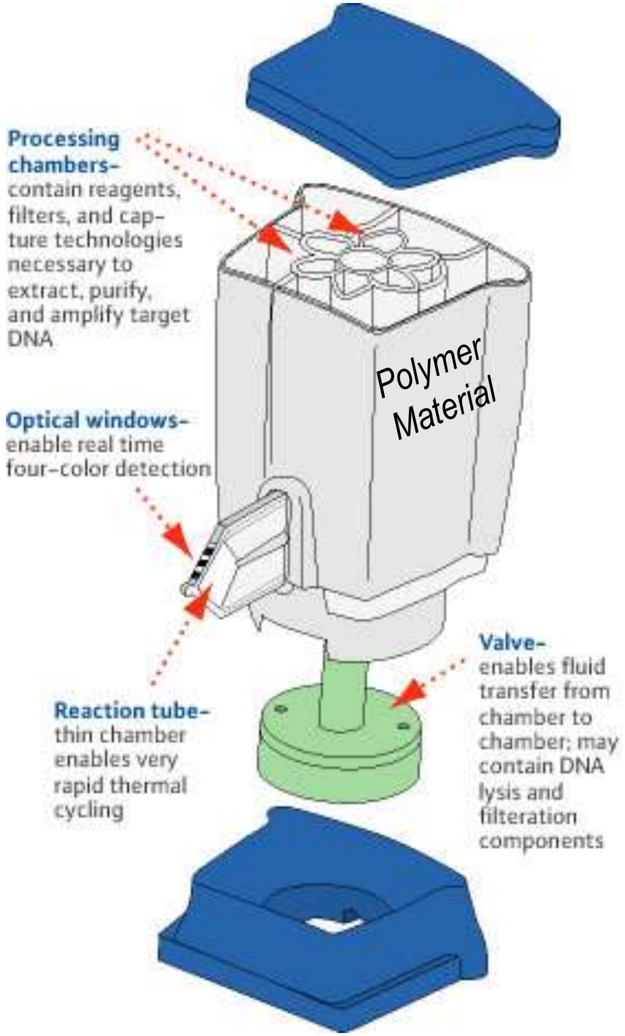
CEPHEID *GeneXpert*



1. Insert swab into cartridge and break at mark
2. Dispense Reagent 1 into port 1
3. Dispense Reagent 2 into port 2

Total hands-on time = 2 minutes

4. Insert cartridges and start assay. Results in 70 minutes.



Processing chambers– contain reagents, filters, and capture technologies necessary to extract, purify, and amplify target DNA

Optical windows– enable real time four-color detection

Reaction tube– thin chamber enables very rapid thermal cycling

Valve– enables fluid transfer from chamber to chamber; may contain DNA lysis and filteration components

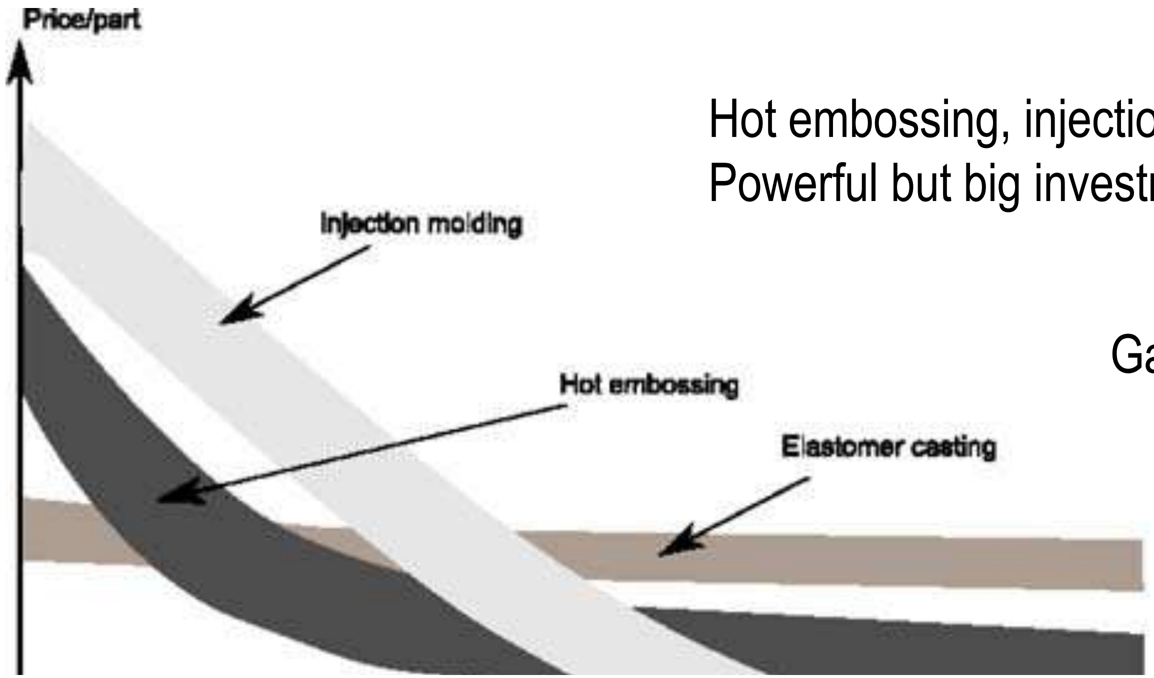
Polymer Material

Anthrax, MRSA, Flu, C. Difficile, Enteroviral meningitis, …

http://www.cepheid.com/tests-and-reagents/

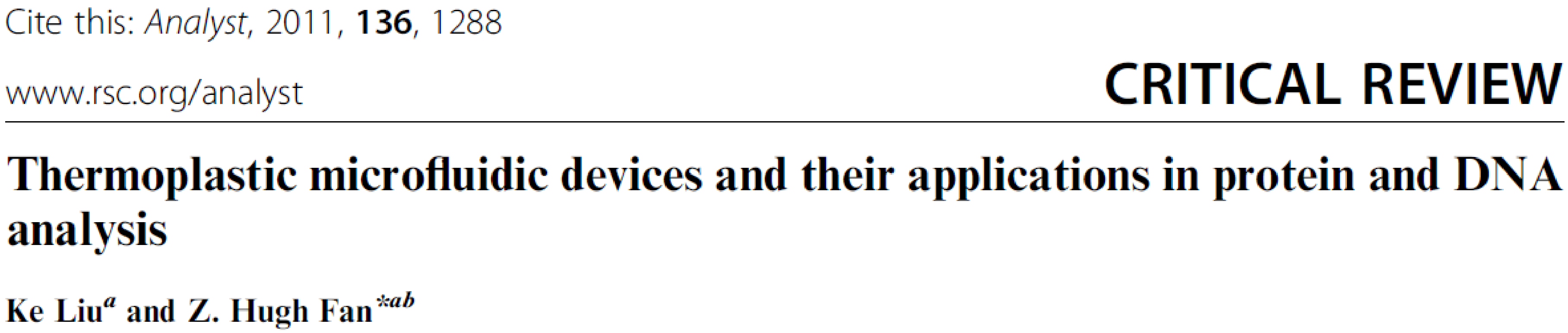
Packaging, reliability, « FDA approval», Market…

Replication methods: academy/industry



Hot embossing, injection molding:
Powerful but big investment (machine cost)

Gap academy/ industry…


Cite this: *Analyst*, 2011, **136**, 1288

www.rsc.org/analyst

CRITICAL REVIEW

Thermoplastic microfluidic devices and their applications in protein and DNA analysis

Ke Liu[a] and Z. Hugh Fan*[ab]

Maturity / commercialization

FluidicMEMS

PERSPECTIVES ON LAB-ON-A-CHIP, MICROFLUIDIC, AND BIOMEMS TECHNOLOGY

285 companies (2019)

~60 : components, microfabrication

~60 : development, consulting

~60 : Research tools

~100 : diagnostics

http://fluidicmems.com/

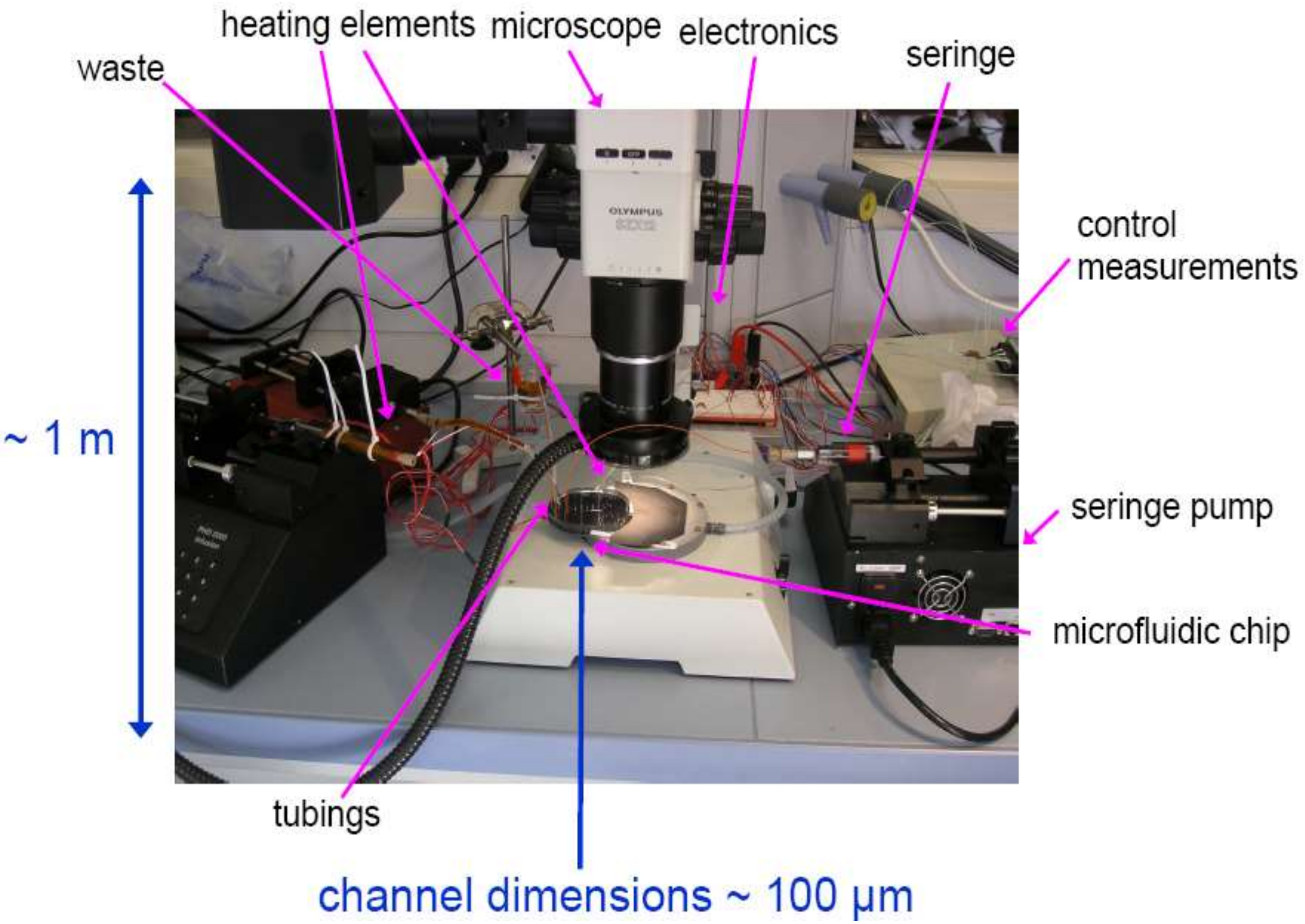
Very active Research domain

>10000 players, Conf.µTAS ~2000 participants

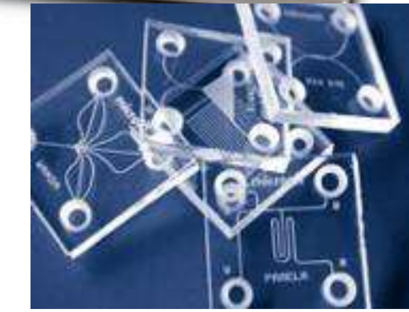
Applications pull →Industry

(start-ups & big companies)

Experimental microfluidics: « a chip in a lab »



∃ commercial chips & setups (Fluigent, cascade microtech, micronit…)



Chip | fluidics + control + measurements

But fabrication may enable to integrate that

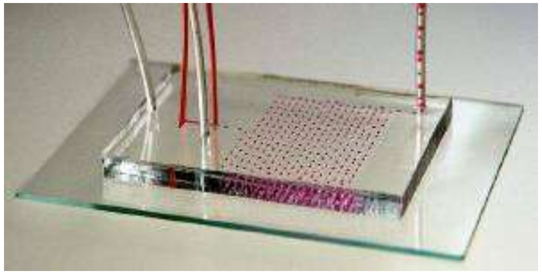
The only aspect developed here

Intro: Basis of « PDMS technology »

➢ History : from microelectronics … to alternative technologies

Polymer technologies (ex: PDMS)

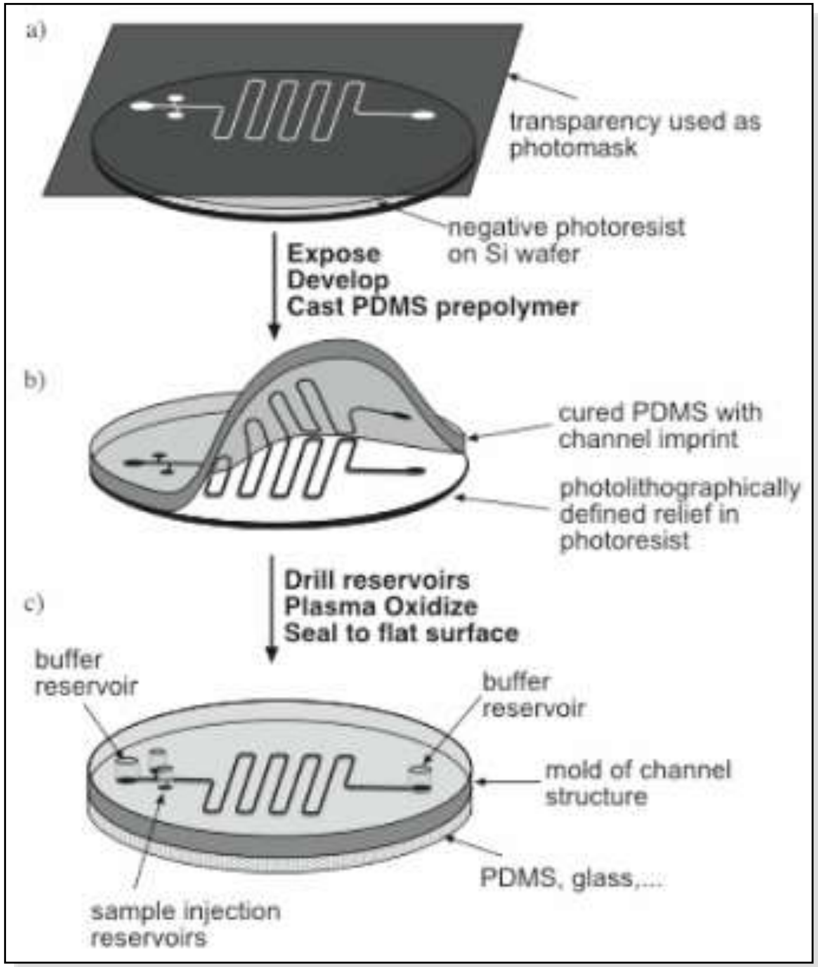
- ✓ simple, cheap, reliable,
- ✓ no need for highly specific equipments
- ✗ solvant compatibility, deformations
- ✗ multi-layer alignment



[LOF-CNRS]

PDMS Soft-lithography

[G. Whitesides, 1995]



~ 1-100 µm channels, choice on materials

I. Intro: criteria to choose material / process

II. PDMS

III. What else?

IV. Openings

II. PDMS for microfluidics

1. Mold (master)
    a) Microfabrication & Photolithography
    b) SU8 processing
    c) Alternative ways to realize a master

2. Channel
    a) PDMS, Casting & Curing
    b) Bonding

3. Properties
    a) Deformation
    b) Permeation
    c) Multi-level, modified
    d) Chemistry & bio

Microfabrication: main steps (1/2)

:Starting substrate

:Deposit layer of desired material

Not done for SU-8 / PDMS

Deposit photoresist (resin)

Spincoating

Expose photographic emulsion through a mask:

Photolithography

Source: John C. Bean: "We're not in Kansas Anymore!" - A Hands-on Introduction to Nanoscience

Microfabrication: main steps (2/2)

:Develop photographic emulsion

Etch desired materal:

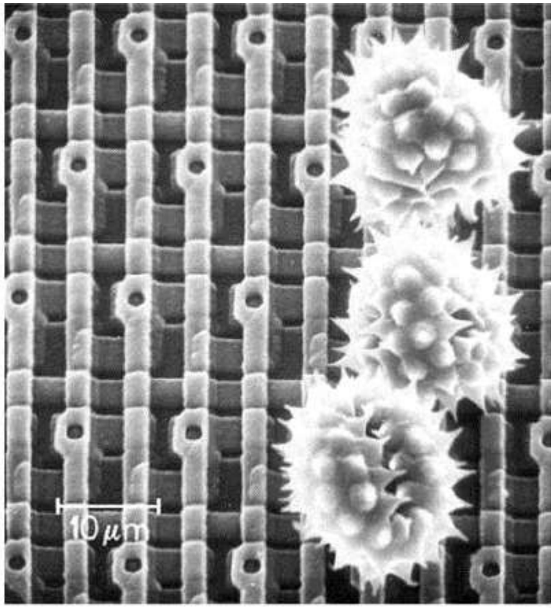
Remove photographic emulsion:

Not done for SU-8 / PDMS

Note: also several thermal cycles (bakes)

Source: John C. Bean

Where to do microfabrication ?



Pollen on microelectronic circuit

Dirt on a necklace

Avoid micron-sized contaminants…

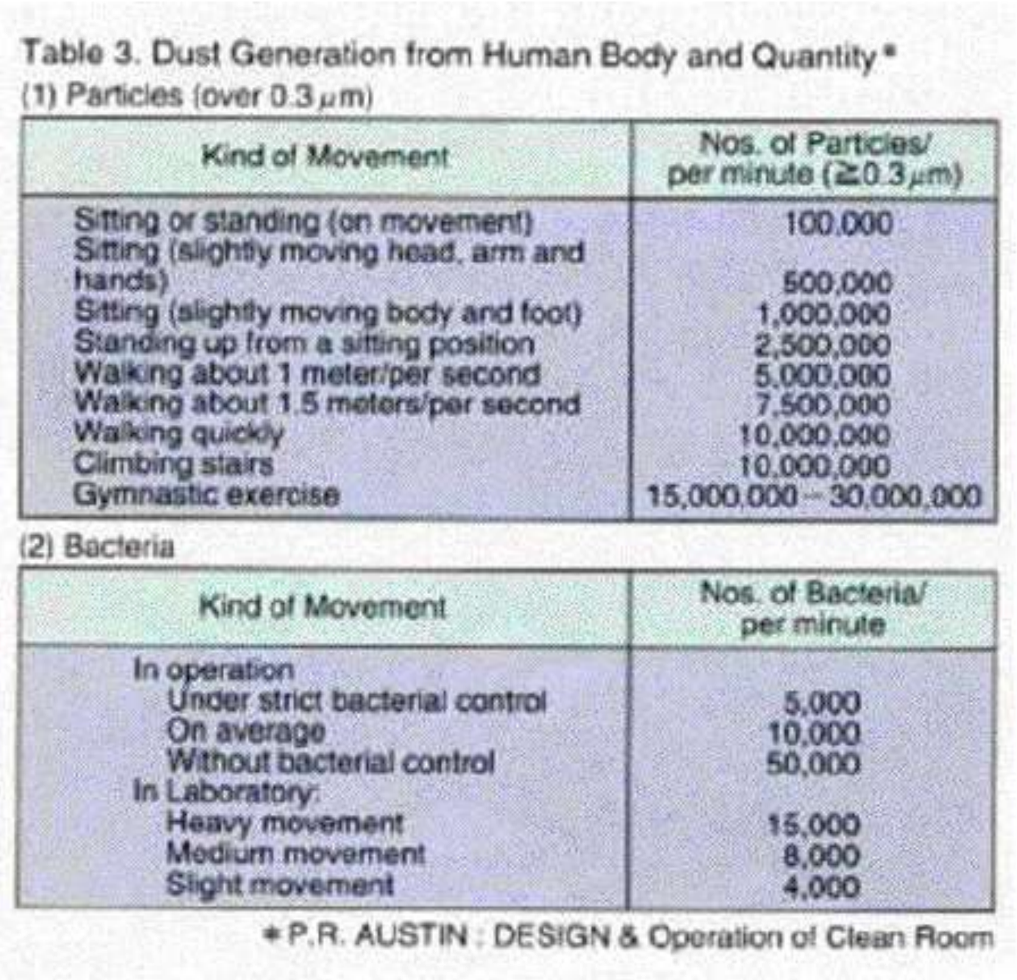


Table 3. Dust Generation from Human Body and Quantity*

(1) Particles (over 0.3 µm)

Kind of Movement	Nos. of Particles/ per minute (≧0.3 µm)
Sitting or standing (on movement)	100,000
Sitting (slightly moving head, arm and hands)	500,000
Sitting (slightly moving body and foot)	1,000,000
Standing up from a sitting position	2,500,000
Walking about 1 meter/per second	5,000,000
Walking about 1.5 meters/per second	7,500,000
Walking quickly	10,000,000
Climbing stairs	10,000,000
Gymnastic exercise	15,000,000 ~ 30,000,000

(2) Bacteria

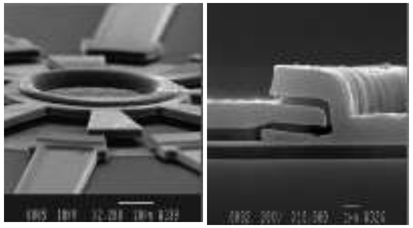
Kind of Movement	Nos. of Bacteria/ per minute
In operation	
Under strict bacterial control	5,000
On average	10,000
Without bacterial control	50,000
In Laboratory:	
Heavy movement	15,000
Medium movement	8,000
Slight movement	4,000

* P.R. AUSTIN : DESIGN & Operation of Clean Room

Source Gardeniers, MESA+, Twente

How ? - Fabrication in a clean room

Ex in LAAS (Toulouse)
National platform,
Equipment total value: 25 M€
30 engineers and technicians



From Mask fabrication

Optical photolithography

Electronic lithography

Thin film deposition

Chemistry

Wet Etching

M.B.E.

Metallization

Plasma Etching

Electrochemical deposition

Ion implantation

Packaging

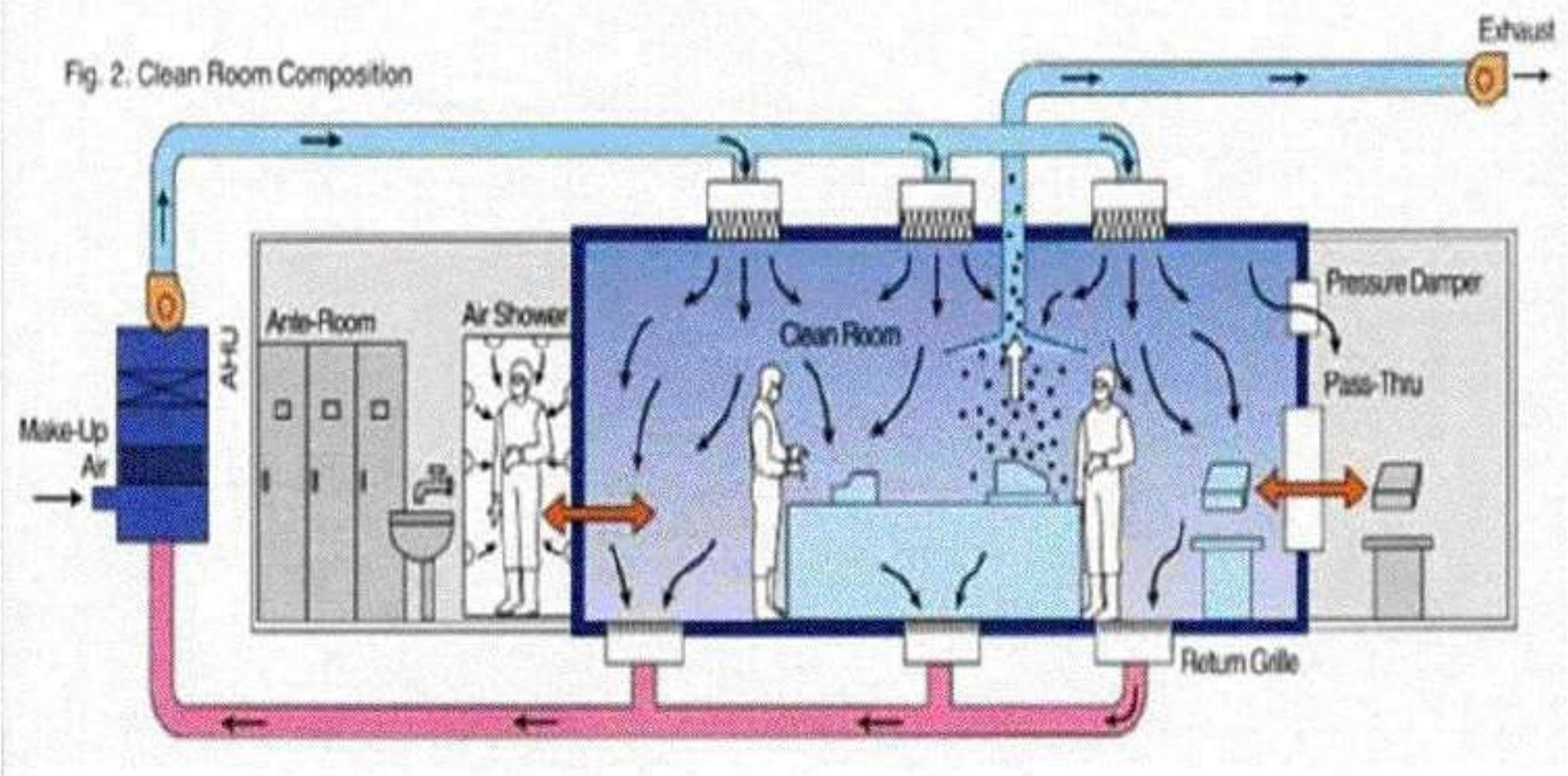
To Characterisation

Infrastructure and support

virtual visit: http://www.cnrs.fr/cnrs-images/multimedia/laas/360/hall.html

Where to do microfabrication ?

…clean room

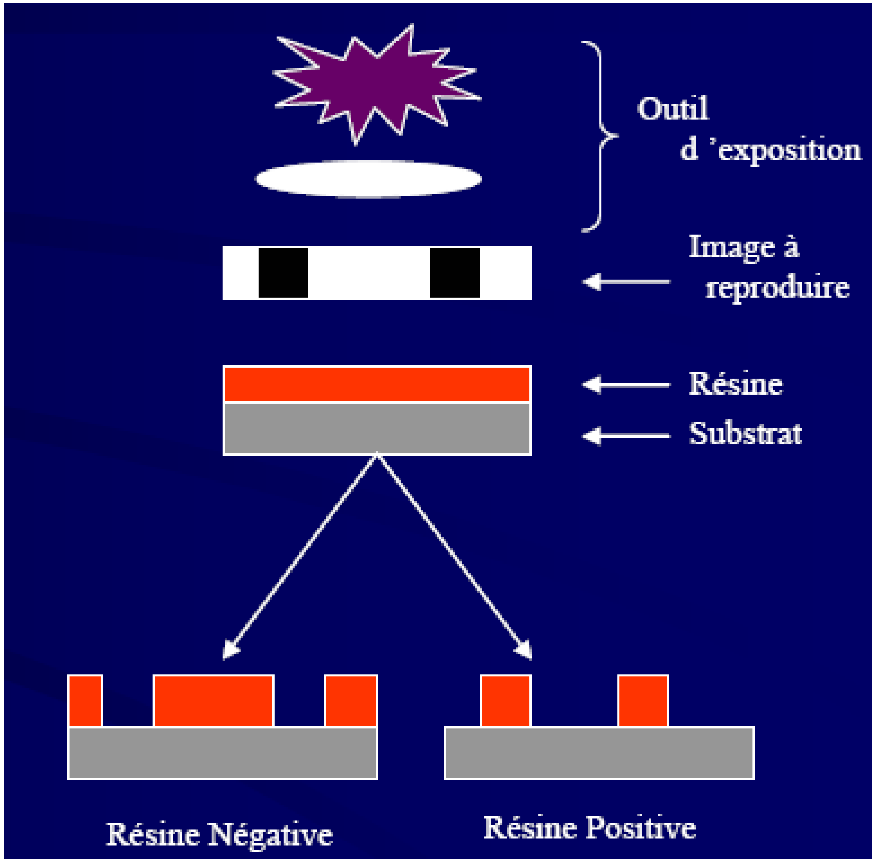


Source : Gardeniers

Note: for some applications/dimension,
Laminar flow hood can be enough

Photolithography: basics

Principle: reproduce an image on a substrate covered by a layer of resin



(1) Resin undergo chemical transformation under **UV (photo)** (could be X ray, ions, electrons…)

(2) Solubility to a specific solvent change for exposed zone (selective dissolution = revelation)

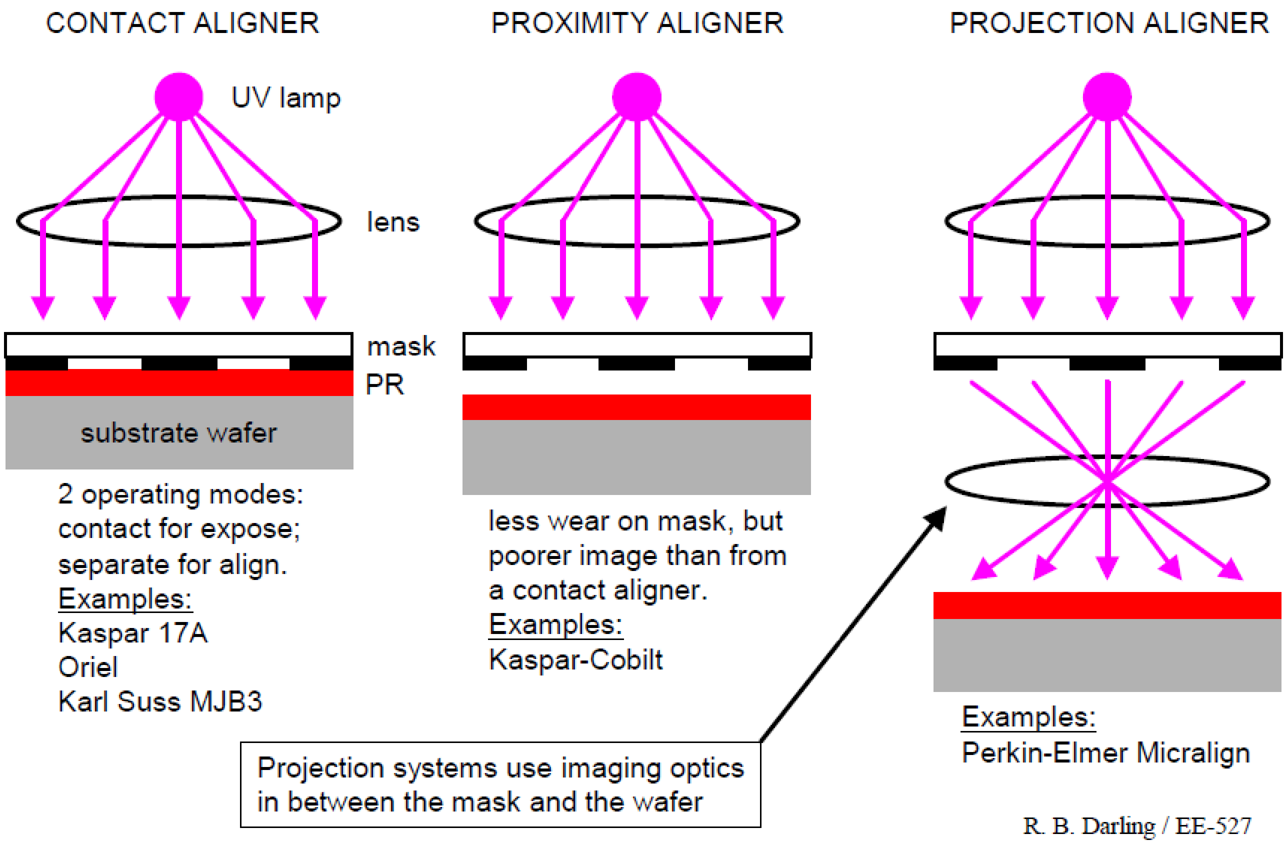
(3) (After photolitho)
on non protected zone of substrate : etching, deposition, doping…

Photolithography: basics

Principle: reproduce an image on a substrate covered by a layer of resin

- Important properties of a resin:
  - Deposition on a substrate: homogeneous, adhesion
  - Low mechanical stress
  - Temperature stability
  - Chemical resistance
  - Easy to be dissolved after use
  - High sensitivity to UV, strong contrast

Optics: 3 modes:



2 operating modes:
contact for expose;
separate for align.
Examples:
Kaspar 17A
Oriel
Karl Suss MJB3

less wear on mask, but poorer image than from a contact aligner.
Examples:
Kaspar-Cobilt

Examples:
Perkin-Elmer Micralign

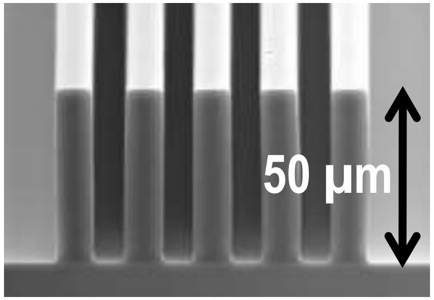
Projection systems use imaging optics in between the mask and the wafer

Source R.B. Darling, Univ. Washington

Mold materials: SU-8

Data-sheet (advertising...): MICRO•CHEM

www.microchem.com



SU-8 3000 is a high-contrast, epoxy based photoresist designed for micromachining and other microelectronic applications, where a thick, chemically and thermally stable image is desired. SU-8 3000 is an improved formulation of SU-8 and SU-8 2000, which has been widely used by MEMS producers for many years. SU-8 3000 allows has been formulated for improved adhesion and reduced coating stress. The viscosity range of SU-8 3000 allows for film thicknesses of 4 to 120 µm in a single coat. SU-8 3000 has excellent imaging characteristics and is capable of producing very high, over 5:1 aspect ratio structures. SU-8 3000 has very high optical transmission above 360 nm, which makes it ideally suited for imaging near vertical sidewalls in very thick films. SU-8 3000 is best suited for permanent applications where it is imaged, cured and left on the device.

What ?

SU-8 3000 is a high contrast, epoxy based photoresist

What for?

suited for **permanent applications**

↳ reusable molds

Properties ?

improved adhesion and reduced coating stress

high, over 5:1 aspect ratio structures

} Freedom / geometry, design

thick, chemically and thermally stable

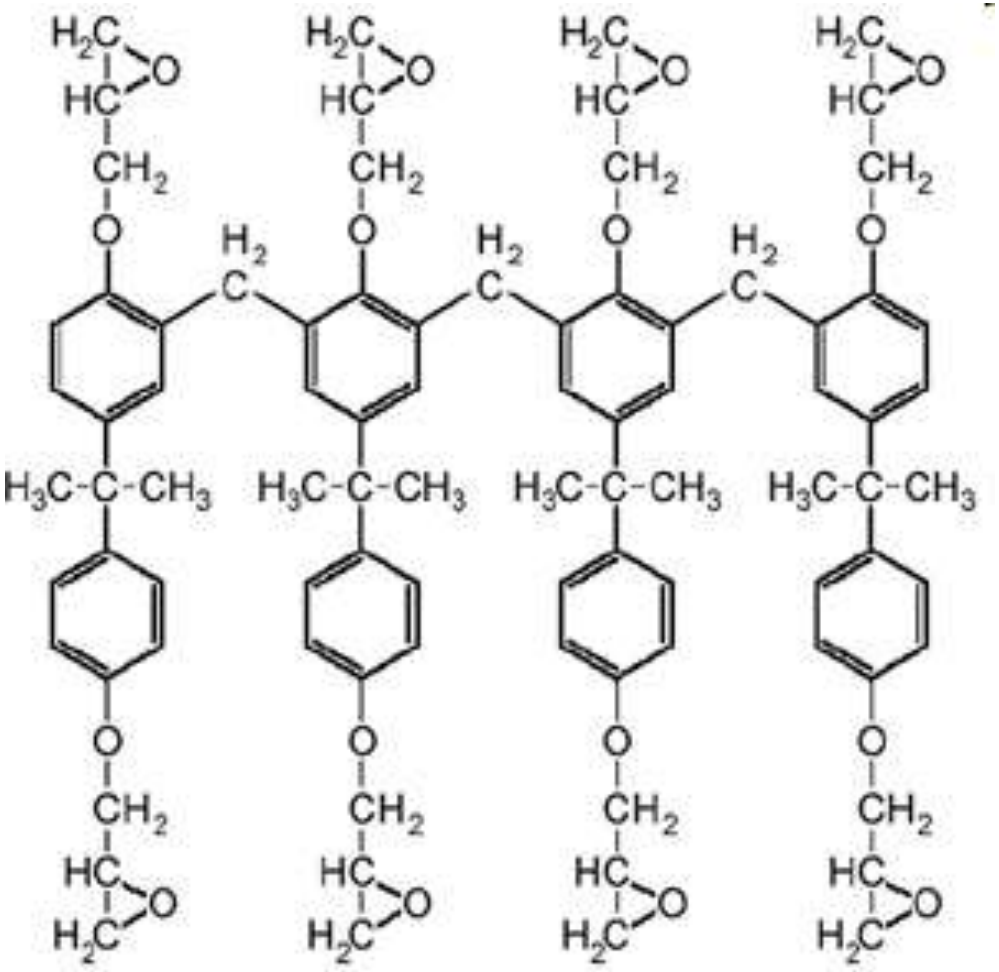
very **high optical transmission above 360 nm**

} Also a good structural material (see III.3)

SU-8 composition: (1) resin

3 components : (1) EPON epoxy resin + (2) Organic solvent + (3) Photoinitiator.

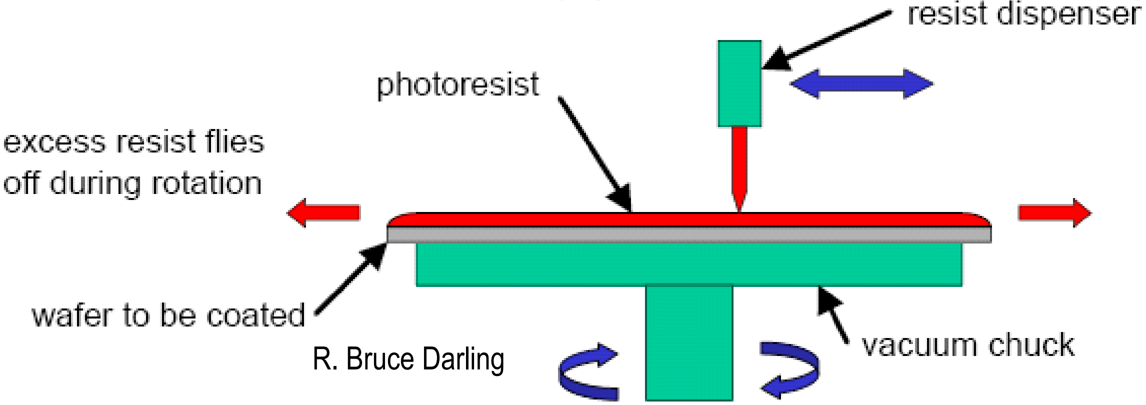
(1) EPON epoxy resin: « glycidyl ether derivative of bisphenol-A novolac »



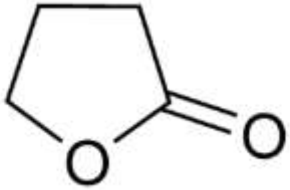
SU-**8** because 8 epoxy groups

SU-8 composition: (2) solvent

- Important for **spin-coating (step 1 in microfabrication)**



R. Bruce Darling



GBL

Solvent quantity

- Viscosity→ thickness of the film
- Evaporation also influences thickness
- (spin coating time also…)

SU-8 3000	% Solids	Viscosity (cS
3005	50	65
3010	60.4	340
3025	72.3	4400
3035	74.4	7400
3050	75.5	12000

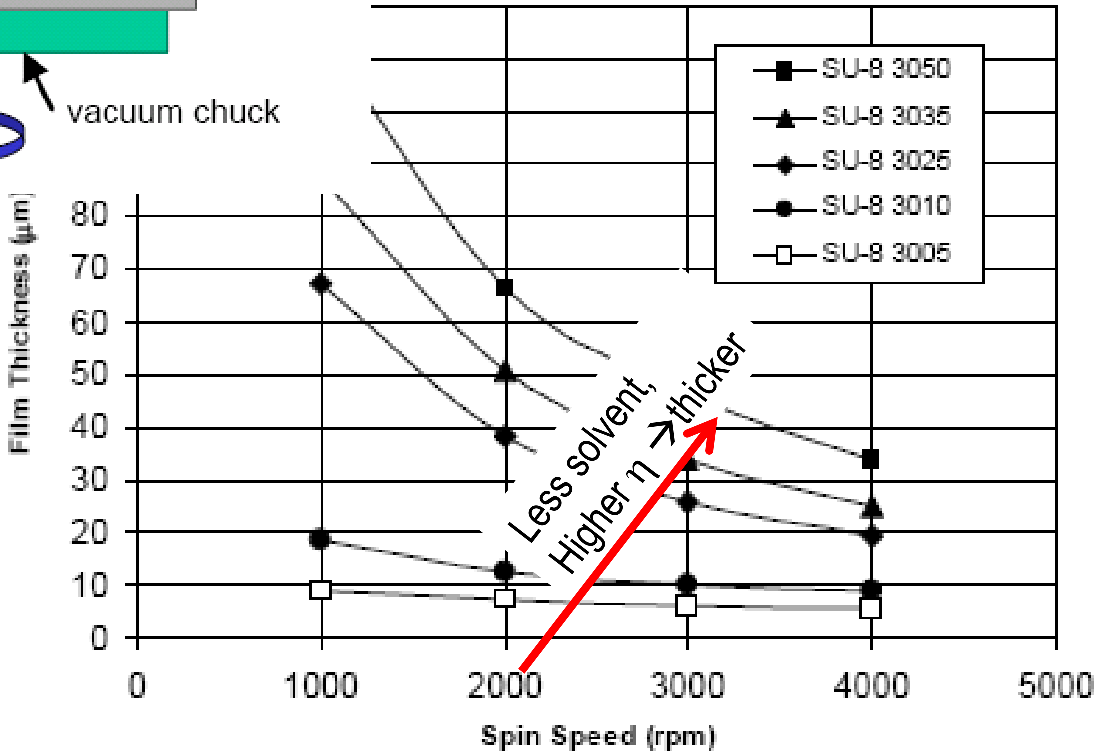
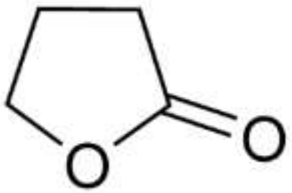


Figure 2. Spin speed vs. Thickness
for SU-8 3000 resists (23^{o}C Japan & Asia)

SU-8 composition: (2) solvent

- Important for **soft-bake (step 2)**

(After spin-coating) solvent evaporation



GBL

Inside a oven

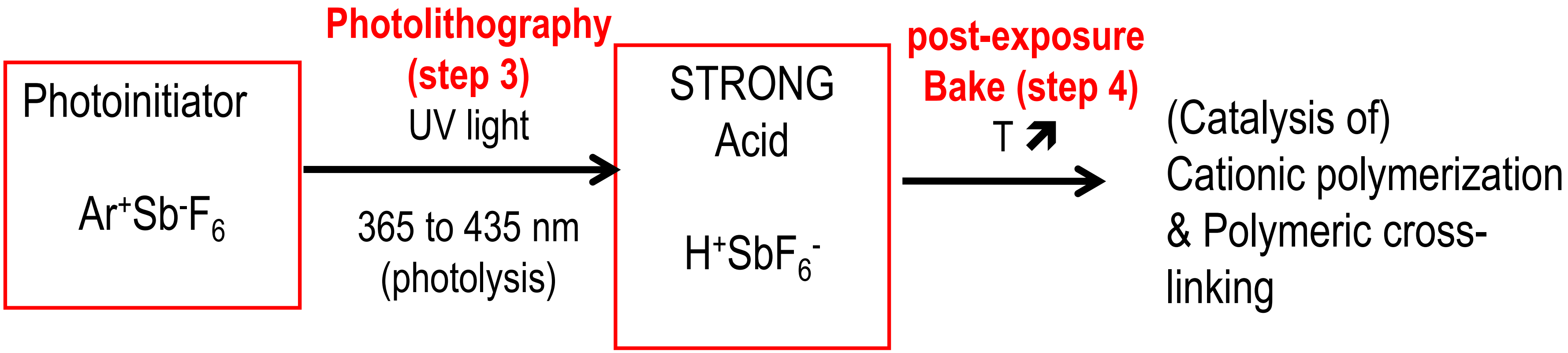
On a hotplate

Good evaporation…

Note: T ramp to reduce stress

SU-8 composition: (3) Photoinitiator

3 components : EPON epoxy resin + Organic solvent + **Photoinitiator.**
(3)Photoinitiator: triarylium-sulfonium salts (CYRACURE® UVI from Union Carbide), ~10 wt %.
(mixed with hexafluoroantimoniate)



Photoinitiator

$Ar^+Sb^-F_6$

Photolithography (step 3)
UV light

365 to 435 nm
(photolysis)

STRONG
Acid

$H^+SbF_6^-$

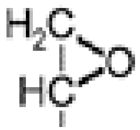
post-exposure Bake (step 4)
T ➚

(Catalysis of)
Cationic polymerization
& Polymeric cross-linking

* Ar^+ aromatic groups→ sensitivity to UV

* SbF_6^- low coordination anion→ VERY strong acid

* H^+ opens epoxy groups → polymerization & reticulation

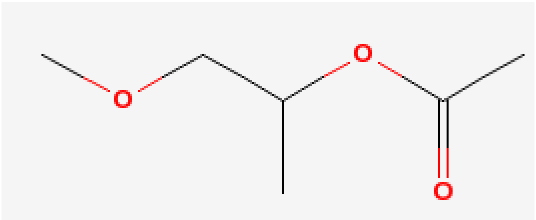


Daniel Sang-Won Park
mail.mems-exchange.org/pipermail/mems-talk/2004-June/013369.html

Finally: **develop (step 5)**, rise, dry

Organic solvent, PGMEA
Propylene glycol methyl ether acetate

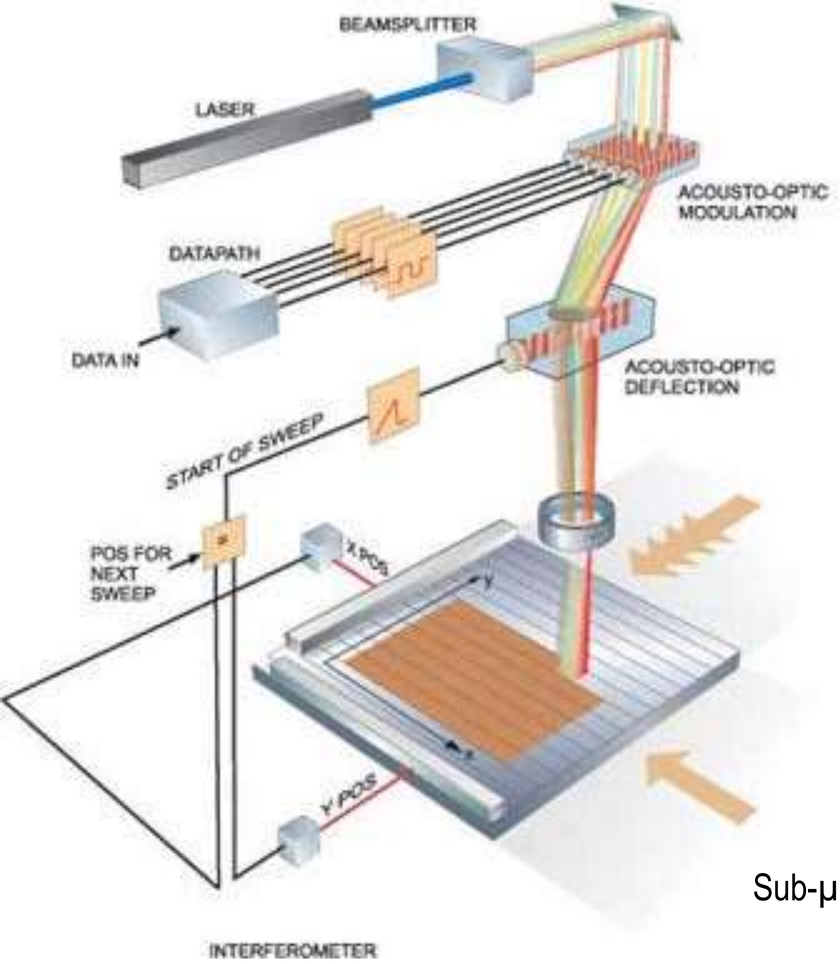
IPA

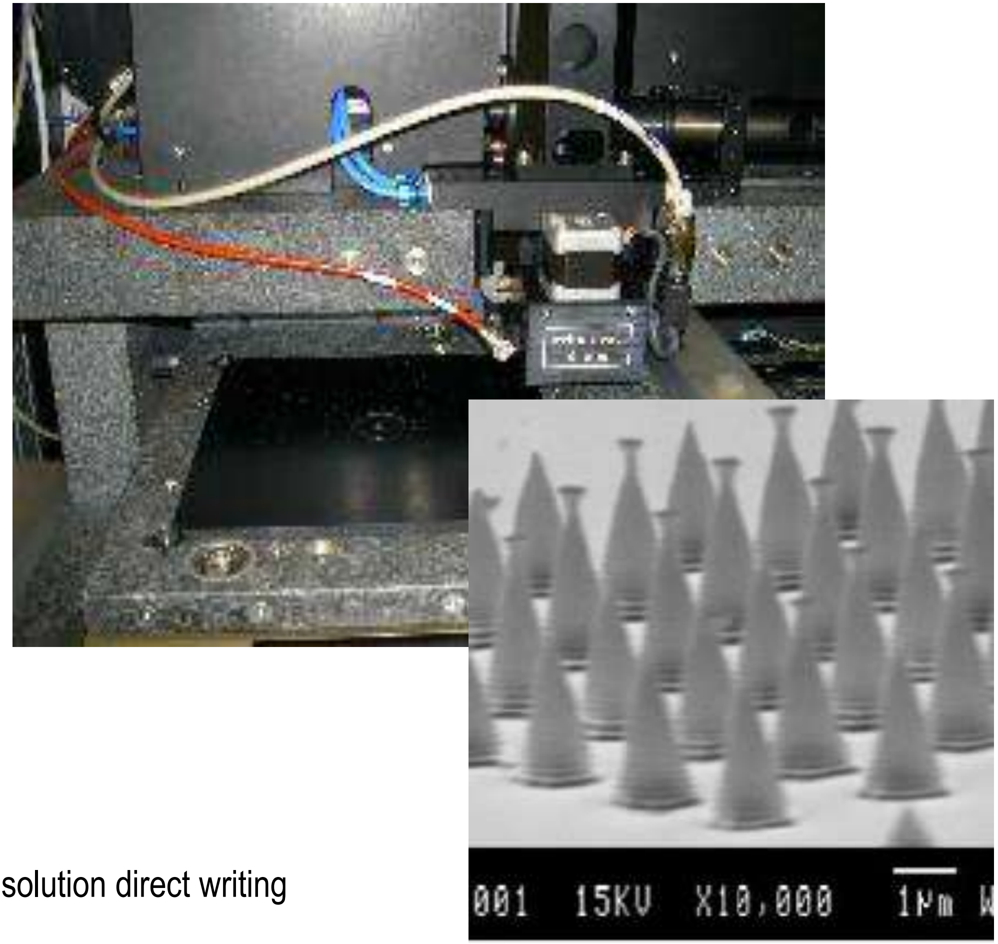


Note: How to realize mask ? →direct writing

- For ~5-25 µm resolution: high-resolution printers on a transparent film.
- For ~λ resolution: Chromium masks, realized by **direct laser writing** (on a resin).

Resolution: ~0.2 µm: nanopositionning system (mechanics) & diffraction (optics)





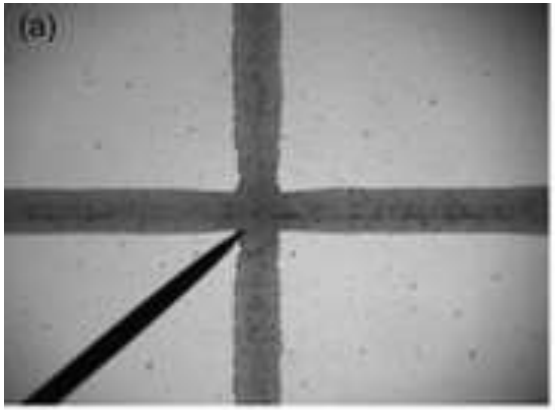
Sub-µm resolution direct writing

Ex at LAAS: laser DWL 200 Heidelberg Instruments, or KLOE Dilase

Other (cheaper than SU8) ways to realize master ?

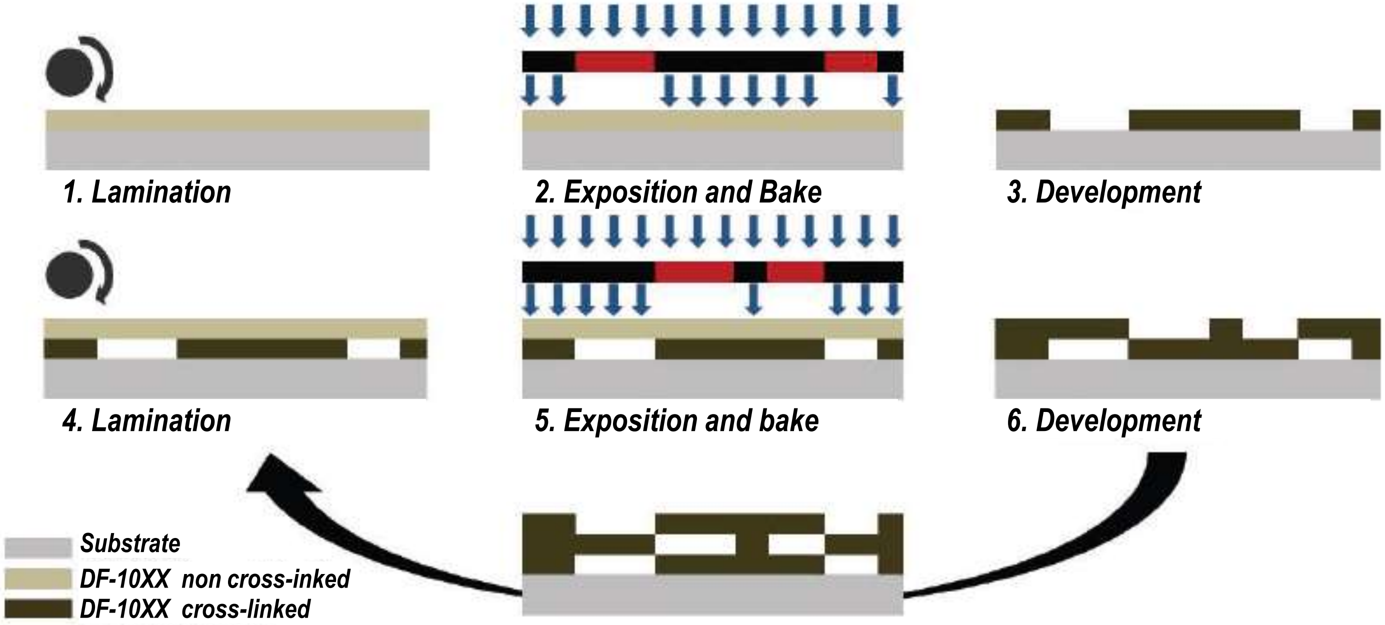
- ➢Wax printer

50 µm X-channel , thermal treatment, on Mylar film



Kaigala, Lab. Chip 2007

- ➢Lamination of dry films (see in part III)



Master fabrication

Micro Machining

Juergen J. Brandner[1]
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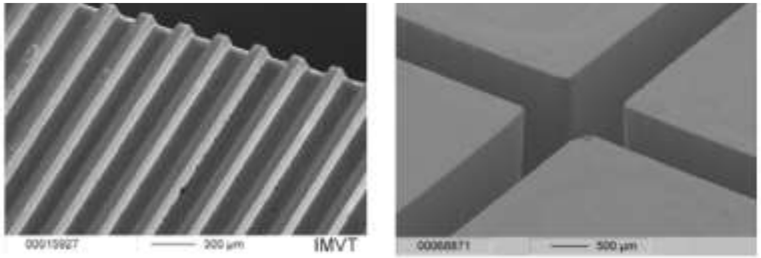


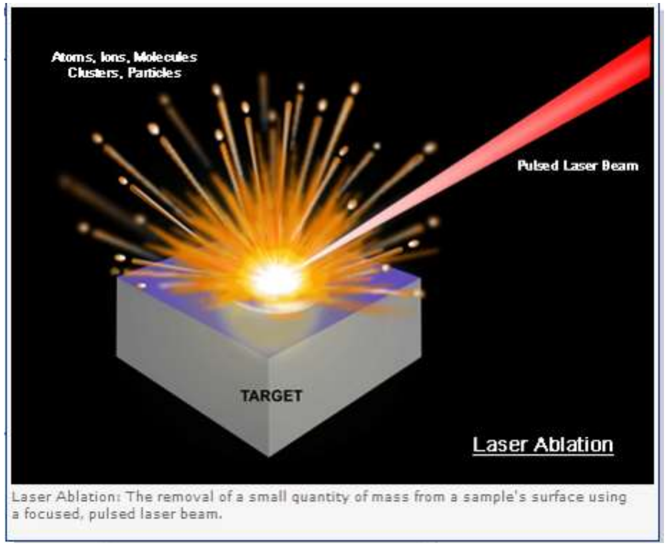
Figure 3 a, b: a (left): Microchannels machined into a stainless steel foil. The channels are about 200µm wide and 100µm deep, the side walls are 100µm wide. b (right): Microchannel cross machined into polymer material. Both structures have been manufactured at IMVT.

Aluminium Master

- Convenient for rapid prototyping
- Large range of materials (metals, polymers …)
- 2,5 D accessible
- Lifetime (metal masters)
- Resolution down to 10 µm
- *Speed ? Roughness ?*

Master fabrication

- **Laser ablation**



Laser Ablation: The removal of a small quantity of mass from a sample's surface using a focused, pulsed laser beam.

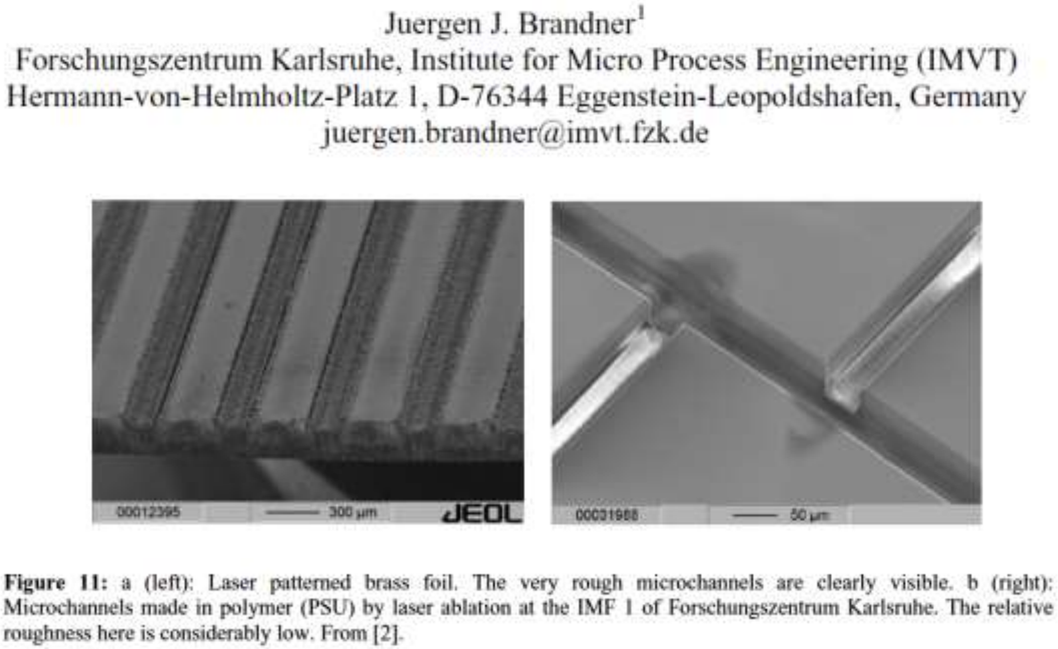


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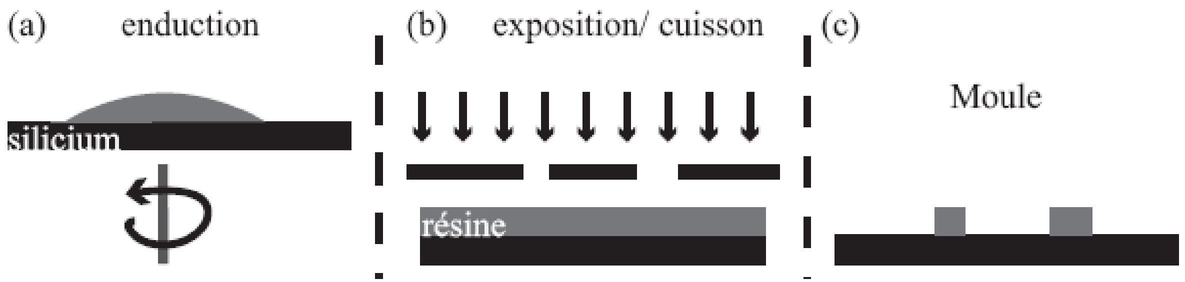
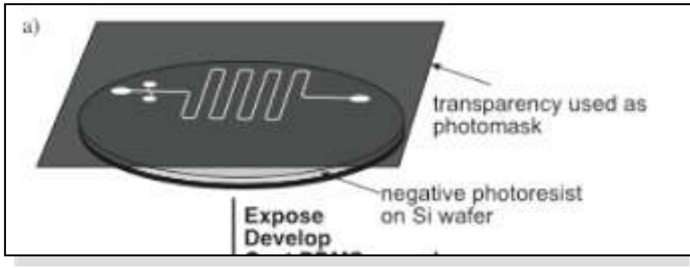
Figure 11: a (left): Laser patterned brass foil. The very rough microchannels are clearly visible. b (right): Microchannels made in polymer (PSU) by laser ablation at the IMF 1 of Forschungszentrum Karlsruhe. The relative roughness here is considerably low. From [2].

- 2,5 D accessible
- Resolution ~ 1µm ?
- *Speed ? Roughness ? Cost*

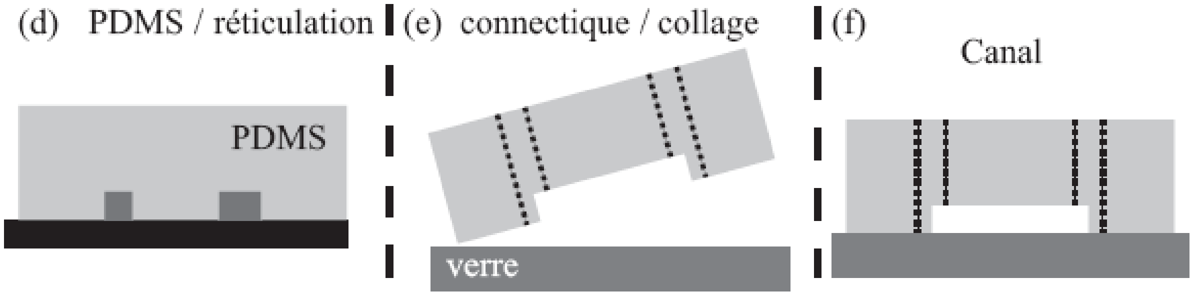
SU8 processing: summary

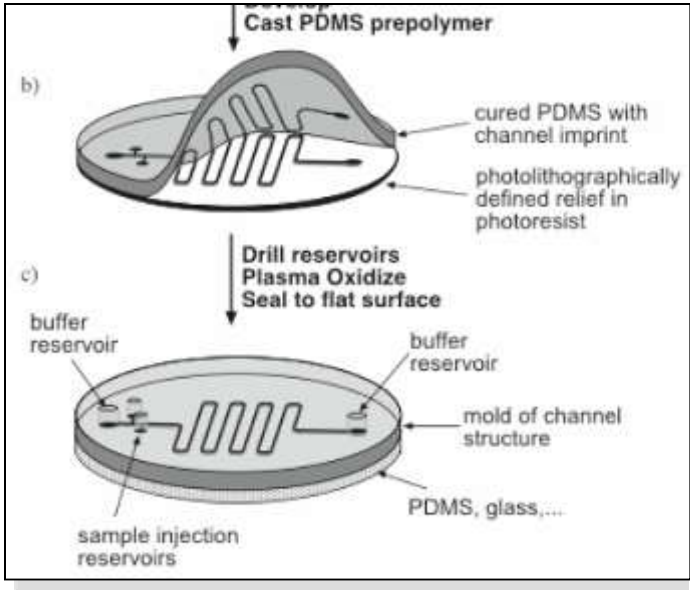
We have done:





Remaining steps:





II. PDMS for microfluidics

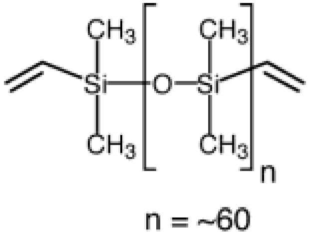
1. Mold (master)
   a) Microfabrication & Photolithography
   b) SU8 processing
   c) Alternative ways to realize a master

2. Channel
   a) PDMS, Casting & Curing
   b) Bonding

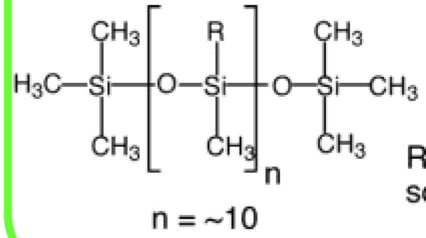
3. Properties
   a) Deformation
   b) Permeation
   c) Multi-level, modified
   d) Chemistry & bio

PDMS reticulation

Siloxane oligomer
(PDMS prepolymer)



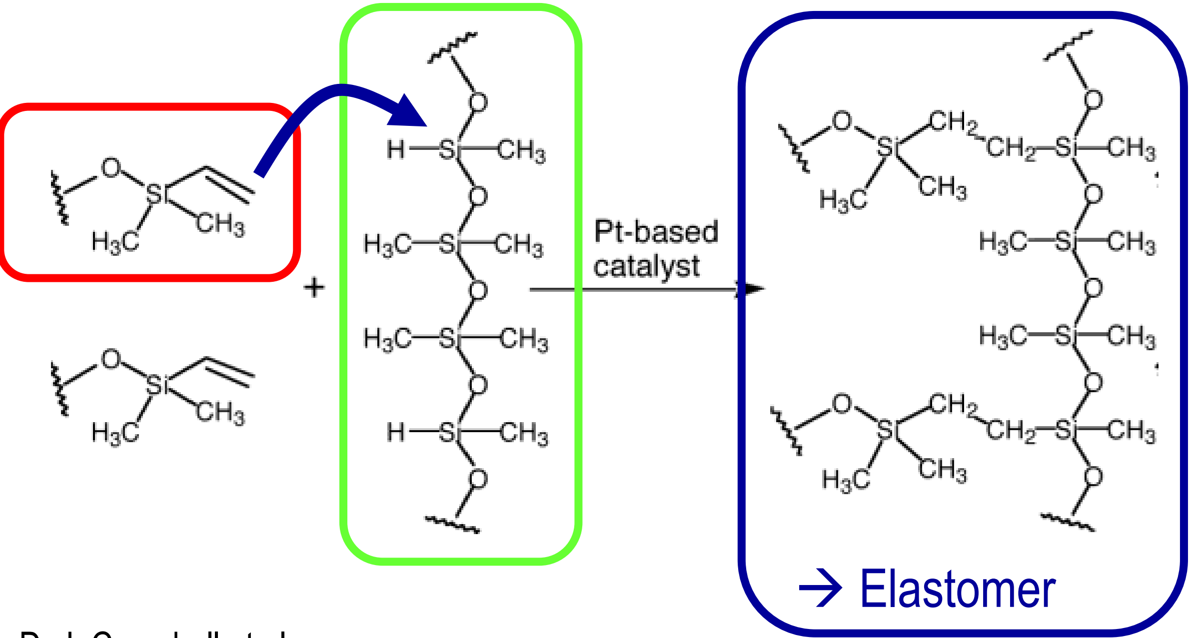
Cross-linker (=curing agent)



R is usually CH_3,
sometimes H

Crosslinking reaction
vinyl groups + silicon hydride bonds
(+ proprietary Pt-based catalyst)

Sylgard 184, Dow Corning



→ Elastomer

* Multiple sites → 3D crosslinking

* No waste products

* ➚ curing agent → harder
(more cross-links)

* Heating accelerates reaction

D. J. Campbell et al,
J. Chem. Educ. (1999)
http://www.mrsec.wisc.edu/Edetc/background/PDMS/index.html

PDMS bonding

* PDMS surface is hydrophobic, low surface energy: **$-Si(CH_3)_3$**

* Activation with O_2 plasma→ hydrophilic: **Si-OH silanol** groups (Silica-like layer)

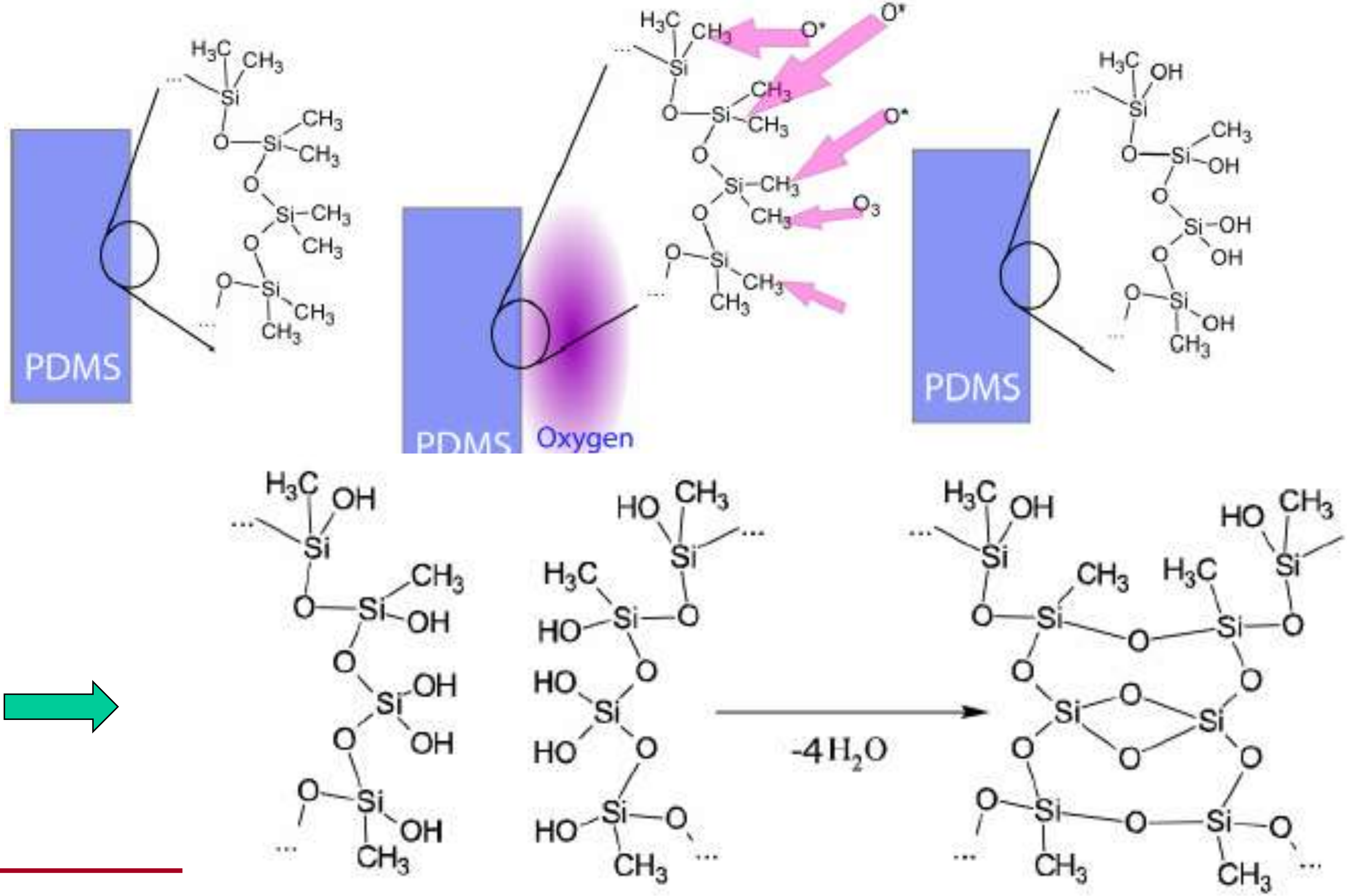
→ After plasma, bonding activated PMDS with Glass (or with PDMS):

Silicone)-Si-OH + (Glass)-Si-OH → (Silicone)-Si-O-Si-(Glass) + H_2O

Chemical bonds, no glue

PDMS bonding

(Silicone)-Si-OH + (Glass)-Si-OH → (Silicone)-Si-O-Si-(Glass) + H_2O



Notes on PDMS bonding

1. Si-OH only for ~30 min because uncrosslinked chains diffuse to the surface

To ➚ stability of hydrophilicity after bonding:

* thermal aging, extraction (before plasma)

Eddington (2006) Vickers (2006)

* stock finished microsystem under water

2. Also with Silicon (native oxyde, surface Si-OH) but lower density, less efficient

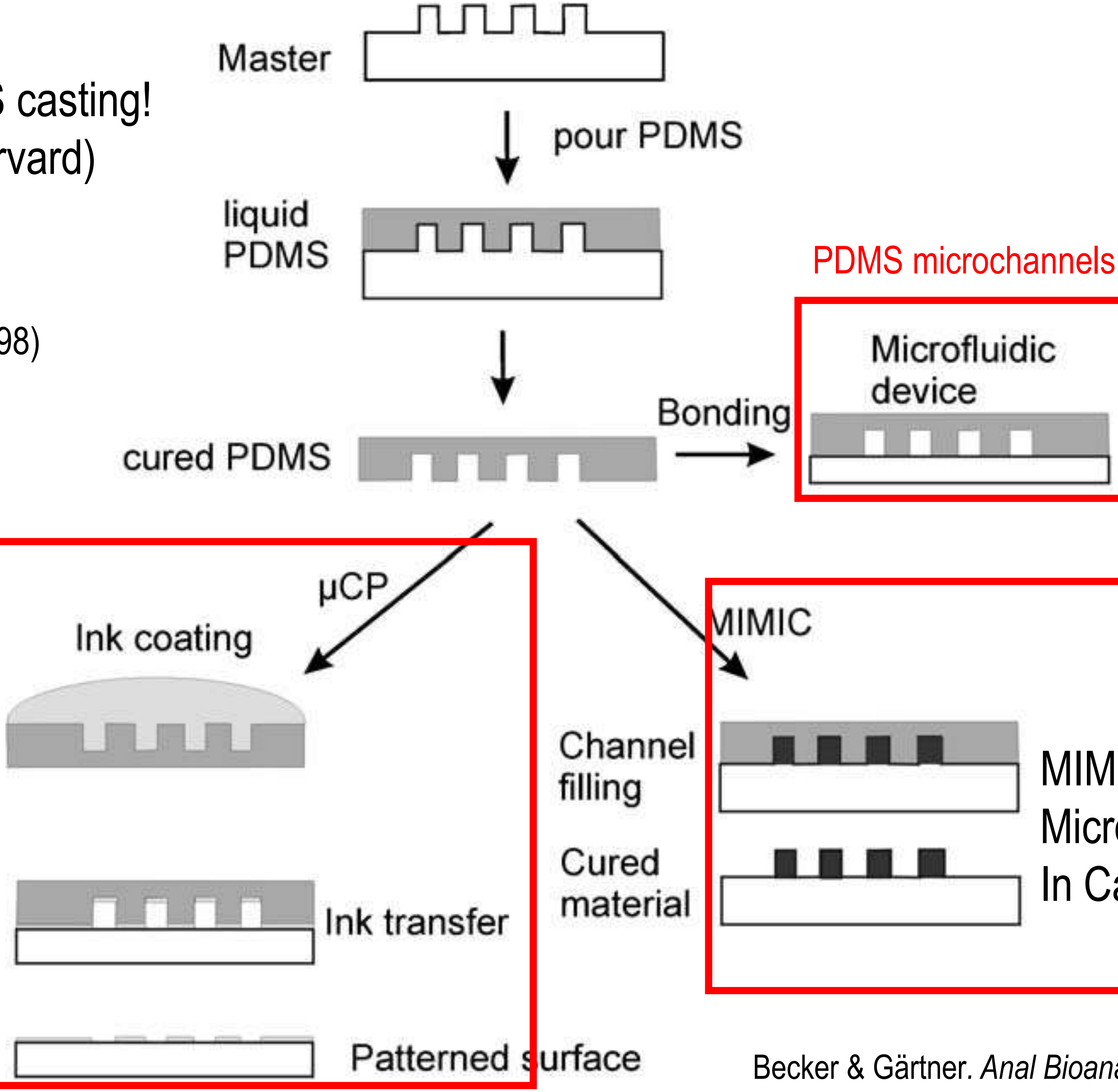
3. Other method to bond PDMS-PDMS: ≠ % of curing agent (ex 5% - 15%)

(again mechanism: diffusion of free chains)

Origin of soft microfluidics : soft-lithography

Potentialities of PDMS casting!
Whitesides group (Harvard)

Xia & Whitesides
Angew Chem Int Ed (1998)



PDMS microchannels (see part I)

Micro Contact Printing…

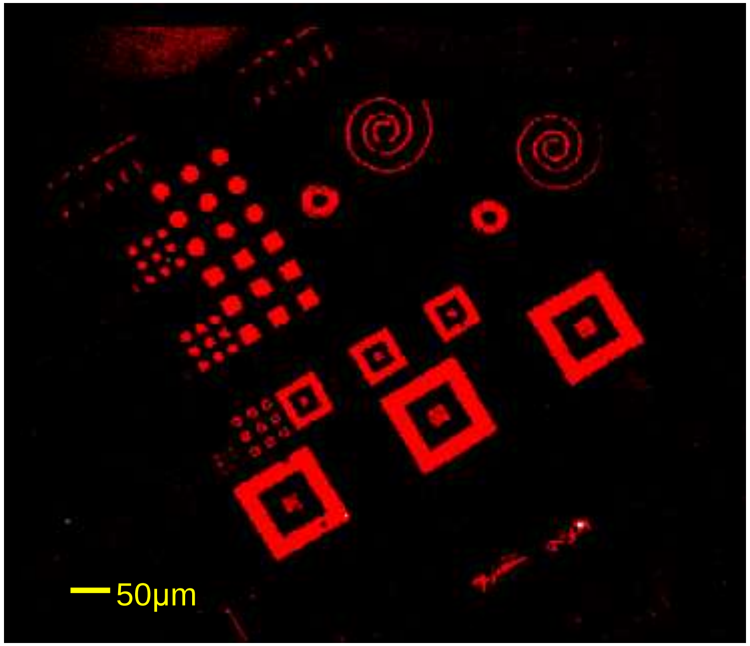
MIMIC:
Micro Molding
In Capillary

Becker & Gärtner. *Anal Bioanal Chem* (2008)

Soft lithography: examples

- Micro-contact printing

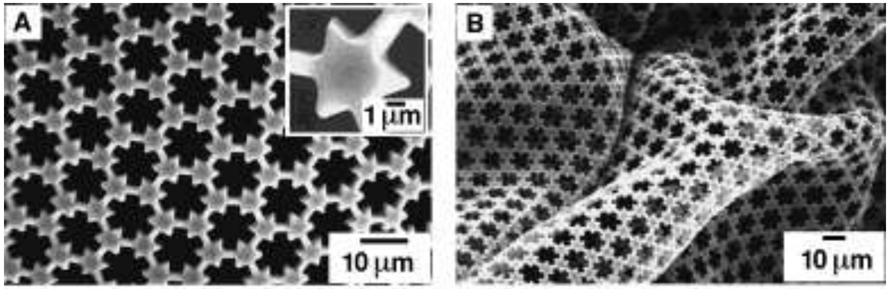
Oligonucleotides 20-mer after hybridization



(courtesy C. Thibault)

- MIMIC: Patterning by capillary flows

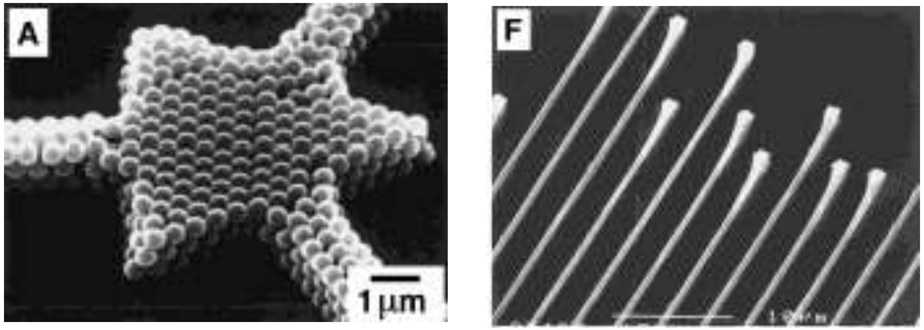
Without solvent



Polyacrylate

Polyurethane

With solvent



Polymer beads in water

Zirconium oxyde ceramics

Xia & Whitesides, Angew Chem Int Ed (1998)

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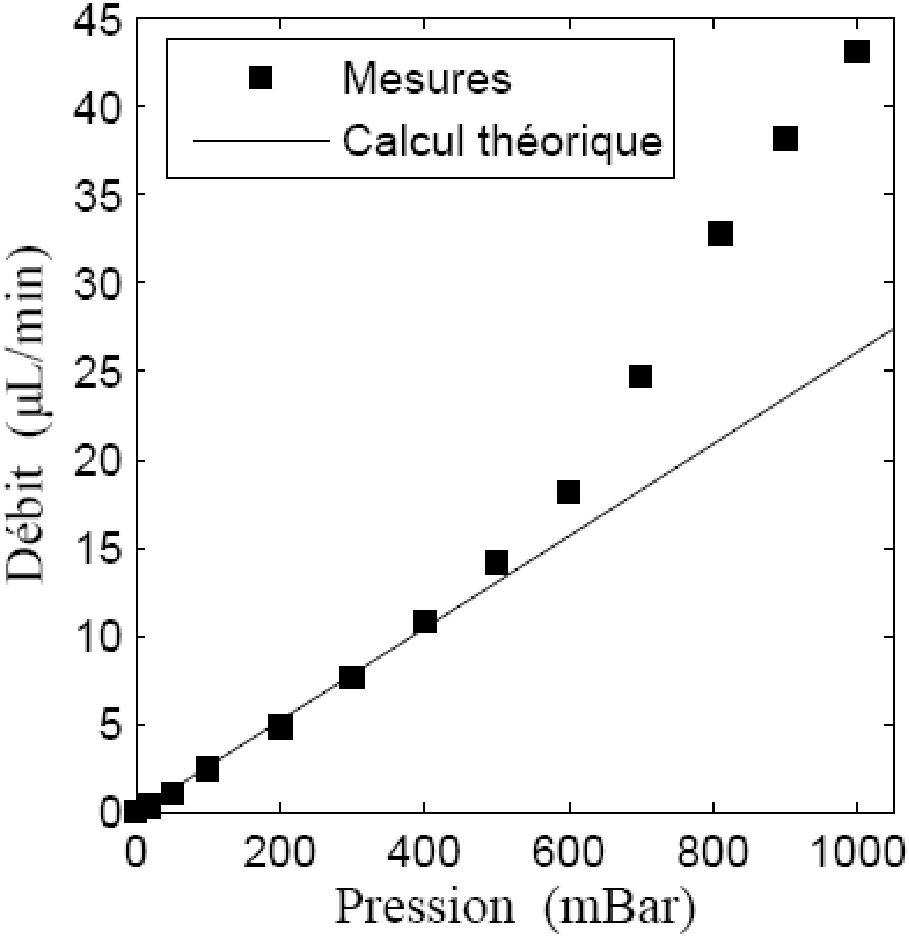
PDMS can be deformed

- **Elastic modulus ~1MPa**



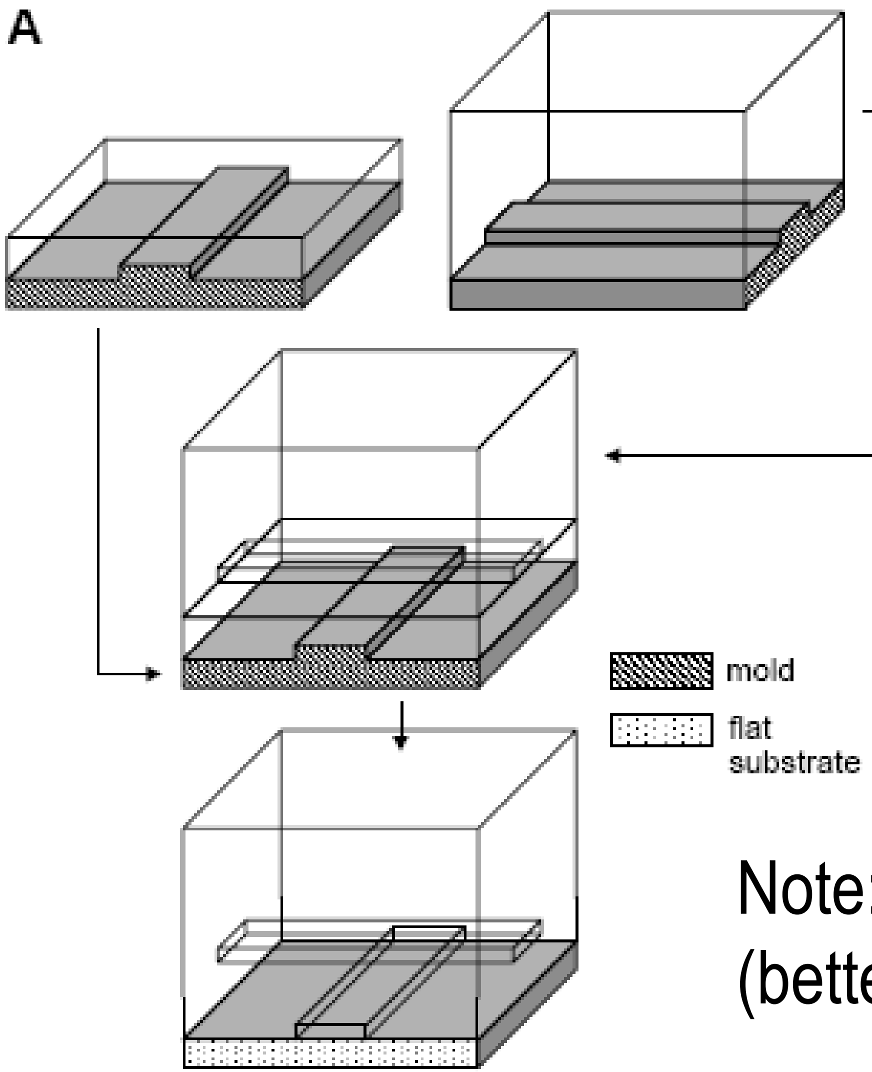
*Drawback:

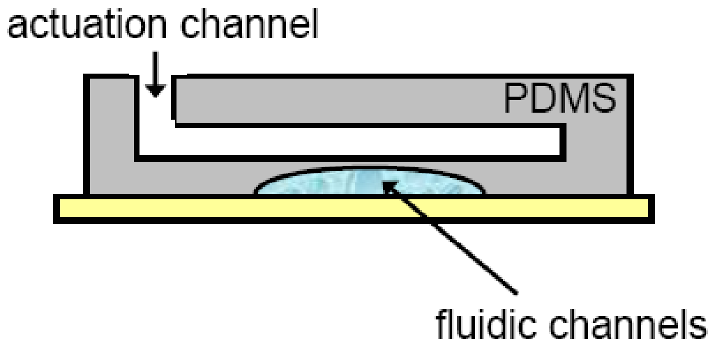
Q(P) non linear

Channel Collapse for low aspect ratio

* Applications : valves, pumps

« Quake Valve » based on deformability





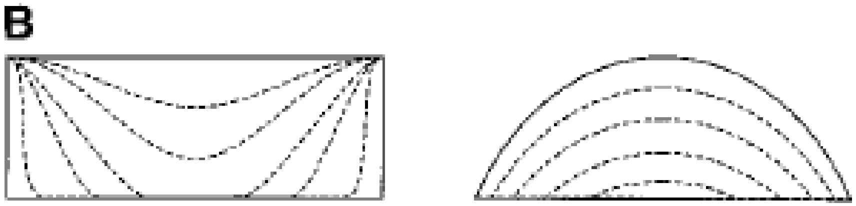
Principle:

2 molds

Deflection of a thin membrane

→close channels

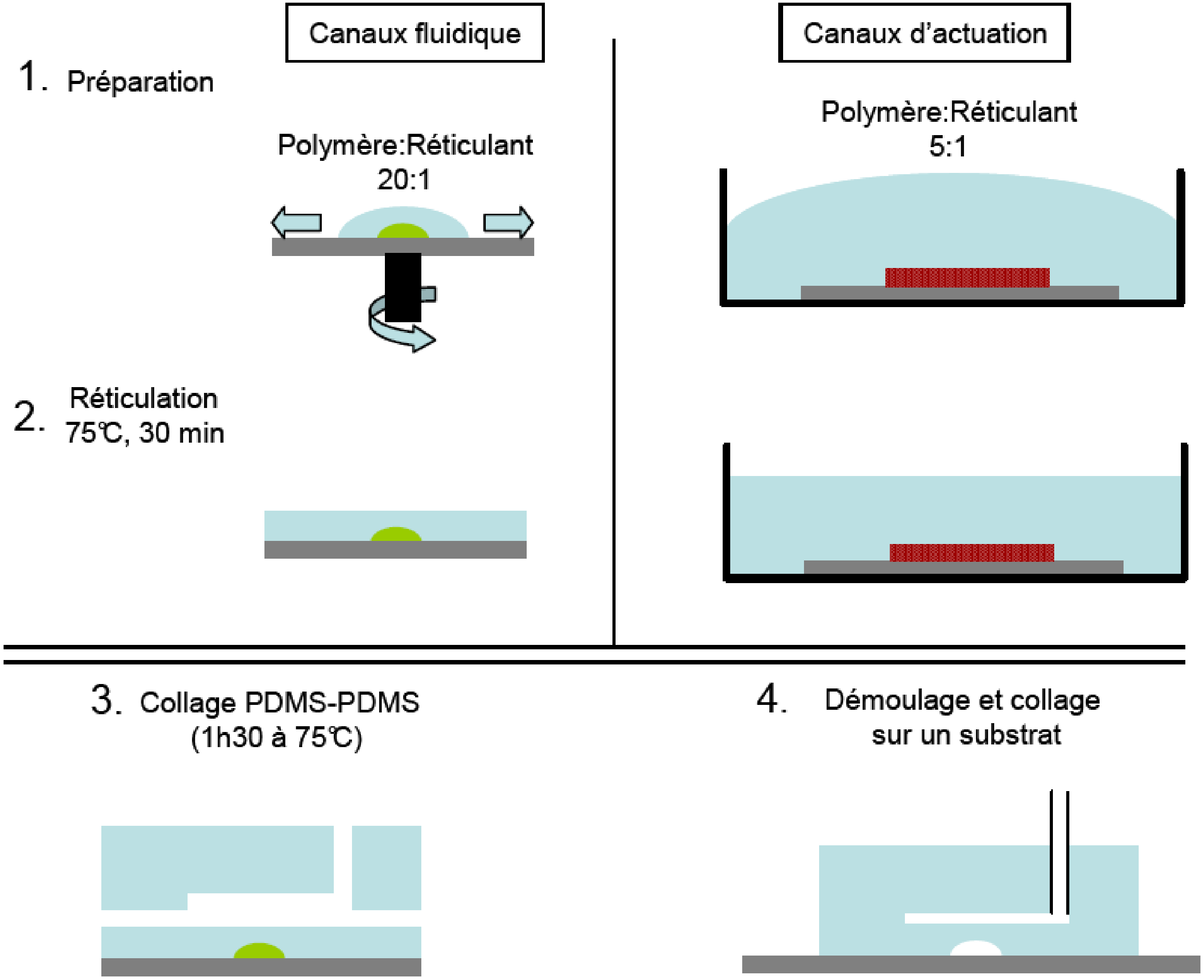
Note: fluidic channels need to be round (better closing)



Unger, Quake, Science 2000

Valve based on deformability

➢ Fabrication protocol



Canaux fluidique

Canaux d'actuation

1. Préparation

Polymère:Réticulant
20:1

Polymère:Réticulant
5:1

2. Réticulation
75℃, 30 min

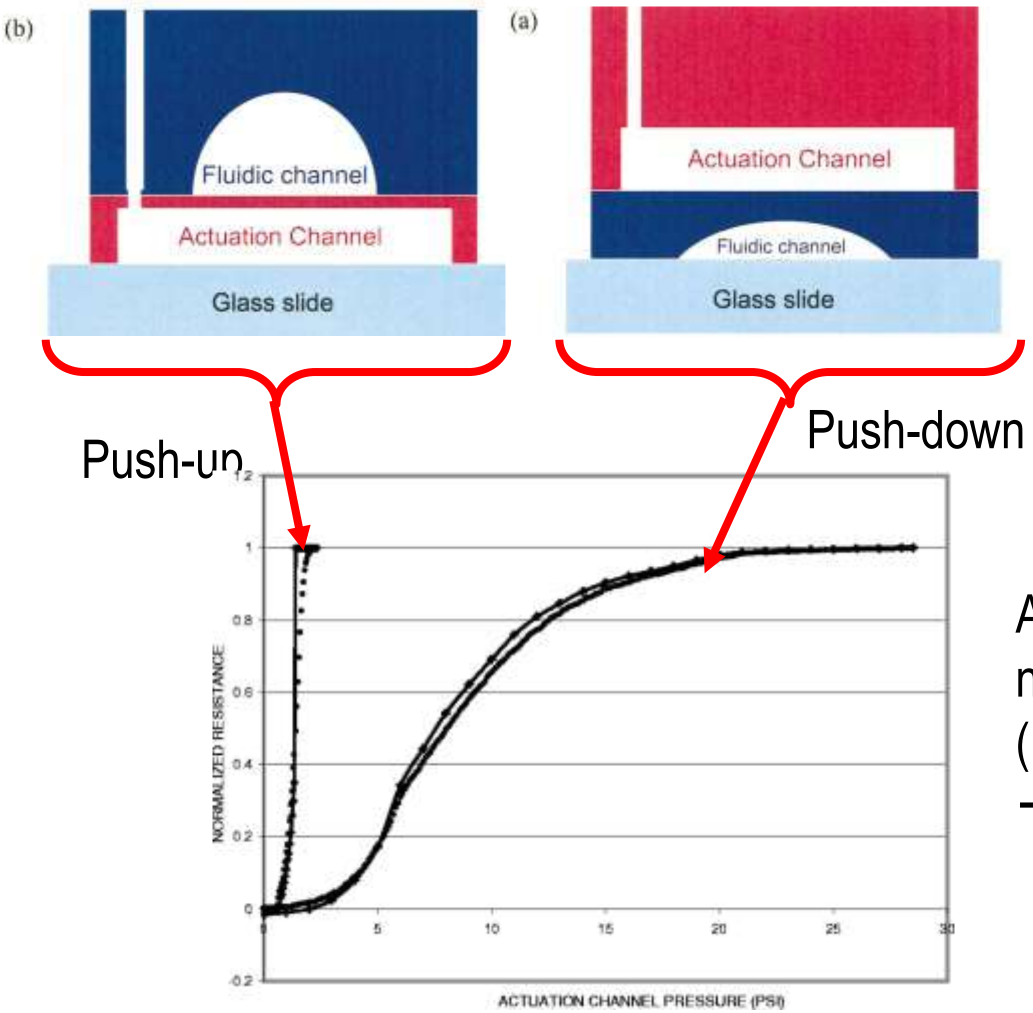
3. Collage PDMS-PDMS
(1h30 à 75℃)

4. Démoulage et collage
sur un substrat

Goulpeau, 2006

Valve based on deformability

- **Design optimization**



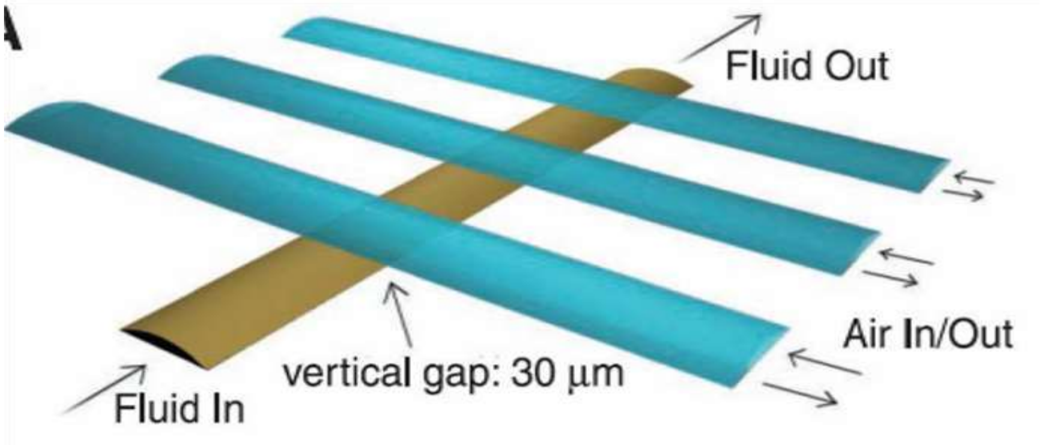
*Fluidic channel need to be round
AZ 100, heated above Tg:
reflowing → round shape
*Actuation channels: SU-8 (rectangular)

Agreement with 3D FEM Model
near-incompressible Neo–Hookean material
(rubber-like, large deformations)
→ E~0.6 Mpa

Studer, Quake, J. Appl. Phys. 2004

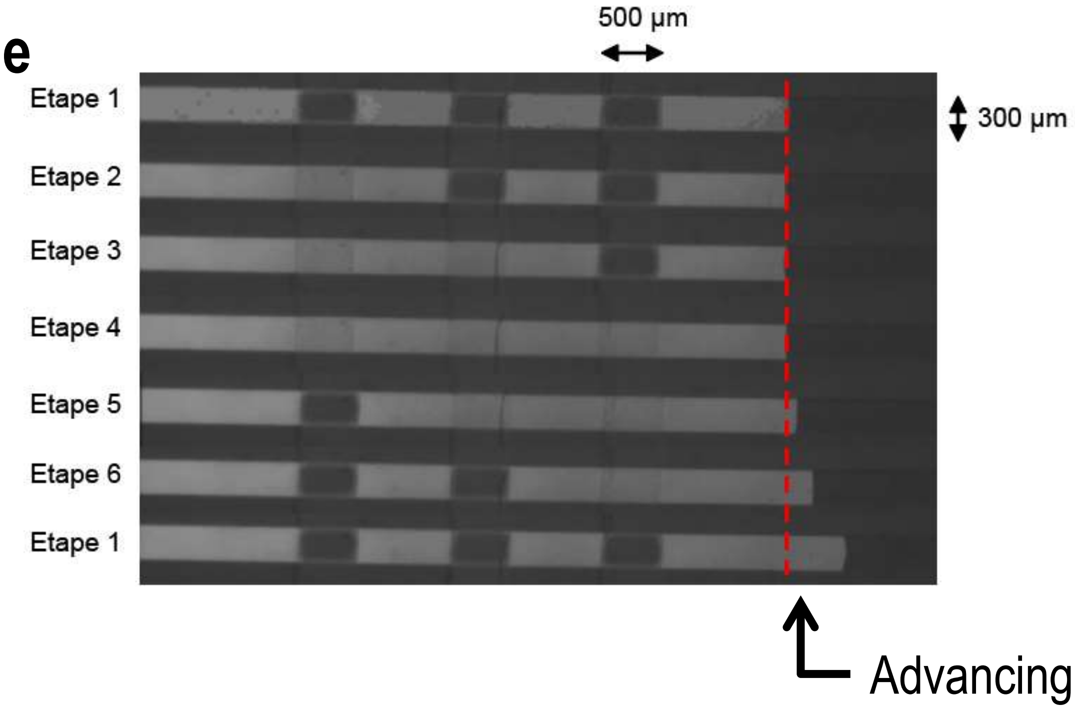
Pumps : principle

- **Design**



Unger, Quake, Science 2000

- **Peristatic cycle**

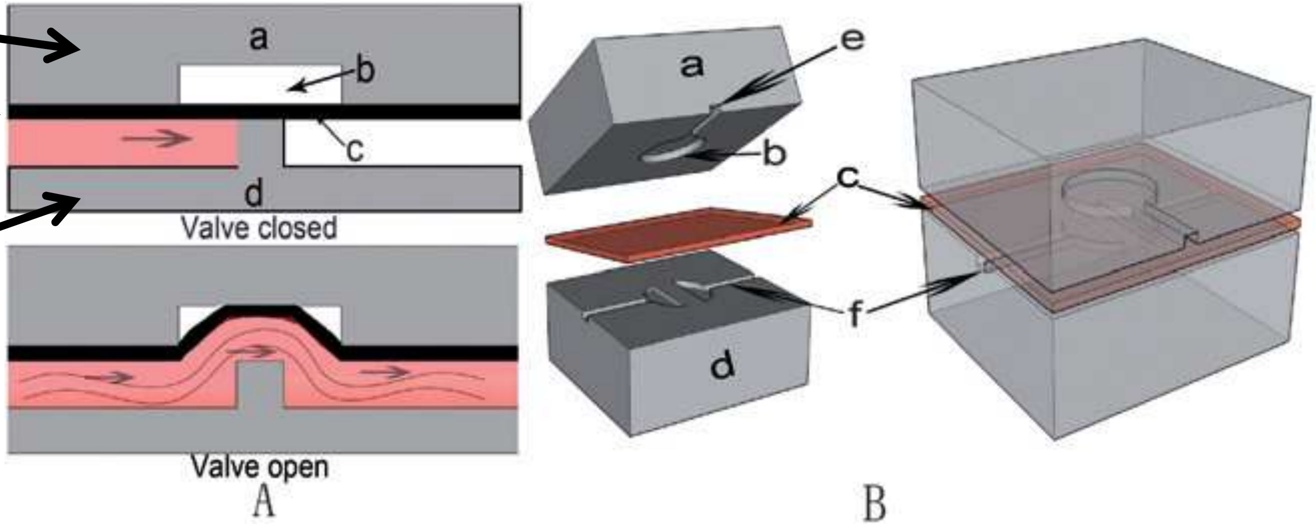


Goulpeau, 2006

Advancing fluorescein front

PDMS/PMMA valves

PMMA channels: harder (see III.2), no deformation…→ integrate PDMS membrane to realize a valve



PMMA actuation wafer

PDMS membrane

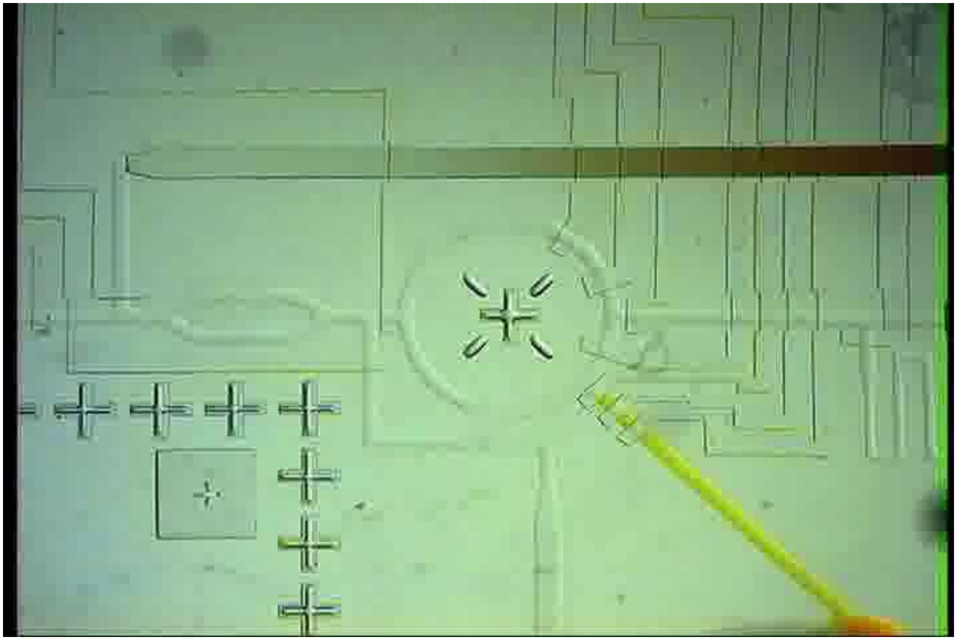
PMMA fluidic wafer

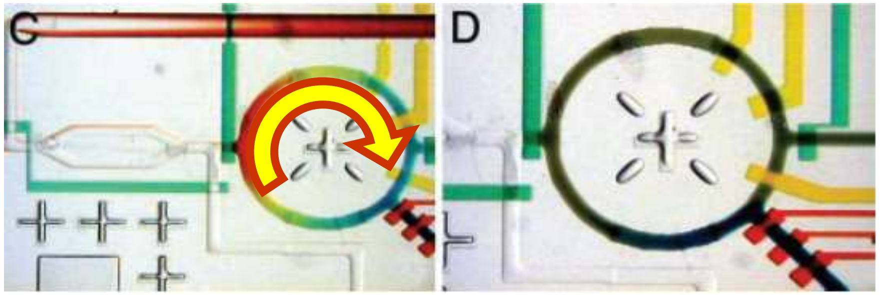
Kuo, LOC 2012 (Review) : hybrid of substrates that takes advantage of each material's attributes.

Zhang et al., Lab Chip 2009

Valves and pumps : microfluidic formulator

http://www.pnas.org/content/suppl/2004/09/17/0405847101.DC1/05847Movie1.mpg





Rotary mixer (V~5nL)

* Rapid mixing of reagents by active peristaltic pumping

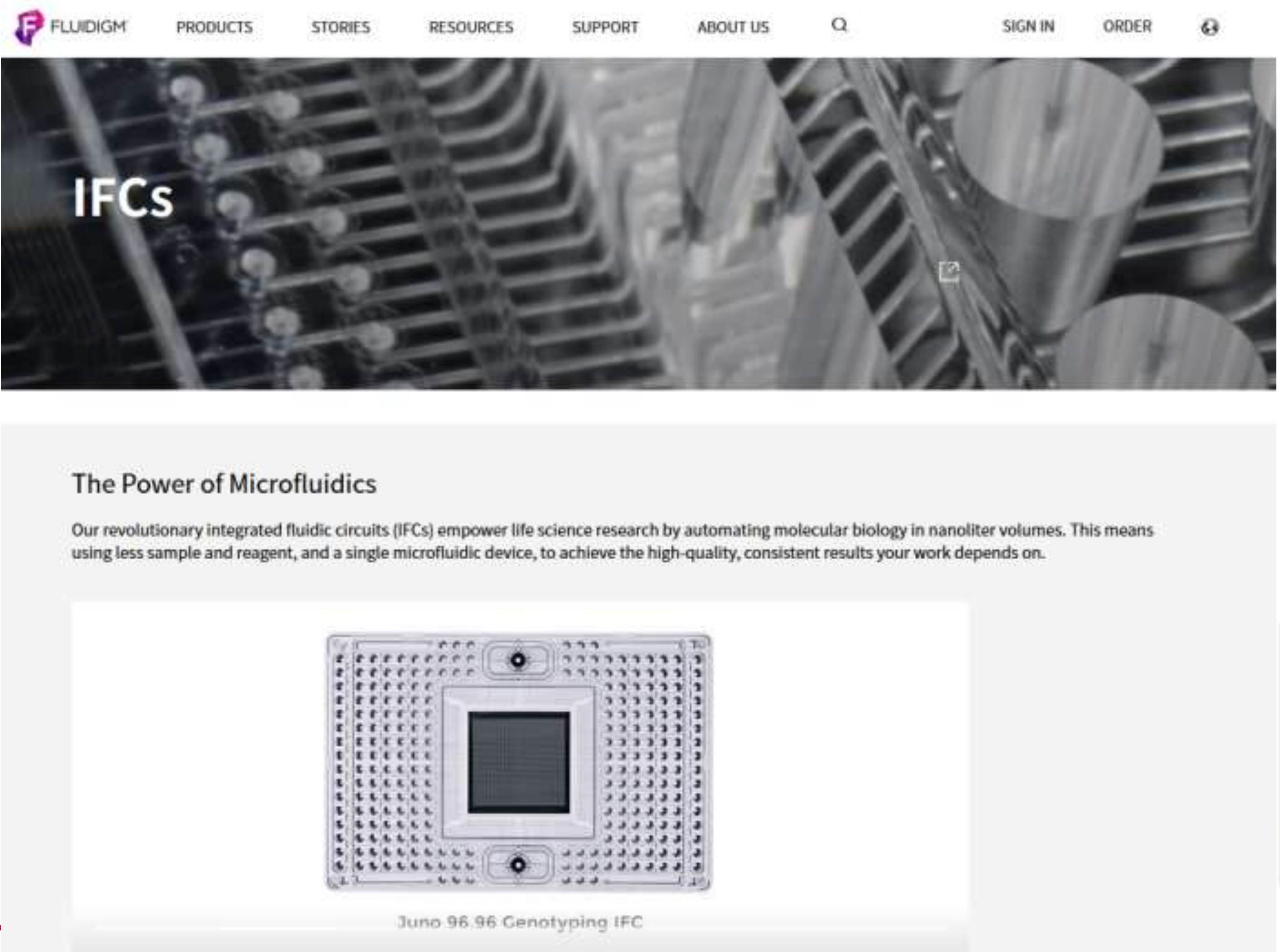
* Combinatorial automated mixing on chip: thousands of exp. with a few µL

→ Systematic investigation of protein phase behavior

Chou et al, Biomed Devices 2001,
Hansen et al, PNAS 2004

Integrating valves

- “Quake’s valves” : → company for life science



IFCs

The Power of Microfluidics

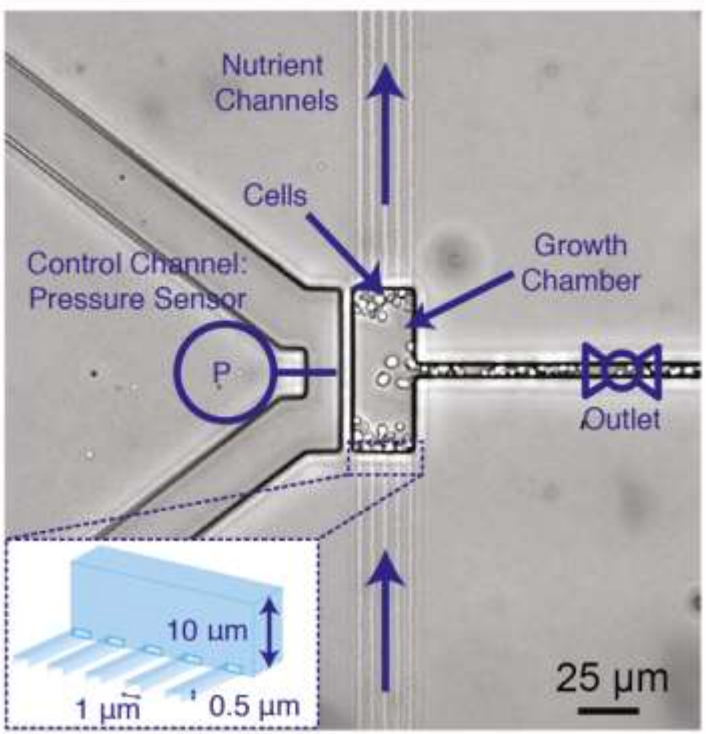
Our revolutionary integrated fluidic circuits (IFCs) empower life science research by automating molecular biology in nanoliter volumes. This means using less sample and reagent, and a single microfluidic device, to achieve the high-quality, consistent results your work depends on.

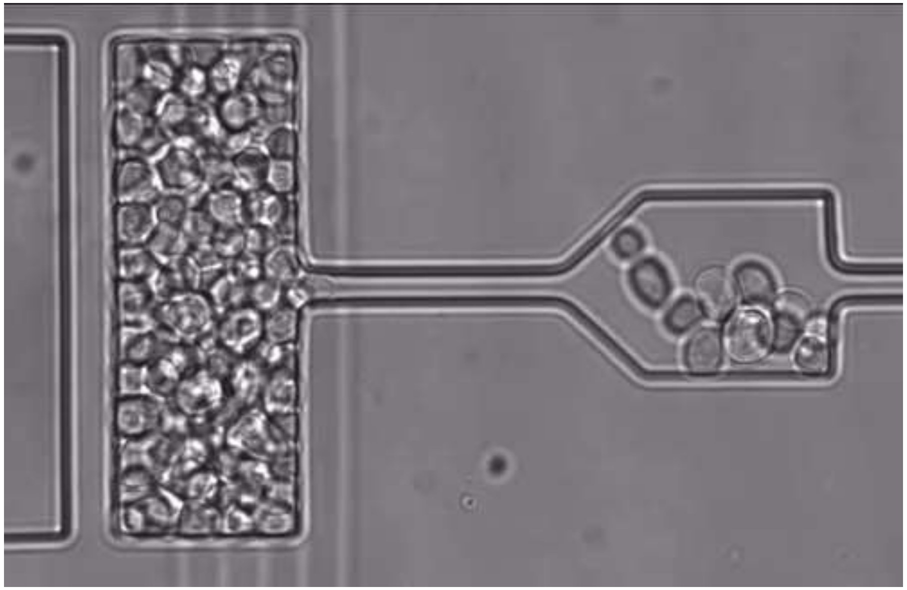
Juno 96.96 Genotyping IFC

- Digital PCR
- Protein cristallization
- Single cell gene expression
- DNA sequencing

PDMS is deformable : Confining chambers for microbes

Use deformation to measure/impose pressure





- ➢ ***Growth-induced compressive stress*** under spatial confinement

In Sète: see Baptiste Alric or Lucie Albert

Morgan Delarue, Nature Physics 2016

PDMS is soft …

- ***Soft Robots***

(G.M. Whitesides)

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   c) Multi-level, modified
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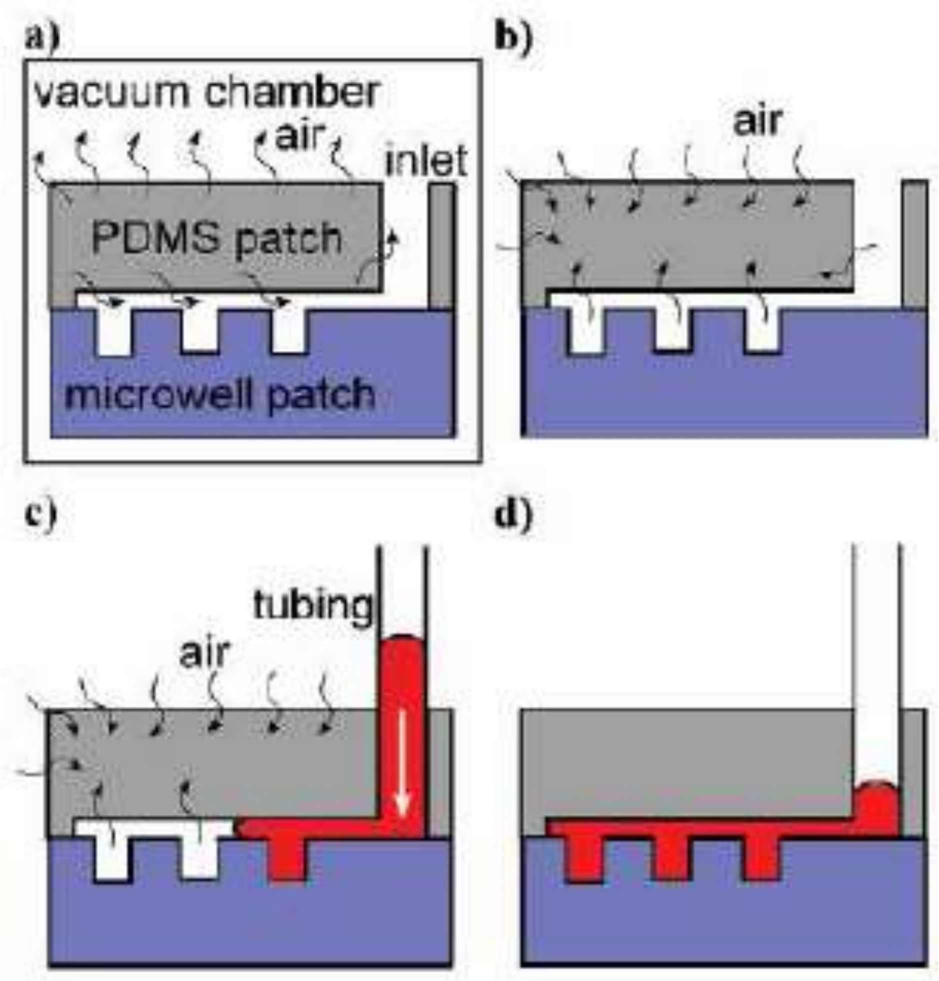
PDMS is permeable to air



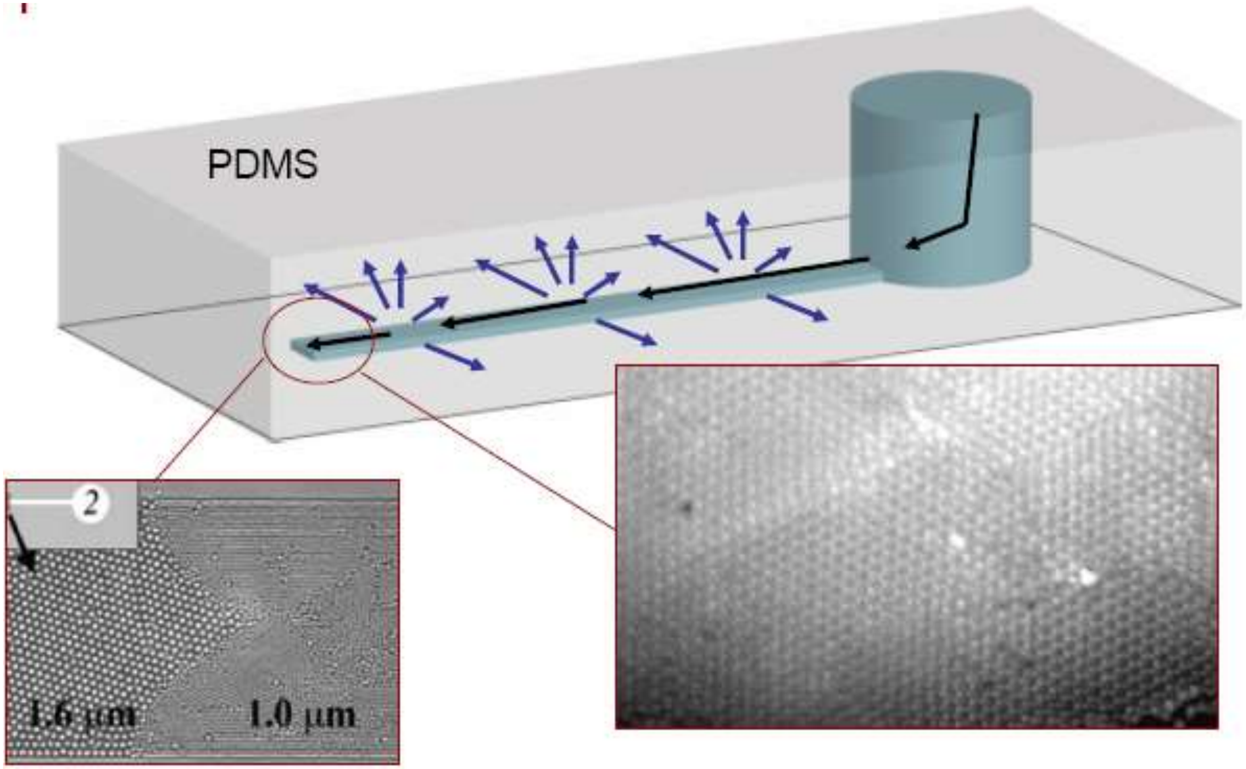
→ filling procedure

Works for closed-end channels

Zhou et al., Anal. Chem. 2007
Goulpeau et al, Brevet 2005

Pumping with permeation

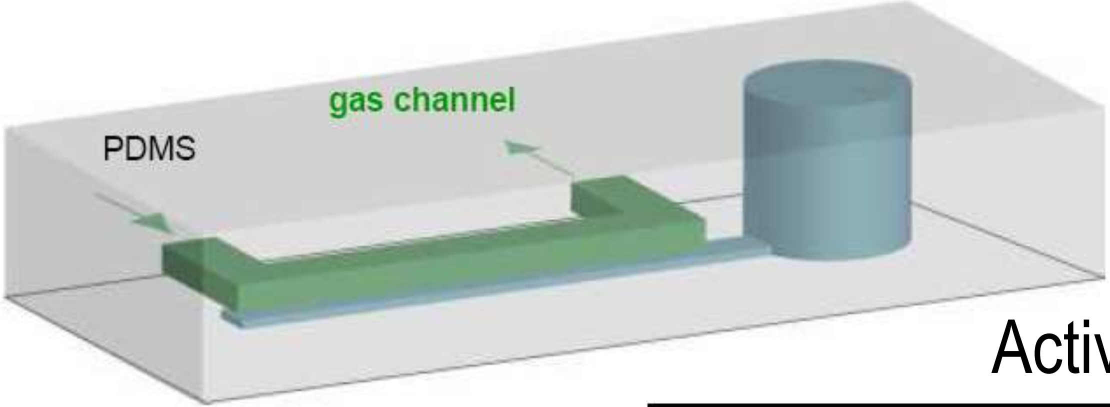
PDMS is permeable to air, but also to liquids



Passive concentration
Permeation-induced flows

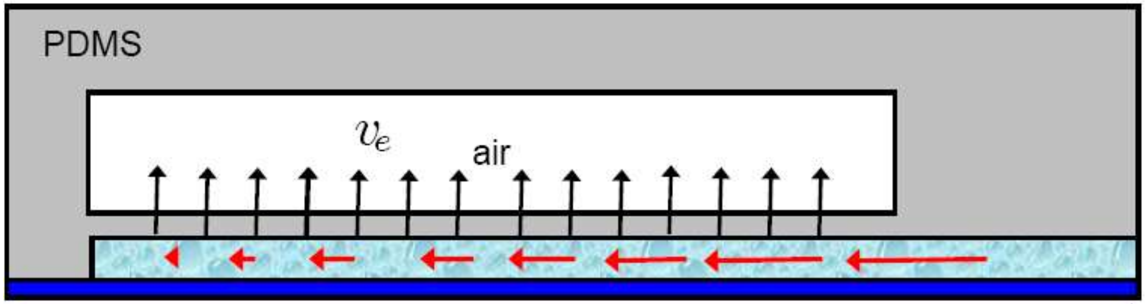
Verneuil et al., EuroPhys. Lett. 2004
Randall et al. PNAS 2005

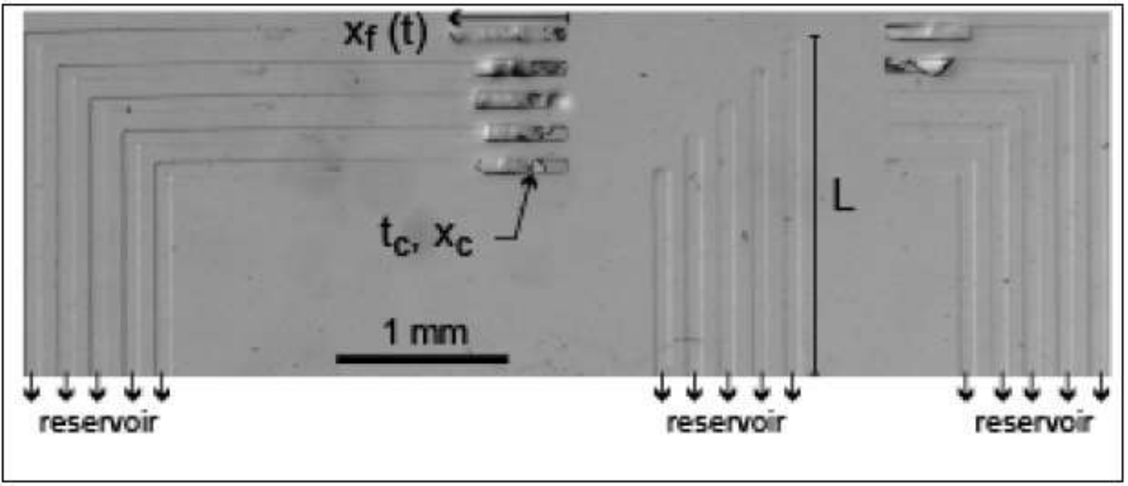
Pumping with permeation



Leng *et al.* Phys. Rev. Lett. 2006
Salmon ESONN 2008

Active control of the permeation





Powerful & versatile tool
to study phase diagrams

In Sete: See JB Salmon

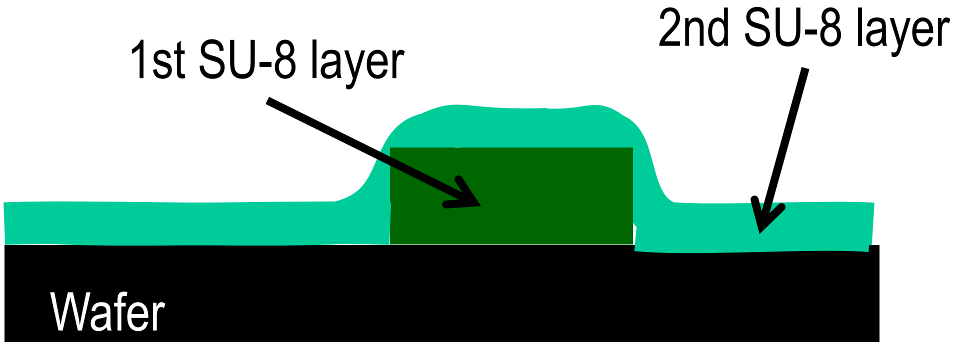
Multi-level channels

- ➢ 2 level master (2 deposition of SU-8)

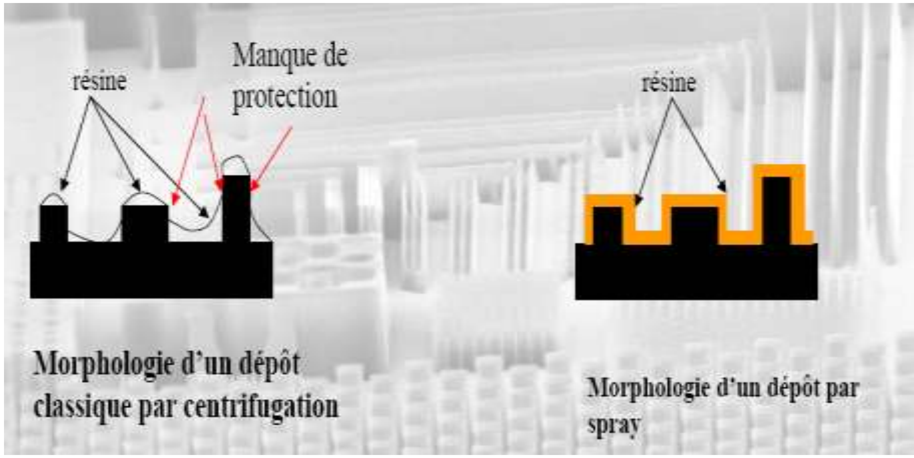
Ex of application:
Super-hydrophobic surfaces in microchannels

Technical challenges :
- Conformity of second level (non-flat substrate)
- Combine hydrophobicity and bonding

- ➢ **Conformity issue** with spincoating

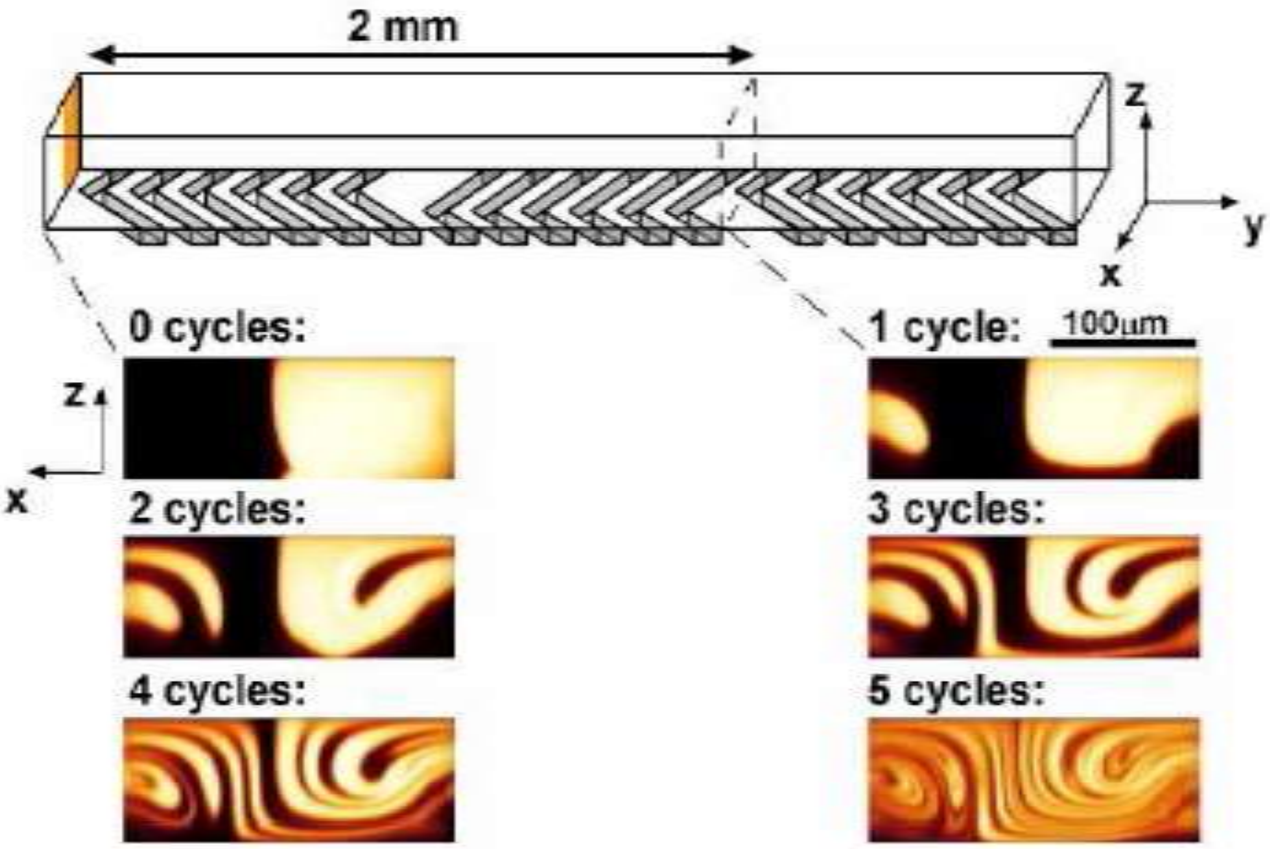


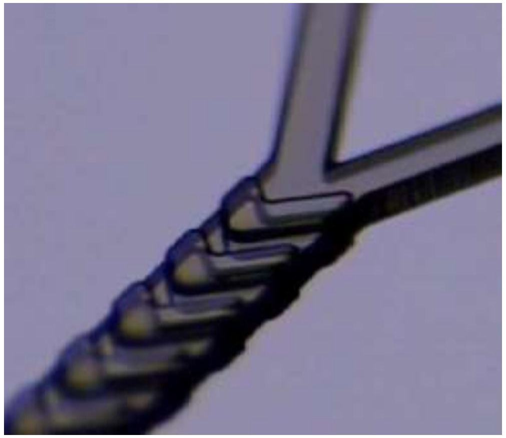
Solution 1: spray deposition



Solution 2: 2nd spincoating before developing 1st layer

Multi-level channels: groove mixer





Mixing only by diffusion:
enhancement by folding interfaces

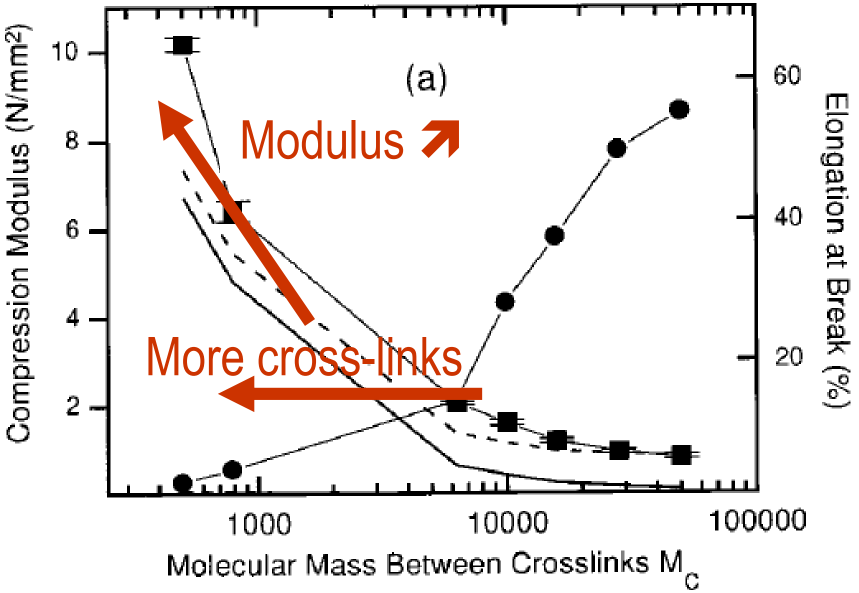
Stroock *et al.*, Science 2002

Modified PDMS: harder ?

- Hard-PDMS

Modified formulation: more cross-links

→E~9MPa



Useful for:

* Nanofluidics (no collapse)

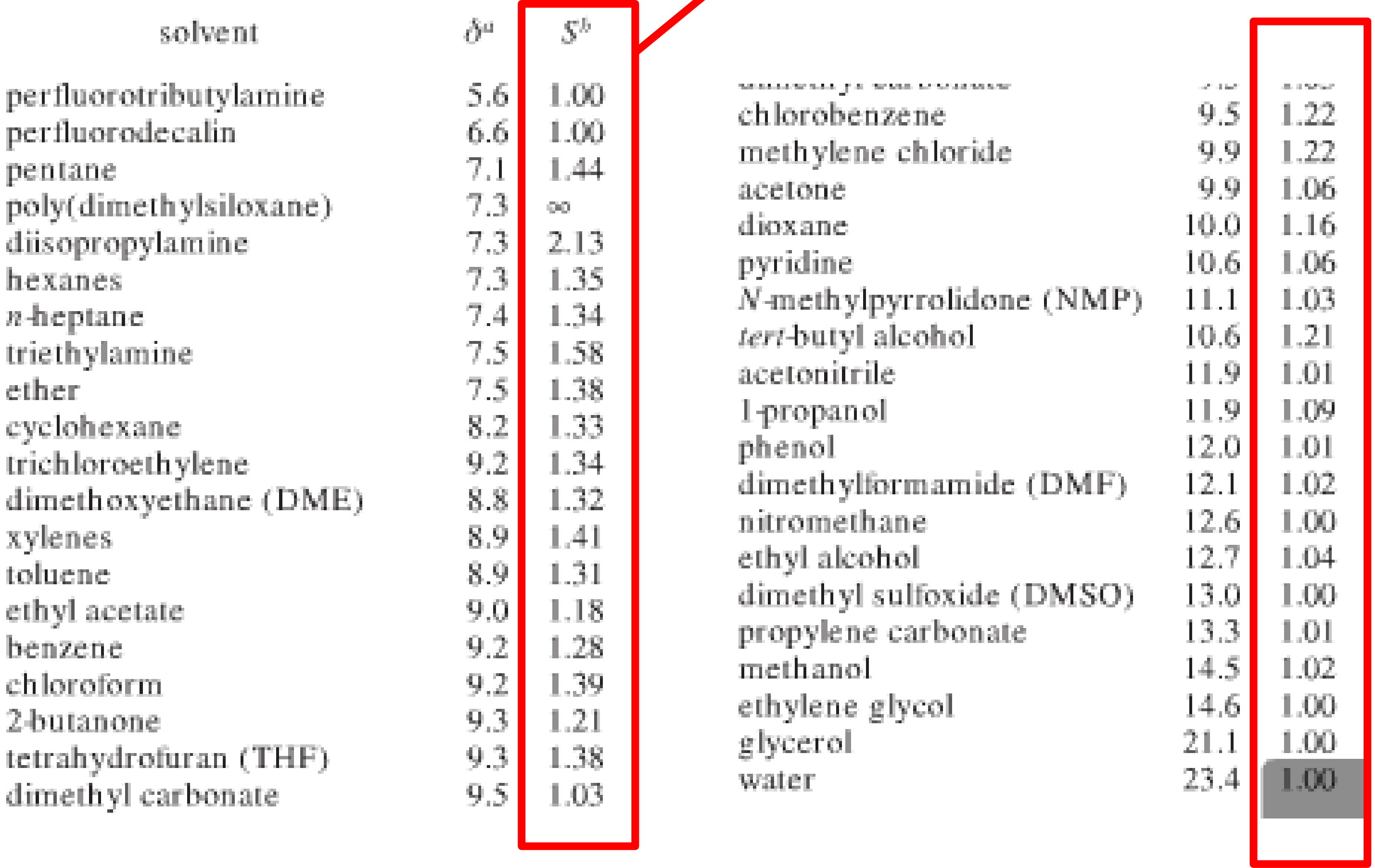
* Increasing soft lithography resolution

Schmid et al., Macromol. 2000

Chemical resistance of PDMS channels

* Bad Chemical resistance and stability:
in table: *S* = swelling ratio

S>1 : swelling by most solvent



solvent	δ^a	S^b
perfluorotributylamine	5.6	1.00
perfluorodecalin	6.6	1.00
pentane	7.1	1.44
poly(dimethylsiloxane)	7.3	∞
diisopropylamine	7.3	2.13
hexanes	7.3	1.35
n-heptane	7.4	1.34
triethylamine	7.5	1.58
ether	7.5	1.38
cyclohexane	8.2	1.33
trichloroethylene	9.2	1.34
dimethoxyethane (DME)	8.8	1.32
xylenes	8.9	1.41
toluene	8.9	1.31
ethyl acetate	9.0	1.18
benzene	9.2	1.28
chloroform	9.2	1.39
2-butanone	9.3	1.21
tetrahydrofuran (THF)	9.3	1.38
dimethyl carbonate	9.5	1.03
chlorobenzene	9.5	1.22
methylene chloride	9.9	1.22
acetone	9.9	1.06
dioxane	10.0	1.16
pyridine	10.6	1.06
N-methylpyrrolidone (NMP)	11.1	1.03
tert-butyl alcohol	10.6	1.21
acetonitrile	11.9	1.01
1-propanol	11.9	1.09
phenol	12.0	1.01
dimethylformamide (DMF)	12.1	1.02
nitromethane	12.6	1.00
ethyl alcohol	12.7	1.04
dimethyl sulfoxide (DMSO)	13.0	1.00
propylene carbonate	13.3	1.01
methanol	14.5	1.02
ethylene glycol	14.6	1.00
glycerol	21.1	1.00
water	23.4	1.00

* Evolution of surfaces (migration of unreticulated chains) : from hydrophilic to hydrophobic
Zeta potential ~-80mV at neutral pH (Si-OH = acid, pKa~4 → SiO^- group)

Lee, Anal. Chem (2003)
Wong, Micro. Nanofluidics, 2009

Surface modification of PDMS is challenging

2

Electrophoresis 2010, *31*, 2–16

Jinwen Zhou
Amanda Vera Ellis
Nicolas Hans Voelcker

School of Chemistry, Physics and Earth Sciences, Flinders University, Adelaide, S.A.,

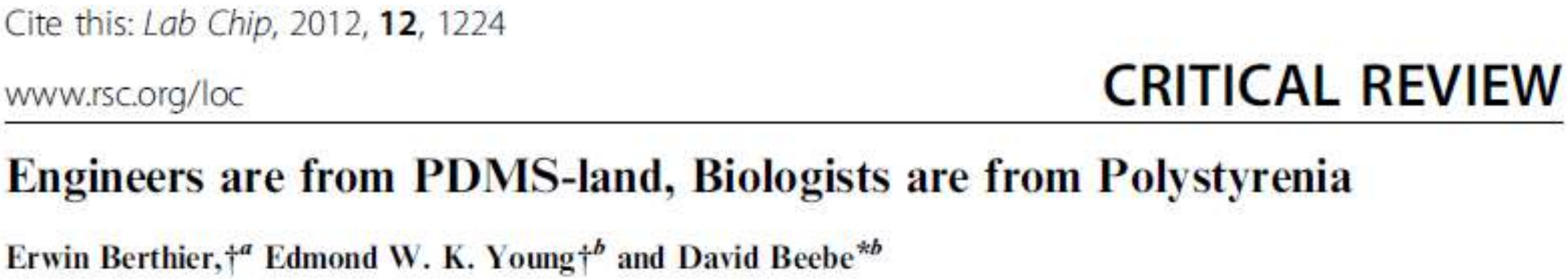
Review

Recent developments in PDMS surface modification for microfluidic devices

-Physical,
dynamic coatings (surfactant treatments)
physisorption of charged or amphiphilic polymers and copolymers
…
- Chemical covalent bonding (SAM self assembled monolayer & thick polymer coating)
- Activation (plasma), Silica-like layer (Si-OH silanol)

Lee, Anal. Chem (2003)
Wong, Micro. Nanofluidics, 2009

Biocompatibility of PDMS?



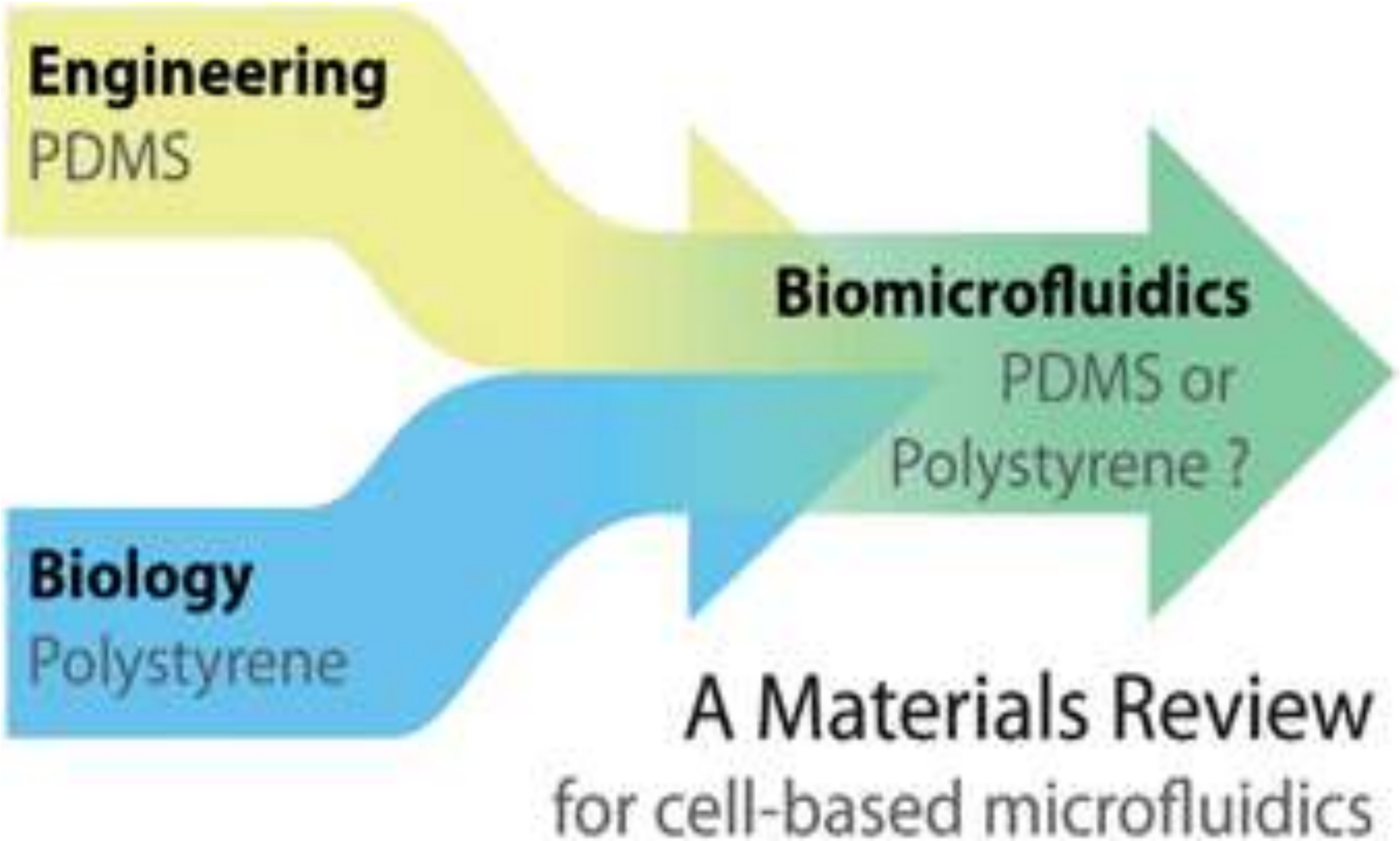
Cite this: *Lab Chip*, 2012, **12**, 1224

www.rsc.org/loc

CRITICAL REVIEW

Engineers are from PDMS-land, Biologists are from Polystyrenia

Erwin Berthier,†[a] Edmond W. K. Young†[b] and David Beebe*[b]



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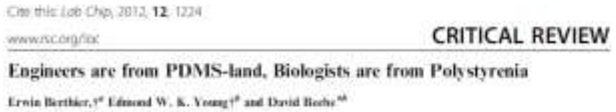

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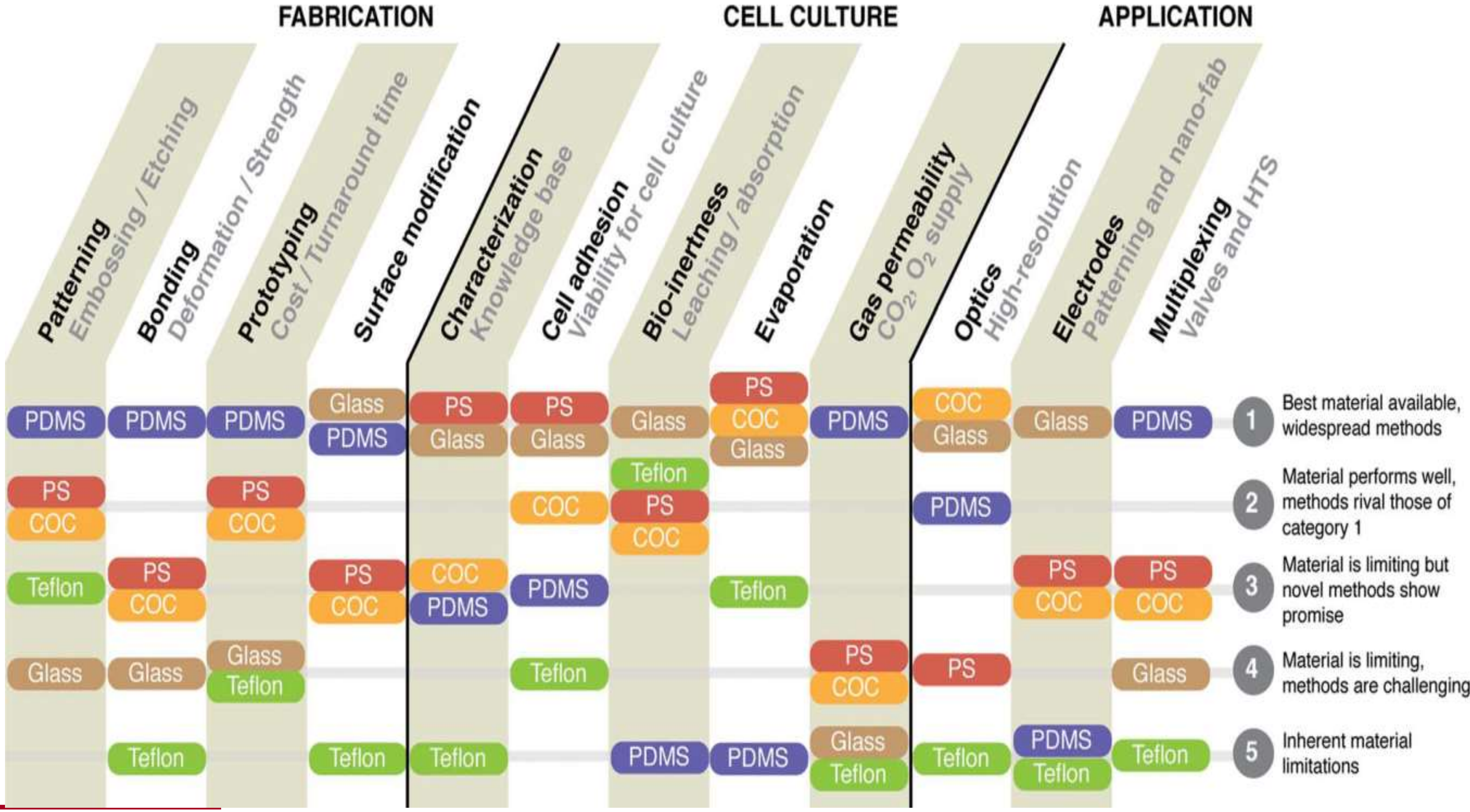


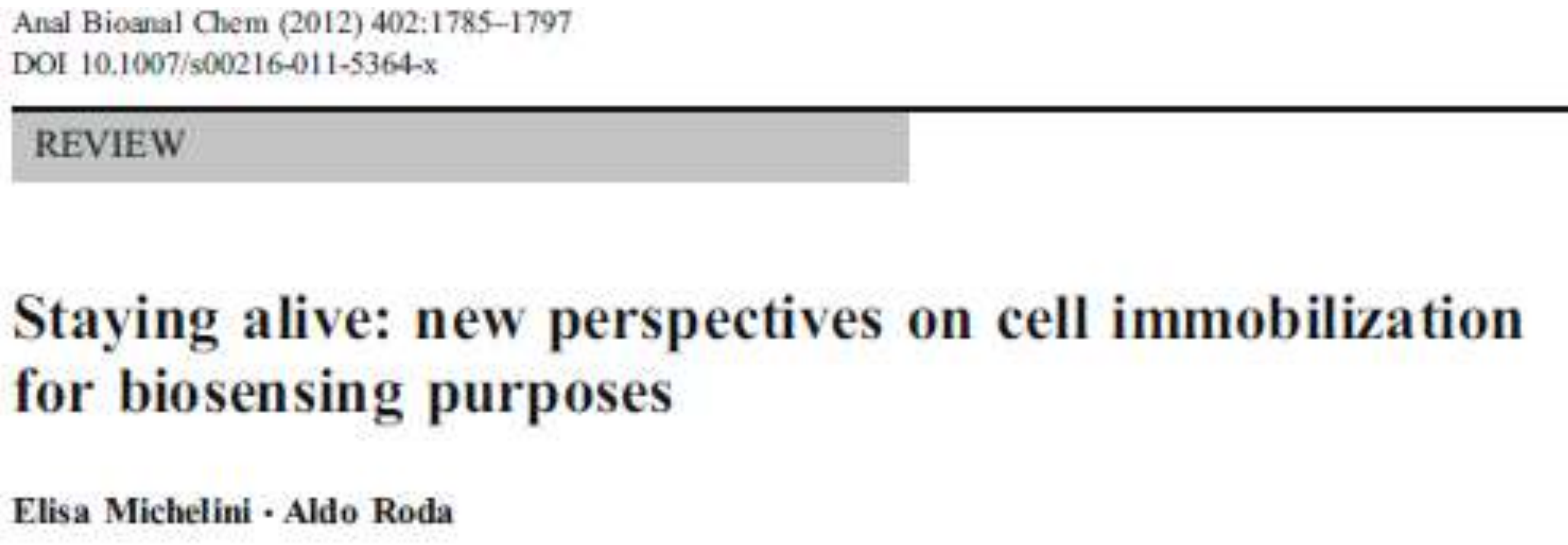
FABRICATION					CELL CULTURE				APPLICATION			
Patterning Embossing / Etching	**Bonding** Deformation / Strength	**Prototyping** Cost / Turnaround time	**Surface modification**	**Characterization** Knowledge base	**Cell adhesion** Viability for cell culture	**Bio-inertness** Leaching / absorption	**Evaporation**	**Gas permeability** CO_2, O_2 supply	**Optics** High-resolution	**Electrodes** Patterning and nano-fab	**Multiplexing** Valves and HTS	
PDMS	PDMS	PDMS	Glass PDMS	PS Glass	PS Glass	Glass	PS COC Glass	PDMS	COC Glass	Glass	PDMS	1 Best material available, widespread methods
PS COC		PS COC			COC	Teflon PS COC			PDMS			2 Material performs well, methods rival those of category 1
Teflon	PS COC		PS COC	COC PDMS	PDMS		Teflon			PS COC	PS COC	3 Material is limiting but novel methods show promise
Glass	Glass	Glass Teflon			Teflon			PS COC	PS		Glass	4 Material is limiting, methods are challenging
	Teflon		Teflon	Teflon		PDMS	PDMS	Glass Teflon	Teflon	PDMS Teflon	Teflon	5 Inherent material limitations

Biocompatibility of PDMS

* PDMS uncured oligomers detected in cells membrane (even after Soxlhet extraction)

* Adsorption of small, hydrophobic molecules from media into the polymer bulk. (ex: PDMS may stock/release oestrogen)

More ? See :



Anal Bioanal Chem (2012) 402:1785–1797
DOI 10.1007/s00216-011-5364-x

REVIEW

Staying alive: new perspectives on cell immobilization for biosensing purposes

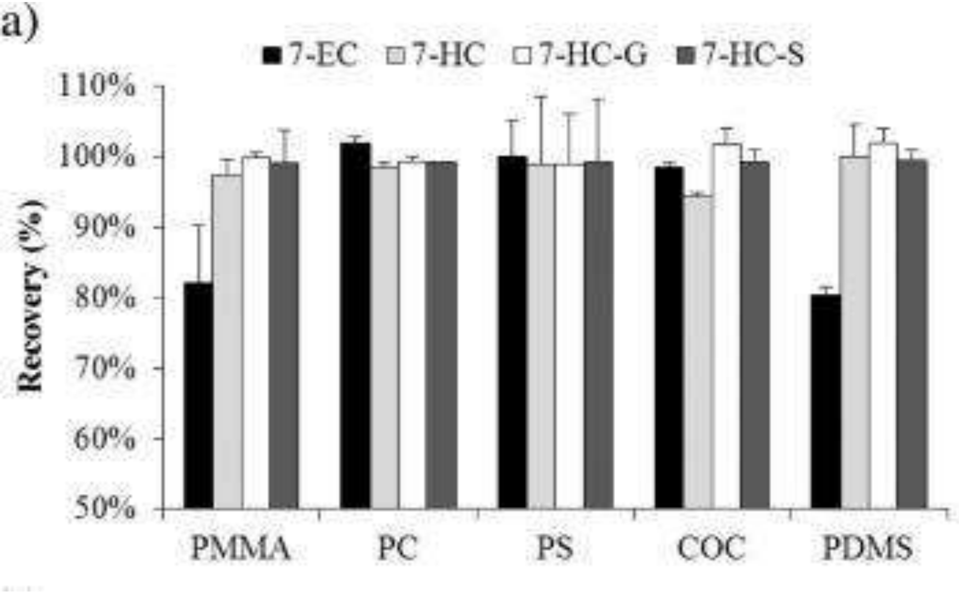
Elisa Michelini · Aldo Roda

Regehr, Beebe LOC2010

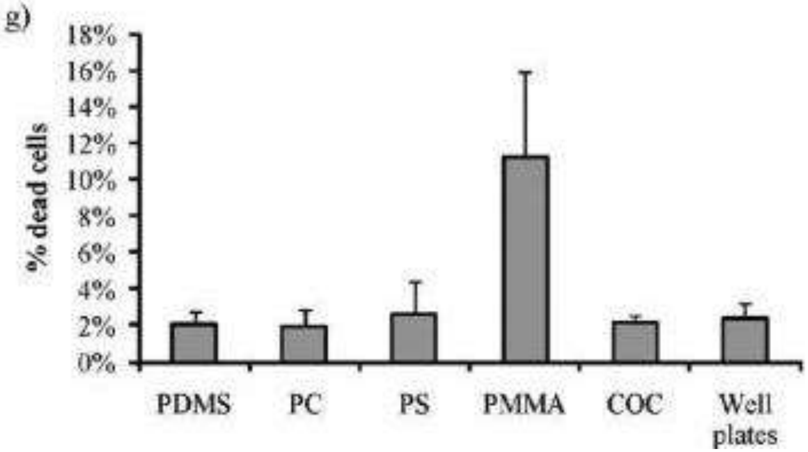
PDMS biocompatibility / other polymers

Study Adsorption & biocompatibility of PC, PMMA, PS, COC, PDMS

Adsorption: Recovery of 7-ethoxycoumarin (7-EC) and its metabolites



% death in cell culture
(Surface coated with collagen)



→PDMS adsorbs ~20% of 7-EC

→PMMA: >10% death: unstable peroxides

PC after 15-min UV-ozone, or COC after a 30-min oxidation, suitable for cells or tissue

Midwoud, Verpoorte Anal Chem 2012

Biocompatibility

Kuo, LOC 2012 Critical Review :
“regulatory approval for disposable microfluidic substrates will be more forthcoming if the substrates are developed with the **United States Pharmacopeia’s biocompatibility compliance guidelines** in mind.”

= choose an already qualified material “FDA approved”

Ex: Chin, Kia, Nature Medecine 2011: HIV / syphilis microfluidic POC diagnostics in Rwanda., with **PC** chip (Elisa-like)

Choosing the right polymer …

When PDMS isn't the best

What are its weaknesses, and which other polymers can researchers add to their toolboxes?

Rajendrani Mukhopadhyay

If a popularity contest for materials were held in the microfluidics community, the silicone PDMS would win hands down. It's easy to pattern by soft lithography, optically transparent, flexible, gas-permeable, and cheap enough for students to use in copious quantities without denting lab budgets. These qualities make PDMS an excellent material for the rapid prototyping of microfluidic devices. In that regard, it's practically irreplaceable.

But experts say that although the material is attractive for quickly testing the fluidics of new device designs and for cell-based studies, it has problems. "There's no perfect material. There's no perfect instrument. There's no perfect technique. PDMS is not an exception," explains Daniel Chiu at the University of Washington. "It's a great material, but you need to know what you're using it for and know its properties."

Issues with PDMS include absorption of organic solvents and small molecules, its innate hydrophobicity, and evaporation of water. Some experts say that PDMS's shortcomings become obvious as you spend time working with it. You soon learn to design around the limitations and use the silicone to its best advantage.

Other experts argue that not everyone is keenly aware of PDMS's shortcomings and that many use it simply because it's convenient, not because it is the wisest choice for the job at hand. Andrew Kamholz of Edge Embossing LLC says, "There are so many papers out there where PDMS is being used. You can get some good results with it, so people are quick to say, 'Look, everyone else is doing it, and I'm going to do it too.' But I'm not sure that everyone goes through the process of thinking about whether PDMS is going to be an issue for them."

Quick 'n' easy

The microfluidics community has embraced PDMS for many reasons. It allows simple, planar systems to be replicated and produced easily. Complex 3D structures and microchannel networks can be fabricated quickly in PDMS by multilayer prototyping approaches. The material is transparent from 240 to 1100 nm, so various optical detection schemes can be used; even optical elements can be created out of it. Because of PDMS's elastic properties, micromechanical valves, developed by groups headed by Stephen Quake at Stanford University and Richard Mathies at the University of California Berkeley, are best made with it. For cell-based applications, the silicone is attractive because it's nontoxic and gas-permeable.

"One reason why people like PDMS is that it doesn't break," points out George Whitesides of Harvard University. "When you're trying to do things with glass, you're always worried about sharps and disposal problems. None of this is an issue with PDMS because it's soft." Christopher Culbertson of Kansas State University adds that using PDMS "requires substantially less skill than making glass chips, is cheaper, and if you drop the chip, it's going to bounce, not break, on you."

PDMS advantages :

✚

- Easy bonding (oxygen plasma)
- Simple to handle
- Valve integration

PDMS limitations :

━

- Permeability
- Mechanical properties (Young modulus)
- Hardly compatible with high throughput fabrication techniques
- Surface treatment often needed

When PDMS isn't the best, Rajendrani Mukhopadhyay
Anal. Chem., 79 (9), 3248-3253, 2007

I. Intro, criteria to choose a material / a method

II. PDMS

III. What else?

1. Back to Material/process Choice

2. Silicon
3. Other replication methods
4. Lamination based processes

5. Other polymers
6 Paper
7 Porous medium

IV. Openings

Some Guidelines

Design for Microfluidic Device Manufacture Guidelines

Editors: Henne van Heeren (enablingMNT), Peter Hewkin (facilitator of the Microfluidics Consortium)

With contributions from the following members of the MF5 Microfluidics consortium: *Dolomite, IMT, Micronit, and EV group and Sony DADC*

This work was commissioned by the Microfluidics Consortium and is supported by the MF manufacturing project.

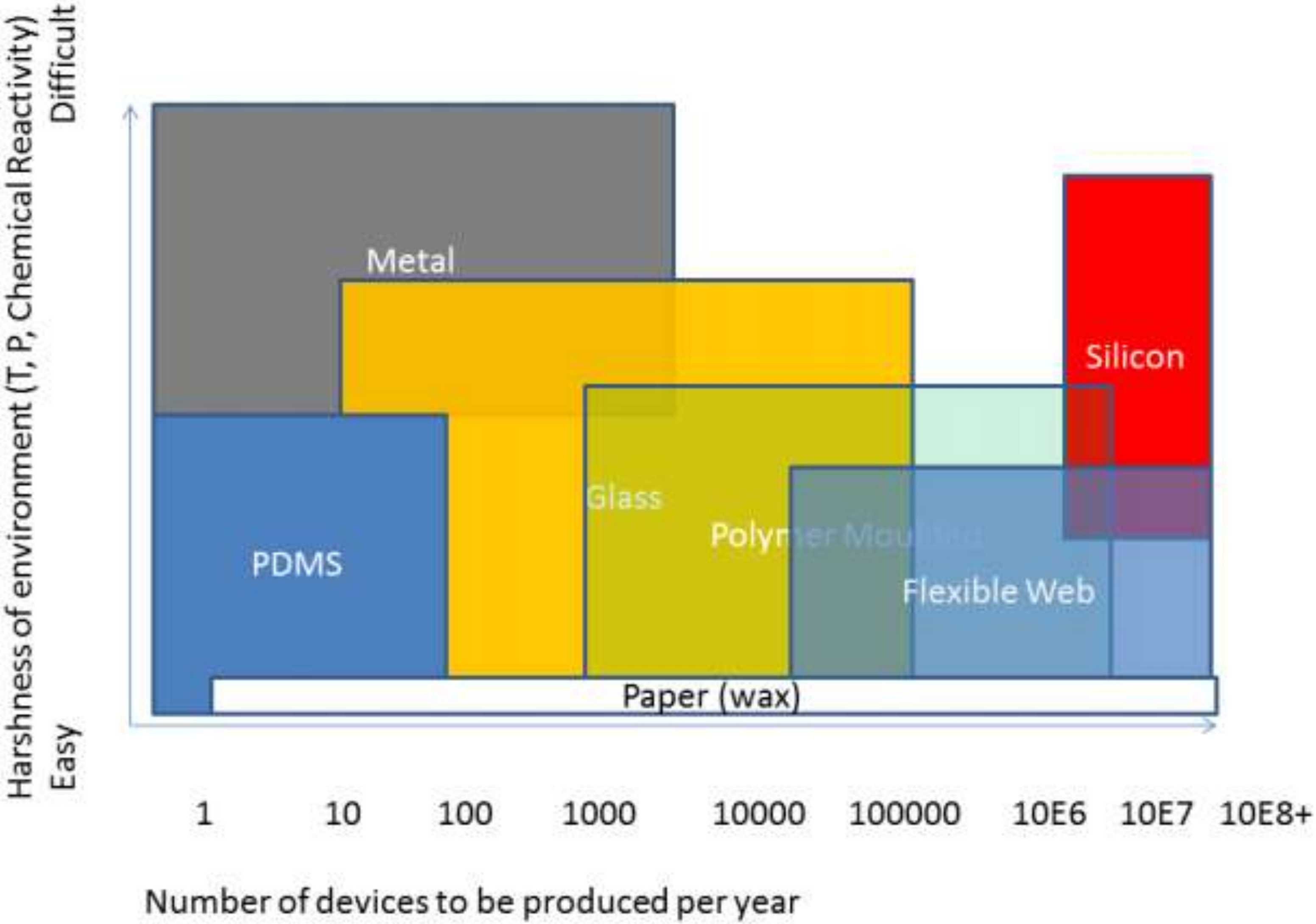
http://www.cfbi.com/microfluidics.htm

Center for Business Innovation

Version 5,April 2014

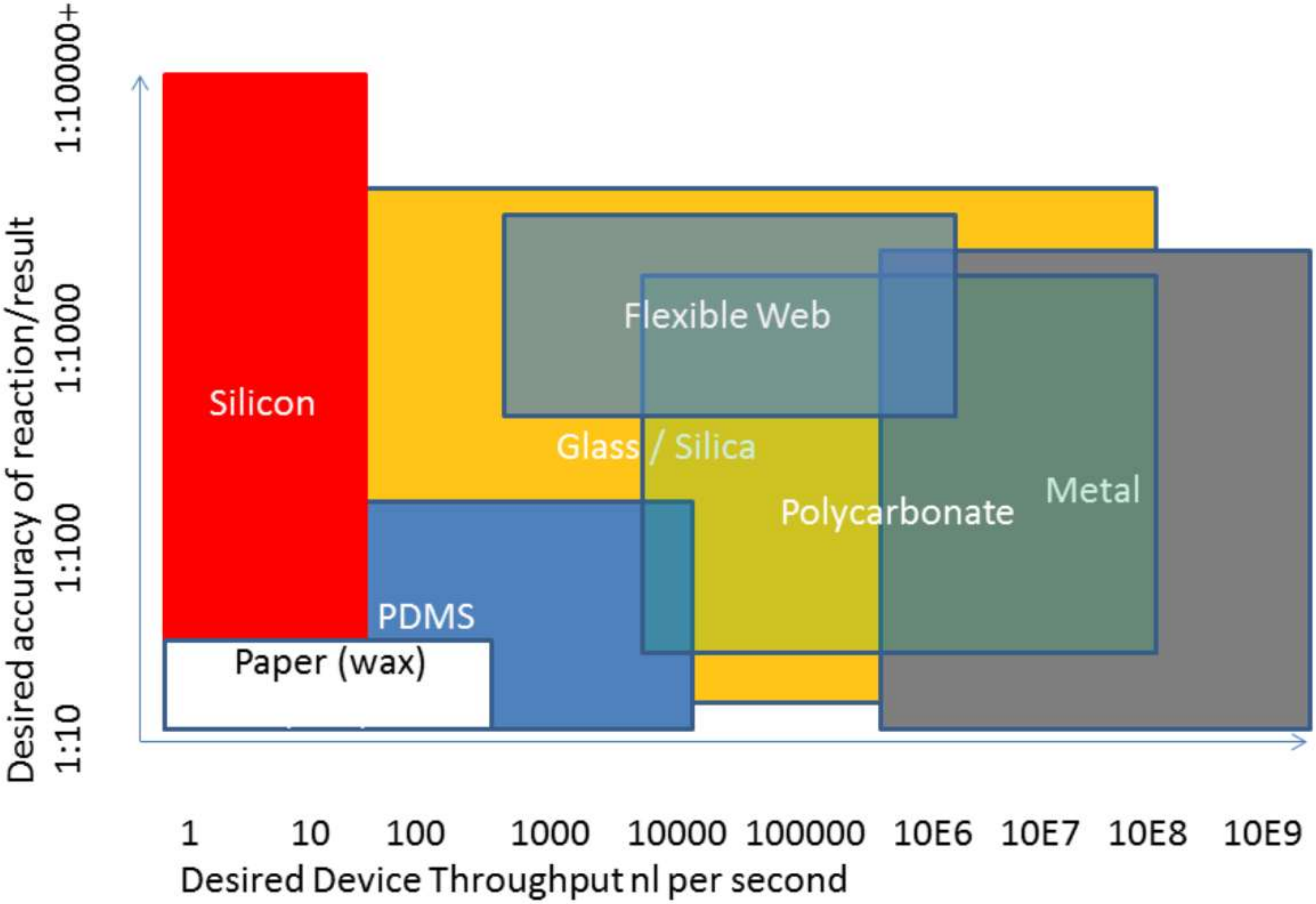
(pdf available if you want)

- **Material Selection Decision Support Chart**



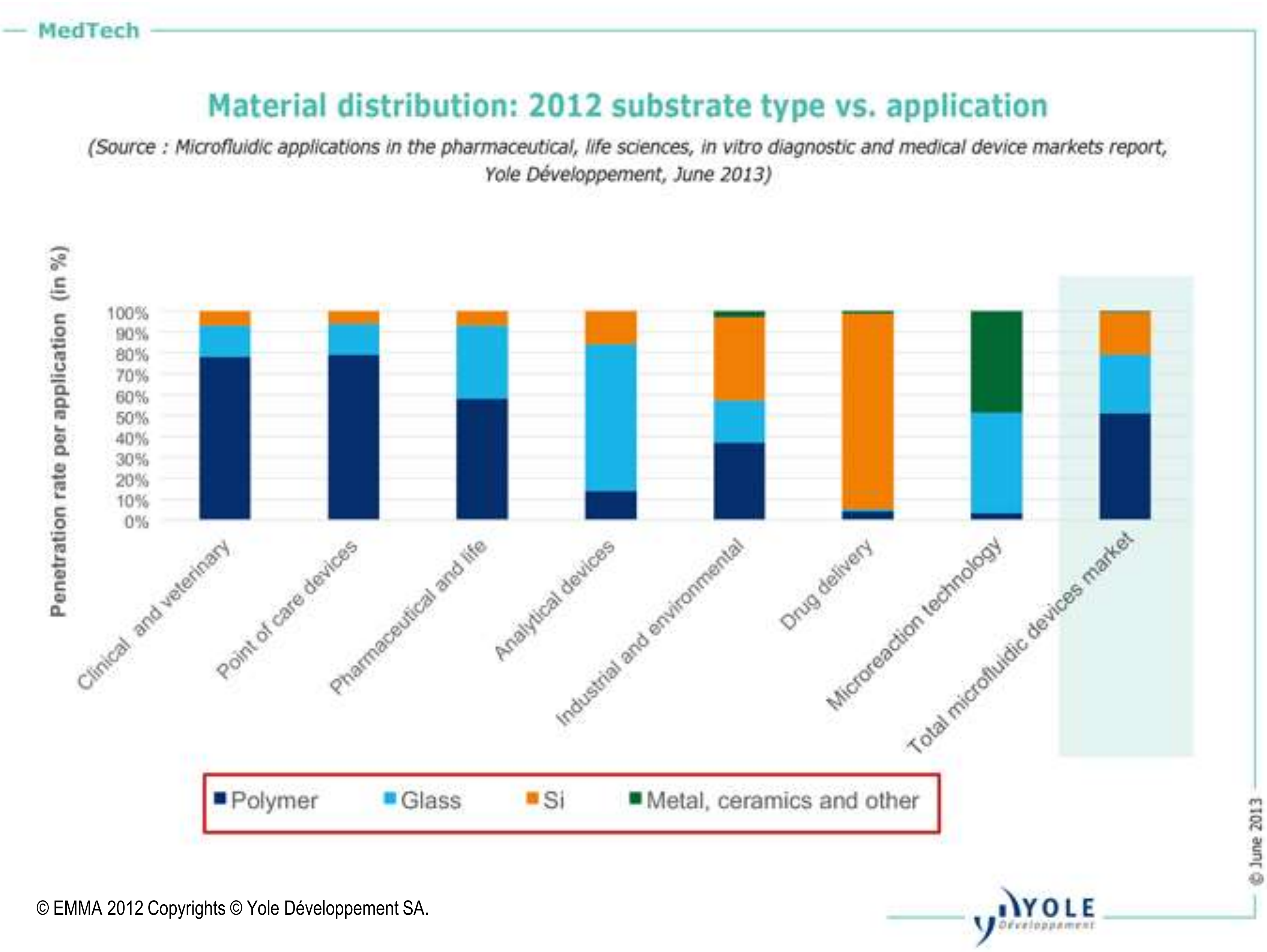
[Design for Microfluidic Device Manufacture Guidelines]()
Editors: Henne van Heeren (enablingMNT), Peter Hewkin (facilitator of the Microfluidics Consortium)

- **Material Selection Decision Support Chart**



Design for Microfluidic Device Manufacture Guidelines
Editors: Henne van Heeren (enablingMNT), Peter Hewkin (facilitator of the Microfluidics Consortium)

Which materials in the biomedical market?



Material distribution: 2012 substrate type vs. application

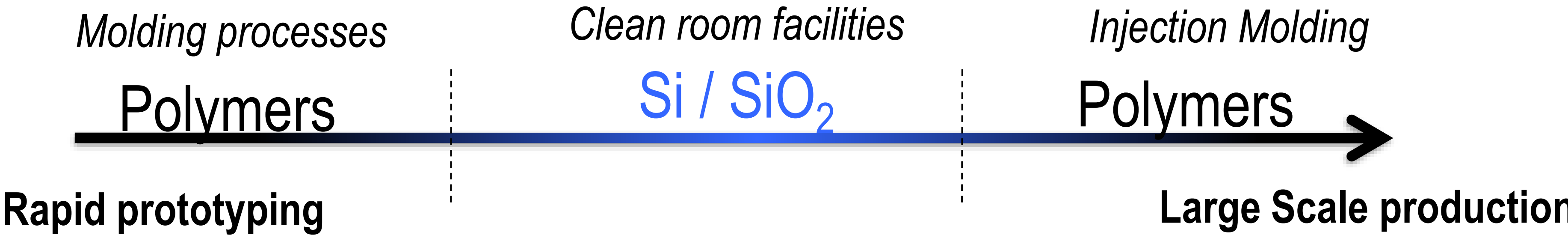
(Source : Microfluidic applications in the pharmaceutical, life sciences, in vitro diagnostic and medical device markets report, Yole Développement, June 2013)

Why Polymers ?

- **The question of Price...**

Price = Funct (material, facilities, process, throughput …)

- **... and throughput**



Molding processes

Polymers

Rapid prototyping

Clean room facilities

Si / SiO_2

Injection Molding

Polymers

Large Scale productio

Choosing the right polymer: criteria …

- Class of polymer (thermoplastics, thermosets, elastomers)

- **physical properties**
  - Optical,
  - Thermal
  - Electric

🟦 Elastomers
🟩 Thermoplastics
🟧 Thermosets

- **Chemical properties**

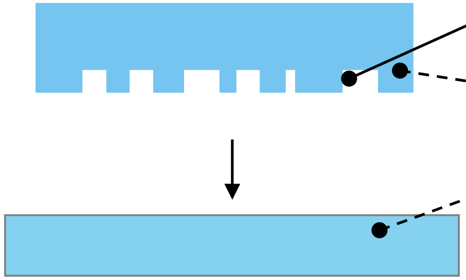
- **Biocompatibility**

- **Processing possibility**

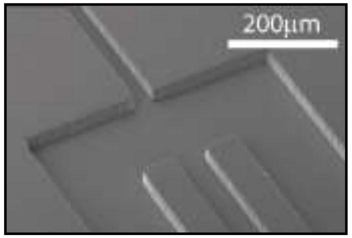
- PDMS : Poly(Dimethyl) SIloxane
- COC : Cycloolefincopolymer
- PC : Polycarbonate
- PE : polyester
- PEEK : Poly Ether Ether Ketone
- PET : Polyéthylène téréphtalate
- PI : Polyimide
- PMMA : Polyméthylmétacrylate
- PP : Polypropylène
- PS : Polystyrène
- Fluorinated polymers (Dyneon, SIFEL..)
- SU8, Dry film resists
- UV curable polymers (NOA, …)
- …

From material to manufacturing process

i)

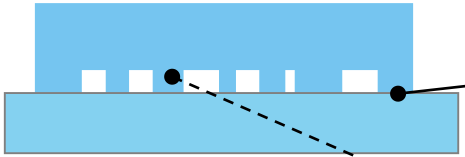


Microchannel fab.



Material's choice

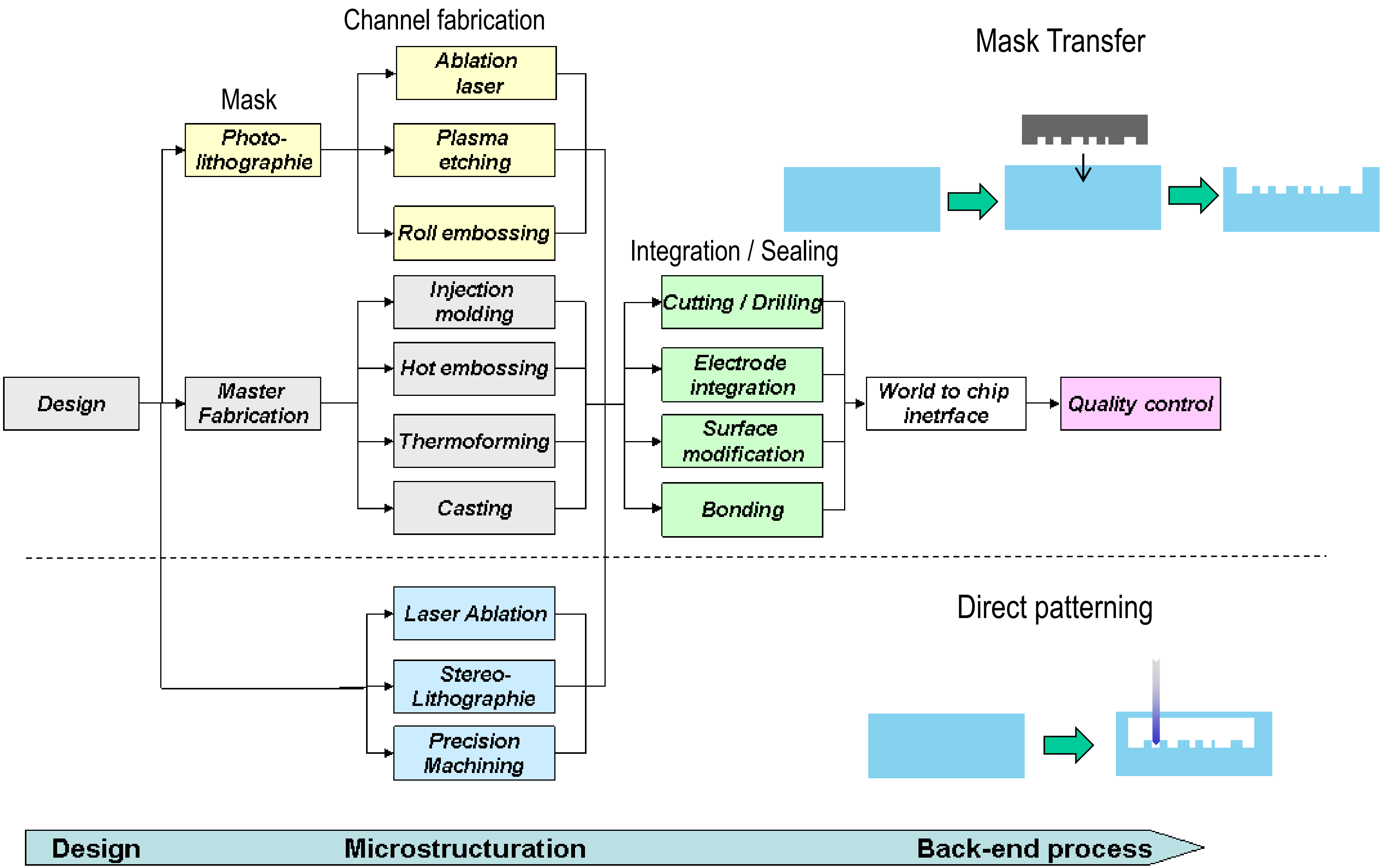
ii)



Microchannel sealing

Electrode integration ?
Surface Treatment ?
World to chip connection ?

From material to manufacturing process



Design

Mask

Photo-lithographie

Master Fabrication

Channel fabrication

Ablation laser

Plasma etching

Roll embossing

Injection molding

Hot embossing

Thermoforming

Casting

Laser Ablation

Stereo-Lithographie

Precision Machining

Integration / Sealing

Cutting / Drilling

Electrode integration

Surface modification

Bonding

World to chip inetrface

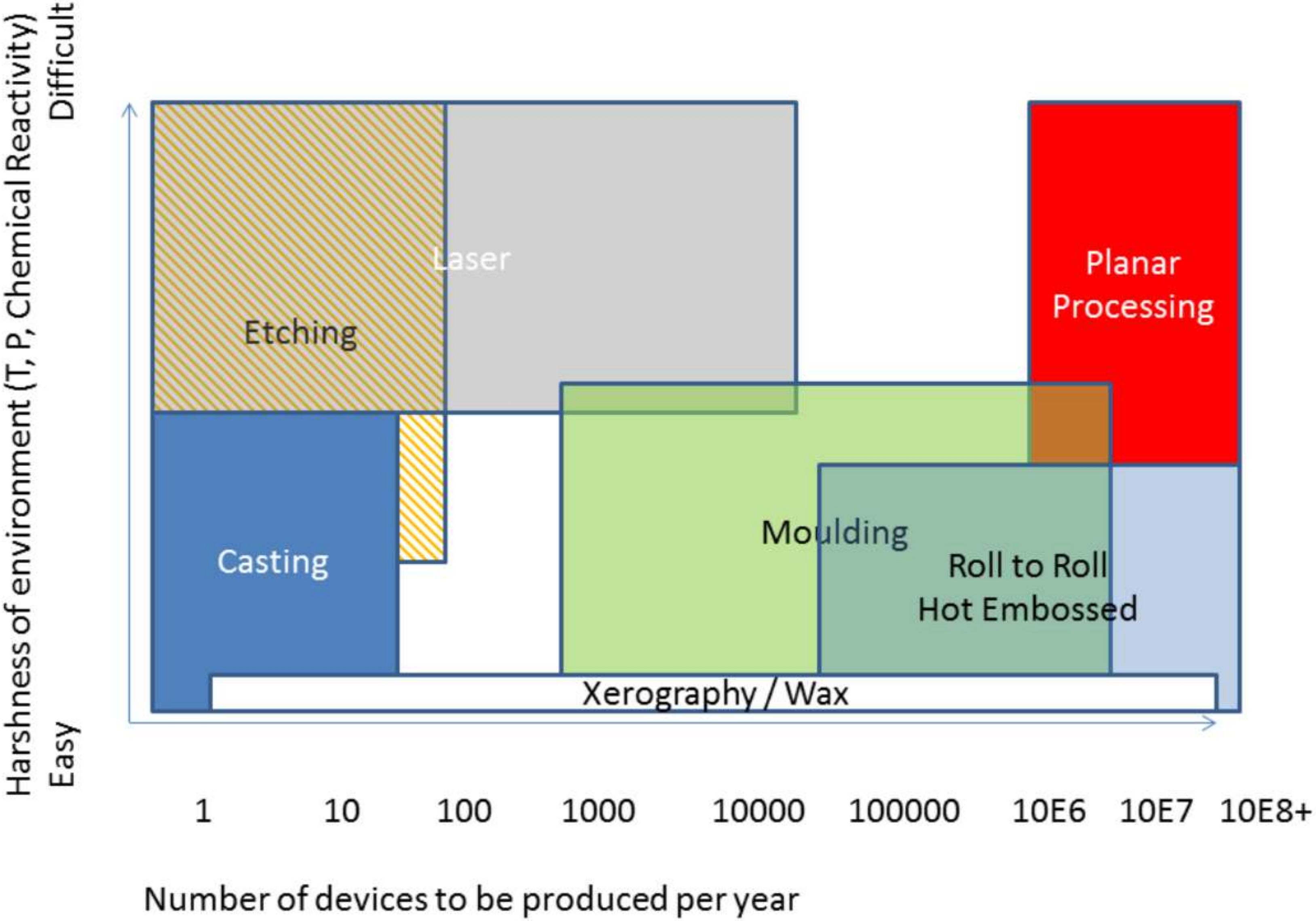
Quality control

Mask Transfer

Direct patterning

Design **Microstructuration** **Back-end process**

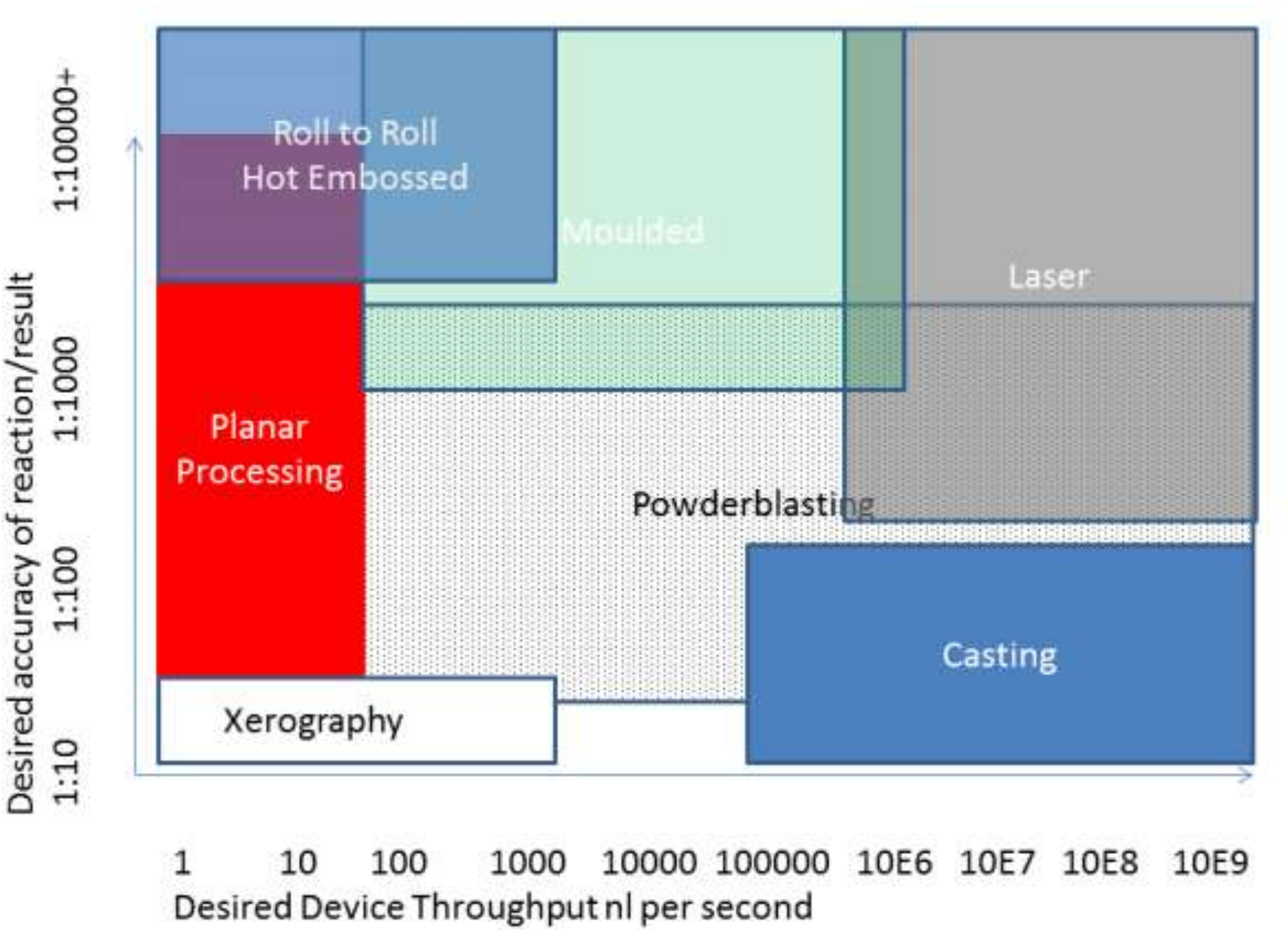
Choosing the right manufacturing process



Design for Microfluidic Device Manufacture Guidelines

Editors: Henne van Heeren (enablingMNT), Peter Hewkin (facilitator of the Microfluidics Consortium)

Choosing the right manufacturing process



Design for Microfluidic Device Manufacture Guidelines

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I. Intro, criteria to choose a material / a method

II. PDMS

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2. **Silicon**
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4. Lamination based processes

4. Other polymers
5. Paper
6. Porous medium

IV. Openings

Silicon and Glass processing

Silicon = Base material of MEMS

* Single crystal wafers

* Workhorse of microelectronics and MEMS

* Comprehensive knowledge based on
  - Material properties (worlds best characterized material)
  - Processing

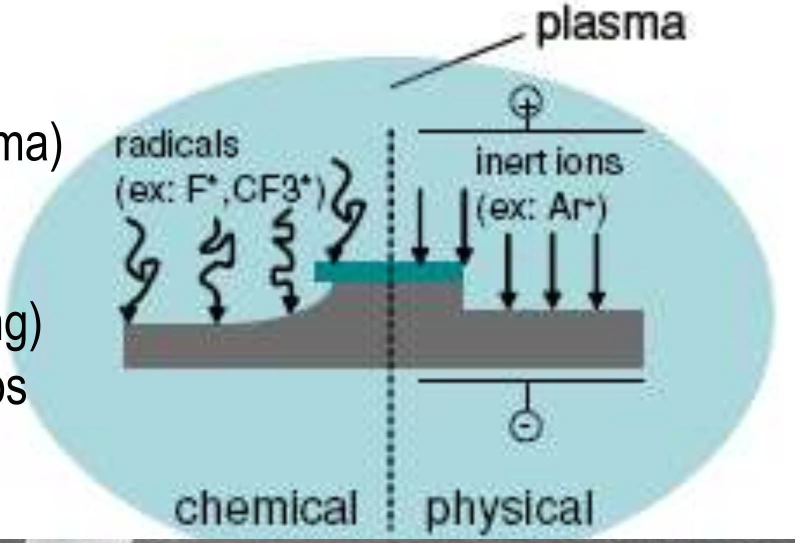
*Micromachining technologies
  - **Surface** micromachining (additive technology for ex. CMOS)
  - **Bulk** micromachining (subtractive technology for ex. wet etching)

Notions on Silicon and Glass processing

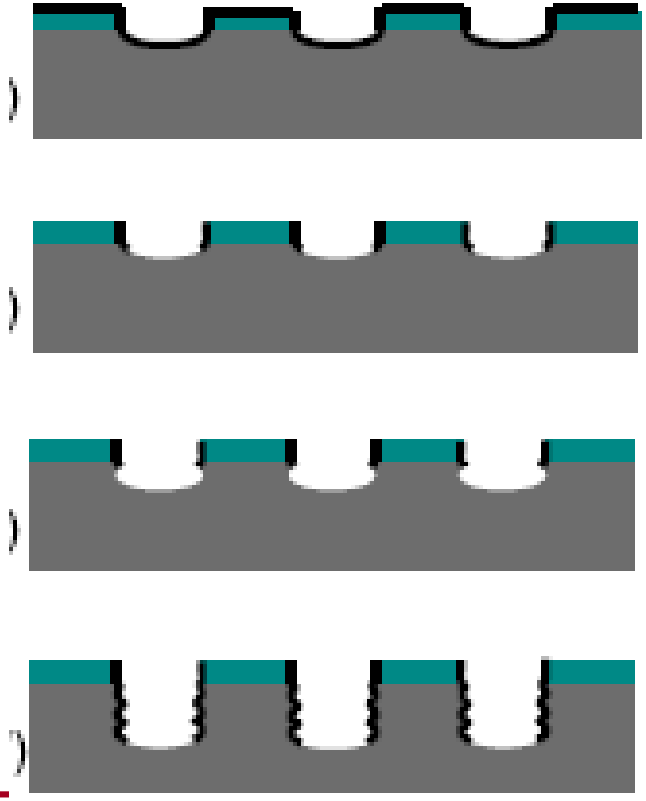
- Silicon dry etching

Removal of material by bombardment with ions (plasma)

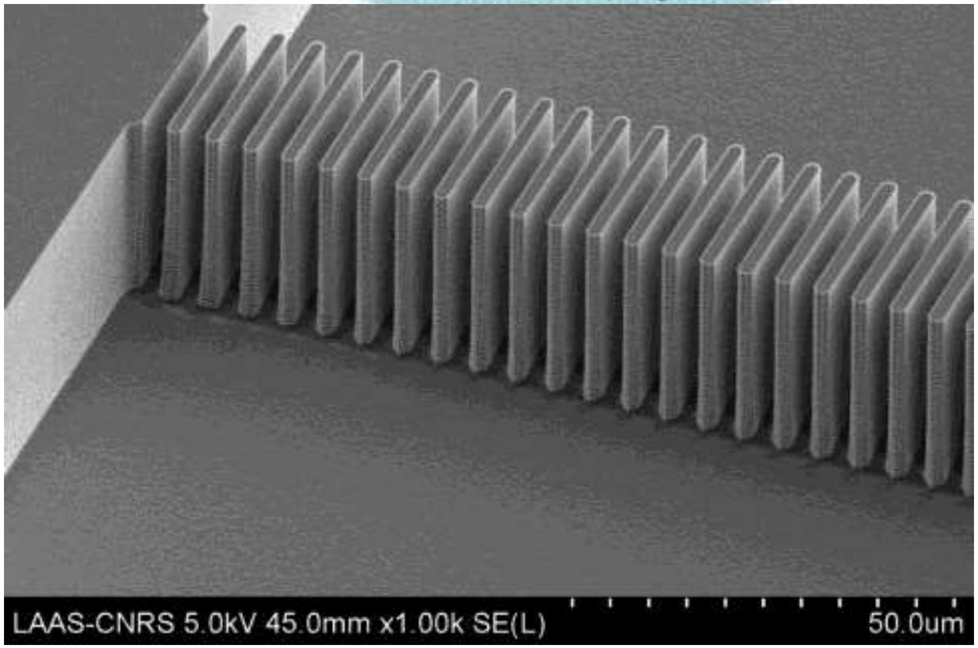
→ Anisotropy : high aspect ratio



Even more anisotropic: DRIE (Deep Reactive Ion Etching)
= succession of protection (CF4) and etching (SF6) steps



Abgrall, JMM 2007

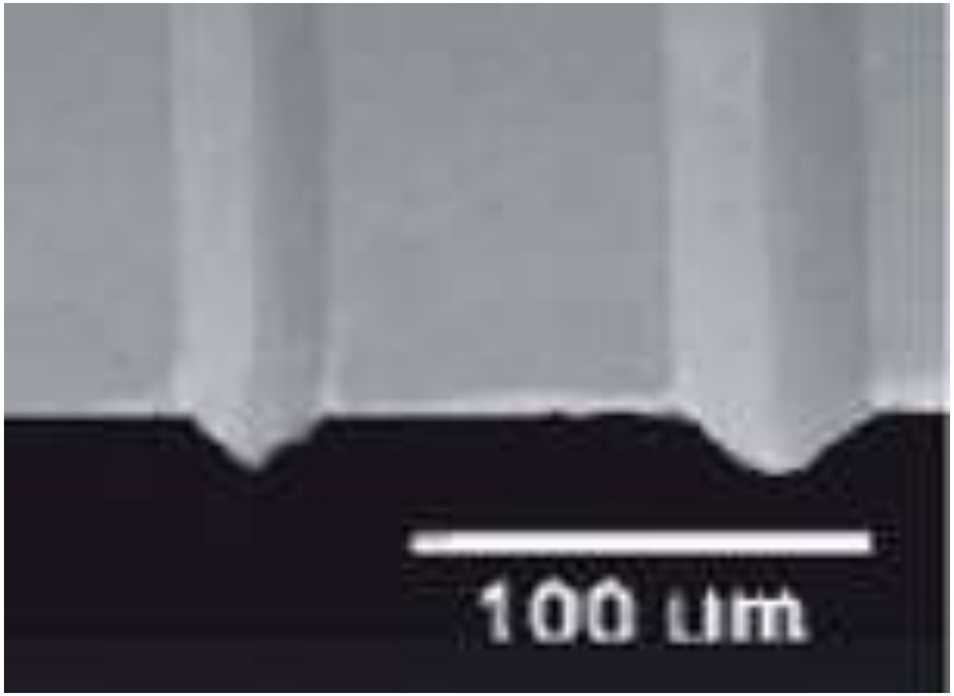


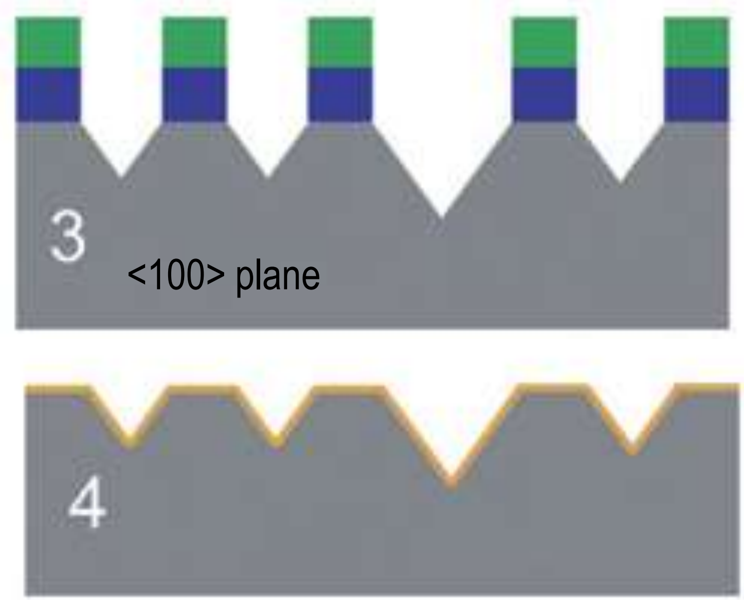
Membranes inside channels, A Valencia, (2017)

Notions on Silicon and Glass processing

- Silicon wet etching

KOH etching solution.
Etch rate dependent on crystal orientation:
→ anisotropic, but crystal impose geometry



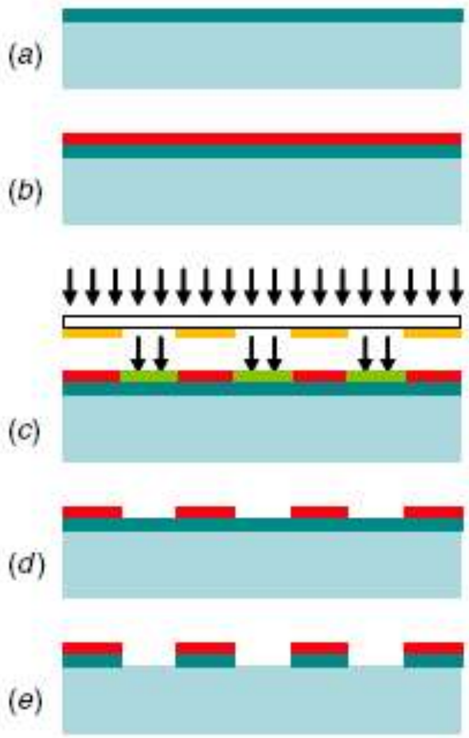


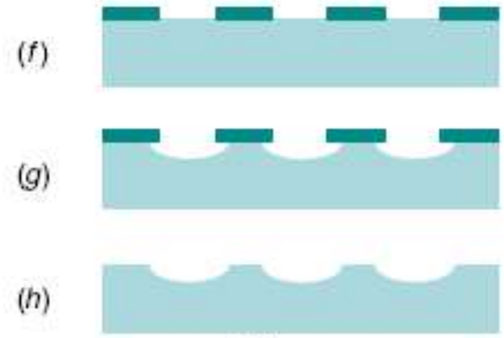
Ex: 3D micromirrors for biology (Hajjoul, Bancaud Lab Chip 2009)

Notions on Silicon and Glass processing

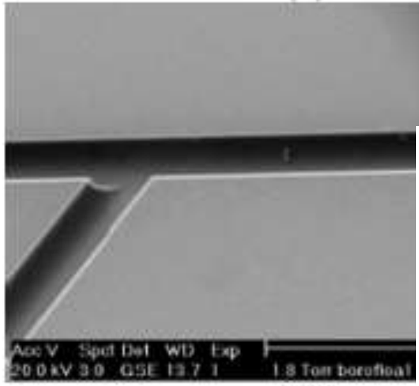
- Glass Wet etching

Chemicals: HF, Fluorhydric Acid





(1)



(2)

Under-etching

Isotropic
→ Low aspect ratio
→ Under-etching, influence of stirring

Abgrall, JMM 2007, and IMT Neuchatel

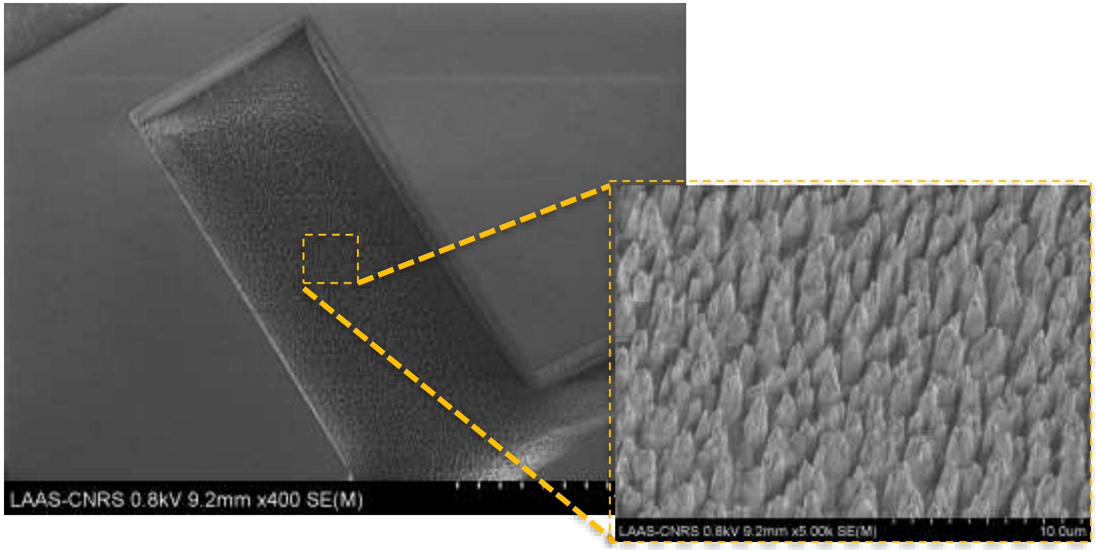
Note: also sand-blasting…

Notions on Silicon and Glass processing

- Glass Dry etching

Most Glasses are not pure

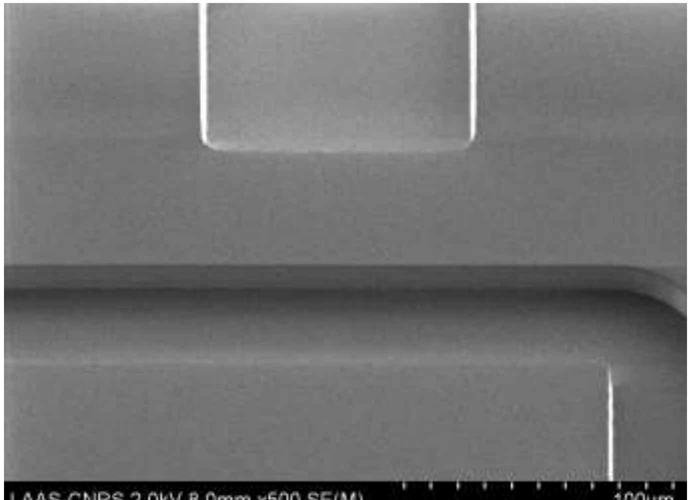
→ Micromasking, roughness



Roughness at the microscale ~ 3 microns

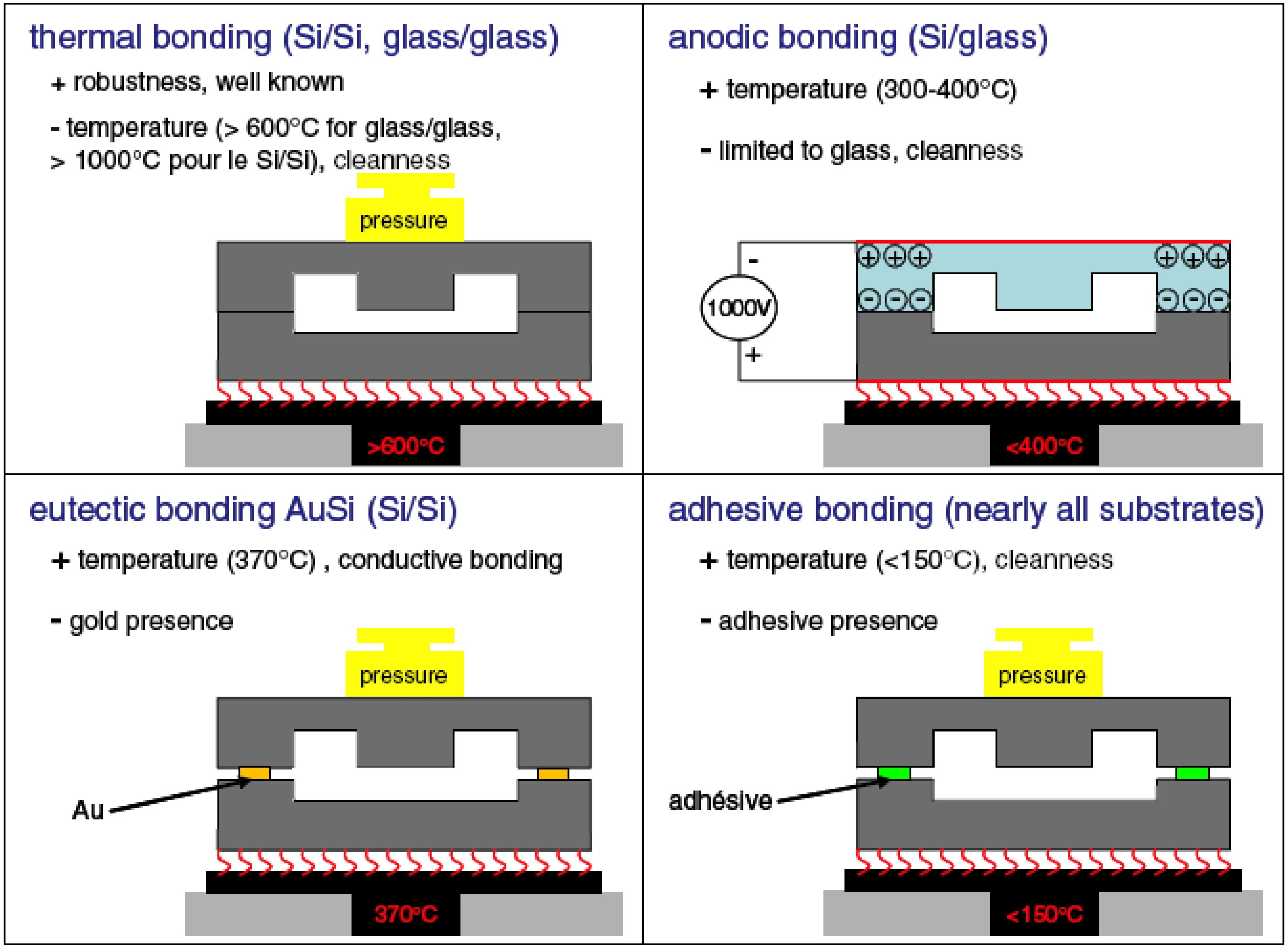
→Additional wet etching step

Mix of :
5 % HF 5%
10 % HCl 37 %
85 % DI Water



III. Notions on Silicon and Glass processing

- Encapsulation (bonding)



thermal bonding (Si/Si, glass/glass)

+ robustness, well known

- temperature (> 600°C for glass/glass, > 1000°C pour le Si/Si), cleanness

anodic bonding (Si/glass)

+ temperature (300-400°C)

- limited to glass, cleanness

eutectic bonding AuSi (Si/Si)

+ temperature (370°C) , conductive bonding

- gold presence

adhesive bonding (nearly all substrates)

+ temperature (<150°C), cleanness

- adhesive presence

More ? See “A practical guide for the fabrication of microfluidic devices using glass and silicon”
Iliescu, Biomicrofluidics2012

Abgrall & Gué, JMM (2007)

I. Intro, criteria to choose a material / a method

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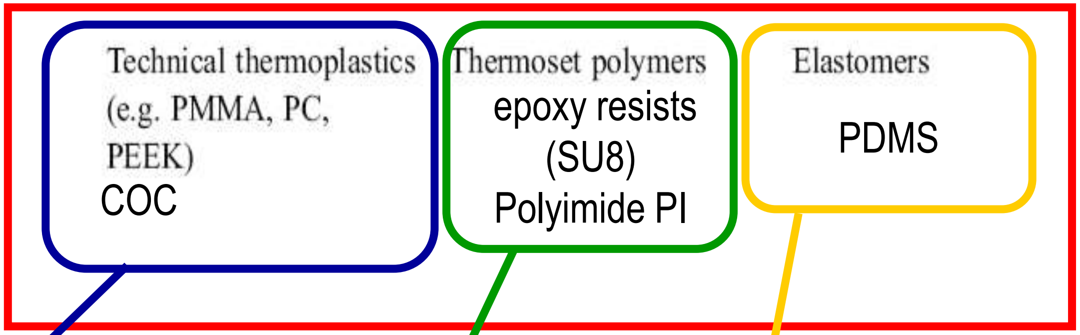
3. **Other replication methods**
4. Lamination based processes

4. « New » polymers
5. Paper
6. Porous medium

IV. Openings

3 classes of Polymers

Polymer Behaviour controlled by the type of bonds existing between the chains



Technical thermoplastics (e.g. PMMA, PC, PEEK)
COC

Thermoset polymers
epoxy resists (SU8)
Polyimide PI

Elastomers
PDMS

Thermoplastics: **weakly bonded chains**
* Typically soluble in organic solvents.
* Soften upon heating (>Tg but needs to be < TD)
* Harden when cooled down (<Tg).

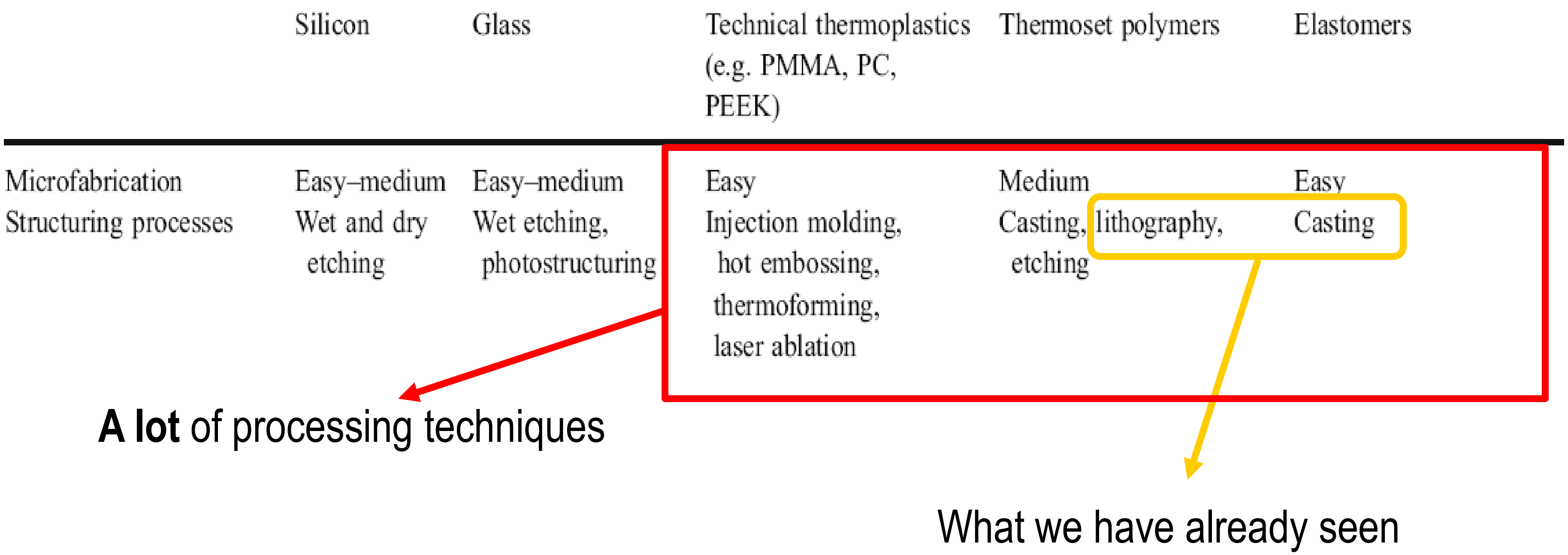
Elastomers : long chains, some physical or chemical cross-linking
Soft, swollen by most solvents

Important Temperatures:
*Tg glass transition, « softening»
* TD decomposition

Thermosetting polymers are cross-linked,
* Not soluble in organic solvents
* Must be shaped before cross-linking (=duroplastic polymers)

Becker & Gärtner. *Anal Bioanal Chem* (2008),
Abgrall & Gué JMM (2007)

How to process polymers ?



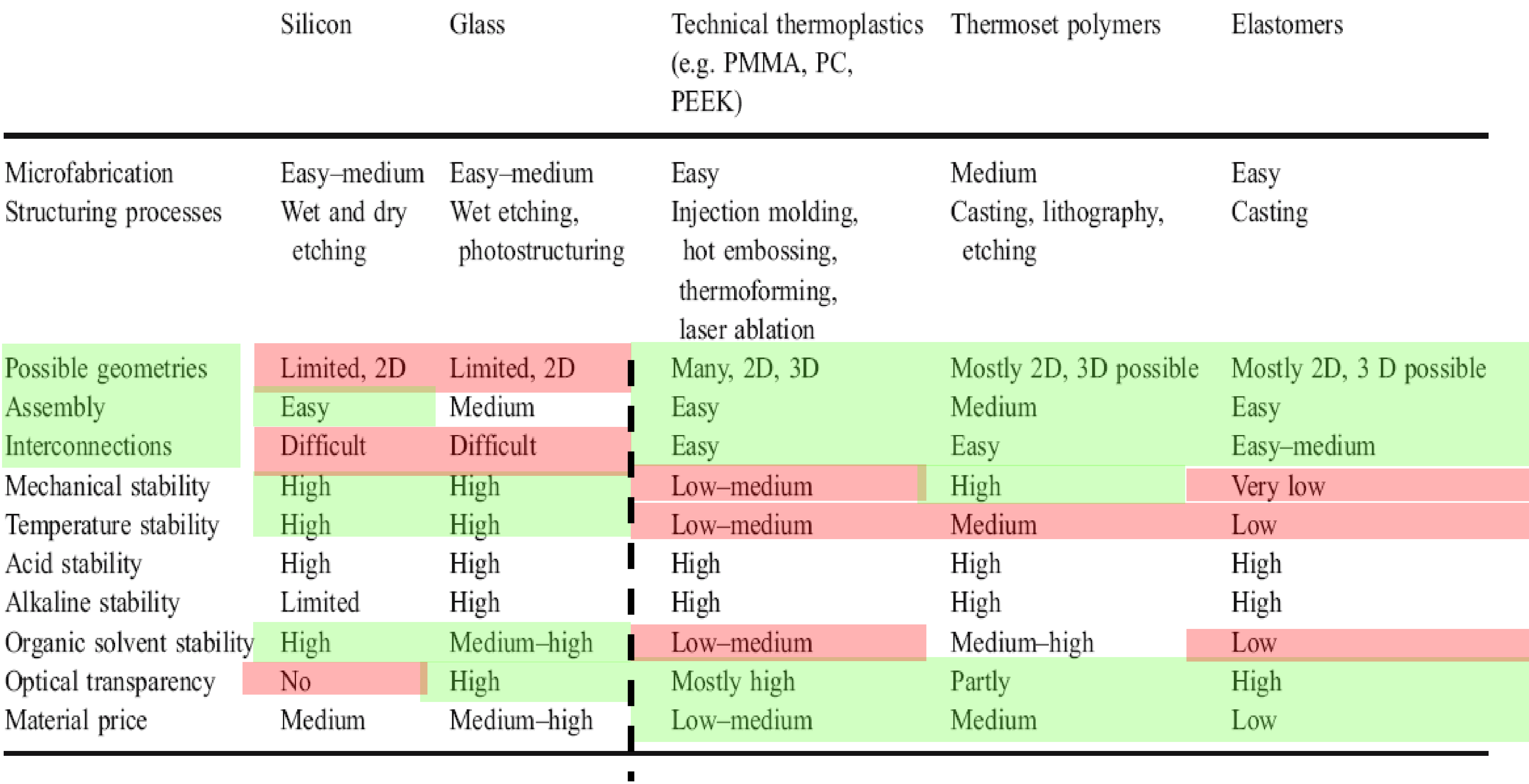
	Silicon	Glass	Technical thermoplastics (e.g. PMMA, PC, PEEK)	Thermoset polymers	Elastomers
Microfabrication	Easy–medium	Easy–medium	Easy	Medium	Easy
Structuring processes	Wet and dry etching	Wet etching, photostructuring	Injection molding, hot embossing, thermoforming, laser ablation	Casting, lithography, etching	Casting

A lot of processing techniques

What we have already seen

Becker & Gärtner. *Anal Bioanal Chem* (2008)

Comparison of materials properties



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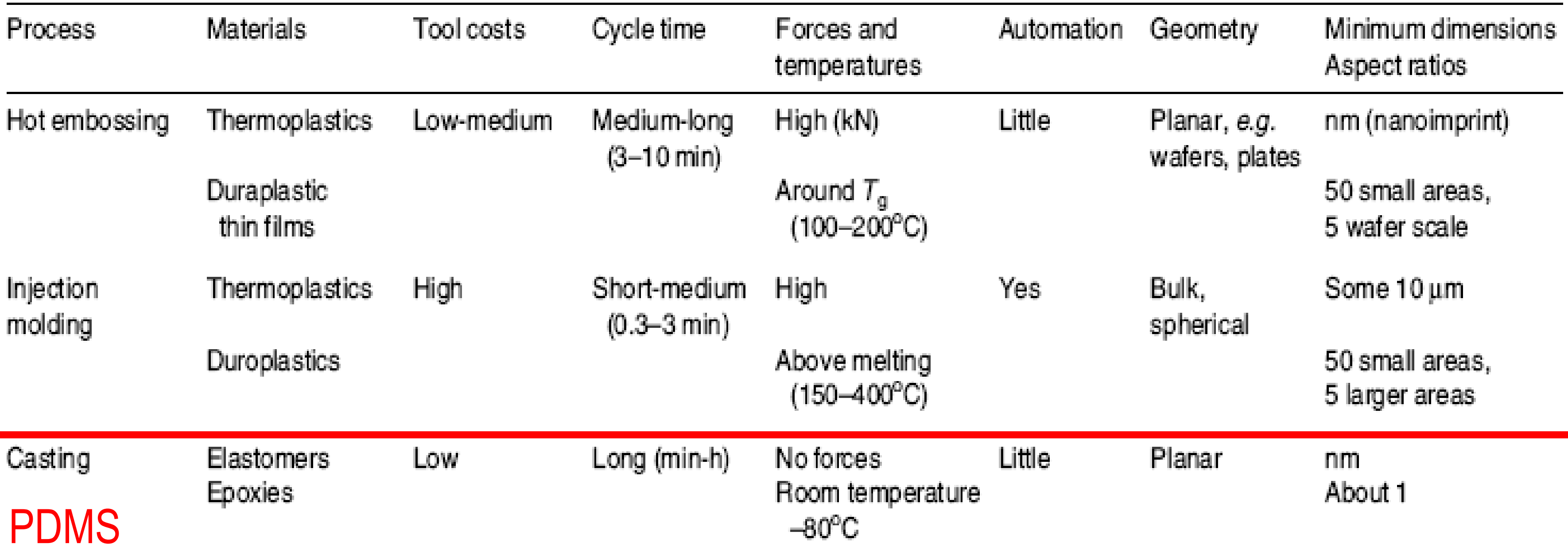
Structuring processes	Wet and dry etching	Wet etching, photostructuring	Injection molding, hot embossing, thermoforming, laser ablation	Casting, lithography, etching	Casting
Possible geometries	Limited, 2D	Limited, 2D	Many, 2D, 3D	Mostly 2D, 3D possible	Mostly 2D, 3 D possible
Assembly	Easy	Medium	Easy	Medium	Easy
Interconnections	Difficult	Difficult	Easy	Easy	Easy–medium
Mechanical stability	High	High	Low–medium	High	Very low
Temperature stability	High	High	Low–medium	Medium	Low
Acid stability	High	High	High	High	High
Alkaline stability	Limited	High	High	High	High
Organic solvent stability	High	Medium–high	Low–medium	Medium–high	Low
Optical transparency	No	High	Mostly high	Partly	High
Material price	Medium	Medium–high	Low–medium	Medium	Low

Polymer : - Solvent compatibility, temperature & mechanical stability

\+ Cheap, transparent, easy 2D & 3D processing,

Becker & Gärtner. *Anal Bioanal Chem* (2008)

Polymers: Other Replication methods



Process	Materials	Tool costs	Cycle time	Forces and temperatures	Automation	Geometry	Minimum dimensions Aspect ratios
Hot embossing	Thermoplastics Duraplastic thin films	Low-medium	Medium-long (3–10 min)	High (kN) Around T_g (100–200°C)	Little	Planar, *e.g.* wafers, plates	nm (nanoimprint) 50 small areas, 5 wafer scale
Injection molding	Thermoplastics Duroplastics	High	Short-medium (0.3–3 min)	High Above melting (150–400°C)	Yes	Bulk, spherical	Some 10 μm 50 small areas, 5 larger areas
Casting	Elastomers Epoxies	Low	Long (min-h)	No forces Room temperature –80°C	Little	Planar	nm About 1

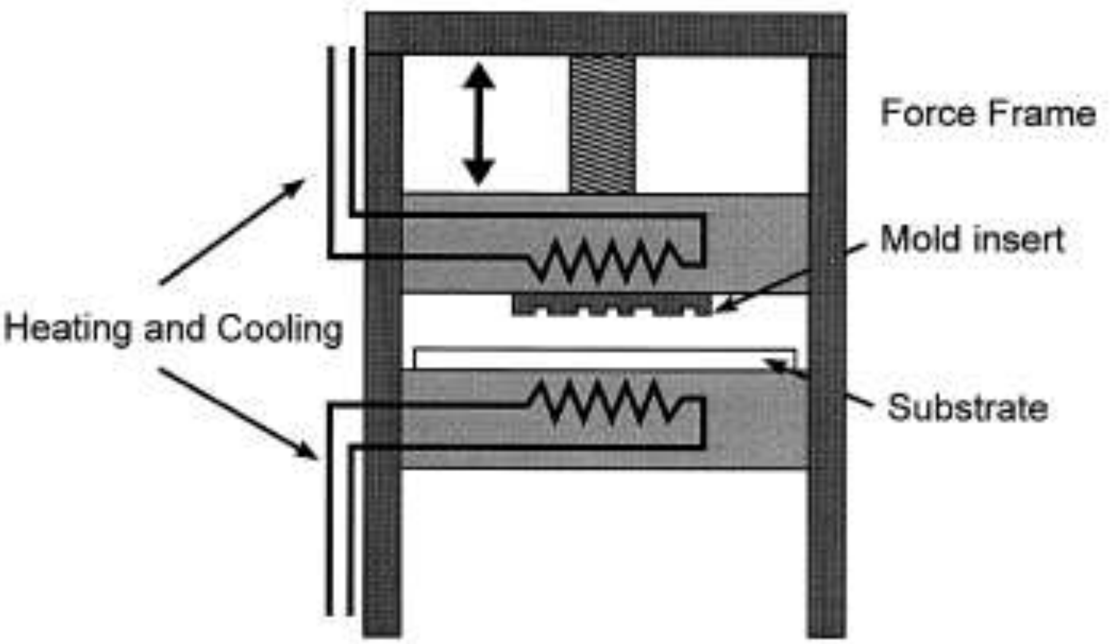
PDMS

Lecture Notes: Zengerle & Ducrée: www.myfluidix.com/

Reviews: Becker & Gärtner. *Anal Bioanal Chem* (2008)
Becker & Gärtner Electrophoresis (2000)
Heckele et al, J. Micromech. Microeng (2004)

Replication methods: hot embossing

- Principle



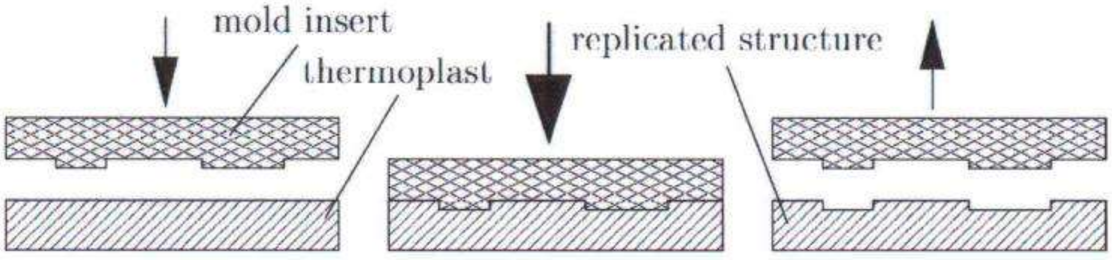
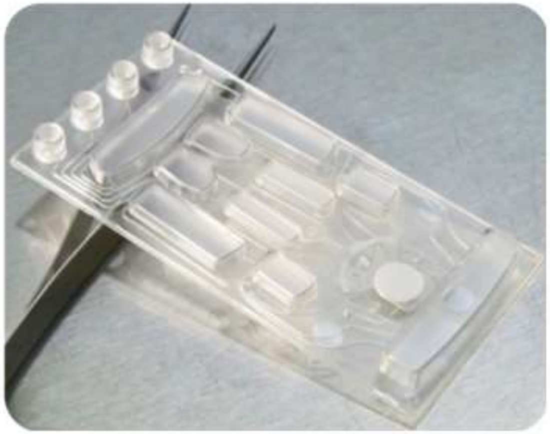


Fig. 4.13. Schematic of hot embossing (HE). The heated mold insert is pressed against a thermoplastic substrate assuming its inverse shape. Upon cooling, the replicated structured is released

A French company working on hot embossing with a biocompatible material

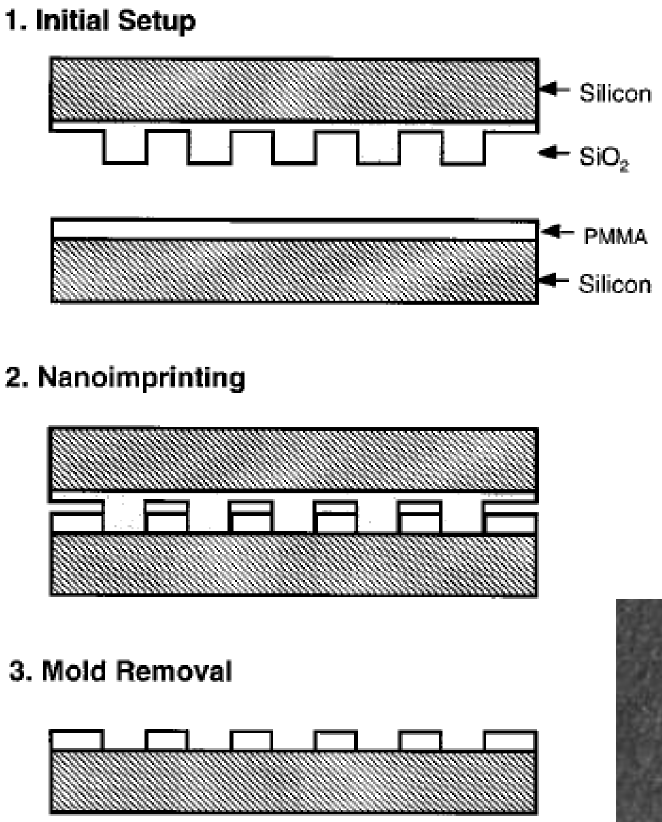
Eden microfluidics



Zengele & Ducrée: www.myfluidix.com/

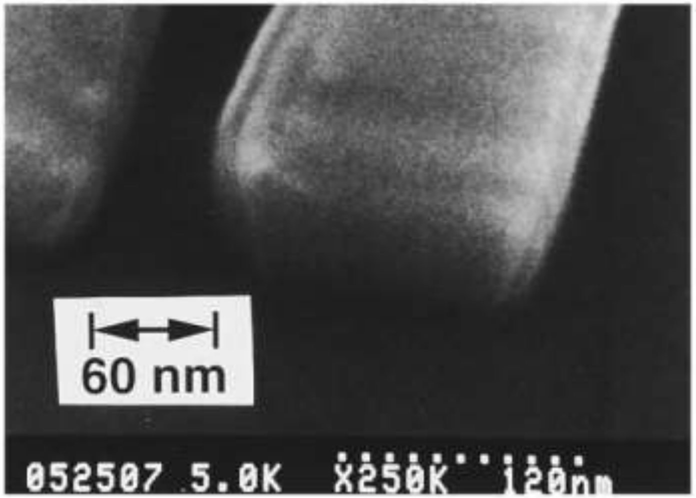
Becker & Gärtner. *Anal Bioanal Chem* (2008)

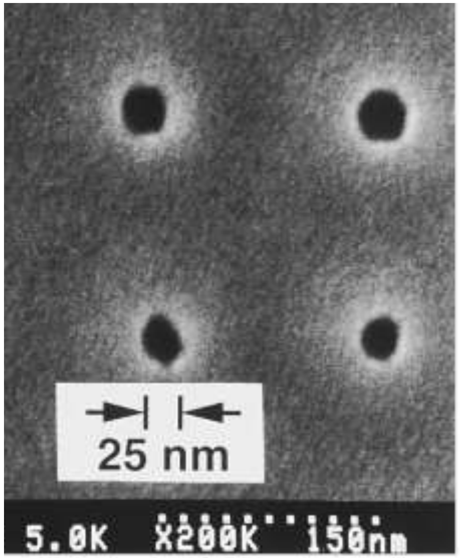
Hot Embossing with nm features: nano-imprint lithography



press a mold into a thermoplastic polymer film on a substrate → vias and trenches
minimum size of 25 nm x 100 nm

60 nm wide trench imprinted into PMMA. The PMMA lines are 100 nm tall.





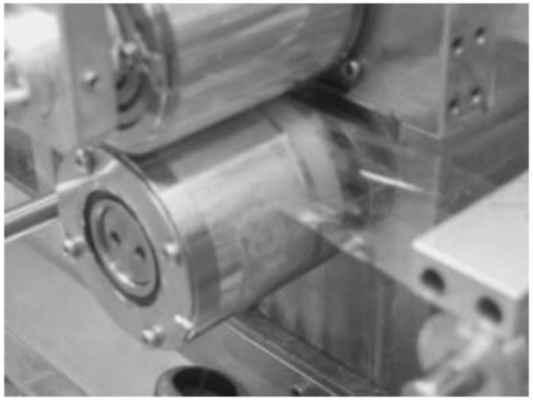
dot pattern imprinted into PMMA.
25 nm diameter and 120 nm period.

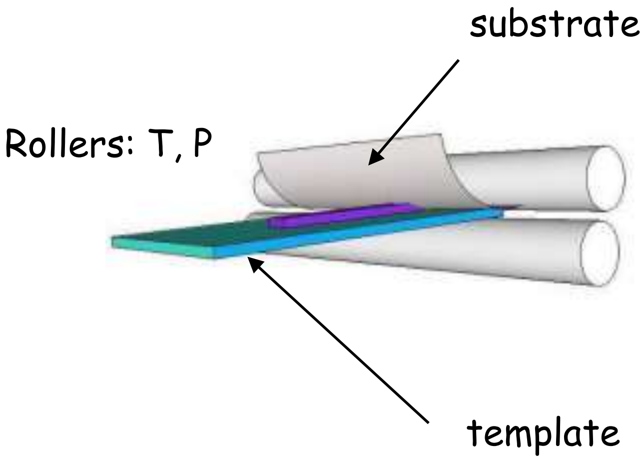
Chou *et al*, Appl. Phys. Lett. 1995
Recent Review: L. Jay Guo,
J. Phys. D: Appl Phys 2004

Roll Embossing= hot embossing+lamination

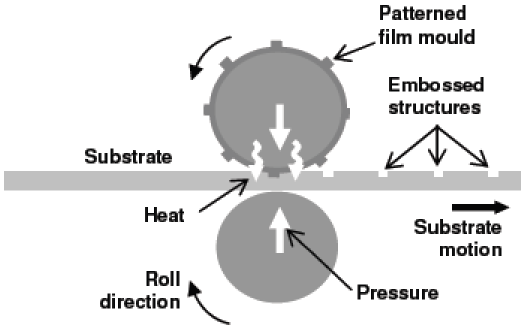
Improving Hot Embossing throughput

(1)

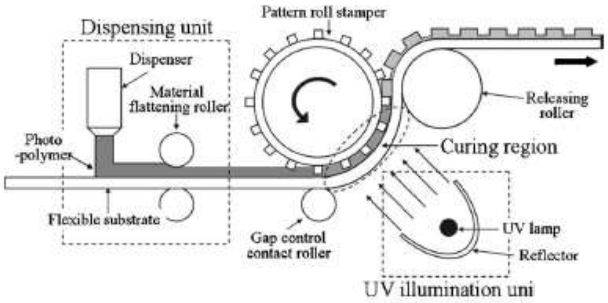




(1)



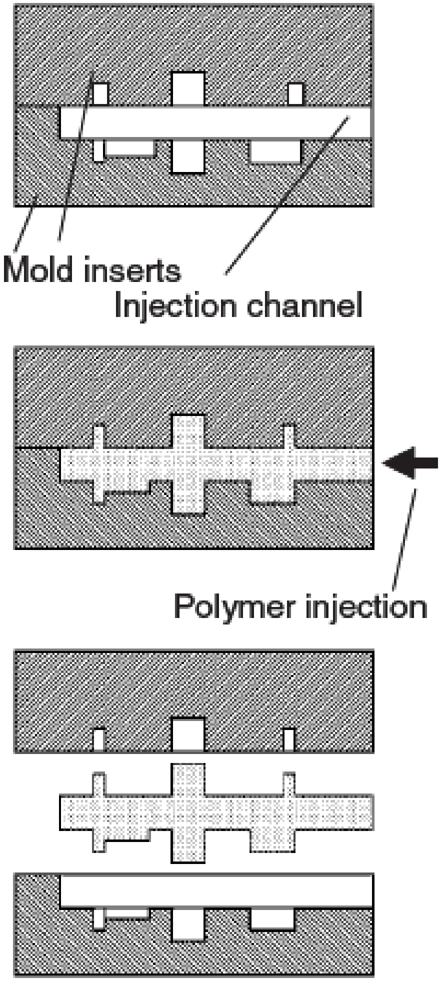
(2)



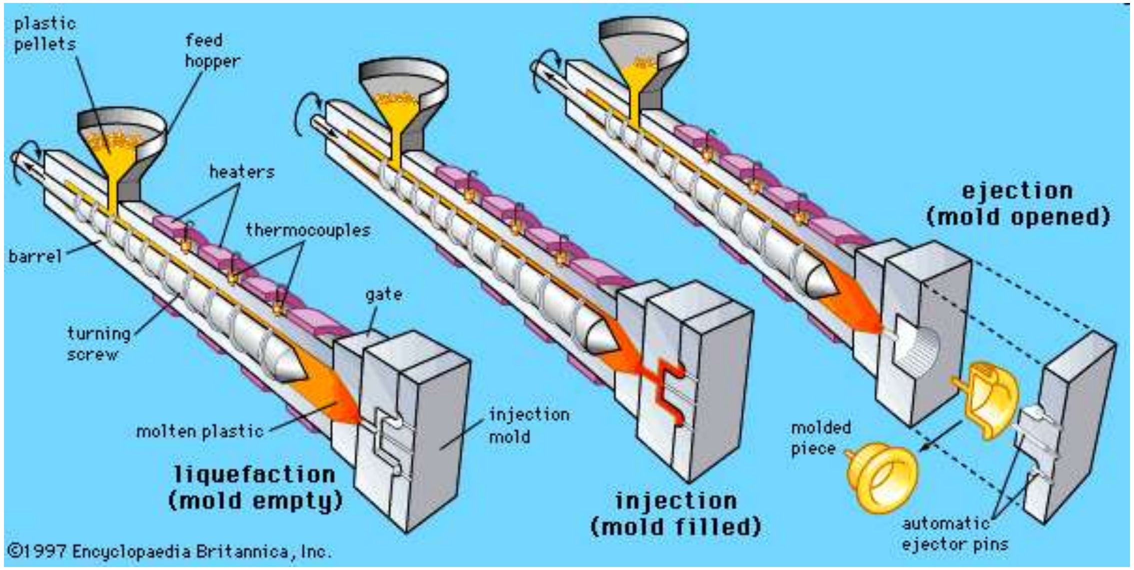
- Master is reusable
- Industrial processes & rapid prototyping
- Compatible with almost any thermoplastic
- Fast process
- No limit in size
- *High résolution ?*
- *Flexible masters !*

Injection molding

- Principle

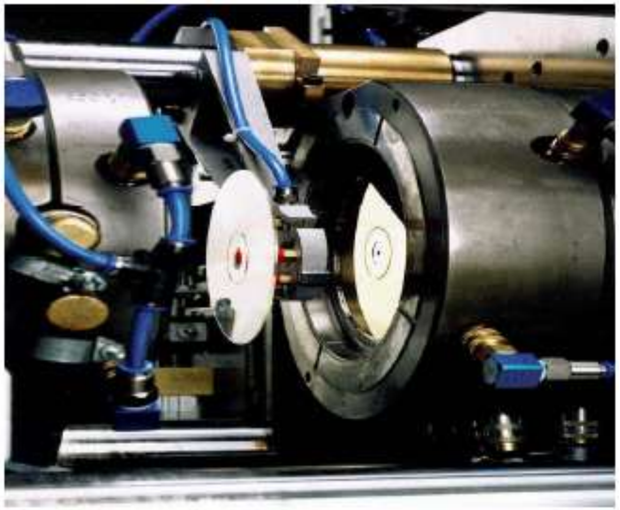


Macro Scale



Base mold with mold insert and automatic ejector

Source: Ferromatik Milacron

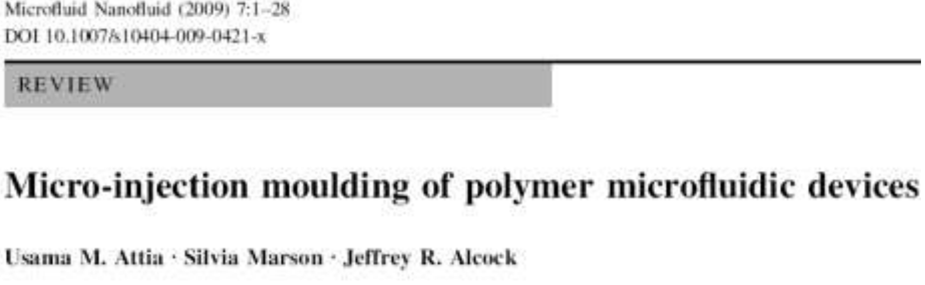


Zengele & Ducrée: www.myfluidix.com/
Becker & Gärtner. *Anal Bioanal Chem* (2008)
Heckele, JMM (2004)

Other Replication methods: injection molding

- ➢ Scaling down is difficult

small injection volumes : need for
« variotherm » process
→increases complexity and cycle time

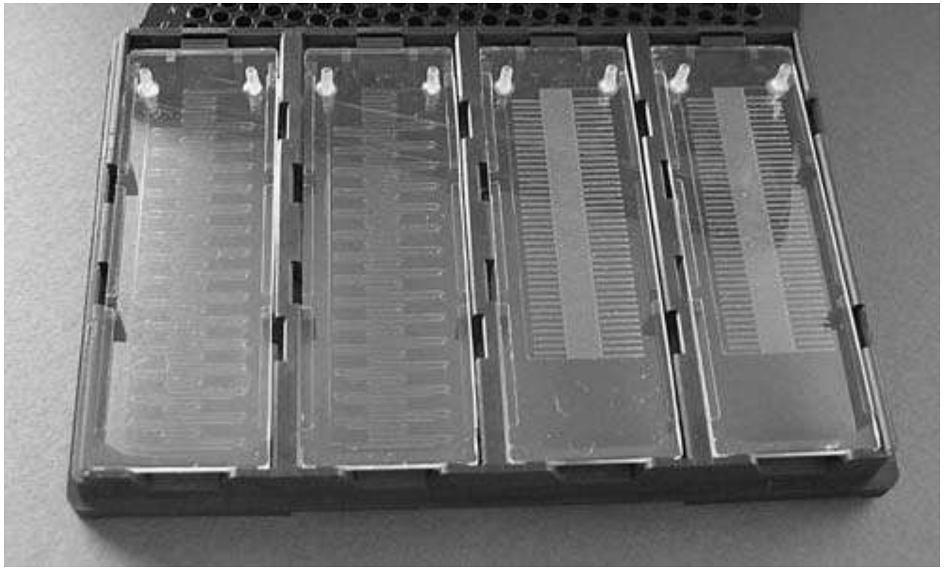

Microfluid Nanofluid (2009) 7:1–28
DOI 10.1007/s10404-009-0421-x

REVIEW

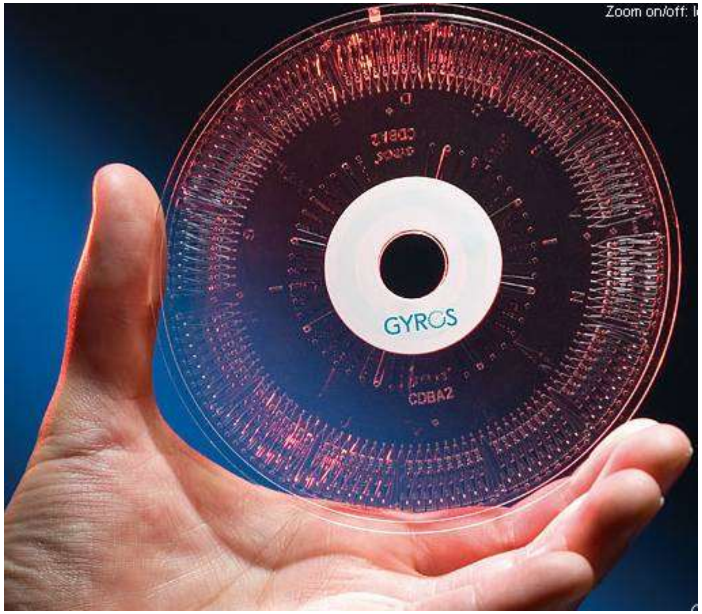
Micro-injection moulding of polymer microfluidic devices

Usama M. Attia · Silvia Marson · Jeffrey R. Alcock

Company Gyros, realization of
« microlaboratory on CD» :
Channels on a CD format
www.gyros.com

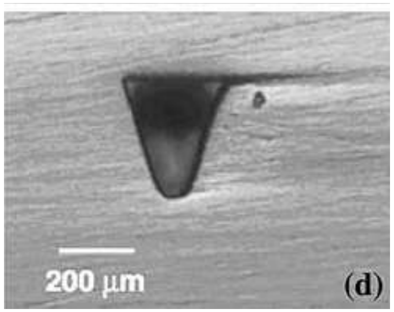


…But feasable, ex: Microfluidic ChipShop
Channels with integrated fluidic interconnects

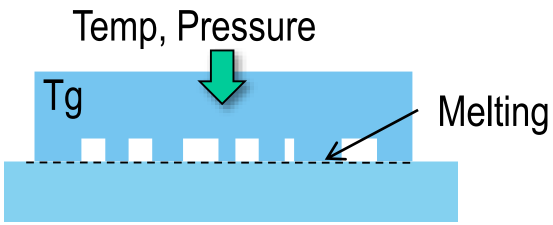


Polymer bonding (encapsulation, sealing)

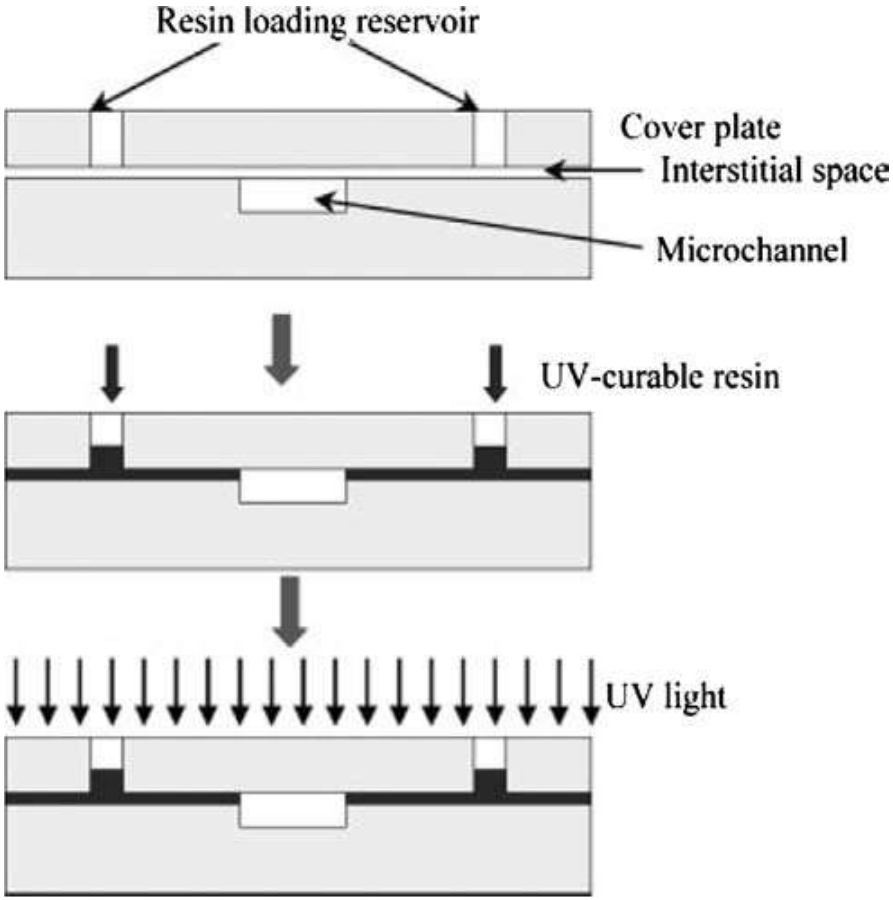
- Thermal bonding



Ex: PMMA, low P, 60°C above Tg



- Adhesive bonding

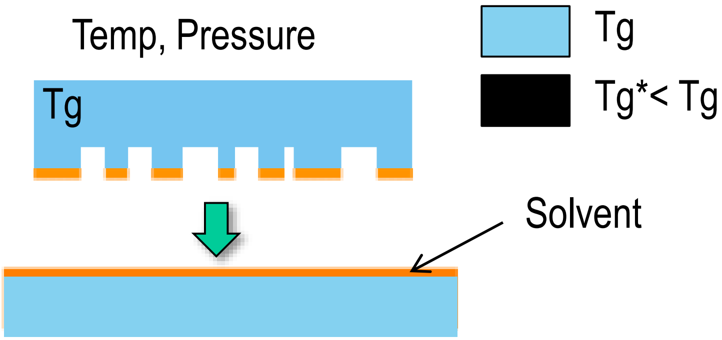


Ex: infiltration of UV sensitive resin

Solvent bonding

Solvent Bonding:
entanglement of polymer chains across the interface.

Exposure to vapour,
can also reduce roughness :



Temp, Pressure

Tg

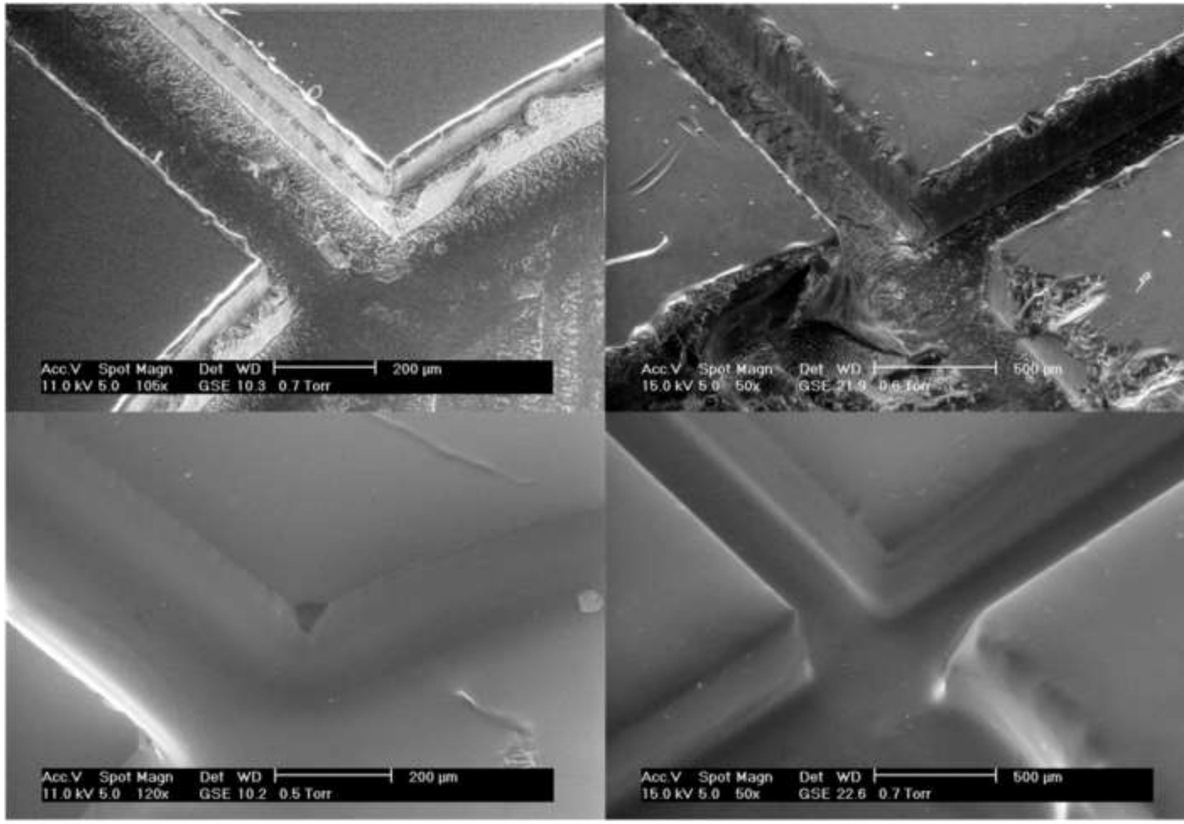
🟦 Tg

■ Tg*< Tg

Solvent

PMMA

COC



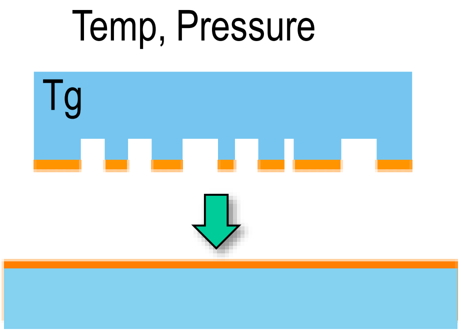
After Chloroform vapor

Cyclohexane vapor

Ogilvie JMM2010

Microfluidic device sealing

- **Using polymers with lower Tg**



🟦 Polymer 1, Tg_1

⬛ Polymer 2 $Tg_2 < Tg_1$

⊕ Monolithic
No deformation

⊖ Polymer deposition

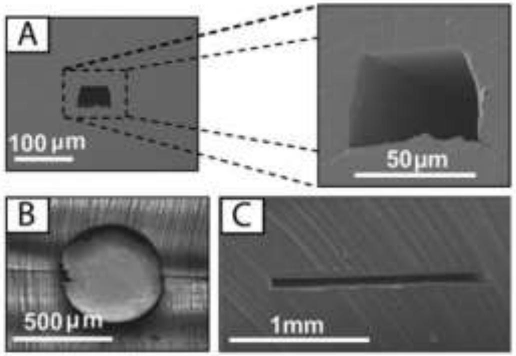
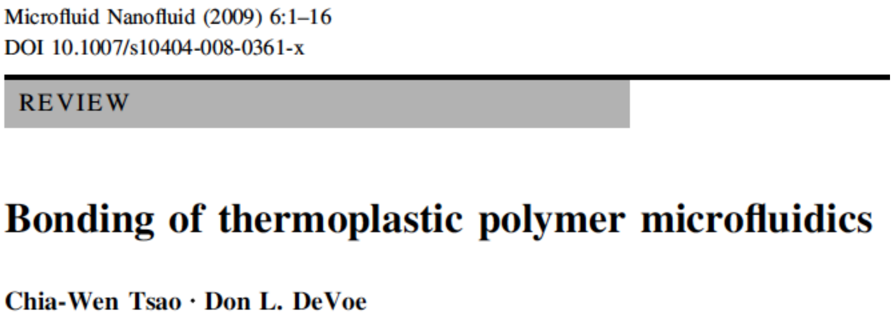


Fig. 4 SEM images of sealed chips with different dimensions and shapes: A. 50 × 50 µm channel; B. Round channel obtained from two semicircular channels (diameter 500 µm); C. 2 mm × 100 µm channel.

S. Begolo et al., 2011 Lab on a Chip

- **Laser welding**
- **Ultrasound welding**
- **Infrared bonding**



Microfluid Nanofluid (2009) 6:1–16
DOI 10.1007/s10404-008-0361-x

REVIEW

Bonding of thermoplastic polymer microfluidics

Chia-Wen Tsao · Don L. DeVoe

Microfluidic device sealing … thermosets

- Microfluidic stickers

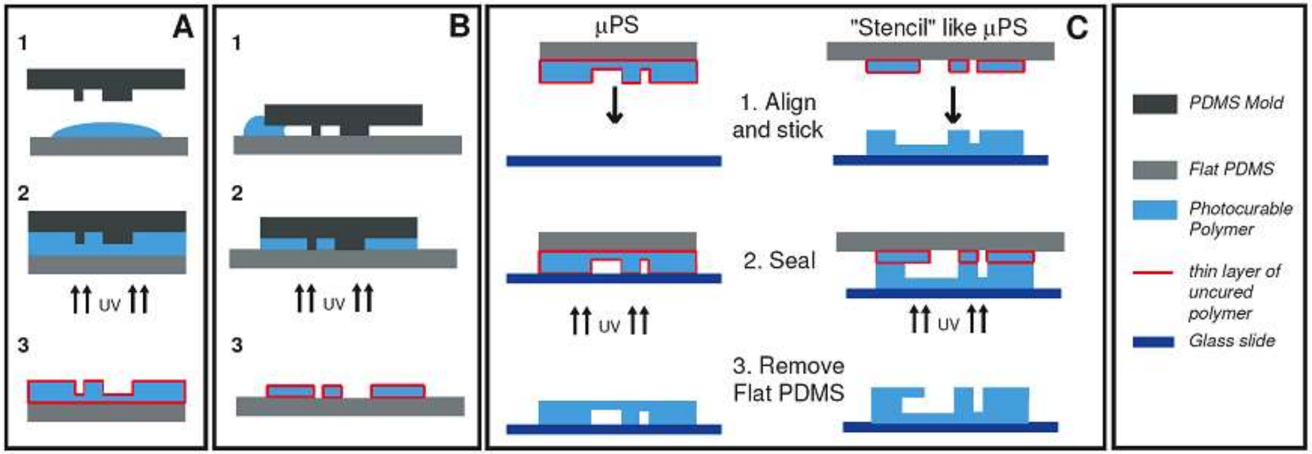
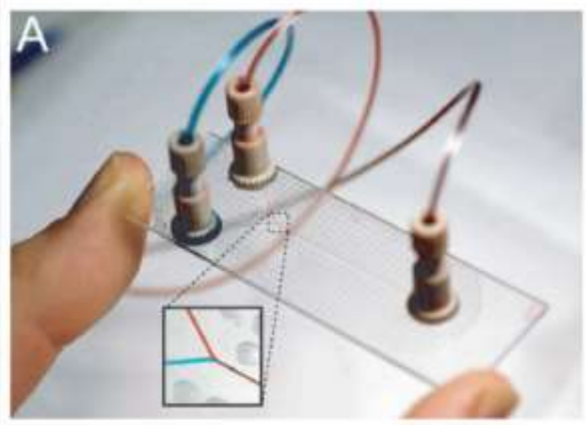


Figure 2. A: Sketch of the fabrication process of a μPS. B: Sketch of the fabrication process of a stencil like μPS. For both methods the two surfaces of the sticker still have reactive sites after UV illumination. C: Construction of microfluidic devices. (Left) One layer device: The circuit imprinted on the μPS is sealed with a glass slide. (Right) Multilayer devices: The stencil like μPS is sealed with a sticker previously bound to a glass slide.



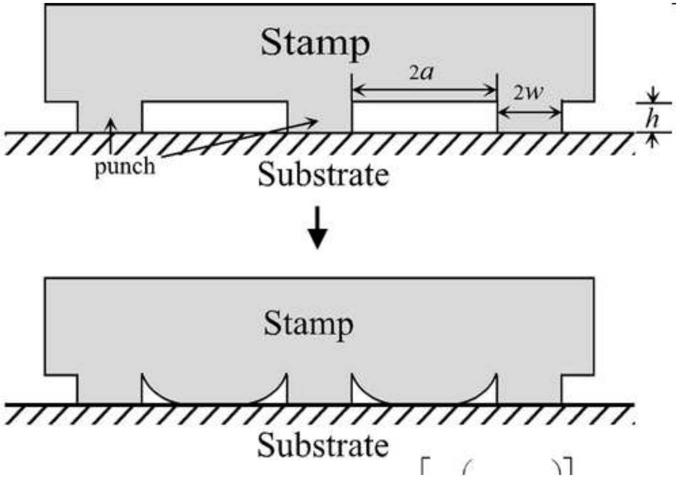
→ Norland optical Adhesive

- *Adapted to rapid prototyping*
- *Easy bonding*
- *PDMS Master*

Bartolo, Studer, Degré LOC 2008

Note on polymer bonding: collapse

- Criterium for collapse:



Criterion of Collapse, $\frac{4a\gamma}{E^{'}h^2}\frac{8}{\pi^2}\left(1+\frac{w}{a}\right)^2 \ln\left|\sec\left(\frac{\pi}{2}\frac{1}{1+\frac{w}{a}}\right)\right| > 0.83$

$E^{'}$ – –plane strain modulus of PDMS

γ – –work of adhesion between PDMS and substrate

For w>>a (single channel), criterium: $\frac{4a\gamma}{E^{'}h^2}\frac{8}{\pi^2} > 0.83$

Collapse of

* thin (h), low aspect ratio (a/h>>1) structure

* with soft (E') and adherent (γ) material

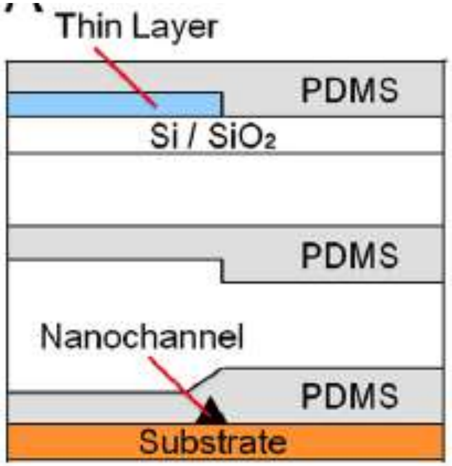
Usually: to be avoided…

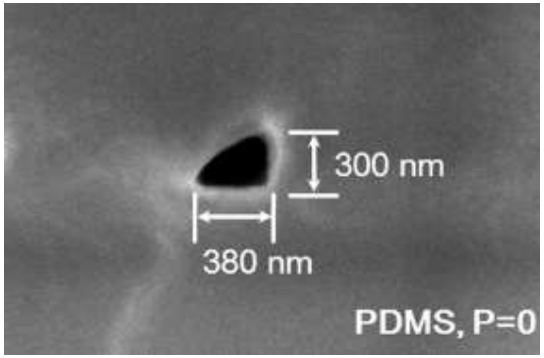
Huang et al, Langmuir (2005)

Note on polymer bonding: use of collapse!

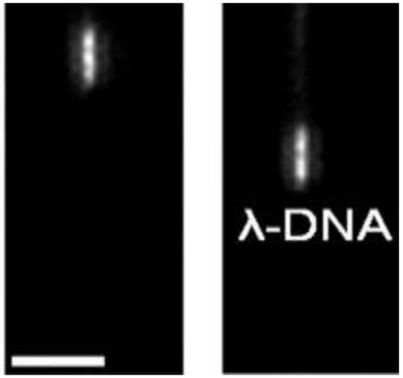
- Use to fabricate polymer nanochannels

Park, Huh, Craighead,Erickson (Cornell), PNAS 2009



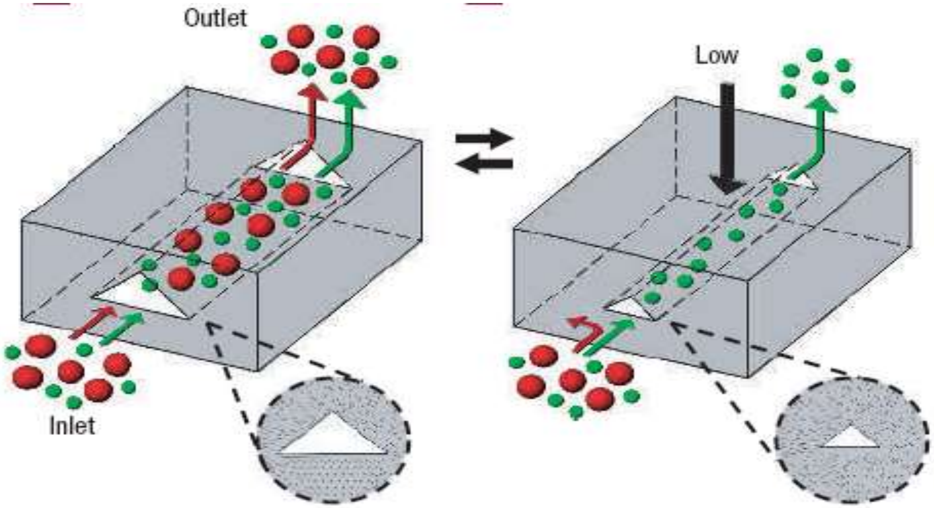


No nanofabrication needed !



Electrophoresis of elongated DNA

- Tunable nanochannels



Cross section function of external load (triangular shape: cracks in PDMS)
→ Tunable filters

Erickson *et al.* Nature Materials (2007)

I. Intro, criteria to choose a material / a method

II. PDMS

III. What else?

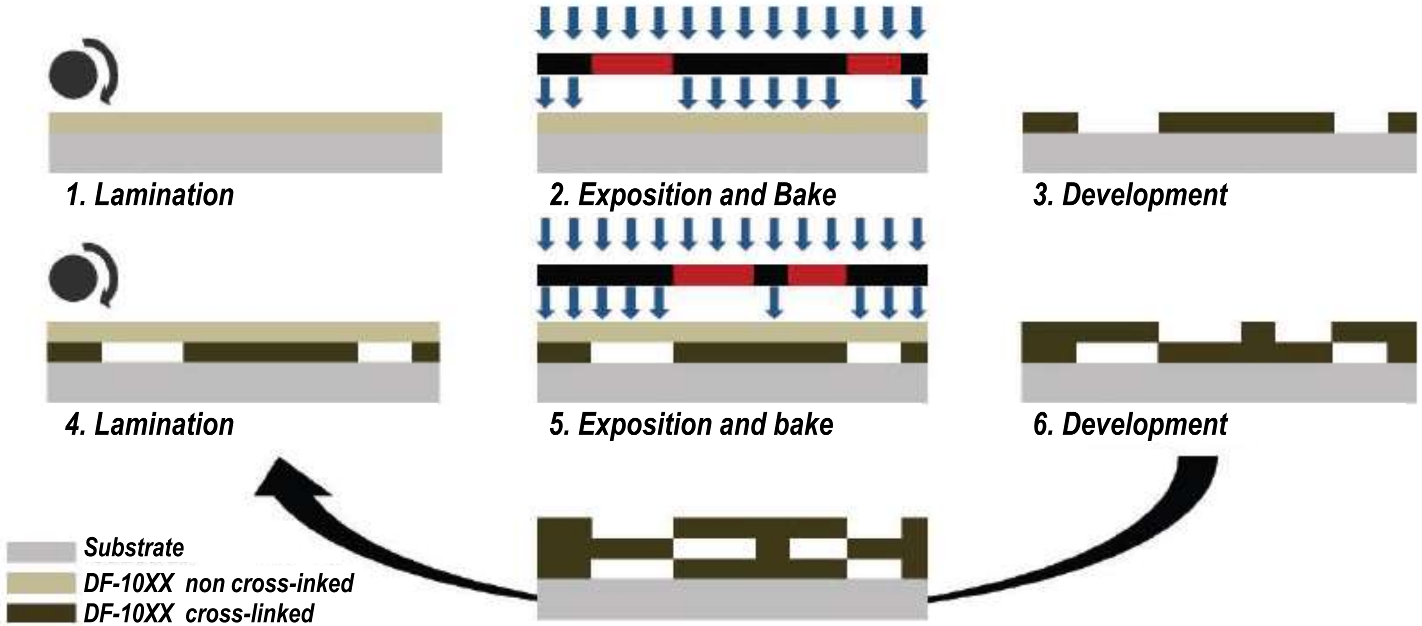
1. Back to Material/process Choice
2. Silicon
3. Other replication methods
4. Other polymers
5. Paper
6. Porous medium

4. Lamination based processes

IV. Openings

Lamination to make 3D devices ?

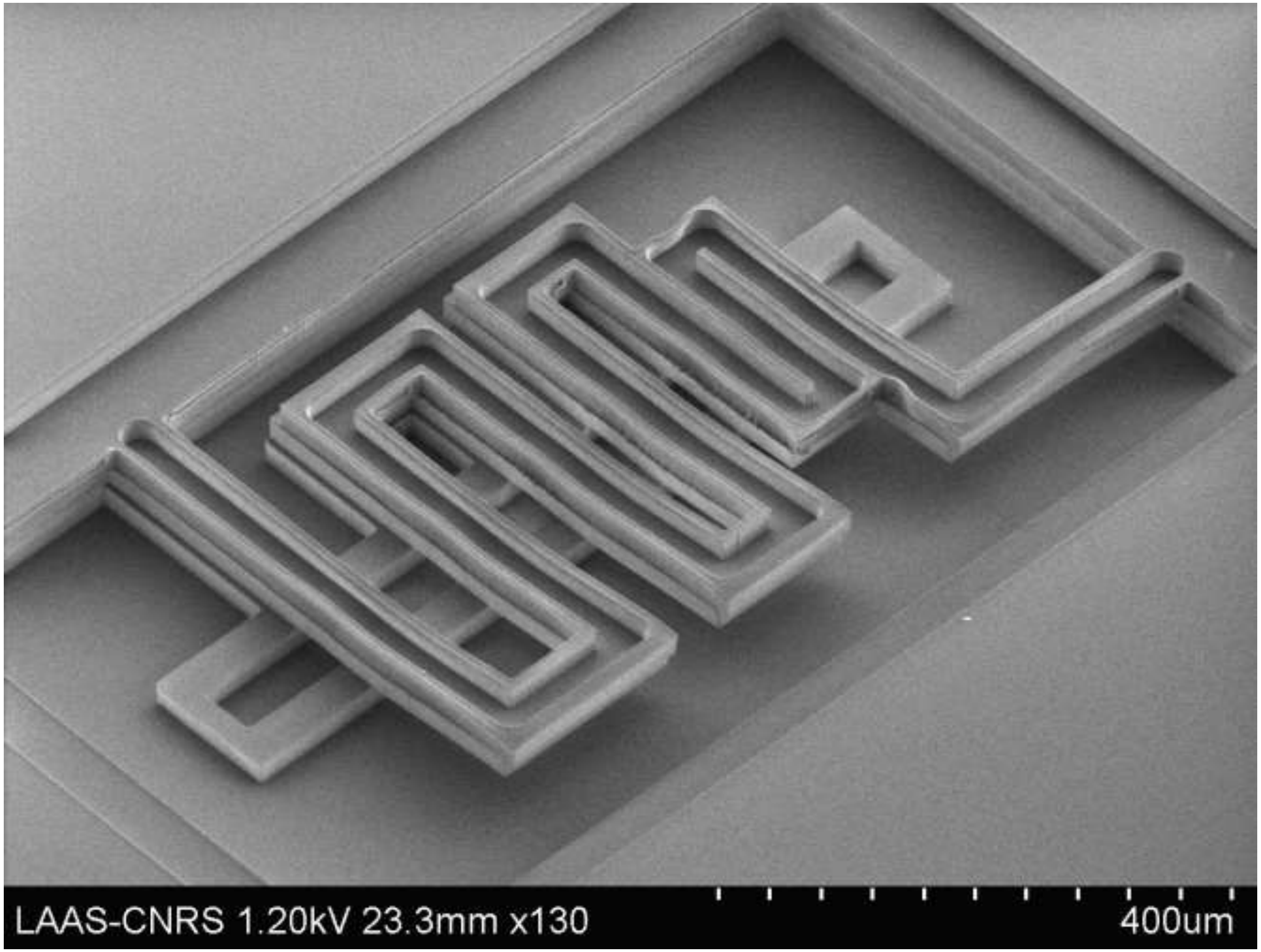
- **SU-8 or cheaper substitute for photolithography**



	SU-8 3050 (1050)	DF-1050 (50µm)
Time to process a layer	1h40	30 min
Cost for a layer on 4’’ wafer	16 €	1,6 €

Courson, Fouet, RSC Adv 2015

Lamination to make 3D devices ?



5 levels of dry film. Floor 5 µm / 4 x 20 µm

Courson, Fouet, RSC Adv 2015

Lamination-based Processes: COC fabrication

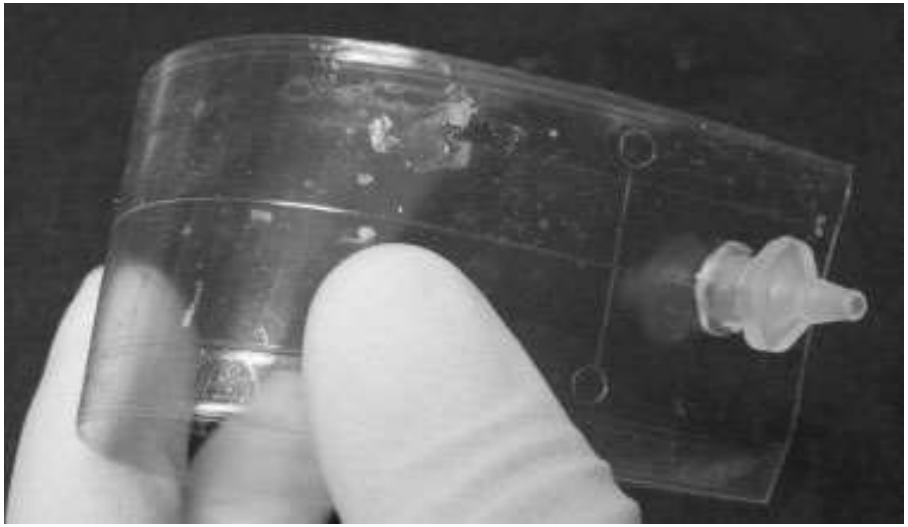
- Material : COC (cycloolefin copolymer)

Good chemical resistance.

Available with ≠ Tg→ easy thermal processing.

Optically transparent down to 250 nm.

Surface treatments OK: for biology!



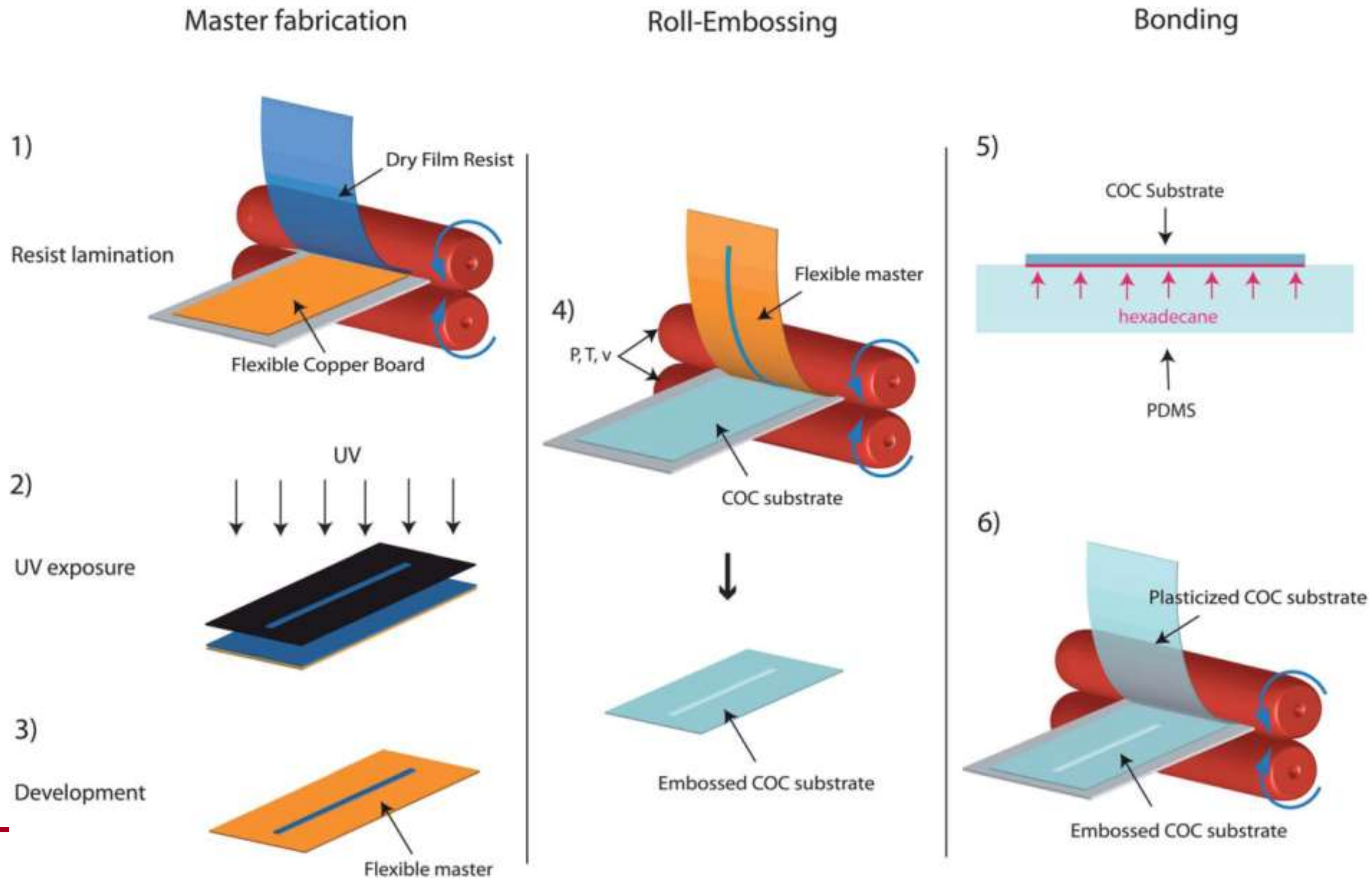
Paul et al., *Electrophoresis* (2007), Miserere LOC 2012, Metwally Khan-Malek, Microsystems Technology 2012

Roll embossing COC

Photopattern a laminated dry film template

Hot embossing COC by lamination against this template

Solvent bonding (hexadecane in isopropanol)



I. Intro: criteria to choose material / process

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4. Lamination based processes

5 A last overview of other polymers

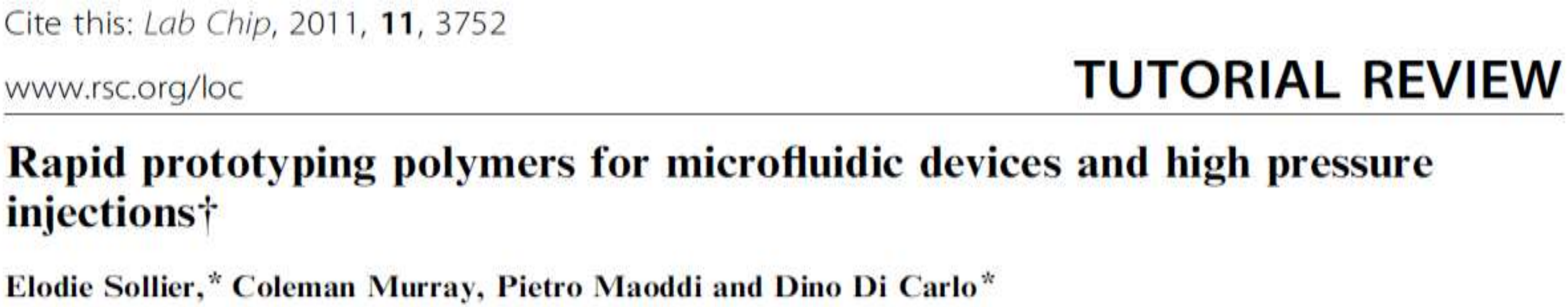
6 Paper

7 Porous medium

IV. Openings

Materials/processing for polymer microfabrication

A simplified view



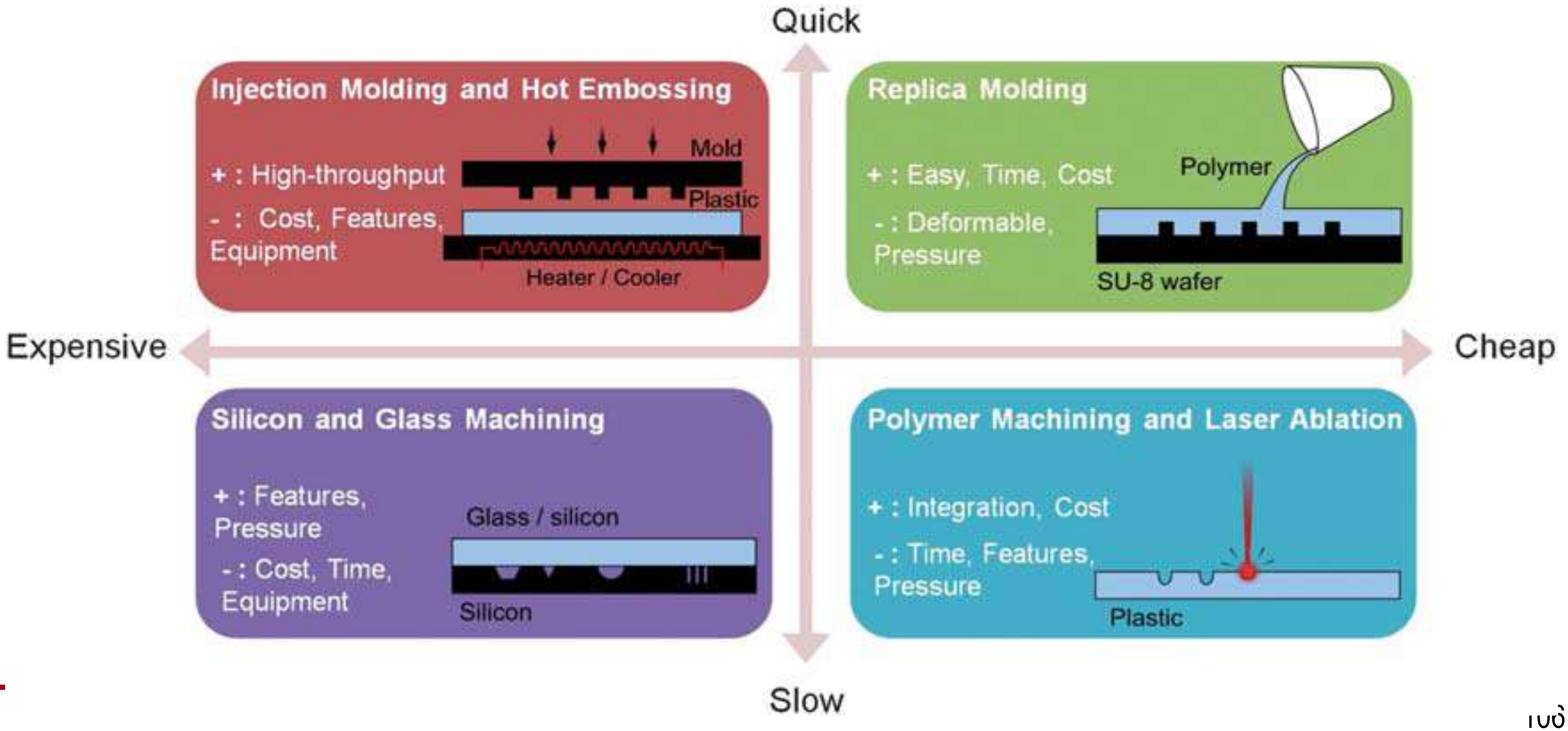
Cite this: *Lab Chip*, 2011, **11**, 3752

www.rsc.org/loc

TUTORIAL REVIEW

Rapid prototyping polymers for microfluidic devices and high pressure injections†

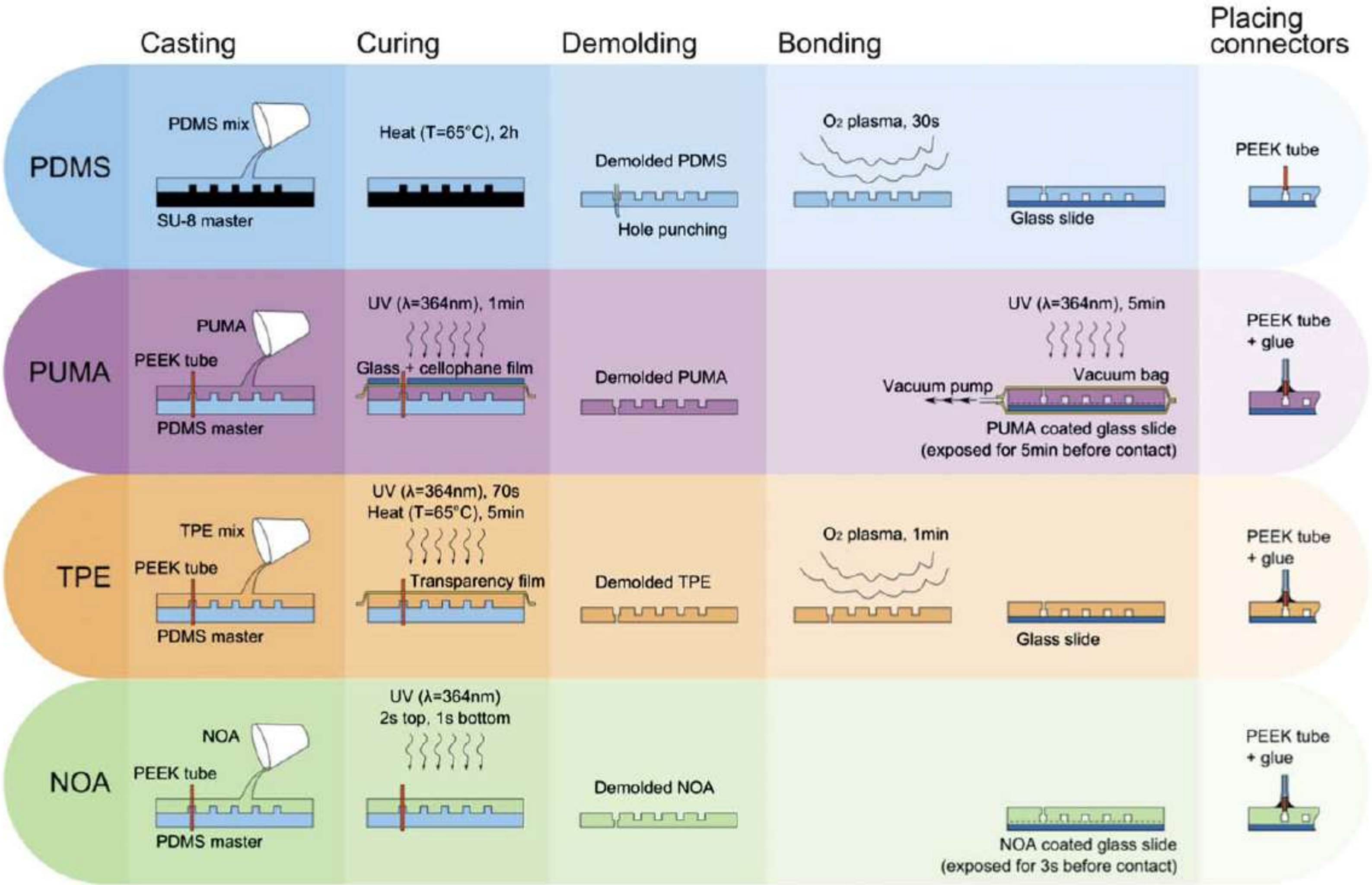
Elodie Sollier,* Coleman Murray, Pietro Maoddi and Dino Di Carlo*



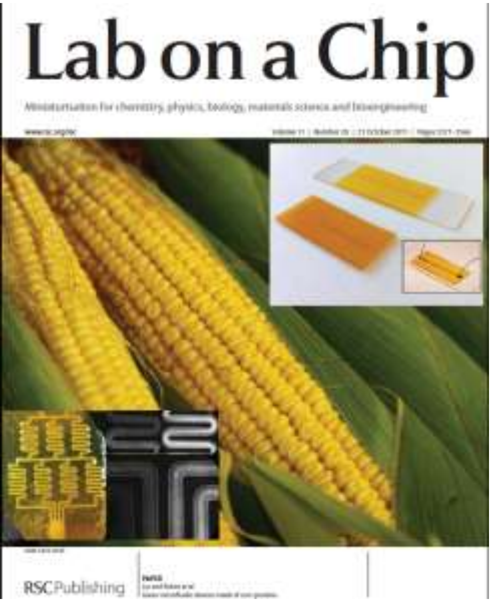
Practical Comparison for casting

Comparison PDMS, TPE, PUMA, NOA (casting)

Main advantage of « no PDMS »: stiffness ! ~100-1000 times harder

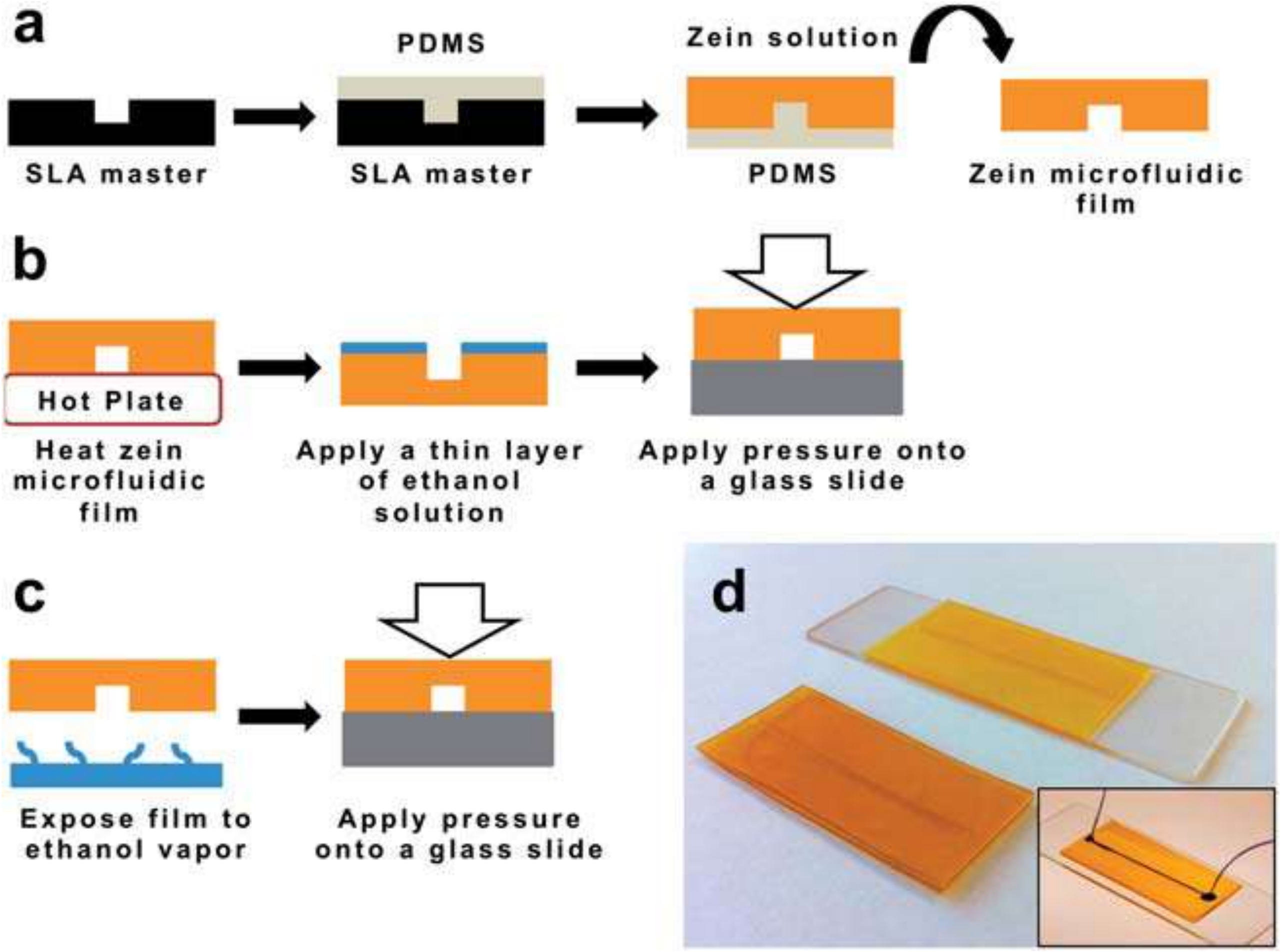


New polymers: green microfluidics ?



Lab on a Chip

RSC Publishing



Luecha LOC 2012
made of zein, a prolamin of corn.
a disposable environmentally friendly microchip
especially in agriculture applications

several other biodegradable materials:
silk fibroin9, gelatin,
poly(DL-lactic-co-glycolide) (PLGA),
poly(glycerolsebacate) (PGS)
calcium alginate

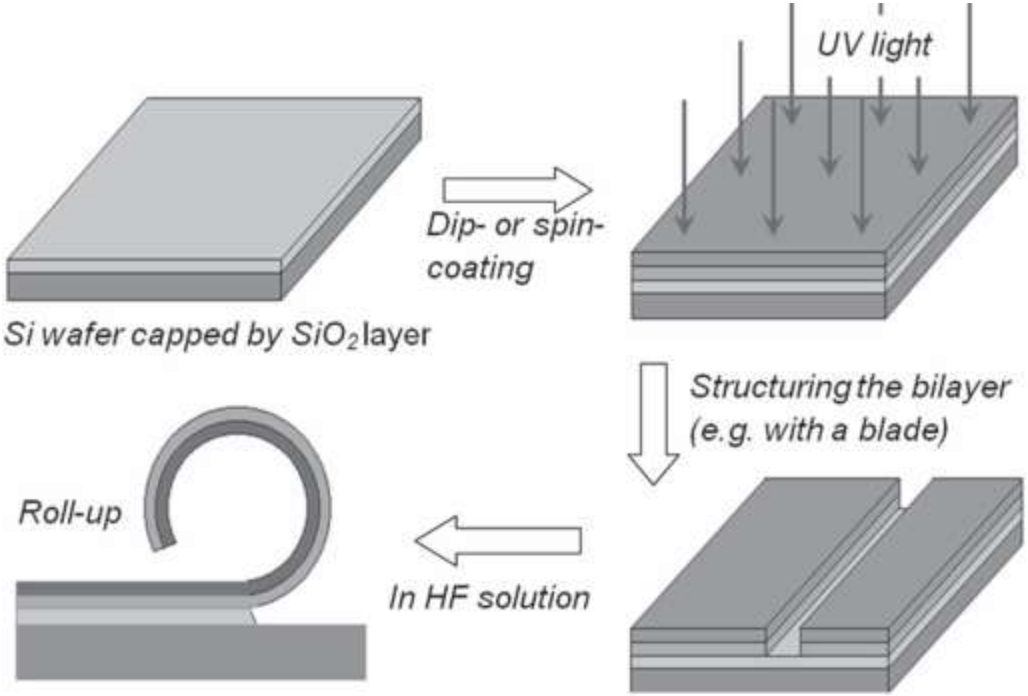
Self-rolling of polymer bi-layers

1. A polymer bilayer
 (P4VP layer in chloroform, PS layer in toluene)

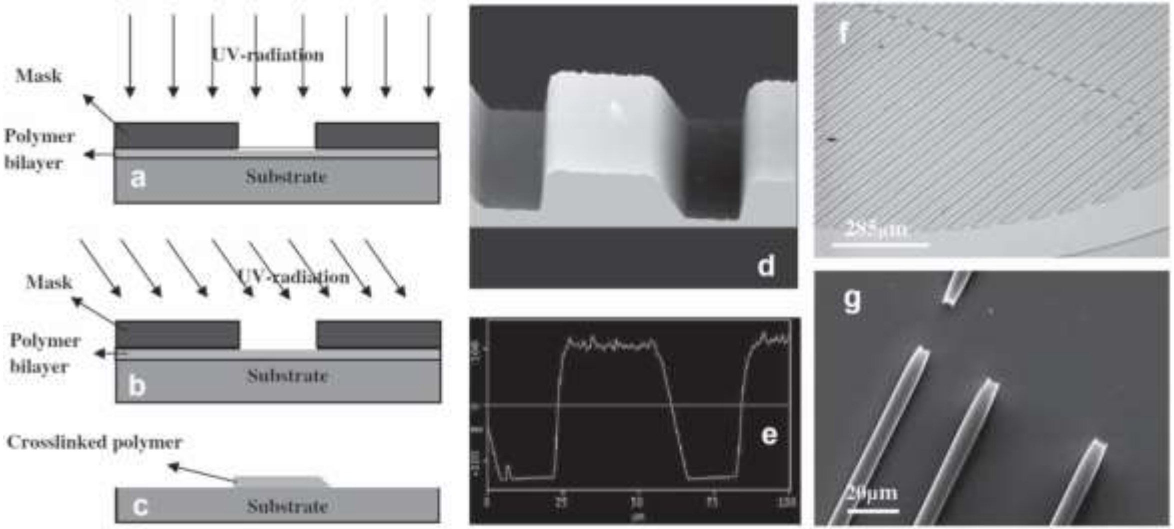
2. UV crosslinking

3. Openings: blade

4. Put in diluted HF solution in water.
 Swelling of the P4VP
→ bending → rolling



+Many recent developments by F Malloggi (CEA)



asymmetric profile→ 1D rolling

Review: Luchnikov,
Macromol Rapid Comm 2011

I. Intro: criteria to choose material / process

II. PDMS

III. What else?

1. Back to Material/process Choice
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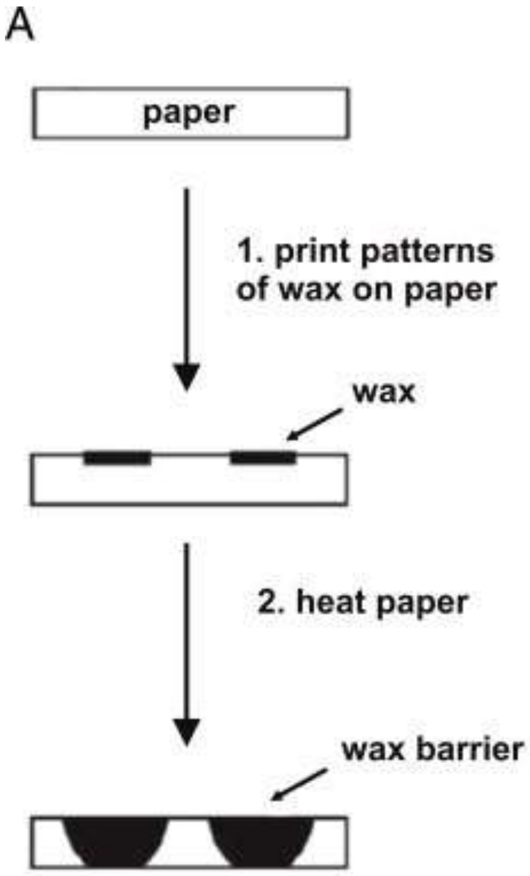
5. A last overview of « New » polymers
6. **Paper**
7. Porous medium

IV. Openings

Paper microfluidics

- Principle

*photolithography or wax printing to define hydrophilic & hydrophobic zones in paper (= channels)
*Bonding: layer of tape



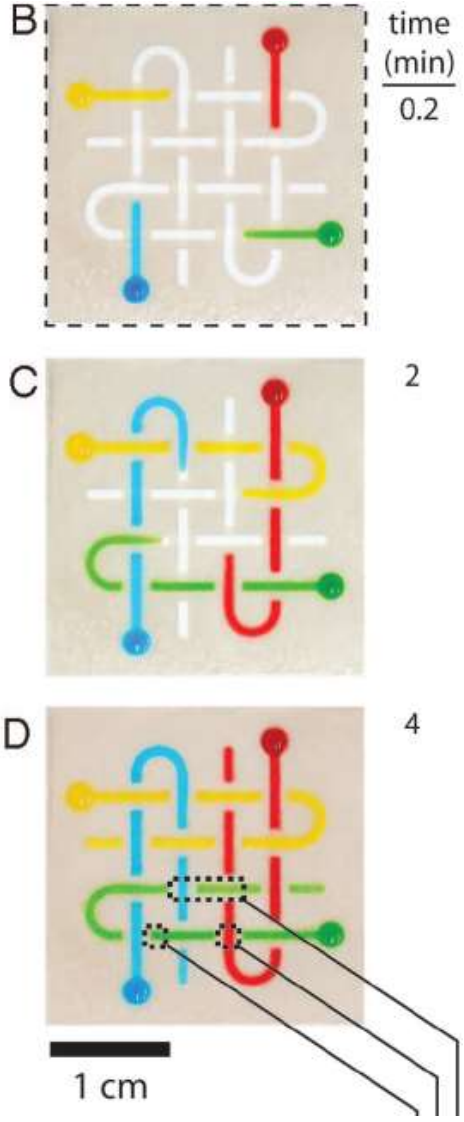
- Advantages

low-cost (~0,03US$)
small sample volumes,
capillary wicking of fluids,
facile multiplexed assays

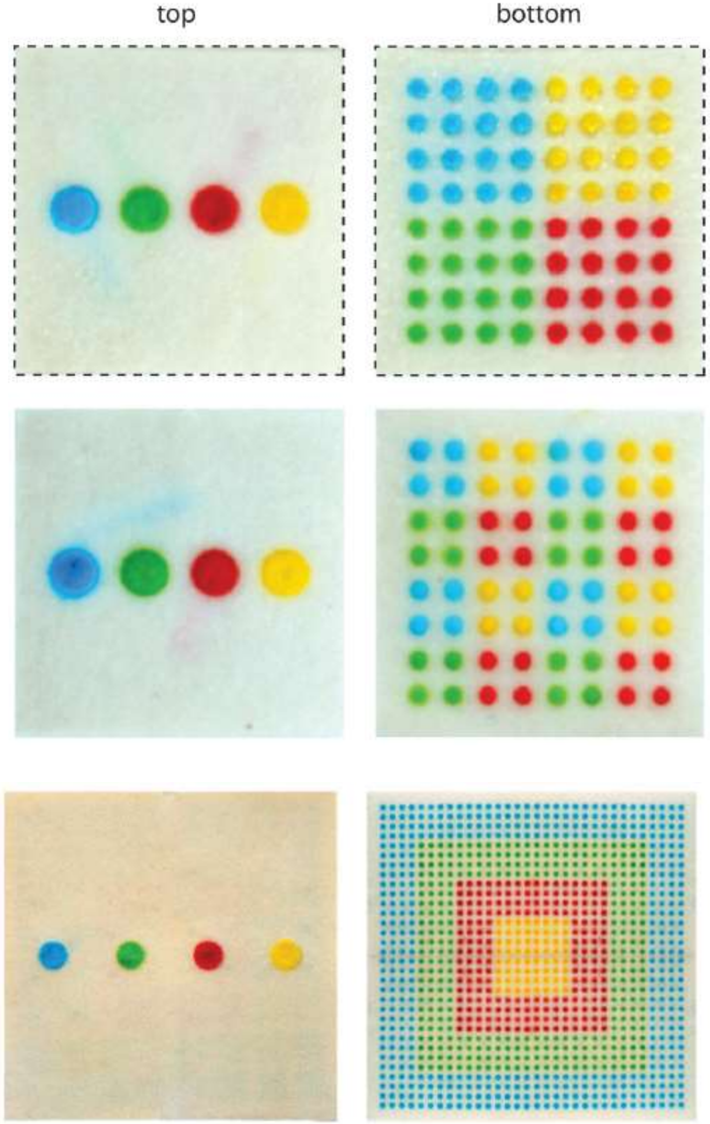
Martinez & Whitesides Anal. Chem 2008
Lewis, LOC2012

III.5. µ-PAD (Paper Analytical Devices)

Capillary Wicking

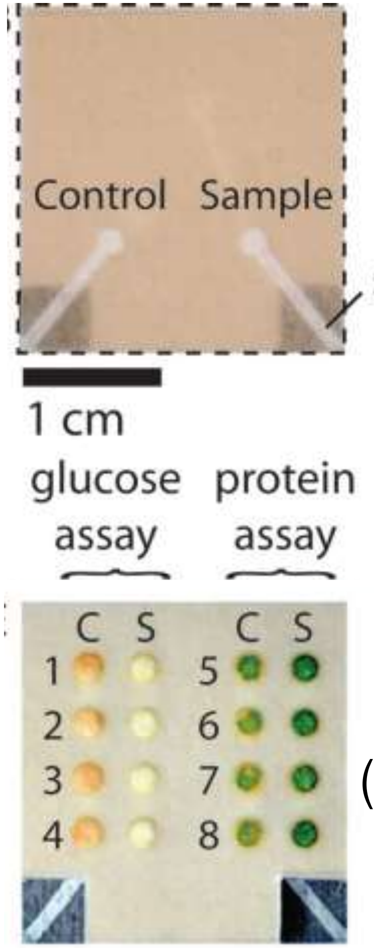


Distribution to detection zones



5 layers of paper, 4 layers of tape, filling in 5 min

Colorimetric detection

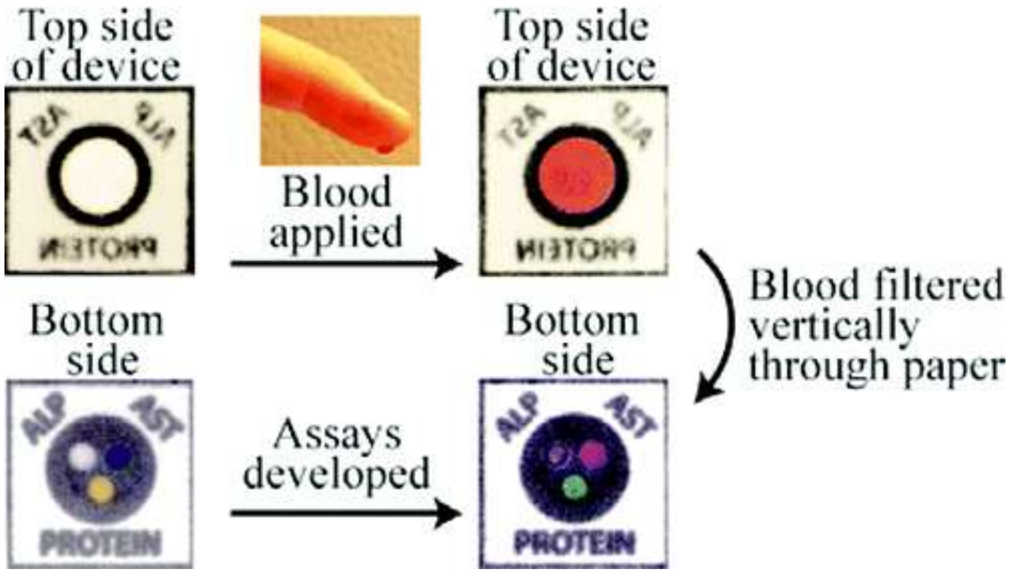


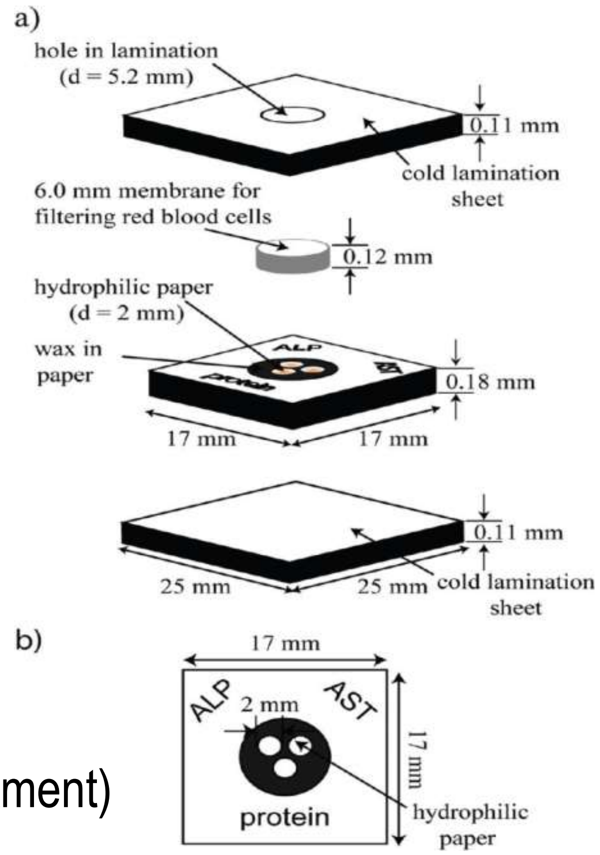
Top

Bottom (detection)

Martinez & Whitesides PNAS 2008

Paper: diagnostics for developing countries





Separation plasma/red blood cells: membranes
Measuring 2 enzymes
→diagnostics of leaver trouble (secondary effects of HIV treatment)
Non profit organization ‘diagnostics for all’

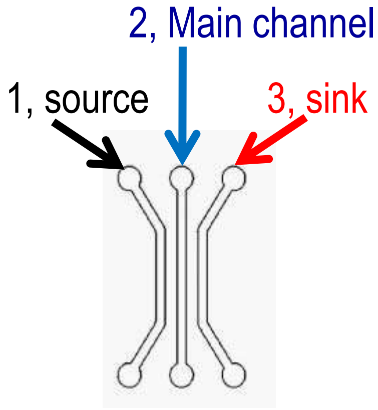
Vella, Whitesides, Anal. Chem., 2012

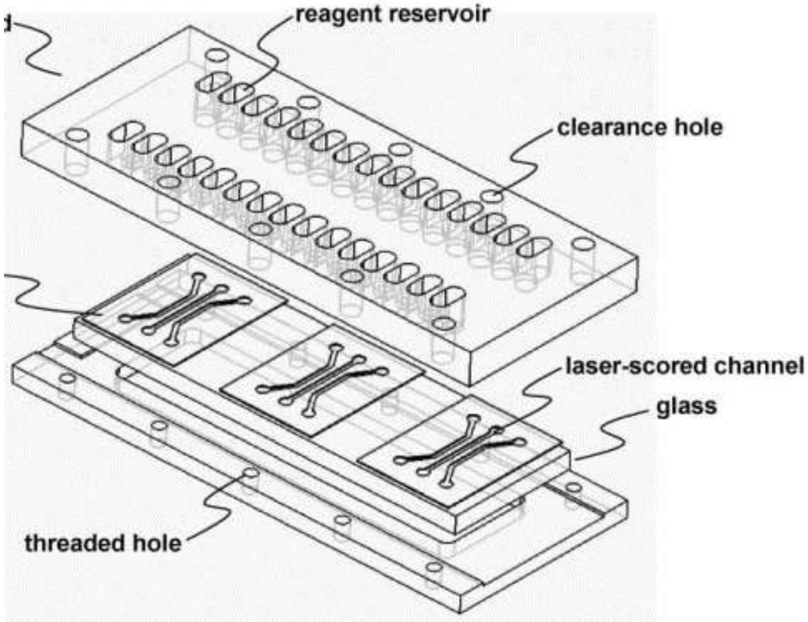
Channel in a Porous structural medium

- **Nitrocellulose membrane: stationary gradients**

Porous membrane: 0.45µm pores, 140 µm thick.
CO_2 Laser photoablation method.
Diffusion of buffers 1 and 3 (sink, source channels) through the membrane towards the center channel

→Interest: stationary gradient with no flow

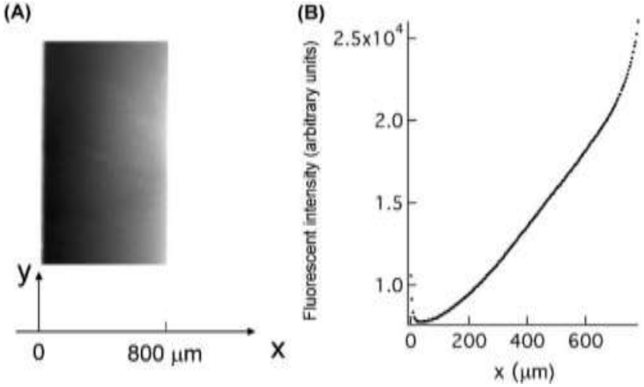




Calibration :

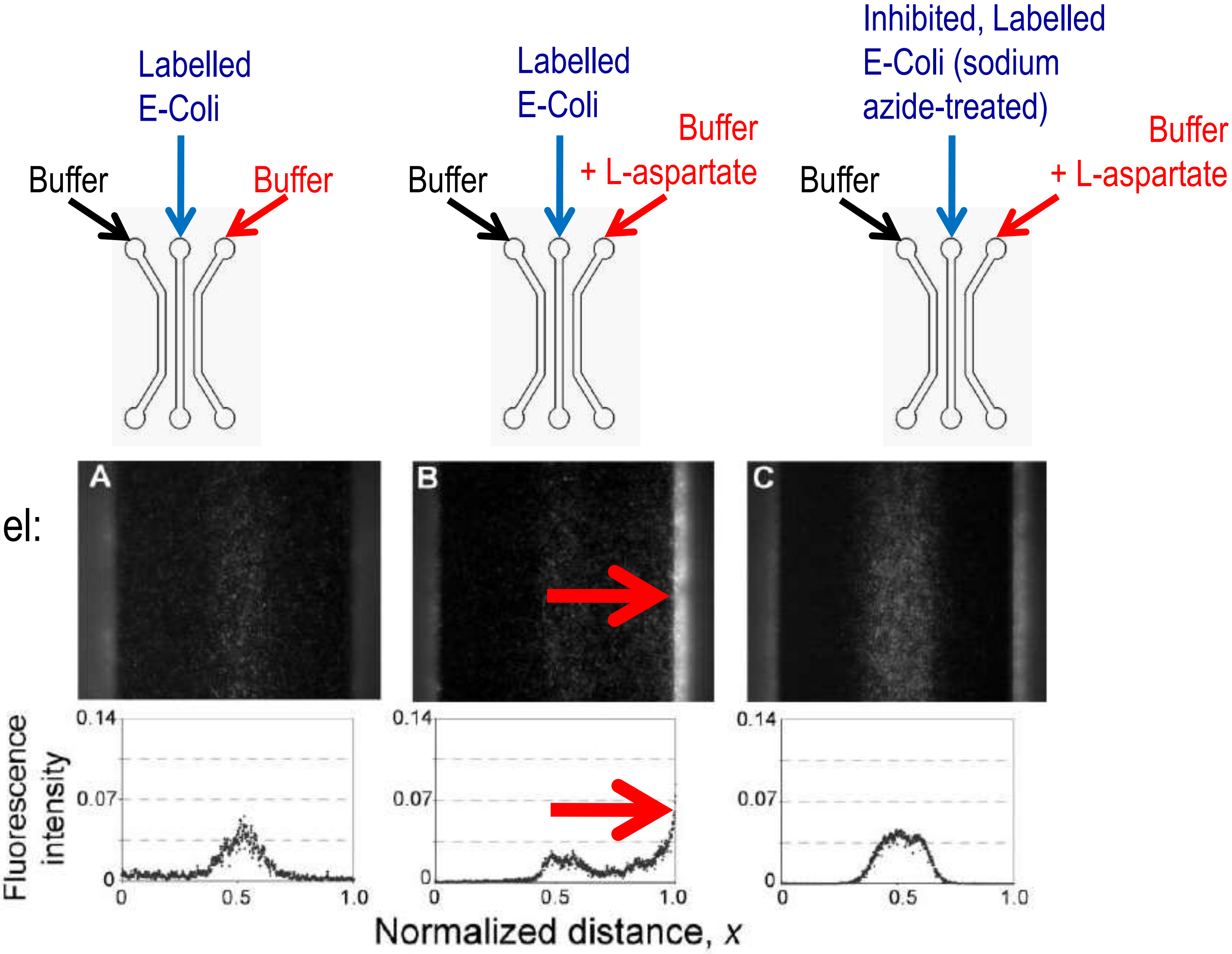
1: 0.1 mM fluorescein
2: Water
3: water

After 35mn,
Fluorescence intensity across center channel



Diao et al., LOC 2006 (DeLisa, Cornell)

Gradients to study bacterial chemotaxis



Bacteries in center channel:

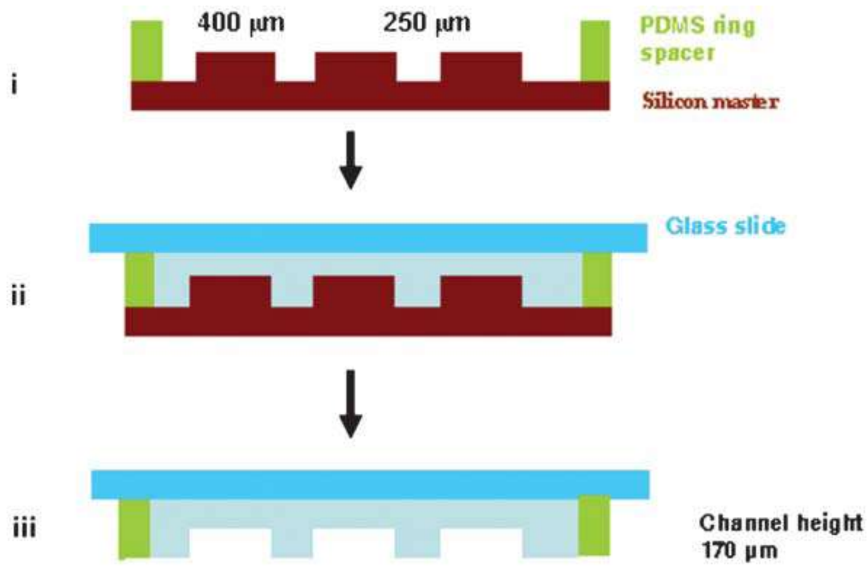
Quantitative studies, but long response time (∃ exp. tricks…)

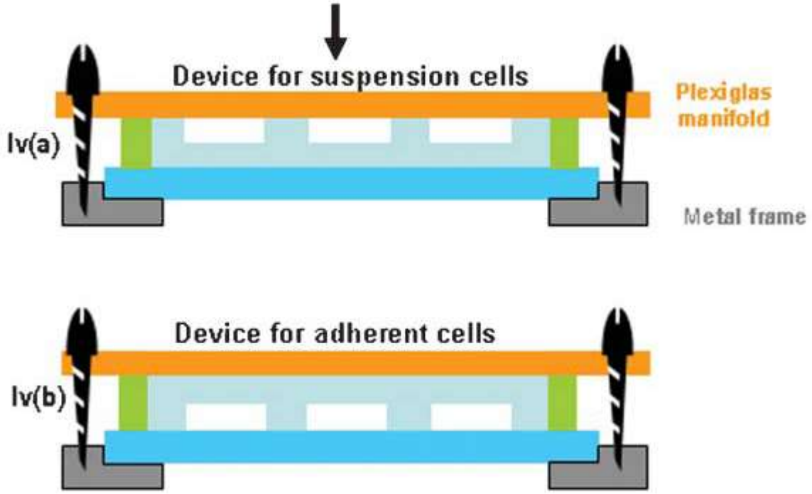
Diao et al., LOC 2006 (DeLisa, Cornell)

Porous medium: Hydrogels

➢ Agarose gel channels: fabrication

Pour 3% hot agarose gel (0.3g agarose, 10ml PBS) onto the silicon master
Peel it off once it is gelled.
Soak the gel membrane in a chemotaxis buffer for at least 30 min.





➢ Advantages

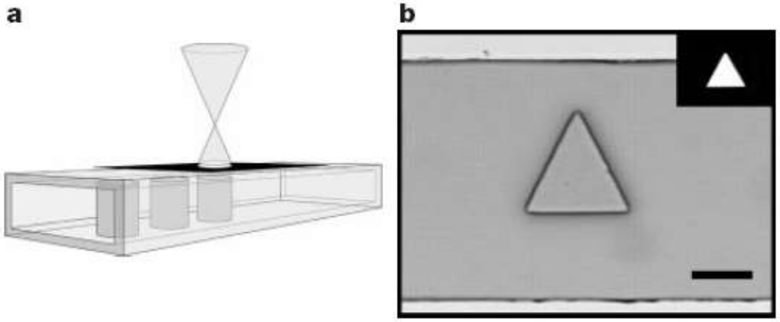
* Good for bio. (proteins & nutrients diffuse in hydrogel)
* capable of applying chemical stimuli indep. of mechanical stimuli
* Straightforward to make

Cheng et al., LOC 2007 (Wu, Cornell)

Kalinin et al., Biophys J. 2009 (Wu, Cornell)

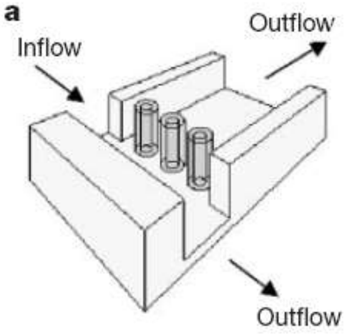
Hydrogels as active elements

- **Liquid-phase photopolymerization**

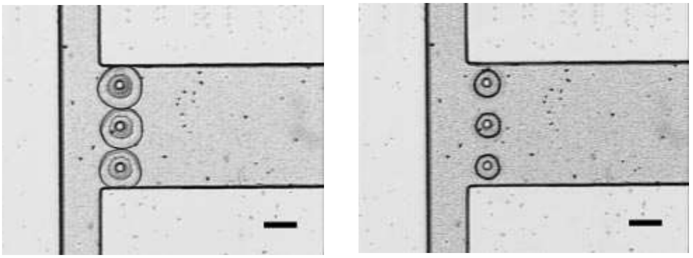


Reticulation through a mask

- **Integrated valve**



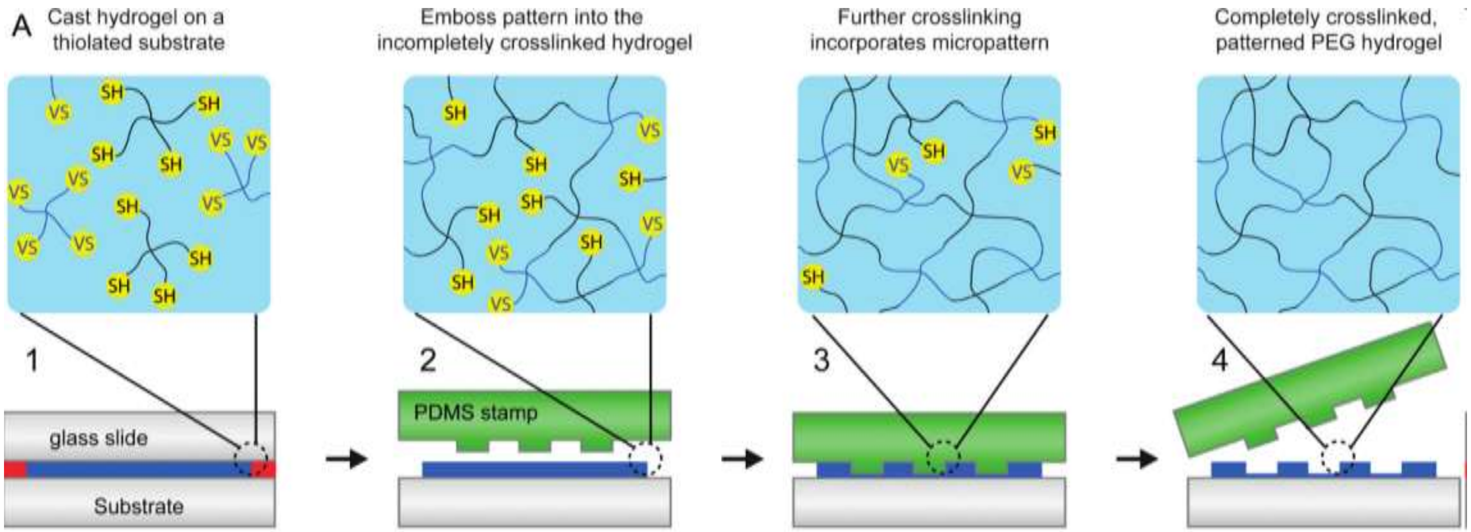
pH responsive polymer

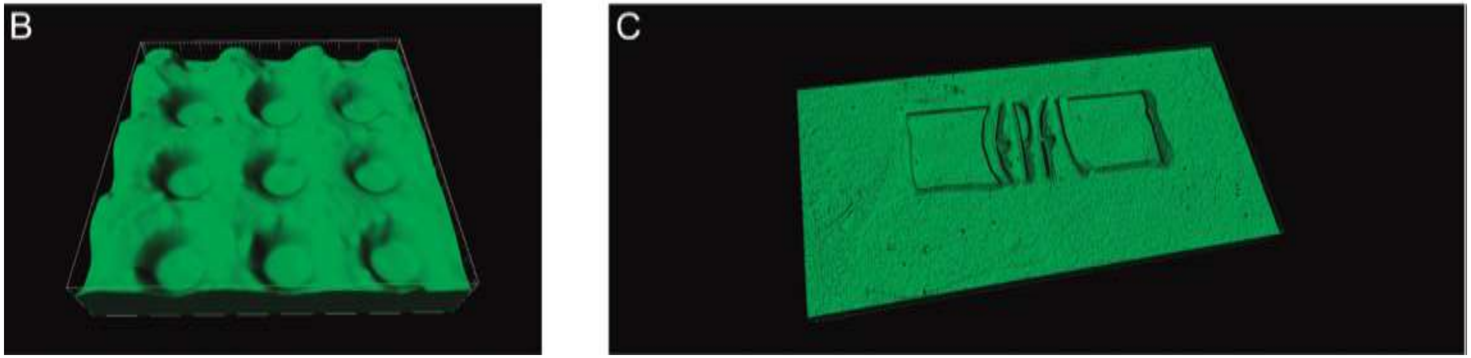


Closed (expanded state) Open (contracted state)

Beebe et al, Nature 2000

Soft Embossing of Hydrogels





* Use a PDMS stamp & finish hydrogel reticulation with the stamp on

* Microwells suited for biology (culturing live single hematopoietic stem cells)

Kobel et al, (Lutolf, EPFL) Langmuir 2009

Hydrogel: great potential for tissue engineering

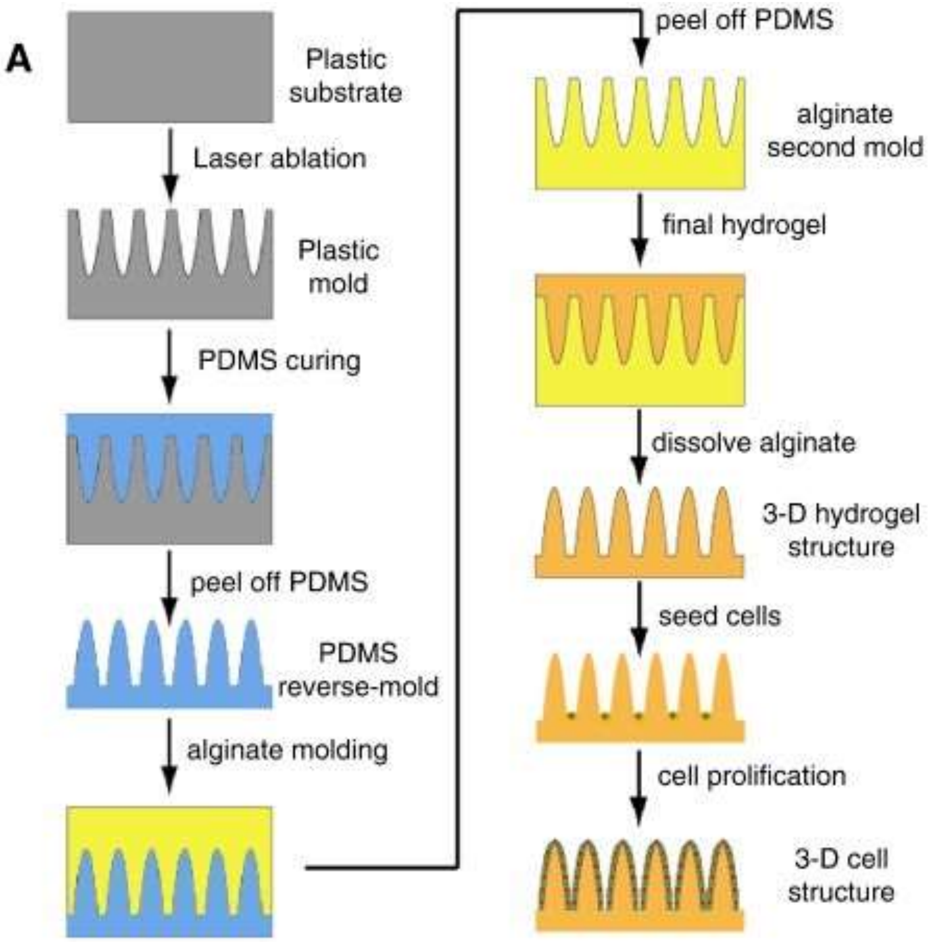

Cite this: *Lab Chip*, 2012, **12**, 45

www.rsc.org/loc

CRITICAL REVIEW

Microfluidic fabrication of microengineered hydrogels and their application in tissue engineering

Bong Geun Chung,*[a] Kwang-Ho Lee,[b] Ali Khademhosseini[cdef] and Sang-Hoon Lee*[g]



Ability to mimick a biological tissue:
Shape;
Stiffness,
Chemical environment

In Sète
→ See Laurent Malaquin, lectures on bioprinting

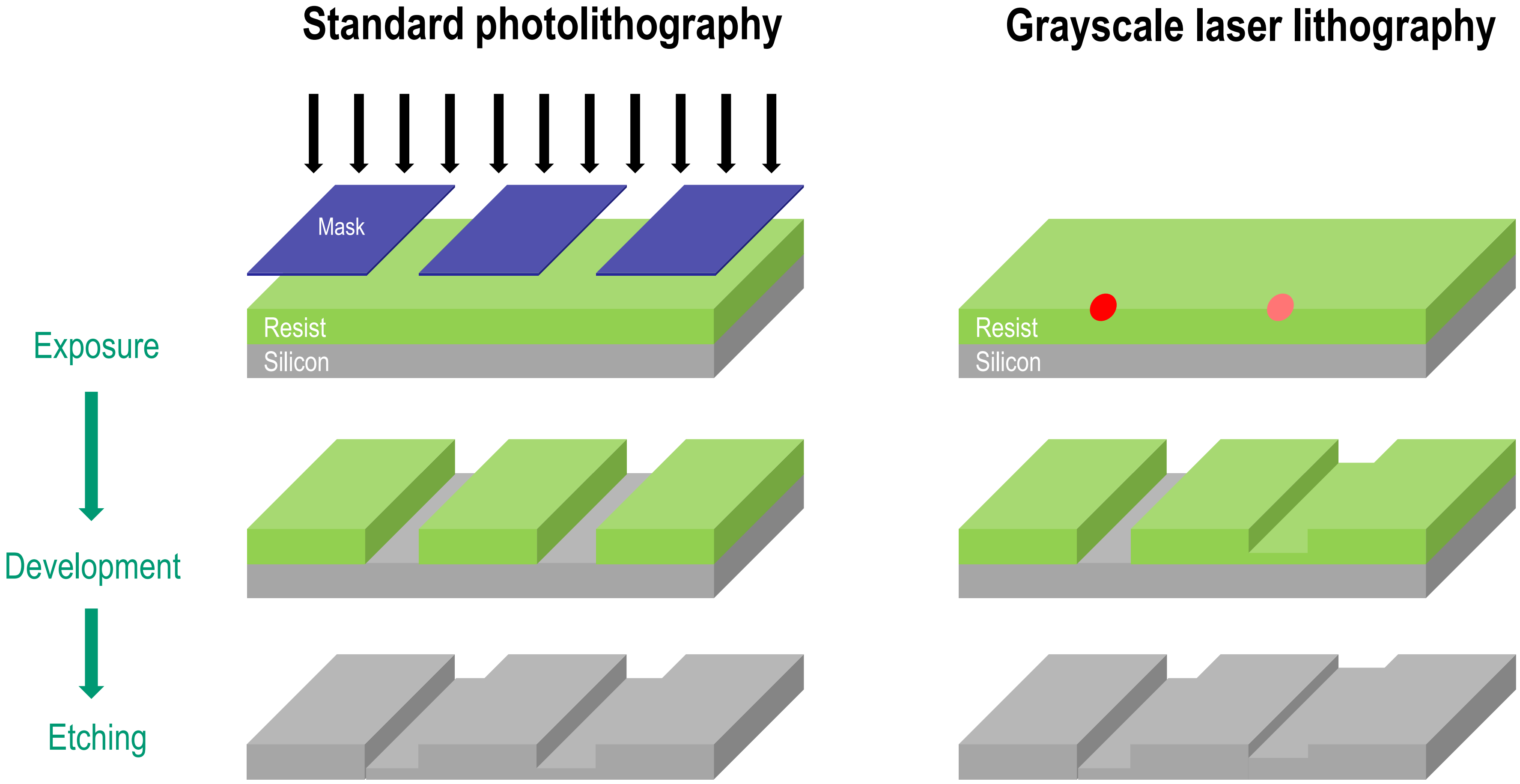
Openings

→ **3D**

Microfluidics FOR fabrication

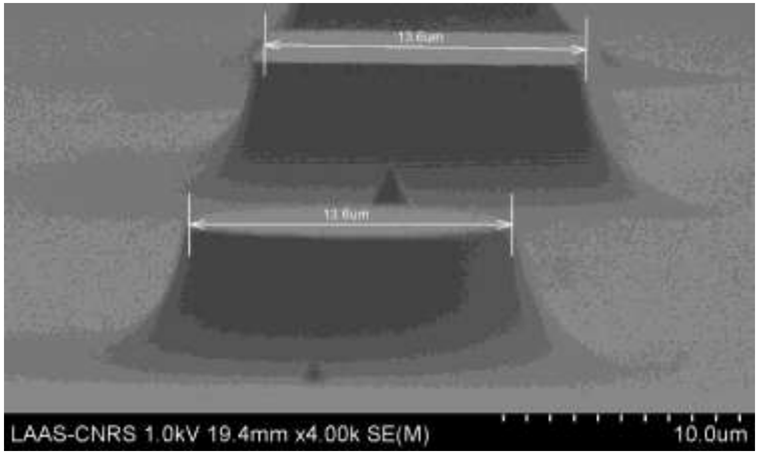
“2.5 D” by gray scale lithography

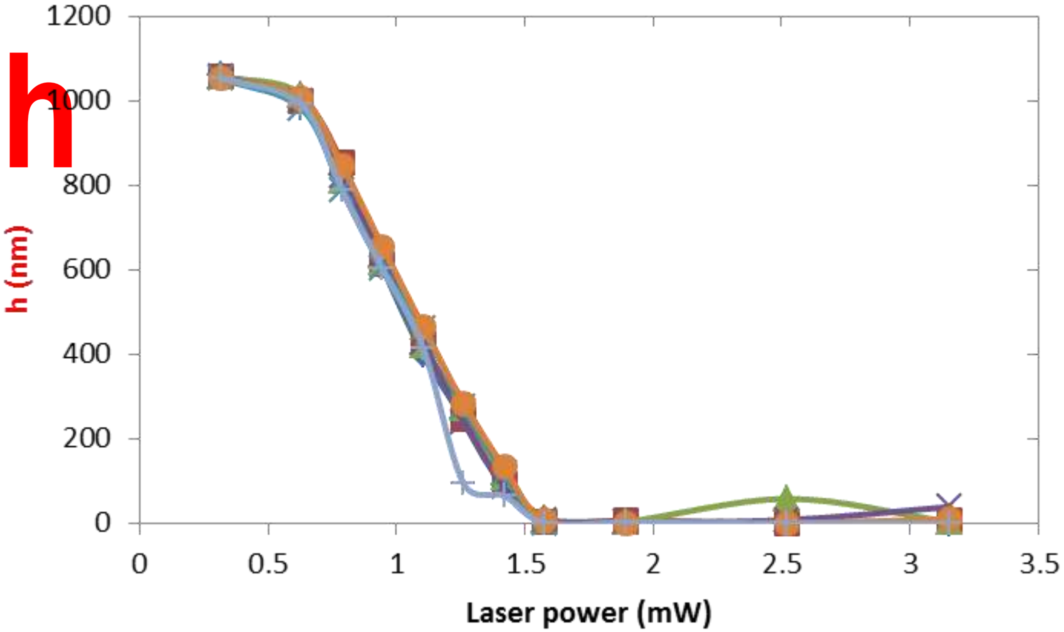
→ variable depth



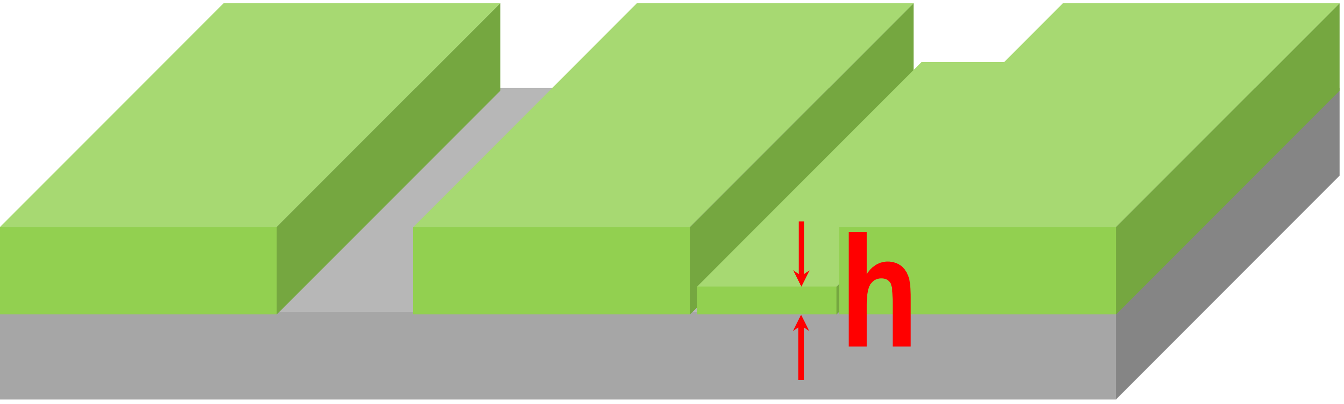
Massadi, Naillon - LAAS

“2.5 D” by gray scale lithography



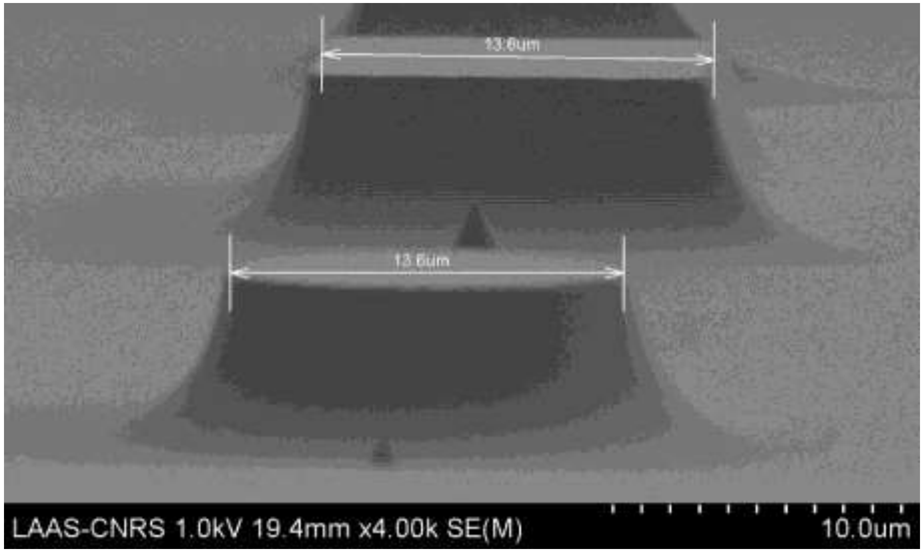


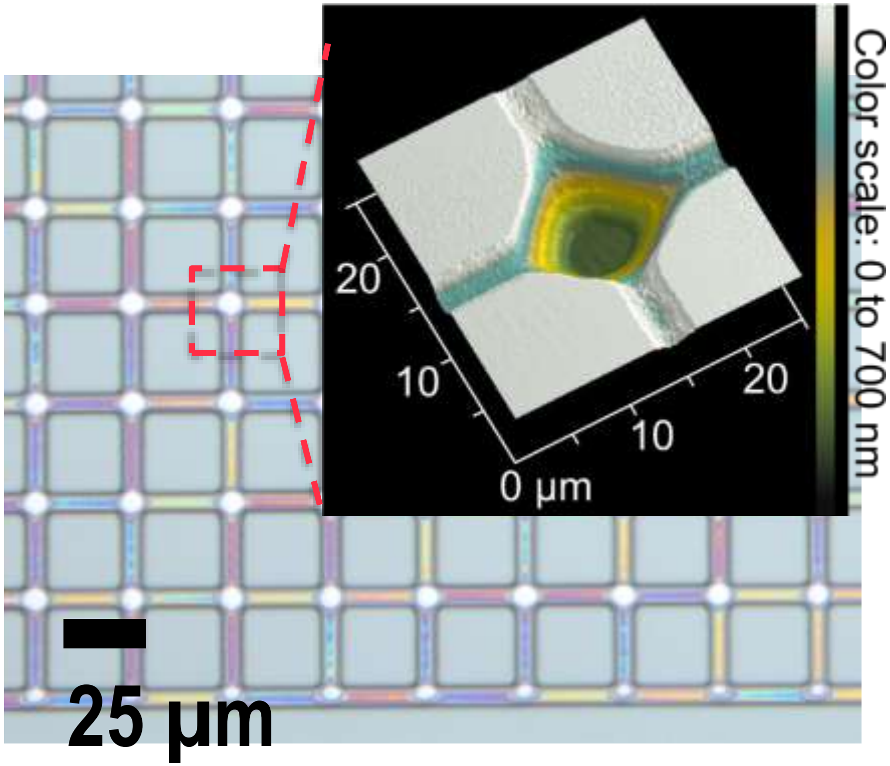
Power

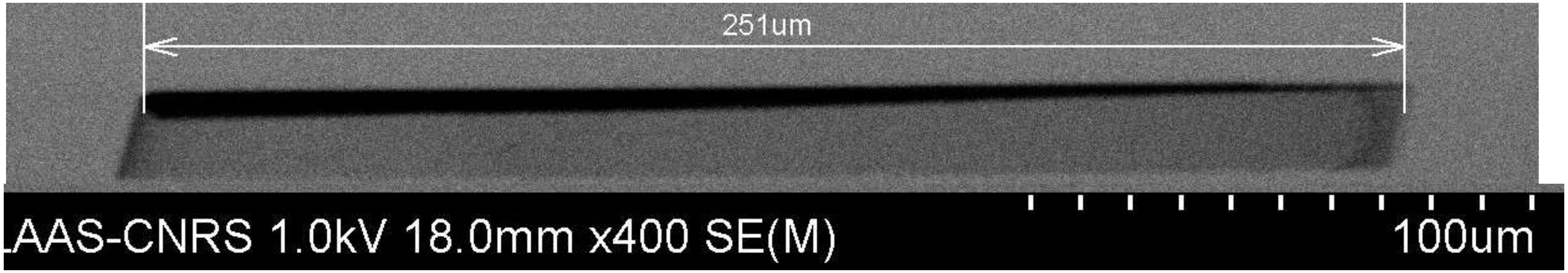


Massadi, Naillon - LAAS

“2.5 D” by gray scale lithography





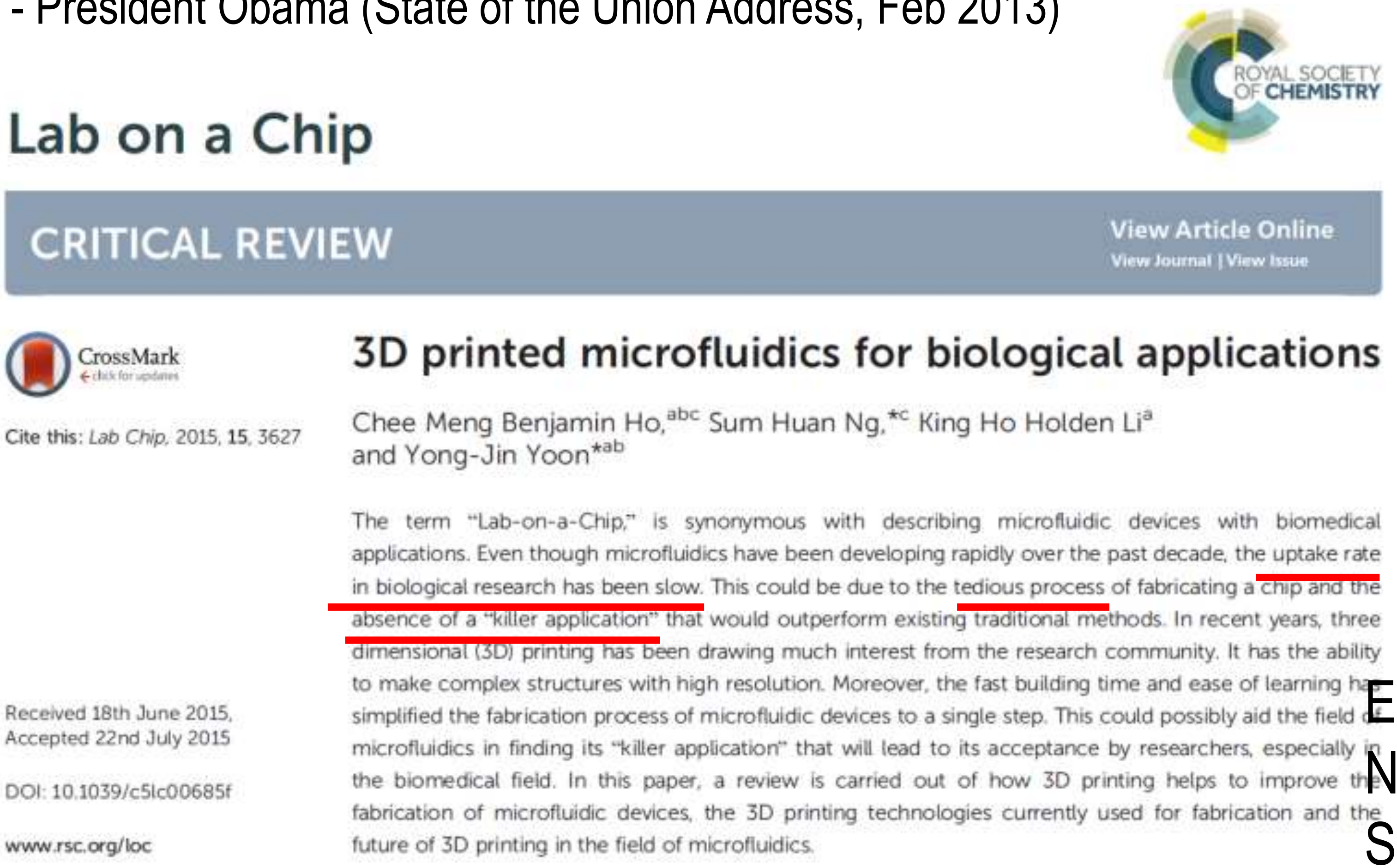


Massadi, Naillon - LAAS

3D printing

“3D printing has the potential to revolutionize the way we make almost everything”

- President Obama (State of the Union Address, Feb 2013)



ROYAL SOCIETY OF CHEMISTRY

Lab on a Chip

CRITICAL REVIEW

View Article Online
View Journal | View Issue

CrossMark

Cite this: *Lab Chip*, 2015, **15**, 3627

3D printed microfluidics for biological applications

Chee Meng Benjamin Ho,[abc] Sum Huan Ng,*[c] King Ho Holden Li[a] and Yong-Jin Yoon*[ab]

The term “Lab-on-a-Chip,” is synonymous with describing microfluidic devices with biomedical applications. Even though microfluidics have been developing rapidly over the past decade, the uptake rate in biological research has been slow. This could be due to the tedious process of fabricating a chip and the absence of a “killer application” that would outperform existing traditional methods. In recent years, three dimensional (3D) printing has been drawing much interest from the research community. It has the ability to make complex structures with high resolution. Moreover, the fast building time and ease of learning ha simplified the fabrication process of microfluidic devices to a single step. This could possibly aid the field o microfluidics in finding its “killer application” that will lead to its acceptance by researchers, especially i the biomedical field. In this paper, a review is carried out of how 3D printing helps to improve th fabrication of microfluidic devices, the 3D printing technologies currently used for fabrication and the future of 3D printing in the field of microfluidics.

Received 18th June 2015,
Accepted 22nd July 2015

DOI: 10.1039/c5lc00685f

www.rsc.org/loc

Resolution
>>10 µm

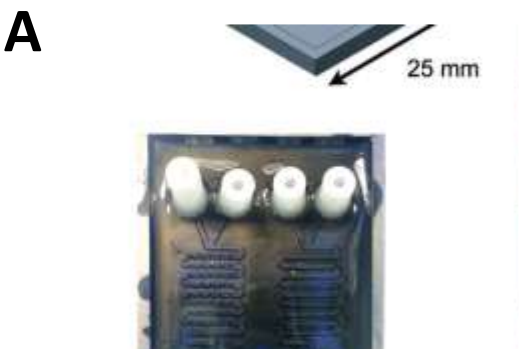
Exception,
Nanoscribe
Sub-µm but
Low speed,
small size, Price…

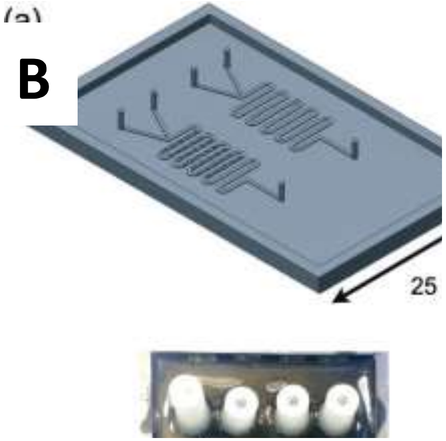
Ho, LOC 2015

L Malaquin

3D printing for microfluidics

- **Master fabrication for molding**

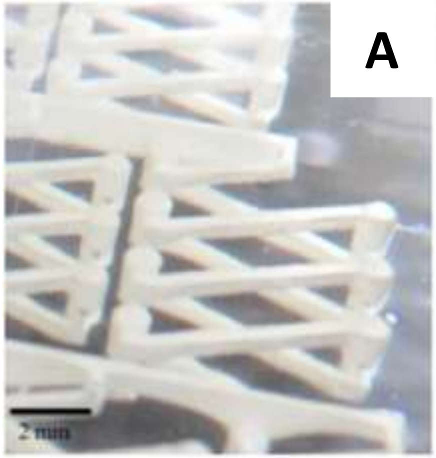


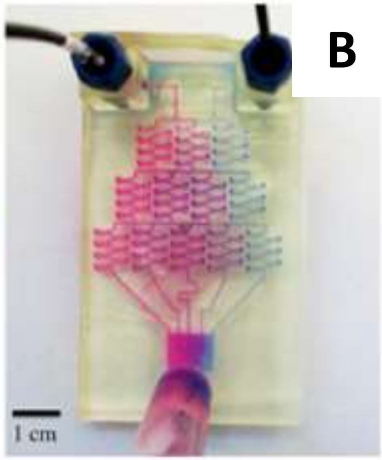


G. Comina, A. Suska and D. Filippini. *PDMS lab-on-a-chip fabrication using 3D printed templates.* Lab Chip 2014, 14, 424-430.

- **Direct fabrication of devices**

A. I. Shallan, P. Smejkal, M. Corban, R. M. Guijt and M. C. Breadmore. *Cost-effective three-dimensional printing of visibly transparnet microchips within minutes.* Anal. Chem. 2014,86, 3124-3130.

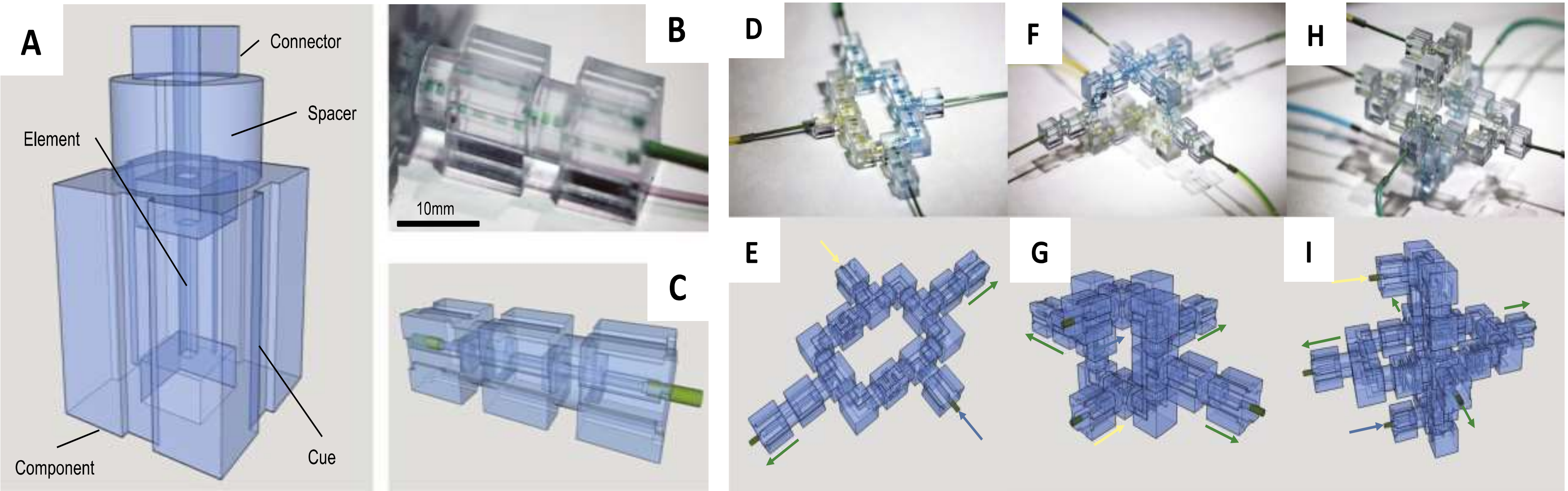




Source: L Malaquin

3D printing for microfluidics

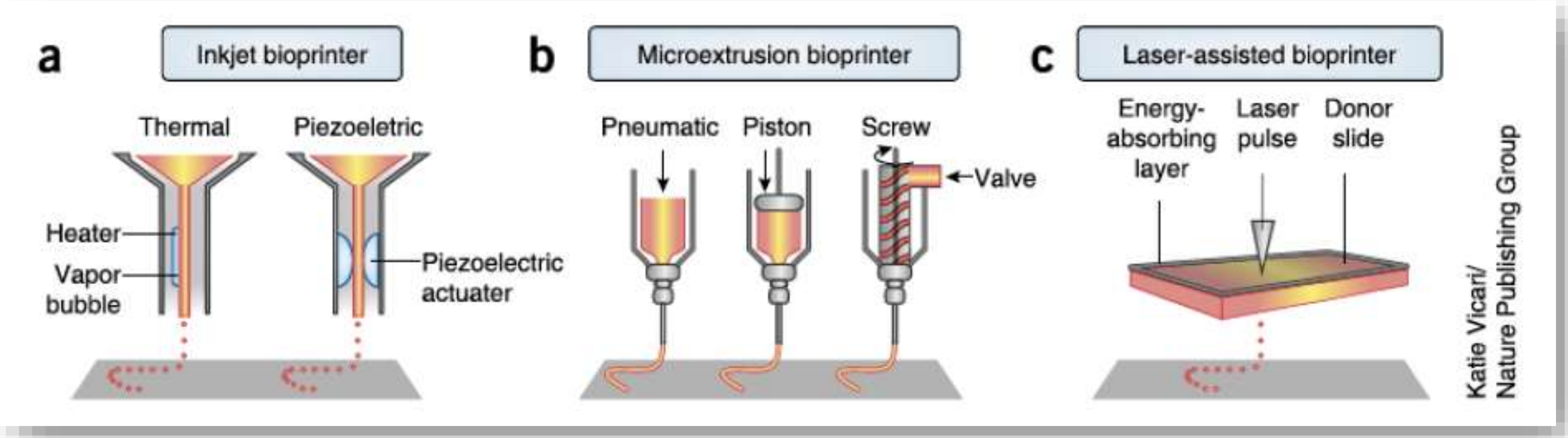
LEGO-like microfluidics



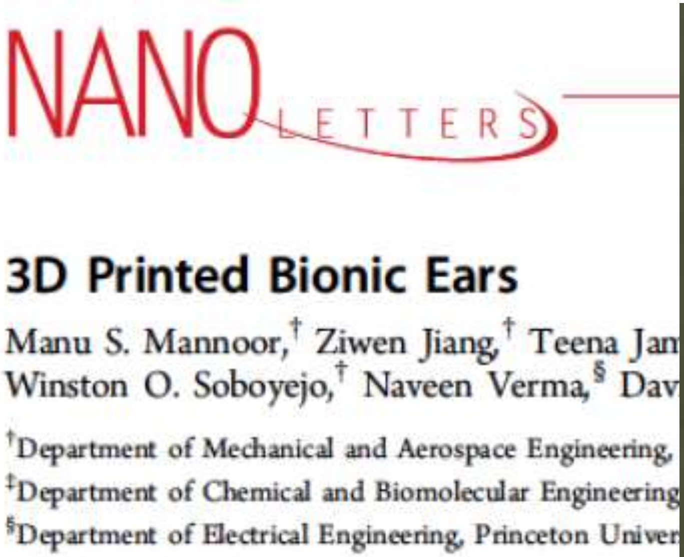
K. C. Bhargava, B. Thompson and N. Malmstadt. *Discrete elements for 3D microfluidics*. PNAS 2014

Source: L Malaquin

3D Bioprinting: tissues and organs



Murphy, S. V., & Atala, A. (2014). 3D bioprinting of tissues and organs. Nature biotechnology


NANO LETTERS

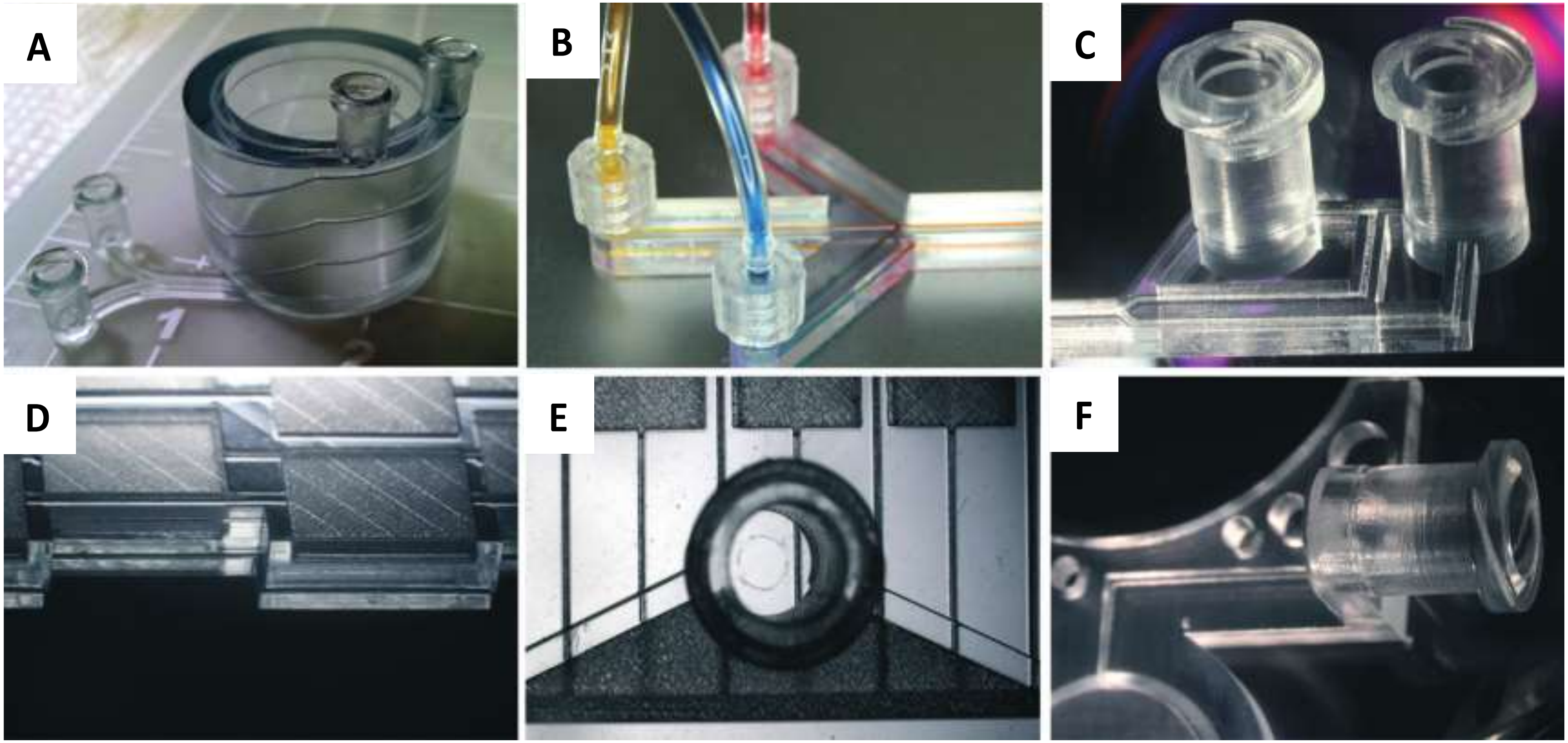
3D Printed Bionic Ears

Manu S. Mannoor,[†] Ziwen Jiang,[†] Teena Jan
Winston O. Soboyejo,[†] Naveen Verma,[§] Dav

[†]Department of Mechanical and Aerospace Engineering,
[‡]Department of Chemical and Biomolecular Engineering
[§]Department of Electrical Engineering, Princeton Univer

3D printing for microfluidics

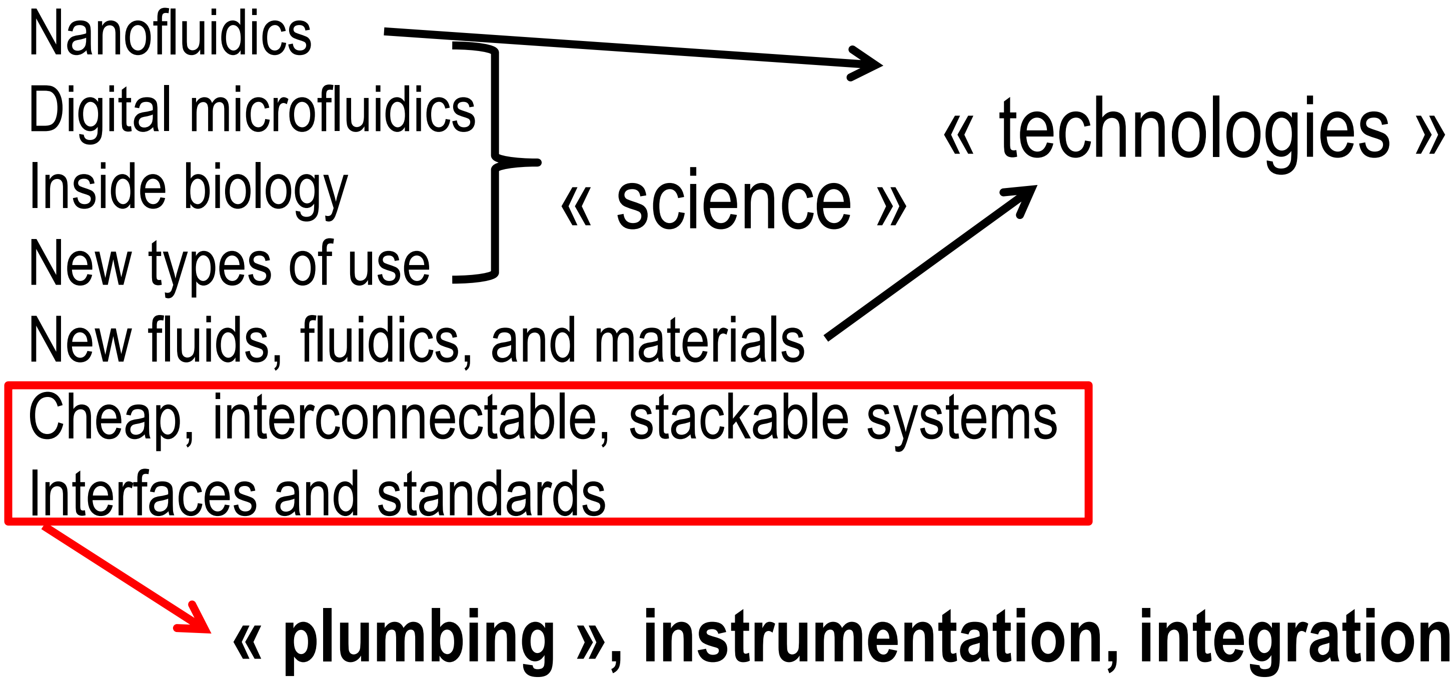
Solving the world to chip interface problem



O. H. Paydar, C.N. Parede, Y. Hwang, J. Paz, N.B. Shah and R.N. Candler. *Characterization of 3D-printed microfluidic chip interconnects with integrated O-rings.* Sensors and Actuators A : Physical 2014, 205, 199-203.

Among challenges: world-to-chip interface

edito Lab Chip 2011,
GM Whitesides (chair, ed Board): « What comes next? », 7 topics



- Nanofluidics
- Digital microfluidics
- Inside biology
- New types of use
- New fluids, fluidics, and materials
- Cheap, interconnectable, stackable systems
- Interfaces and standards

« science »

« technologies »

« plumbing », instrumentation, integration

Standard needed?

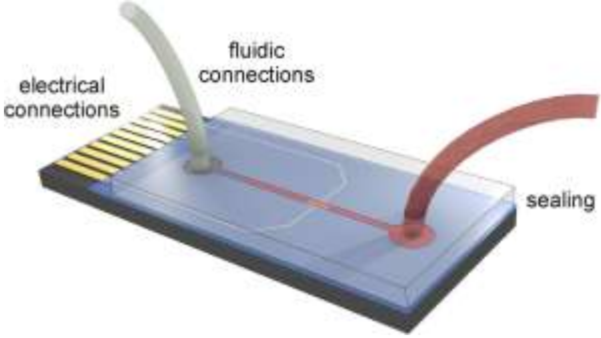
World-chip interface

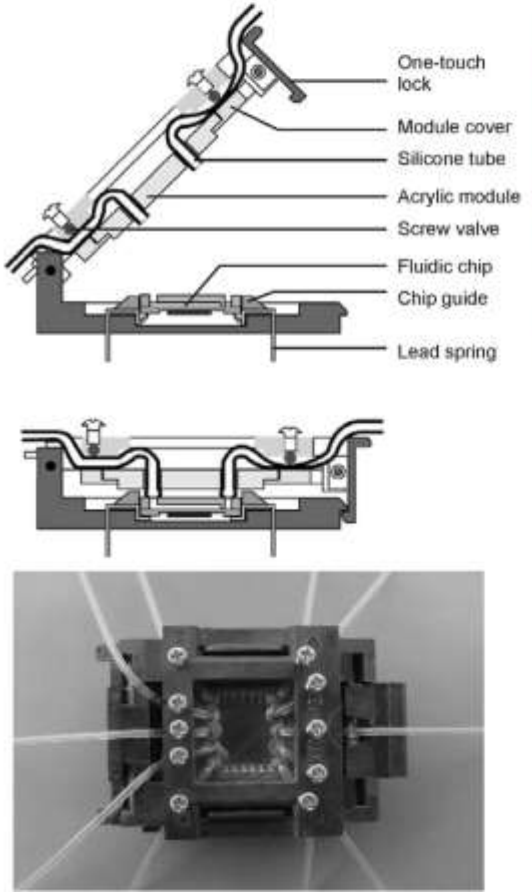
Review Article Microelec Eng 2015

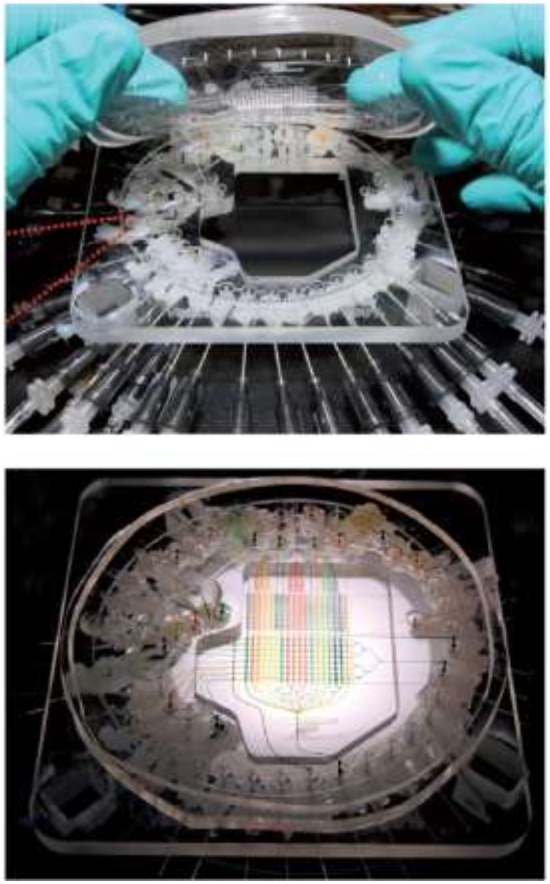
Lab-on-a-chip devices: How to close and plug the lab?

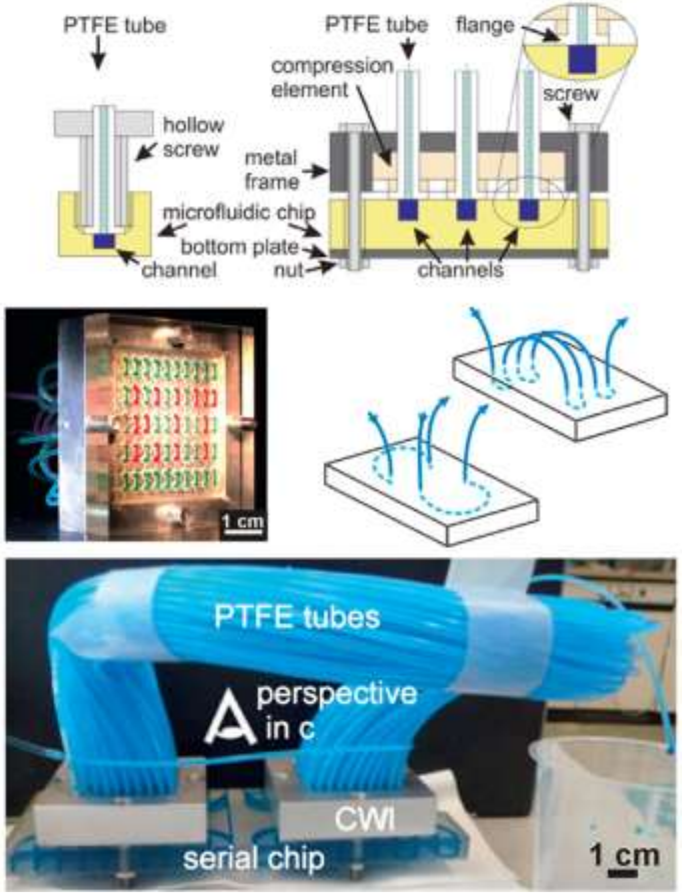
Yuksel Temiz *, Robert D. Lovchik, Govind V. Kaigala, Emmanuel Delamarche *

IBM Research GmbH, Säumerstrasse 4, 8803 Rüschlikon, Switzerland




(a) Socket with built-in valves


(b) Vacuum manifold


(c) Multichannel Chip-to-World Interface

IV. Openings

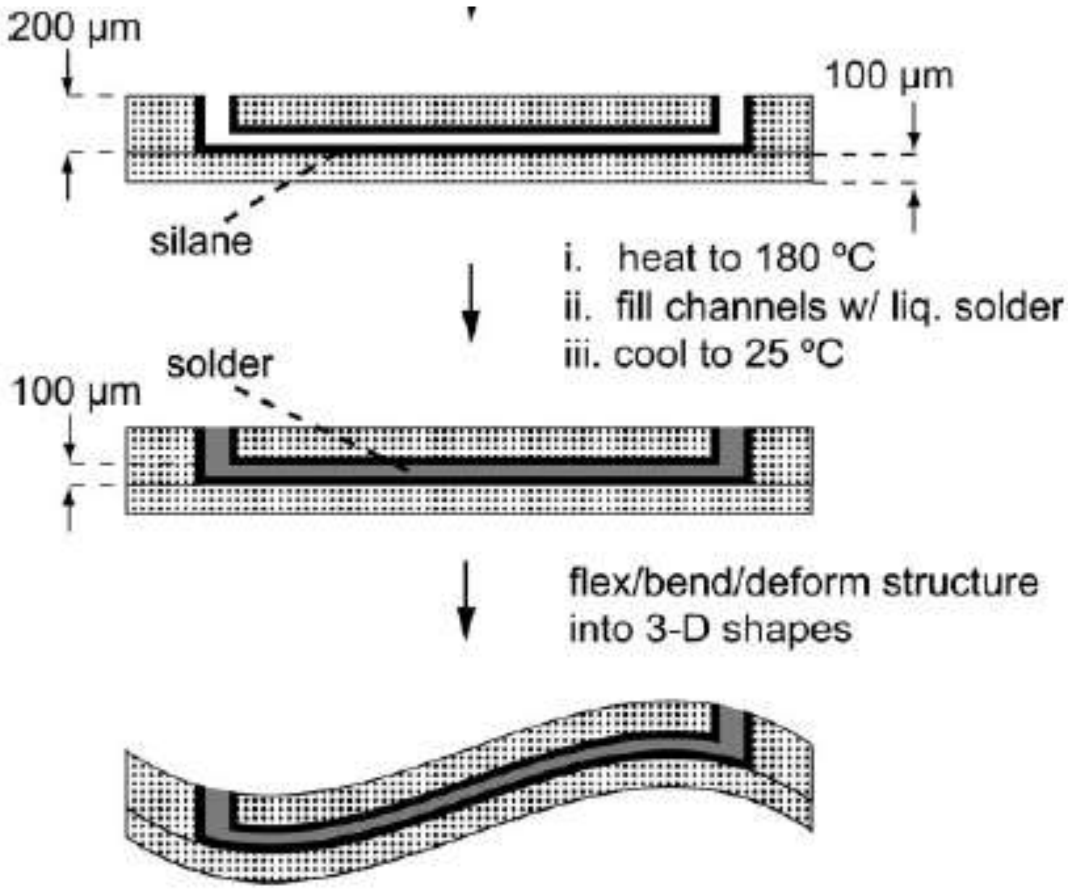
3D?

→ **Microfluidics FOR fabrication**

Electrode integration: microsolidics

Note on classical technologies: Metal evaporation, Electrochemical growth, Conductive ITO layer

Microsolidics: Fill microchannel with metallic solder, then dry

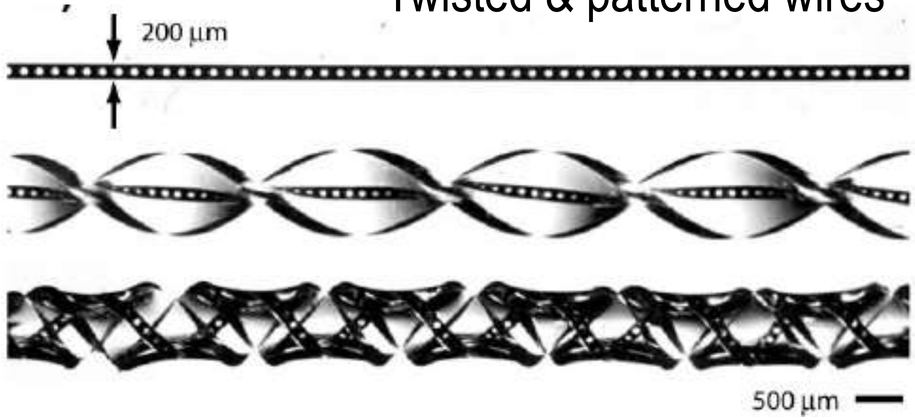


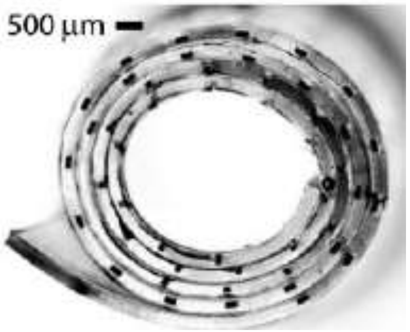
Best Solder is Indium:
Low Melting 158°C, low hardness

Siegel et al., Adv Mater. (2007)

Electrode integration: electronics

Twisted & patterned wires





PDMS/Indium tasting rolled cake

Siegel et al., Adv Mater. (2007)

Soft, reconfigurable electronics

Cite this: *Lab Chip*, 2012, **12**, 2782–2791

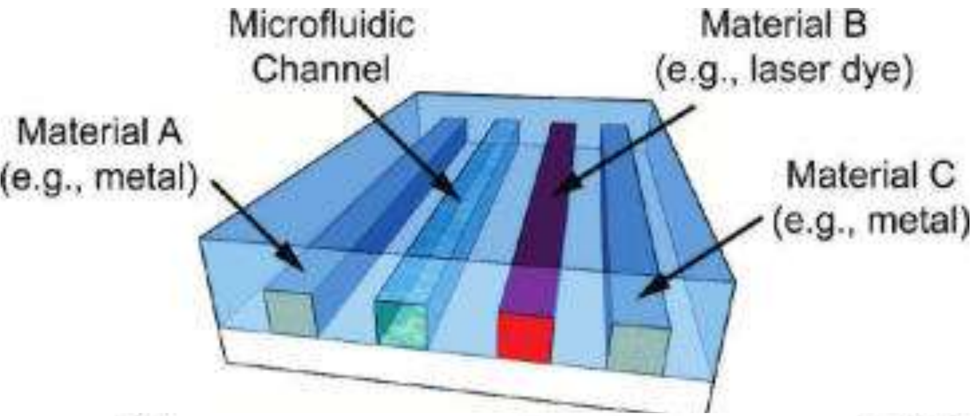
www.rsc.org/loc

CRITICAL REVIEW

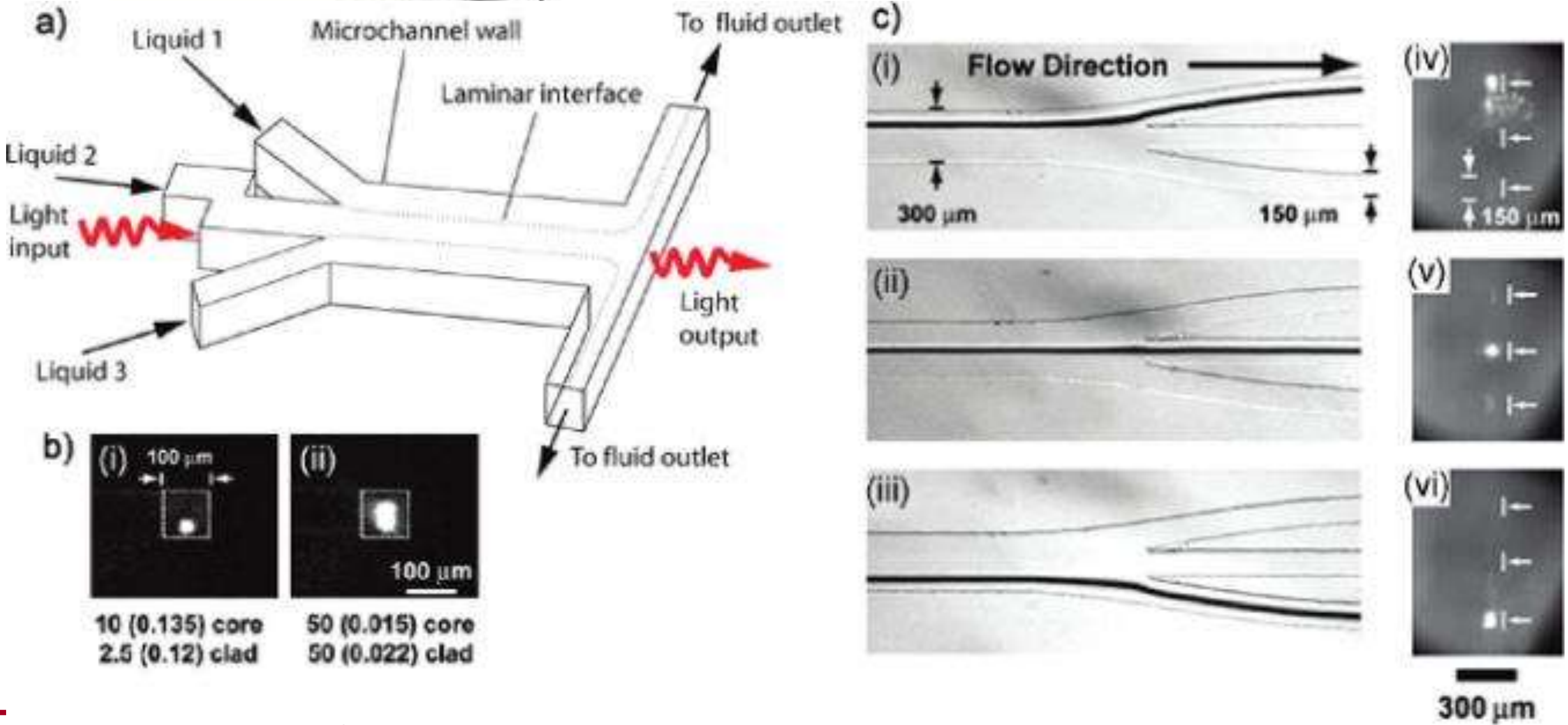
Microfluidic electronics

Shi Cheng*[a,b] **and Zhigang Wu***[a]

Cofabrication (microfluidic assisted fabrication)



Ex: optofluidic waveguide

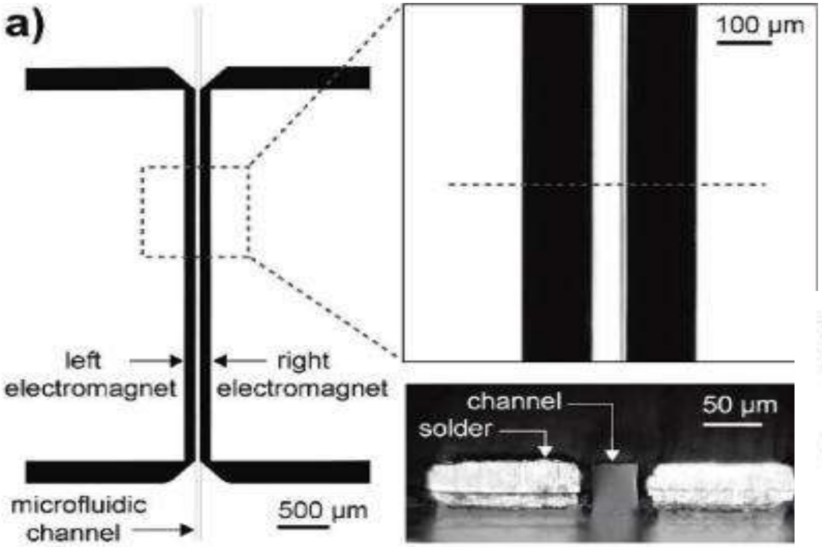


10 (0.135) core
2.5 (0.12) clad

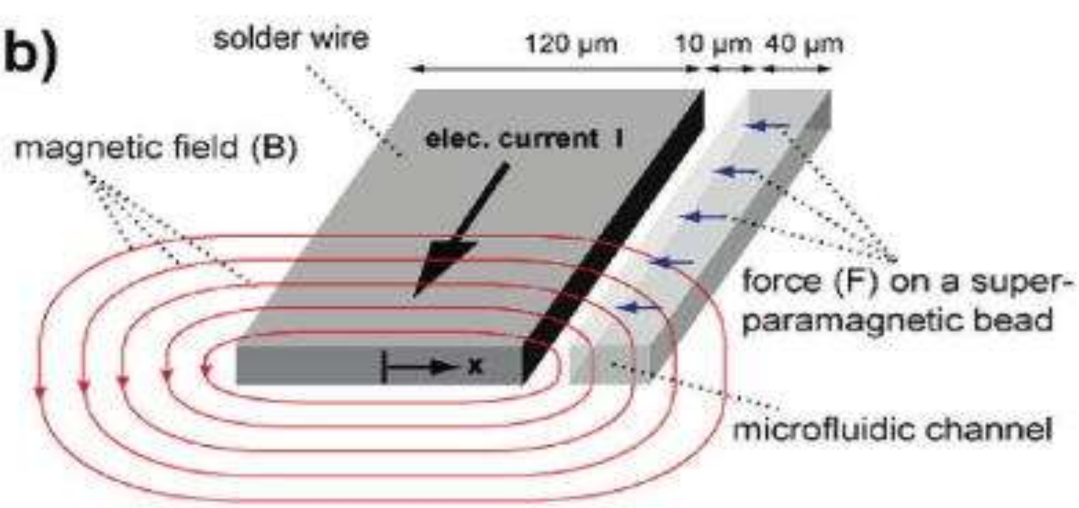
50 (0.015) core
50 (0.022) clad

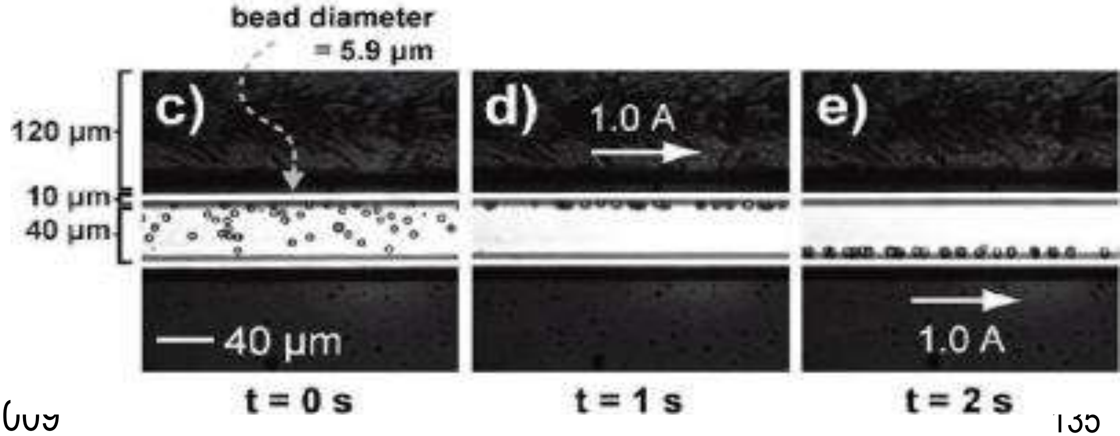
Siegel, Whitesides Accounts Chemical Research 2009

Cofabrication (microfluidic assisted fabrication)



Ex: magnets

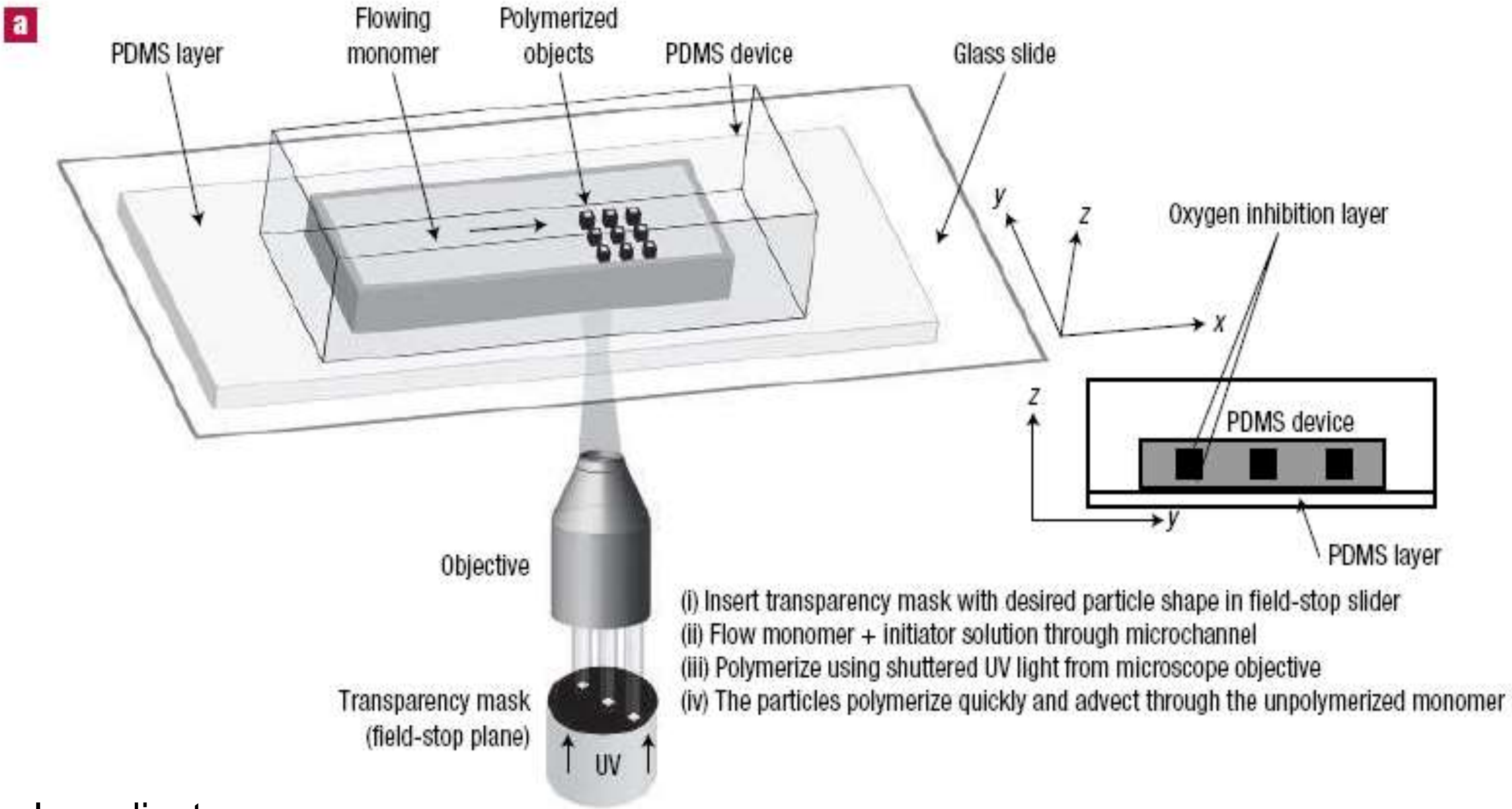




Siegel, Whitesides Accounts Chemical Research 2009

Continuous flow lithography

microfluidics = fabrication tool ! → Continuous fabrication or microparticles



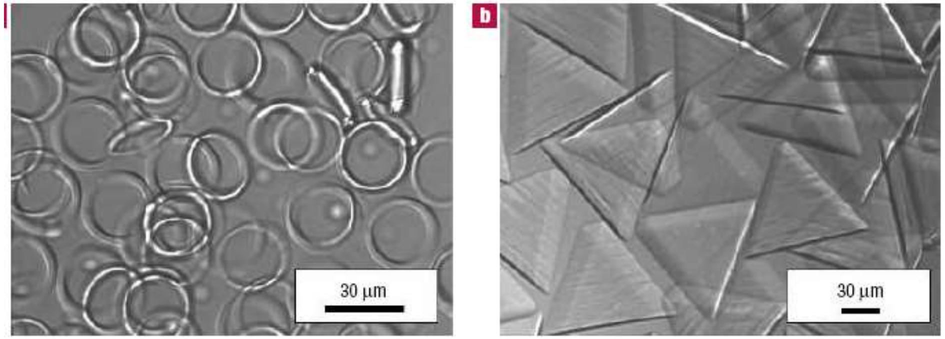
(i) Insert transparency mask with desired particle shape in field-stop slider
(ii) Flow monomer + initiator solution through microchannel
(iii) Polymerize using shuttered UV light from microscope objective
(iv) The particles polymerize quickly and advect through the unpolymerized monomer

Ingredients:
*Flow photosensitive prepolymers
*Photopolymerization through an optical mask (flash exposition)
*Inhibition of reaction by oxygen, PDMS permeable to O2: continue flowing !

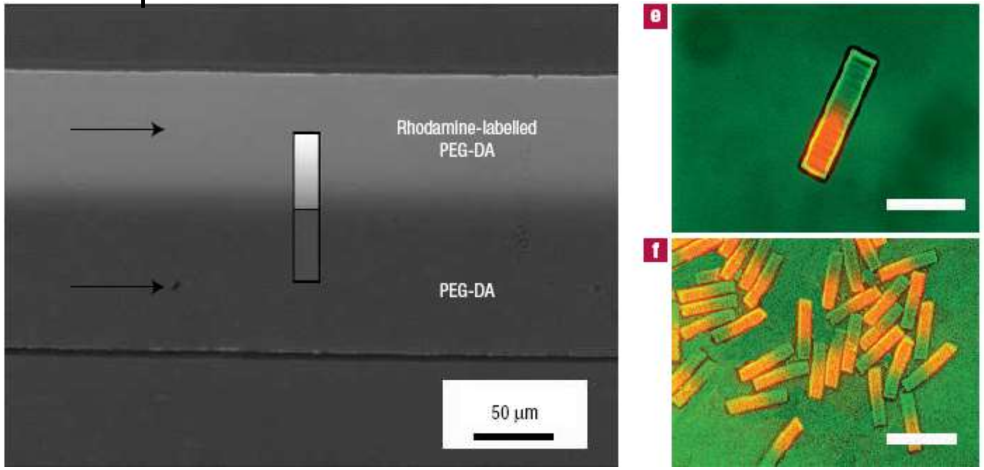
Dendukuri et al (Doyle, MIT) *Nature Materials* 2006

Continuous Flow lithography

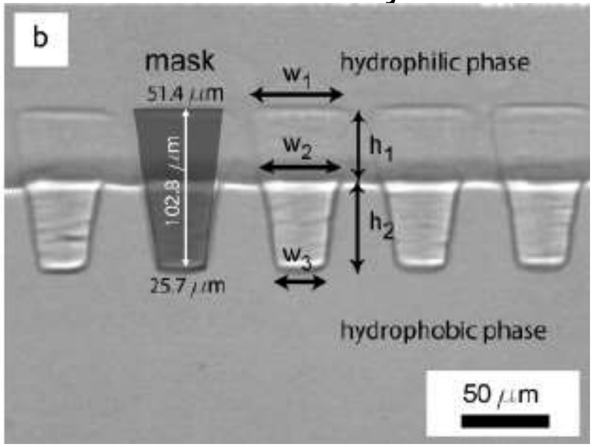
Chosen shape

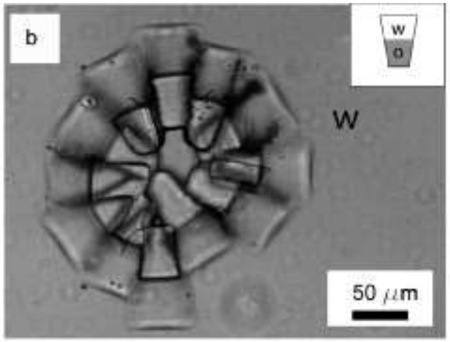


Janus particles



Amphiphilic Polymeric Microparticles
And micelle-like assembly

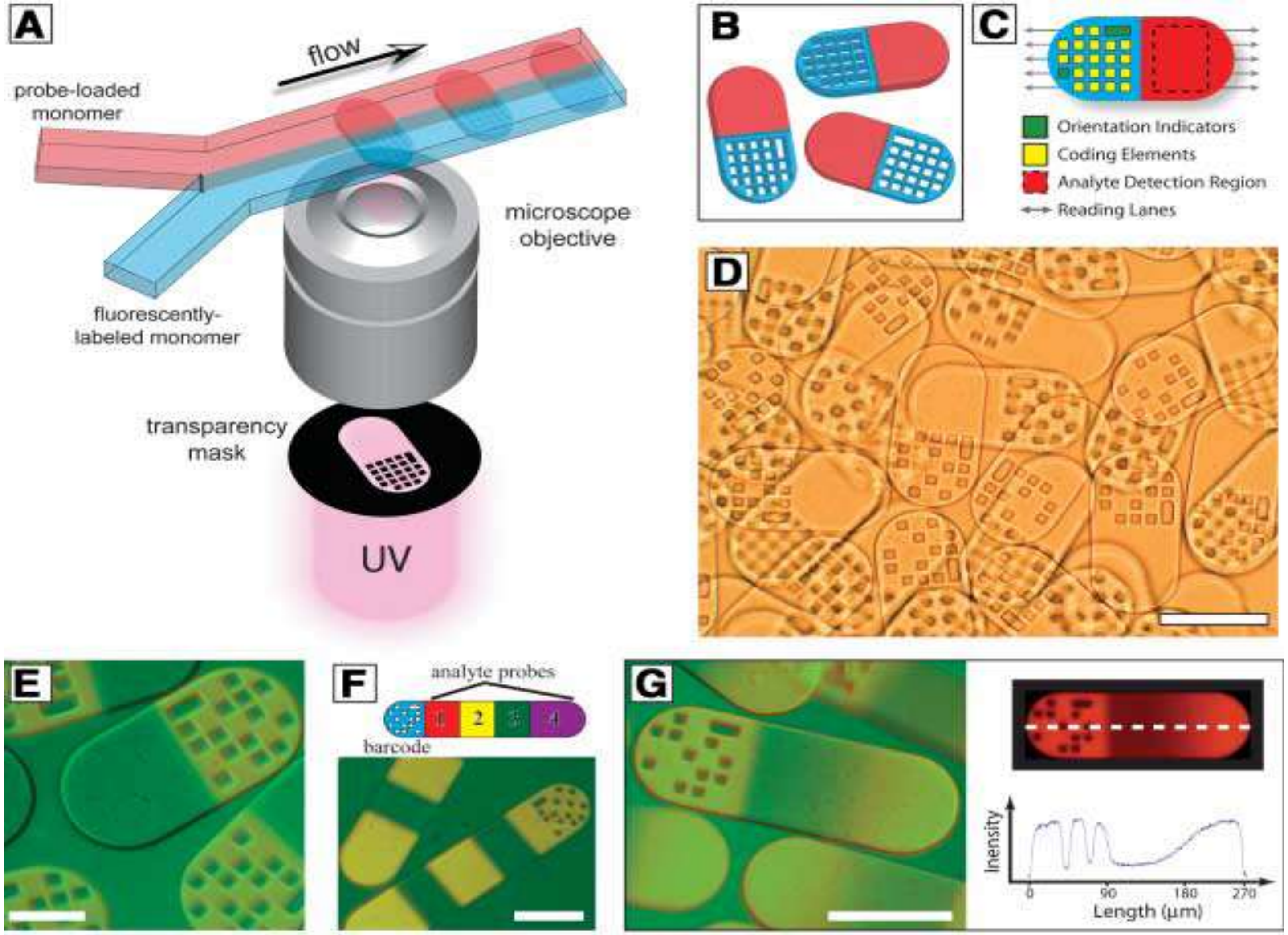




→ Many shapes and functions

Dendukuri et al (Doyle, MIT) *Nature Materials* 2006, Langmuir 2007

Flow Lithography: encoded microparticles



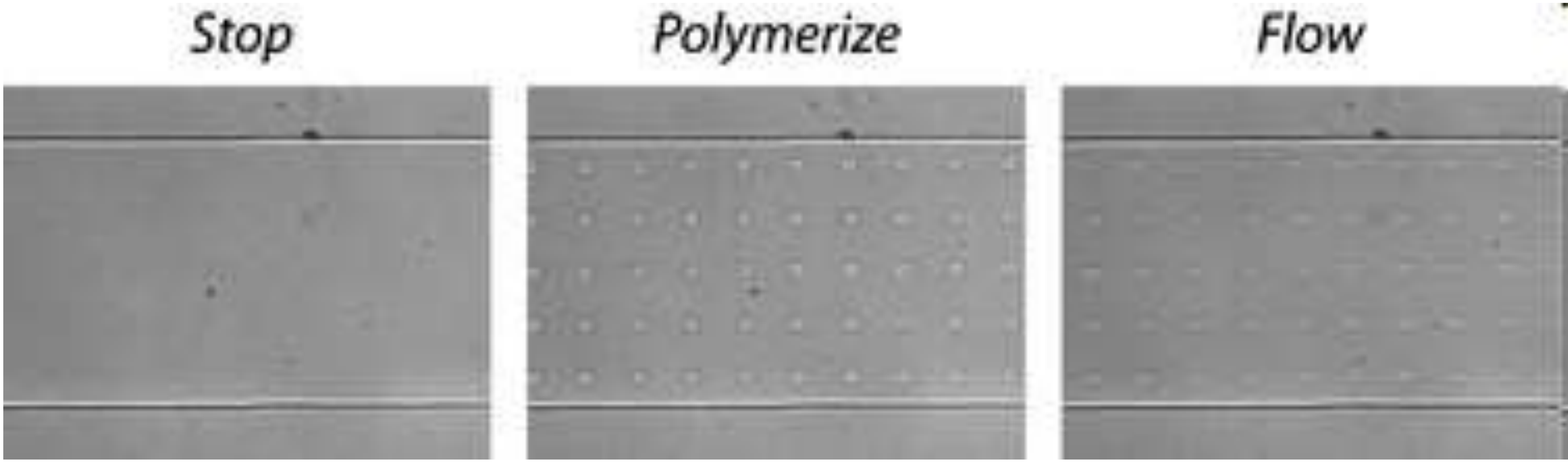
(1) Fabrication: 1/2 identifyer (2D barcode), 1/2 functional material
(2) Analysis for a mixture of particles: high throughput (« Lab On Chip » !)

Pregibon, Toner, Doyle, (MIT), *Science* 2007

Flow Lithography: ameliorations and alternatives

- **Stop-flow lithography**

Faster, higher throughput

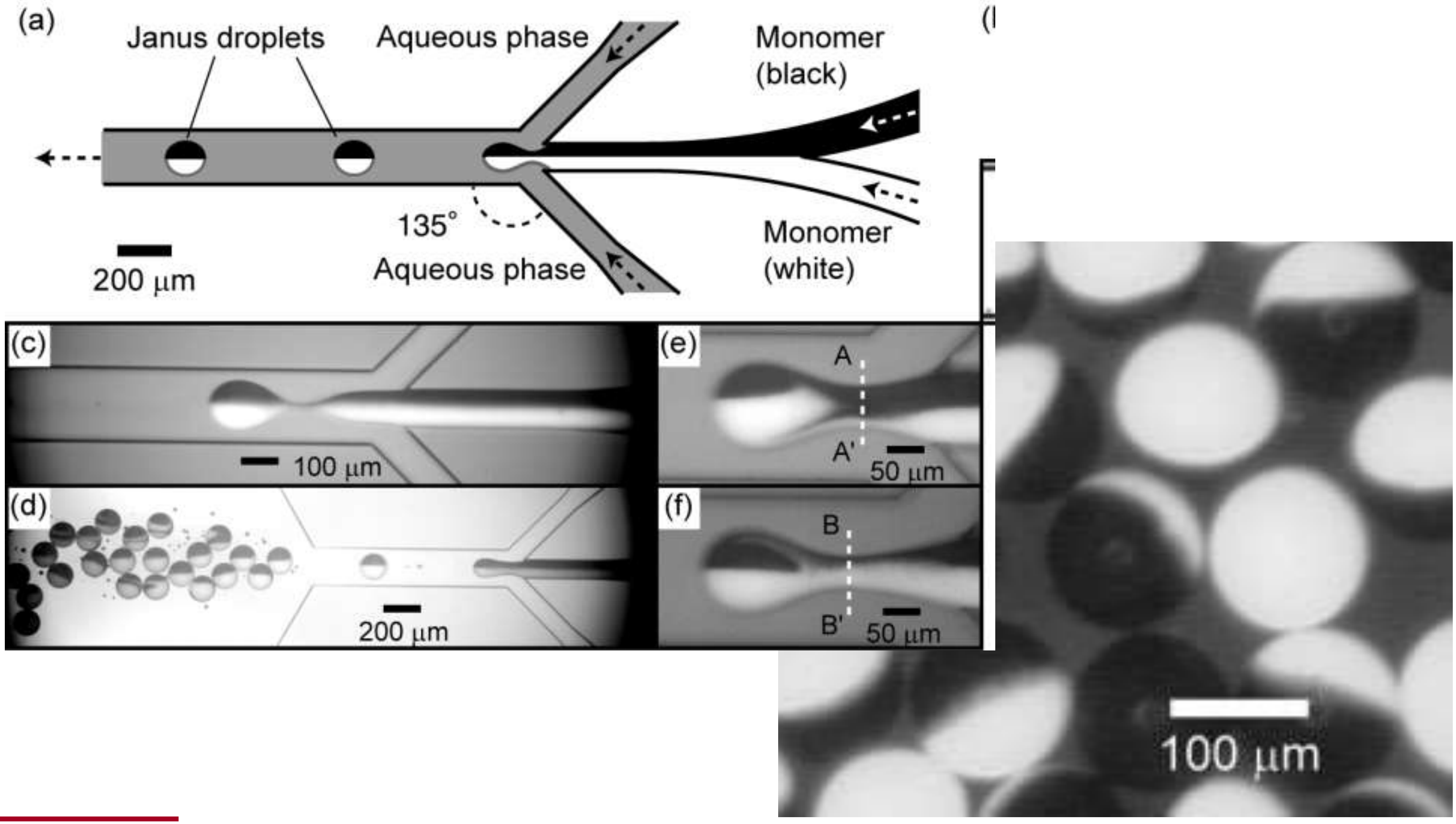


http://www.rsc.org/suppdata/LC/b7/b703457a/b703457a.mpg

Dendukuri et al *Lab Chip* 2007

Microfluidic assisted fabrication from droplets

- **Synthesis of Janus (« bicolor ») particles**

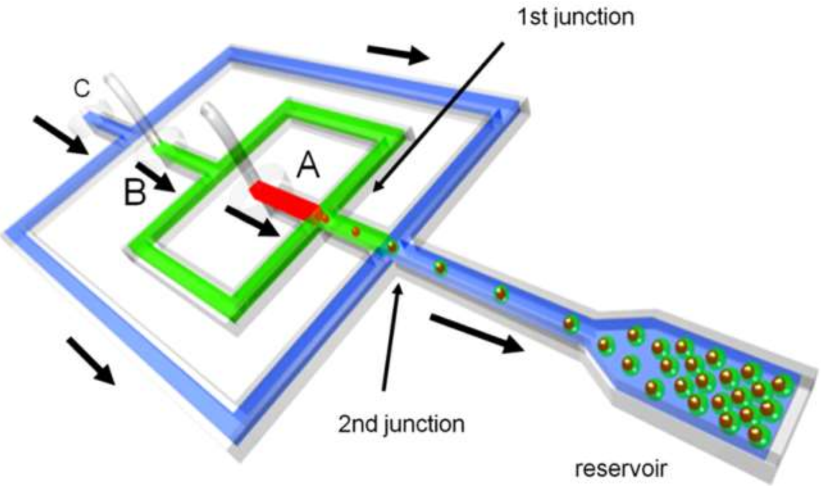


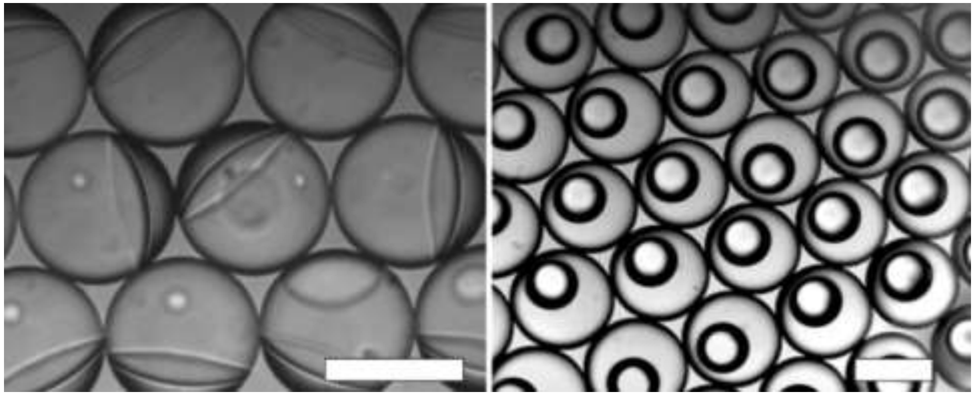
Nisisako *et al. Adv. Mater.* (2006)

Microfluidic assisted fabrication from droplets

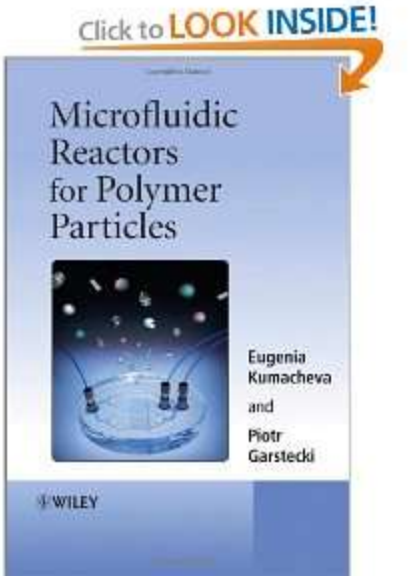
- **Multiple emulsion**

**Tetradecane in
Tripropylèneglycol-diacrylate (TPGA) in
Water**





In-situ reticulation → possibly out of equilibrium patterns


Click to LOOK INSIDE!

Microfluidic
Reactors
for Polymer
Particles

Eugenia
Kumacheva
and
Piotr
Garstecki

WILEY

Pannacci *et al. PRL* (2008)

Conclusion & Opening…

➢ Many technologies

Choose Material & technology according to application & needs
(soft/hard, hydrophobic/philic, transparent, cost important, biocompatibility)

Keep it simple

Trends:
- Integration, Hybrid systems
- Biocompatible, chemically resistant polymers
- 3D printing

➢ Not evoked

Nanofluidics

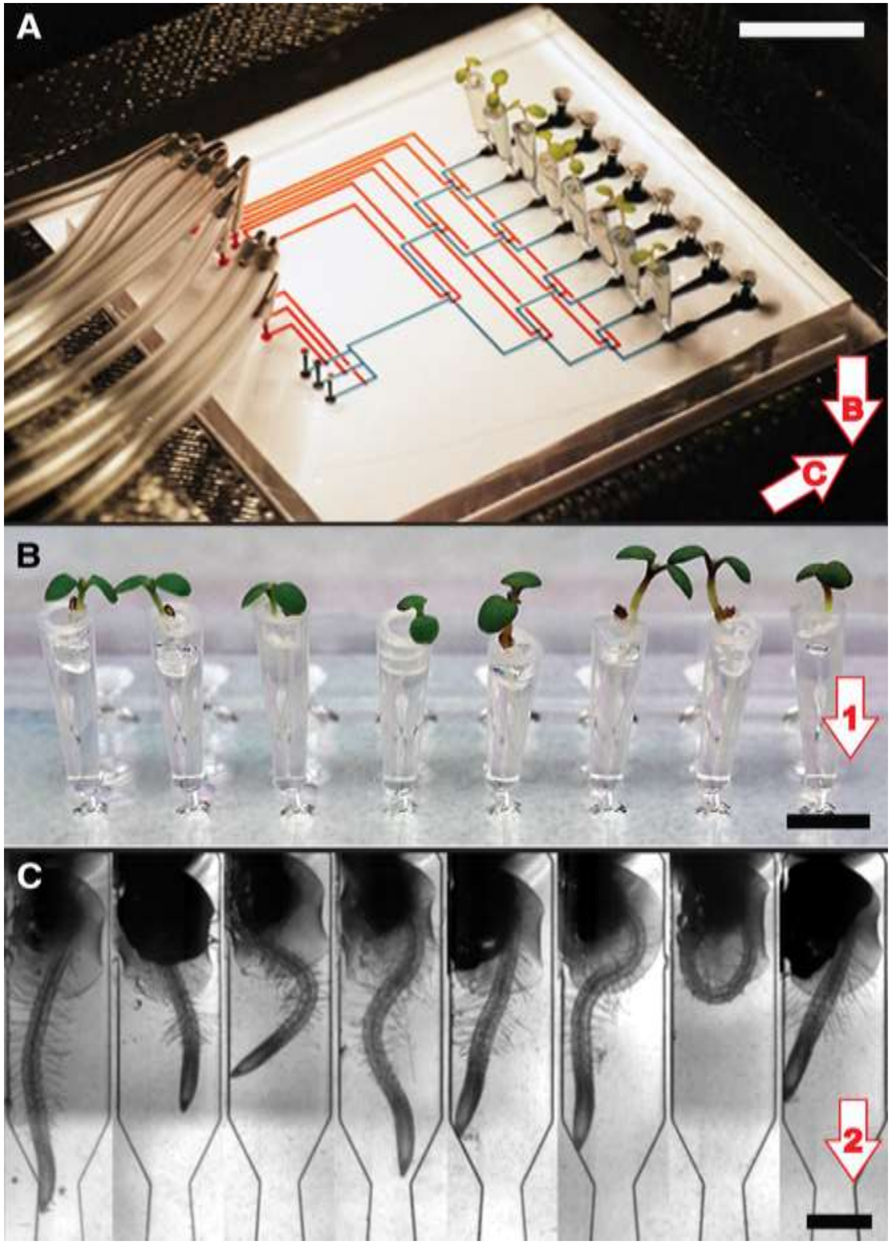
Other techniques (laser ablation, sand blasting, precision micromachining…)

World to chip interface (dark side of microfluidics)

Bottom-up approach (here top-down)

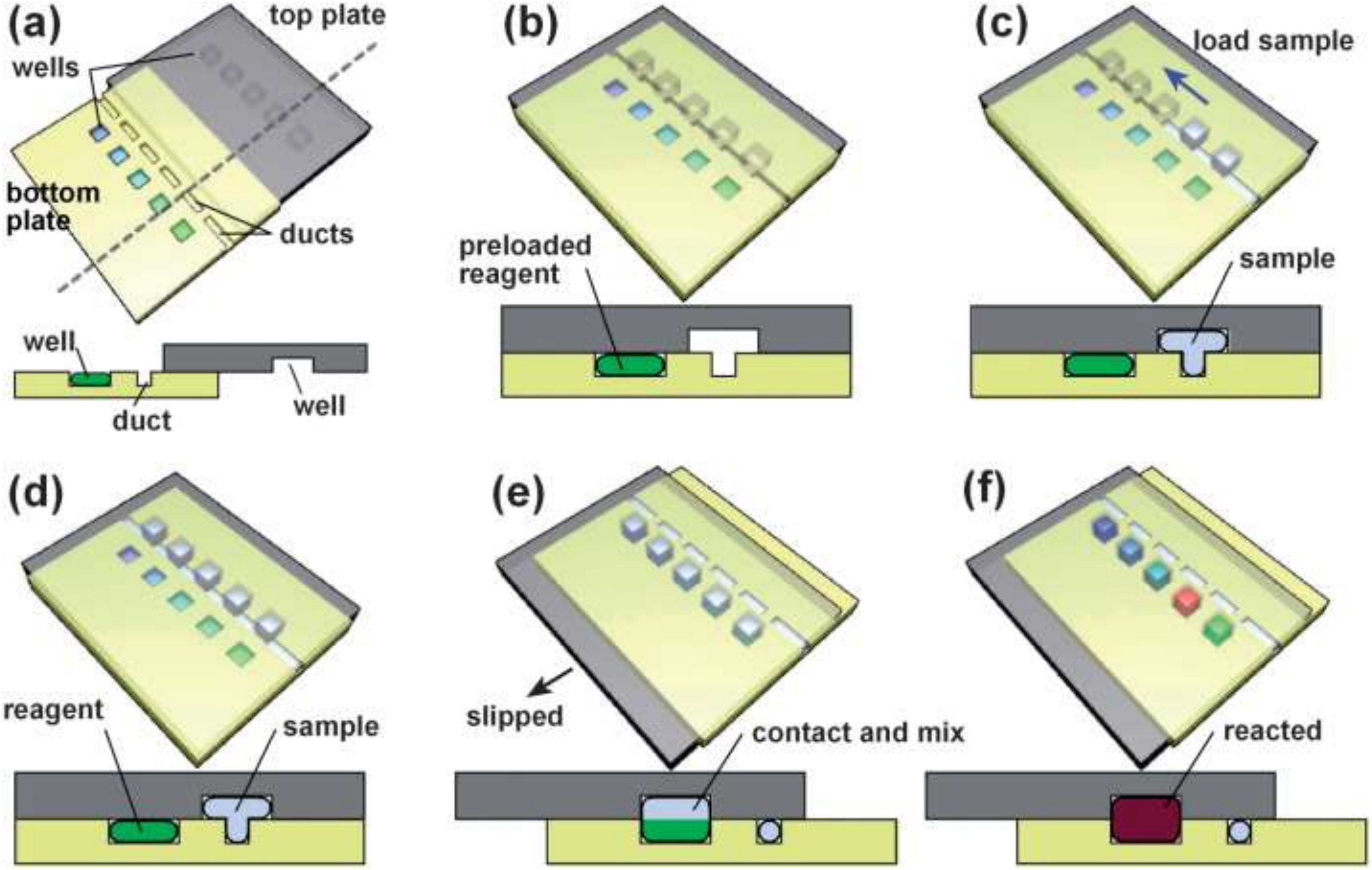
Integration: the root chip

Grossmann, Quake, Plant Cell 2011
regulation of microenvironment



Platform: the slip chip

Slip Chip, LOC2009 Du, Ismagilov



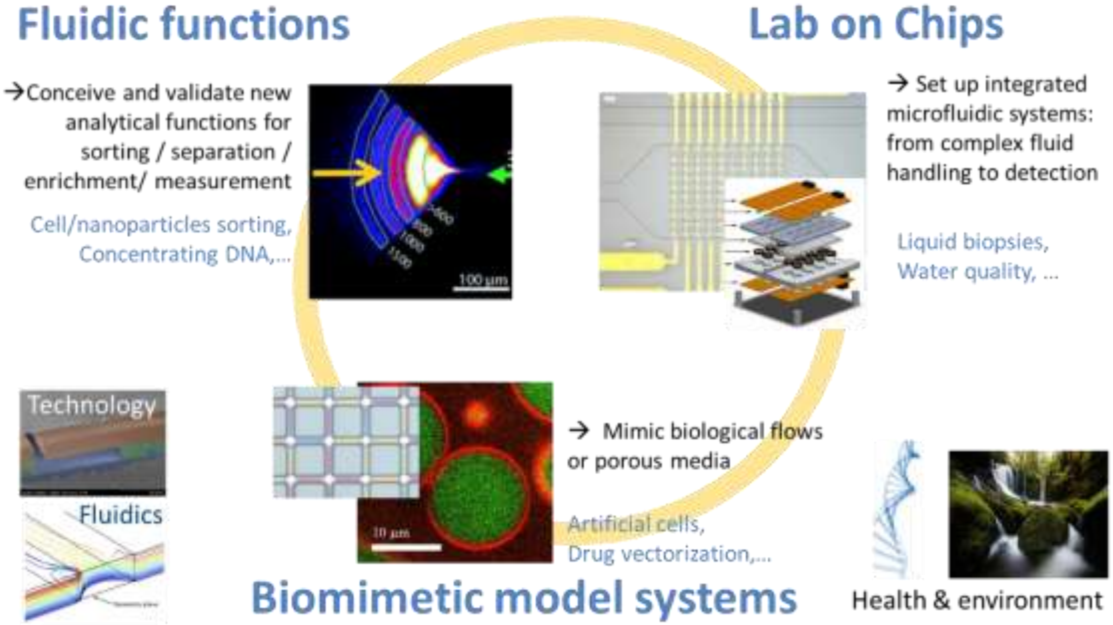
Thank you!

MILE team at LAAS: Micro/nanofluidics for Life Science and Environment

TEAM service at LAAS

L Malaquin

J Espeut
+ Orga Microfluidics'19



Fluidic functions

→Conceive and validate new analytical functions for sorting / separation / enrichment/ measurement

Cell/nanoparticles sorting, Concentrating DNA,...

Lab on Chips

→ Set up integrated microfluidic systems: from complex fluid handling to detection

Liquid biopsies, Water quality, ...

→ Mimic biological flows or porous media

Artificial cells, Drug vectorization,...

Biomimetic model systems

Health & environment