FABRICATION 1
LECTURE 3

Tamás Pardy
TalTech Lab-on-a-Chip

13.01.2022

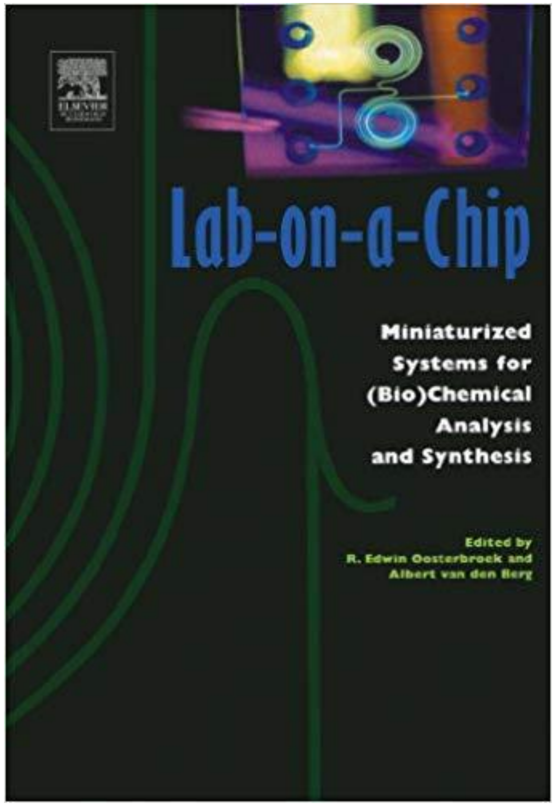
TALLINN UNIVERSITY
OF TECHNOLOGY

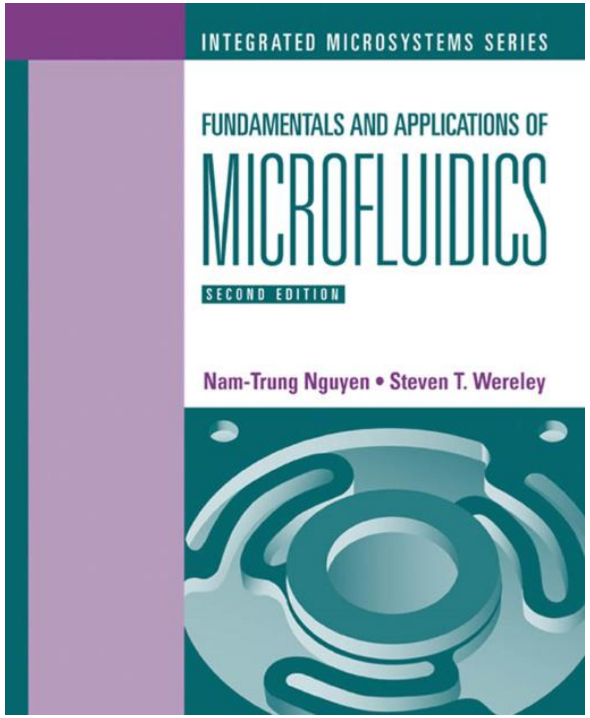
ADDITIONAL MATERIALS

- Lab-on-a-Chip. Miniaturized Systems for(Bio) Chemical Analysis and Synthesis
- **R. Edwin (editor)**
- ISBN: 978-0444511003

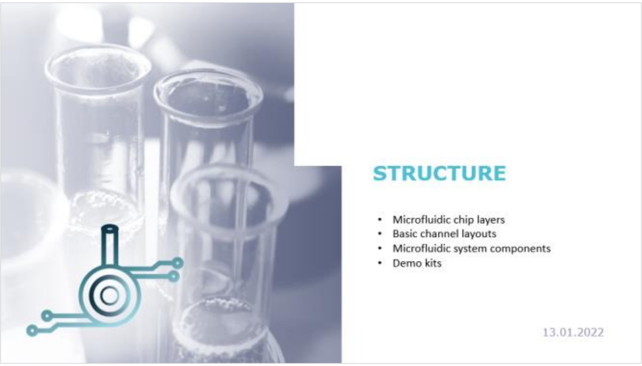
- Fundamentals and Applications of Microfluidics (2^{nd} edition) – **Chapter III**
- Nam-Trung Nguyen, Steven T. Wereley
- ISBN-10 1-58053-972-6
ISBN-13 978-1-58053-972-2

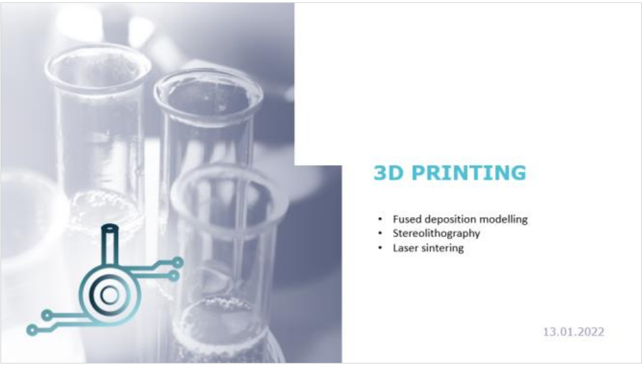
- **Additional materials:**
  - RSC Lab-on-a-Chip journal





OVERVIEW





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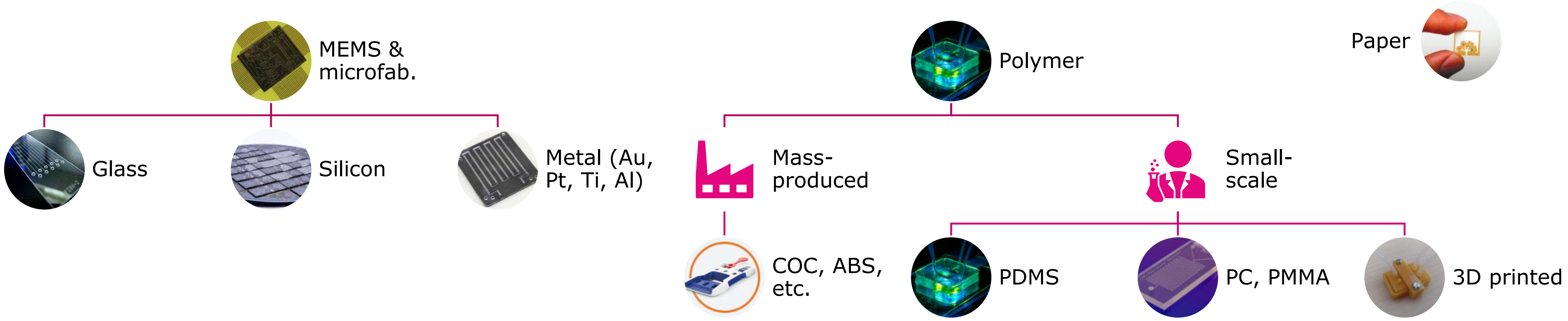
MATERIALS

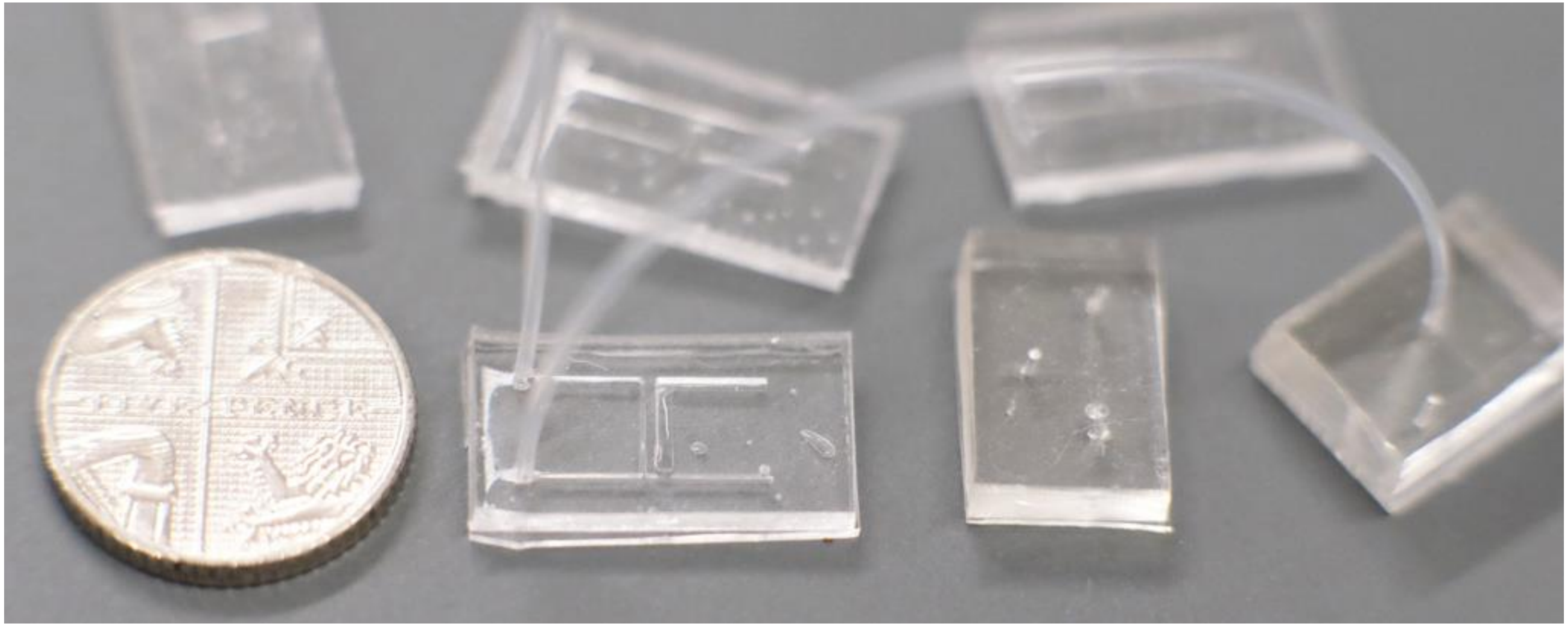
- Common structural materials in microfluidics
- Polymers
- Glass
- Paper

FABRICATION & MATERIALS



MATERIALS

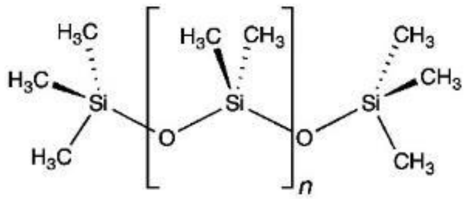
Conventional microfluidics chips made from PDMS, with H and T-junctions connected by microtubing. A five pence coin is shown for scale. Fabricated by friends in the Boutelle lab at Imperial College.



http://www.science-practice.com/blog/2015/01/29/low-tech-microfluidics/

PDMS

- PDMS (polydimethylsiloxane)
  - Elastomer: silicon-based organic polymer. Optically clear, chemically inert, non-toxic and non-flammable.
  - It is a type of silicone that is fully biocompatible and is even used in the food industry as an antifoaming agent.
  - In the labs we use Dow-Corning Sylgard® 18X.



- Pros/cons:
  - (+) Inert, biocompatible
  - (+) 6 nm feature size
  - (-) Bubbles… a pain in mass-production
  - (-) Labor-intensive fabrication and bonding

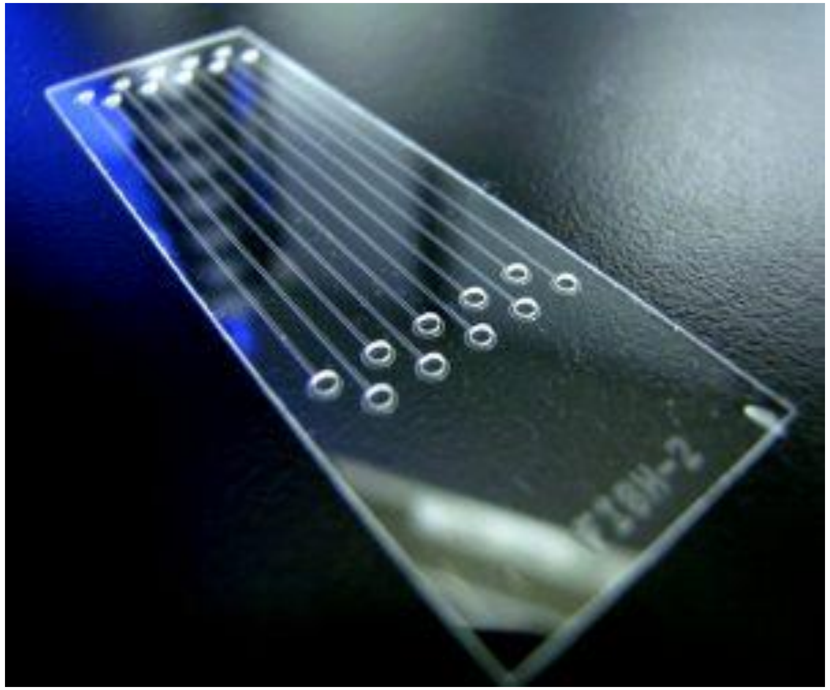
Property	Value
ε	2.68
Heat cure	150 °C, 10 min
k	0.27 W/(mK)
ρ	2.9e14 Ωcm

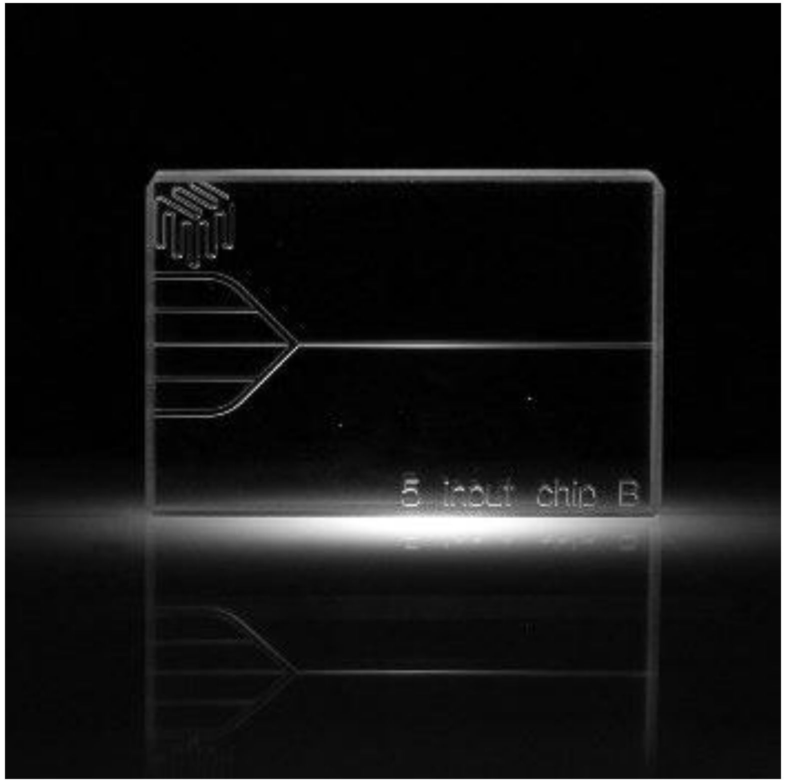
Only in the US…

Stroock, Abraham D., and George M. Whitesides. "Components for integrated poly (dimethylsiloxane) microfluidic systems." *Electrophoresis* 23.20 (2002): 3461-3473.

FABRICATION & MATERIALS

Glass microfluidic chips





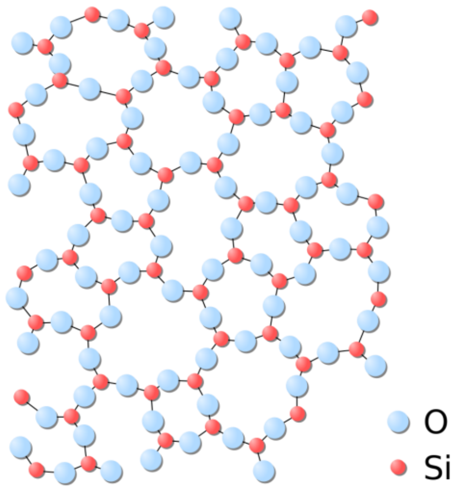
https://www.blackholelab-soft-lithography.com/blackholelab-soft-lithography-stations-faq/microfluidic-foundries
https://www.news-medical.net/5-Input-Chip-e28093-Short-Channel-e28093-Hydrophilic-from-Dolomite

MATERIALS: GLASS

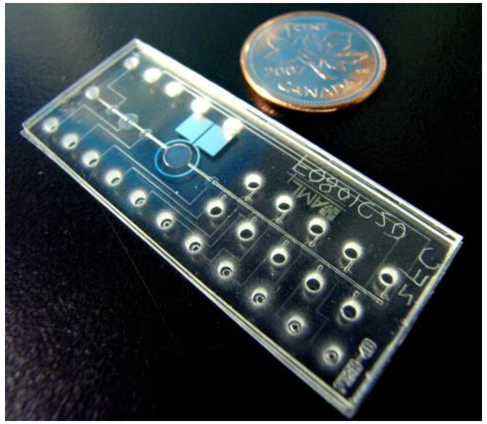
- Glass: often transparent amorphous solid
- Silicate (SiO_2)/borosilicate glass

- Why glass?
  - Temperature and pressure-resistance
  - Chemically resistant (easy to clean)
  - Highly transparent
  - Fully biocompatible
  - Non-permeable to gas
  - Excellent quality control

- Why not glass?
  - Expensive



This Photo by Unknown Author is licensed under CC BY-SA



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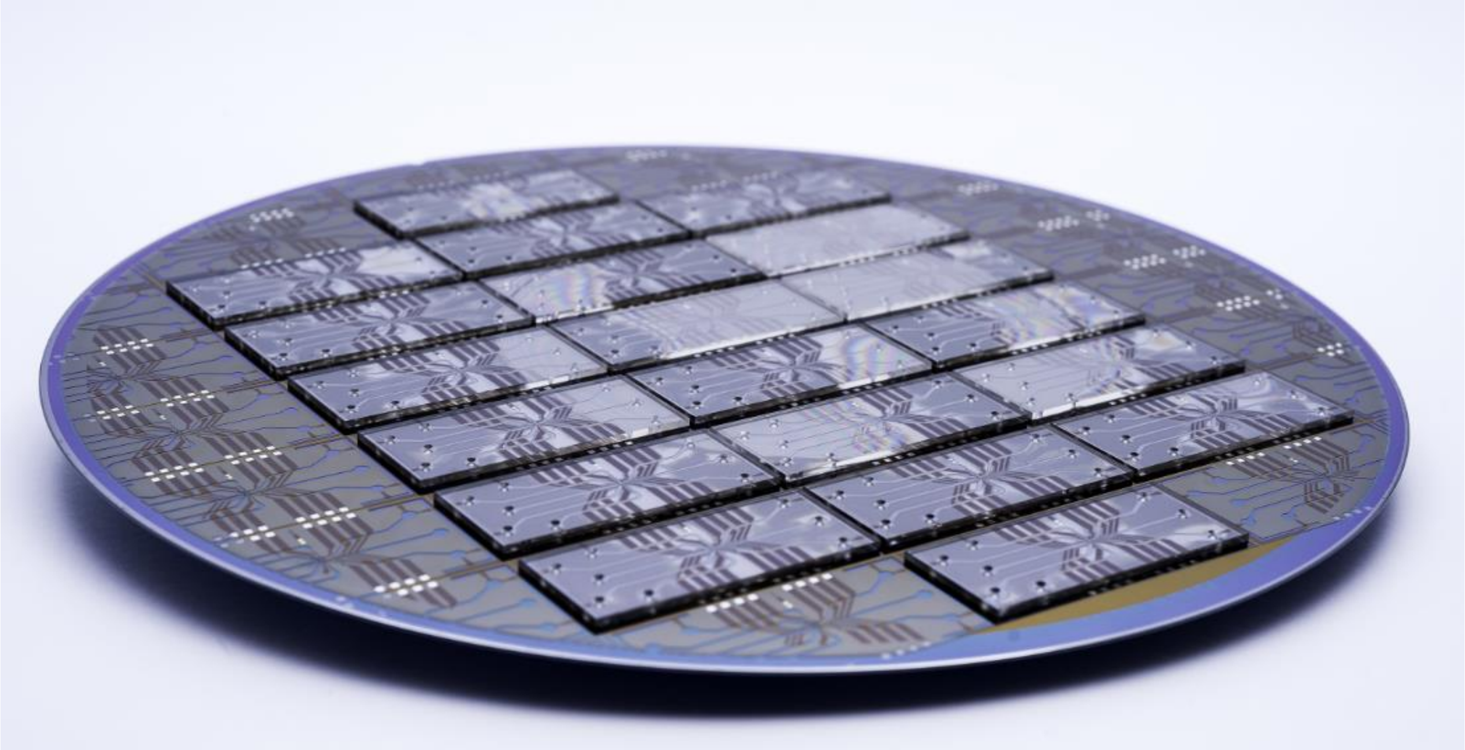
Property	Value
ε	4.7
k	0.8 W/(mK)
ρ	1e0-1e4 Ωm

FABRICATION & MATERIALS

Silicon-glass chips



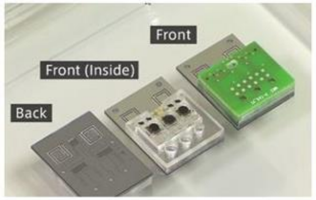
http://phys.org/news/2013-11-microfluidic-material-breakthrough-wafer-scale-mass.html

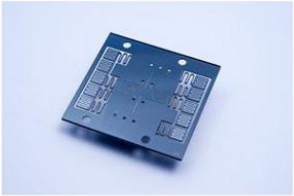
MATERIALS: SILICON

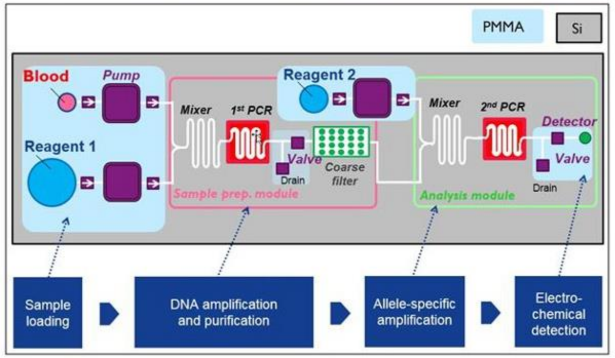
- Silicon: hard, brittle crystalline solid semiconductor
- Sealed by bonding glass/polymer plate

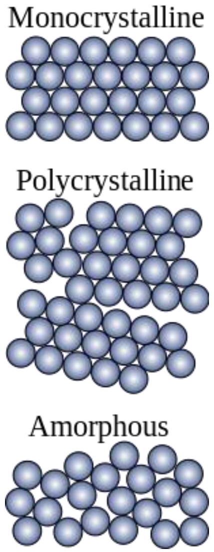
- Why silicon?
  - Temperature resistance but excellent heat conductivity
  - Chemically resistant (easy to clean)
  - Biocompatible
  - Micromachining yields high aspect ratio structures
  - Excellent quality control

- Why not silicon?
  - Expensive









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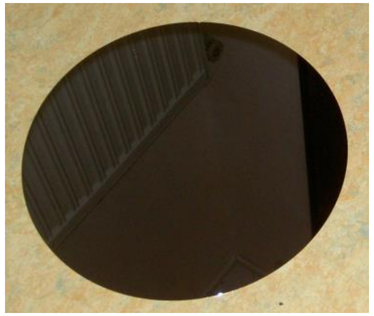
Property	Value
ε	11.68
k	149 W/(mK)
ρ	2.3e3 Ωm



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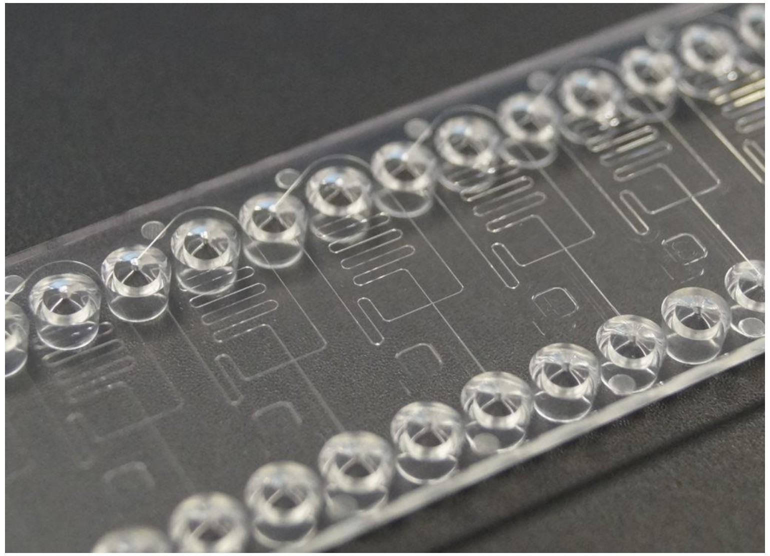
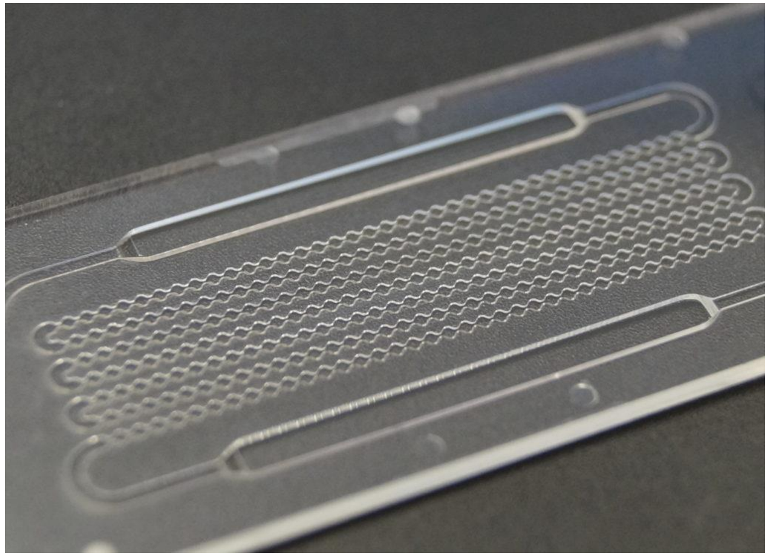
https://www.meddeviceonline.com/doc/silicon-a-material-with-huge-potential-for-lab-on-chips-0001

FABRICATION & MATERIALS

Thermoplastics: polyethylene (PE), polystyrene (PS), polyethylene terephtalate (PET), polypropylene (PP), polycarbonate (PC) or cyclic olefin (co)polymers (COC/COP)





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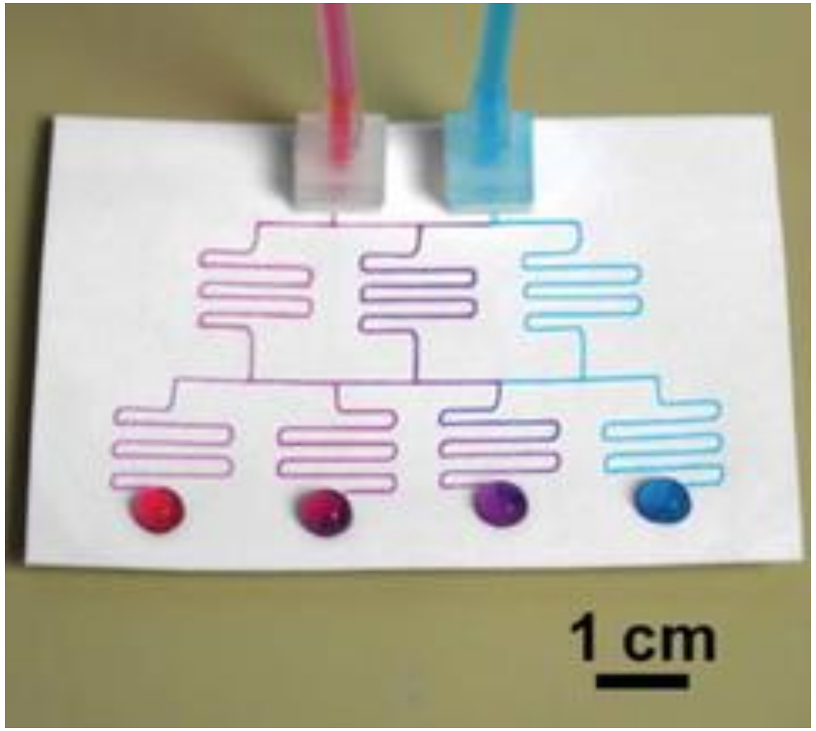
http://www2.technologyreview.com/tr35/profile.aspx?TRID=962
https://www.microfluidic-chipshop.com/microfluidics/

FABRICATION & MATERIALS

Paper LoC



http://thefutureofthings.com/3482-lab-on-a-chip-made-of-paper/
https://darwin-microfluidics.com/pages/microfluidic-chips-a-quick-overview

MATERIALS

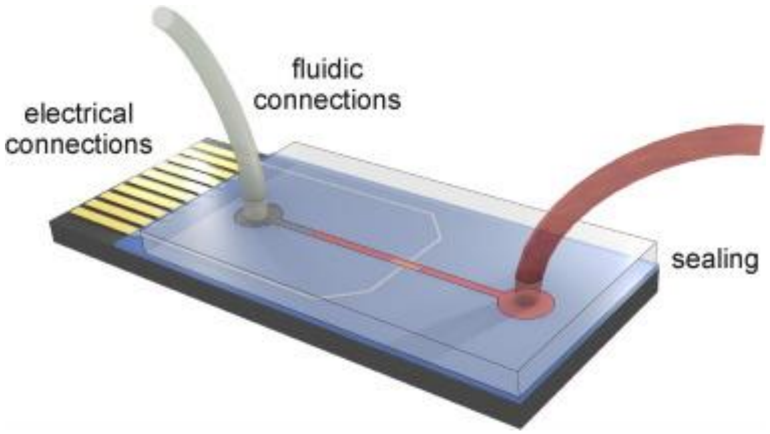
- Common structural materials in microfluidics
- Polymers
- Glass
- Paper

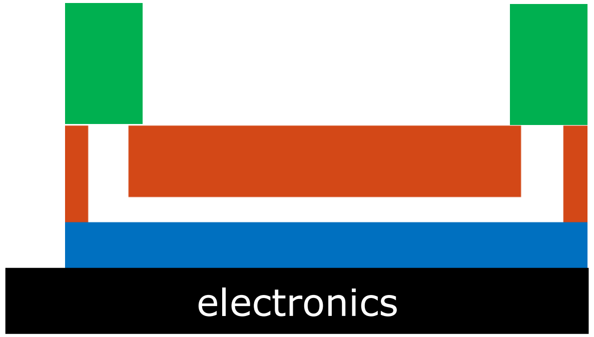
STRUCTURE

- Microfluidic chip layers
- Basic channel layouts
- Microfluidic system components
- Demo kits

MICROFLUIDIC DEVICE COMPONENTS

- Before we learn **how** to fabricate, let's see **what** we fabricate…
- Layers
  - **Fluidic I/O layer (fluidic connections)**
    - Teflon (PTFE) tubes OR on-chip integrated reservoirs
  - **Liquid handling layer (chip body)**
    - Channels
  - **(optional) Sealing layer**
    - Glass OR plastic film
    - Sometimes a PCB
  - **Electronics layer**
    - PCB or silicon

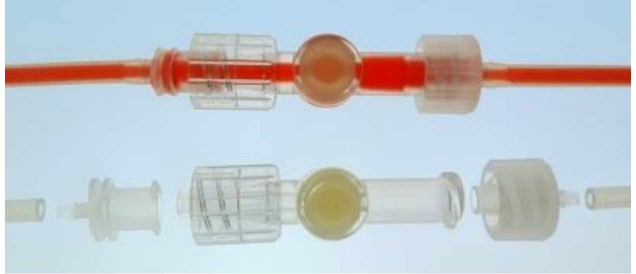




2. EXTERNAL SYSTEM COMPONENTS: LIQUID PATH

- **Reservoir**:
  - Closed: pressure vessel, syringe
  - Open: Beaker, on-chip reservoir
- **Tubing**:
  - Teflon tubes (1/16”)
  - Silicone tubing
- **Fittings, connectors**:
  - HPLC screw joint
  - Luer-Lok™
- **Chip holder**
- **Product collector:**
  - External: e.g. beaker, pressure vessel (don’t forget degassing ☺)
  - Internal: e.g. paper wicking pad

https://www.dolomite-microfluidics.com/product/mitos-fluika-pressure-vessel-100ml/



http://gonagen.com/wp-content/uploads/2014/11/luer-lock-connector-male-2.jpg

http://iris.fishersci.ca/LitRepo.nsf/0/37A8D30084EEF537852579A500746038/$file/72370172.pdf

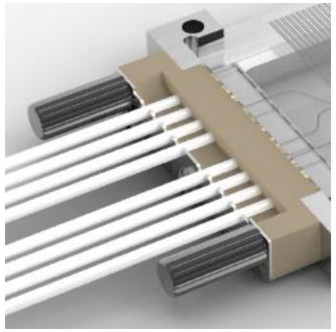
https://www.micronit.com/products/microfluidic-starter-kit.html

MICROFLUIDIC CHIP COMPONENTS

Layers

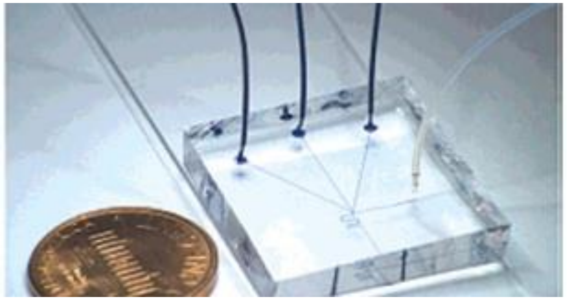
- **Fluidic I/O layer: typically Teflon (PTFE) tubes**
- Liquid handling layer
- Electronics layer

Pressure contact (Dolomite)



http://www.dolomitemicrofluidics.com/images/stories/microfluidic-images/newsupdate/dolomite_cavendish_optical-stretcher_1a.jpg

Plug-in tubing (HPLC equipment)



http://2010.igem.org/wiki/images/e/eb/ESBS-Strasbourg-fluidfig1.jpg

Screw joints

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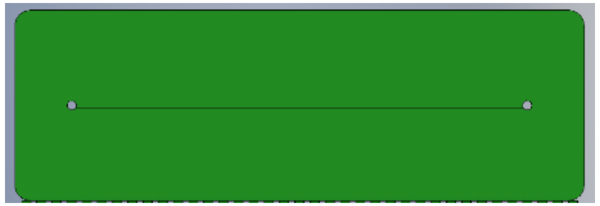
MICROFLUIDIC CHIP COMPONENTS

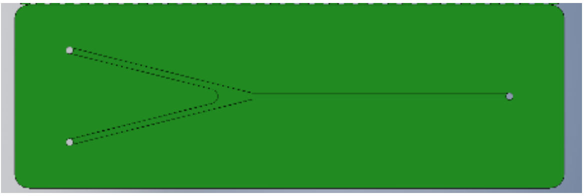
Layers
- Fluidic I/O layer
- **Liquid handling layer**
- Electronics layer

Straight chip

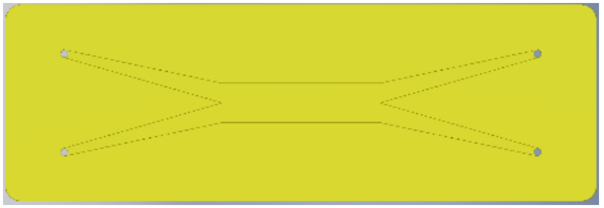


T chip (mixer)

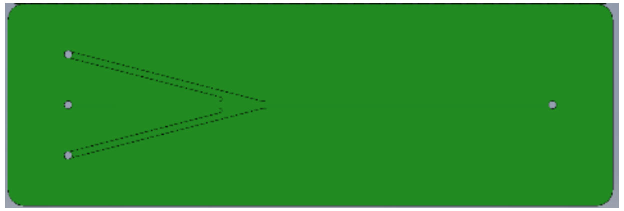
Y chip (mixer)



H chip (reactor/separator)



Focusing chip

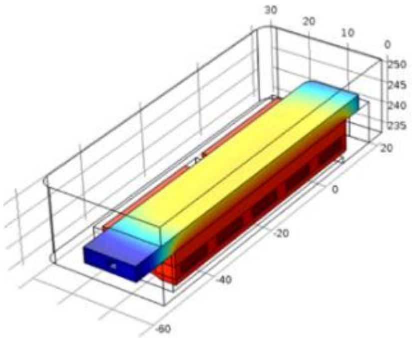


These example chips are all made by rapid prototyping and are available at TJS ELIN in 3D printing

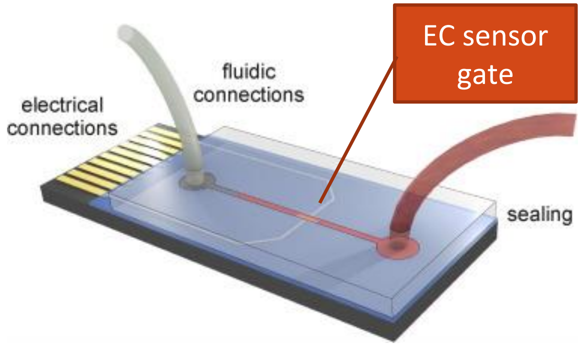
MICROFLUIDIC CHIP COMPONENTS

Layers
- Fluidic I/O layer
- Liquid handling layer
- **Electronics layer (integrated electronics)**

Temperature regulation (more in a later lecture)

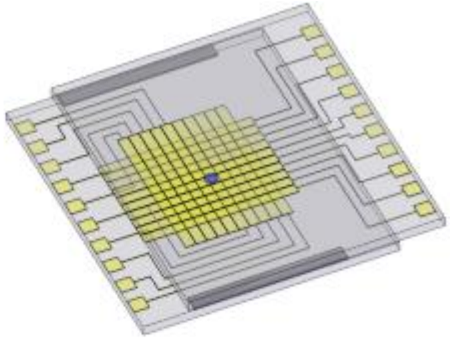


Sensors (more in a later lecture)



https://ars.els-cdn.com/content/image/1-s2.0-S0167931714004456-gr1.jpg

Fluidic actuators (more in a later lecture)



DEMO KITS

- **Demo kit ~5-10 k €**
  - Most microfluidics producers these days offer a starter kit in the 5-10 k€ range. Why?
  - To get you to use their ecosystem ☺
  - To build and test basic proof-of-concept fluidic layouts for your idea
- **Contents: pumps, chips, etc.**
  - Microfluidic pump(s)
  - Microfluidic chips
  - Microfluidic chip holder(s)
  - Tubing, fittings, etc.
- **How does it work?**
  - A bit like LEGO®. You liked that as a kid, you'll probably like microfluidic starter kits. You just need to plug and play.
  - Chips are slides (mostly 25 mm * 75 mm, same as microscope slides for obvious reasons)

- Micronit starter kit

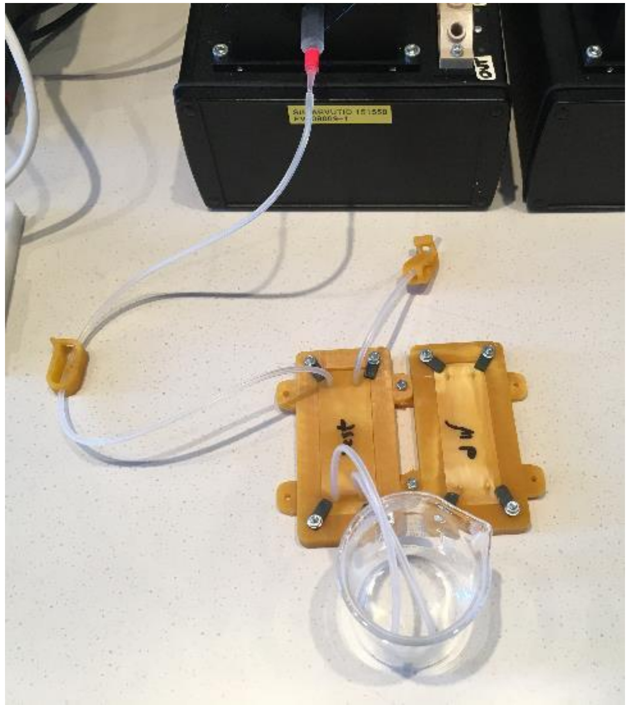
https://www.micronit.com/products/microfluidic-starter-kit.html

https://microscopy-news.com/wp-content/uploads/2017/01/76cdb59ad4fa88891c88d57584984a82.jpg
http://www.minifab.com.au/services/product-development-and-prototyping/
http://www.medicaldevice-developments.com/uploads/newsarticle/989322/images/198048/large/fig%202.jpg

DEMO KITS: WE HAVE OURS!

- At TJS ELIN, we have…
  - 3D printed chips designed and fabricated in-house. Designs are available for printing in the R&D team's cloud.
  - 2 Syringe pumps
  - Thermostat with chip interface and camera
  - Accessories and consumables

- In the labs, you'll use this kit to experiment and measure.
  - Should you choose to stay and write your thesis with us, you'll gain access to the design library.



STRUCTURE

- Microfluidic chip layers
- Basic channel layouts
- Microfluidic system components
- Demo kits

RAPID PROTOTYPING

- Polymers - PDMS
- Milling
- Paper and screen printing

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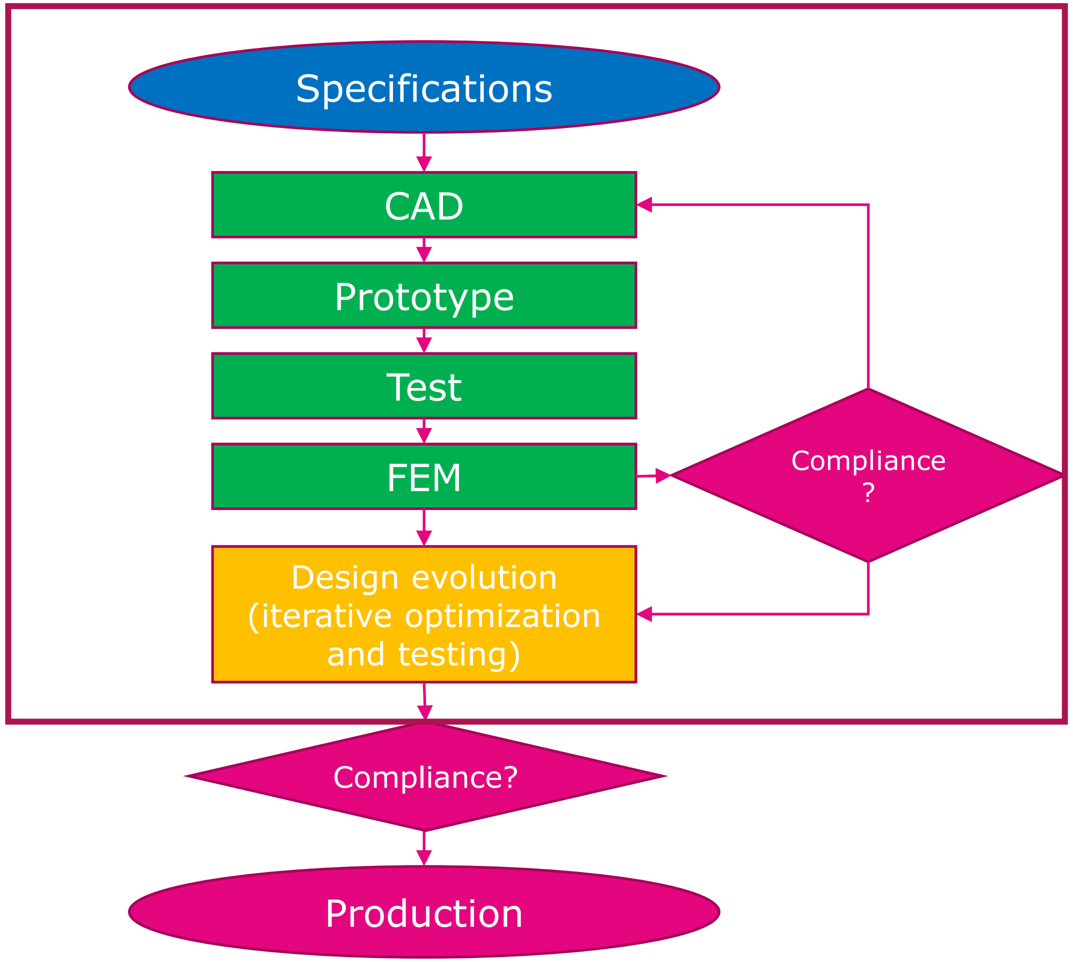
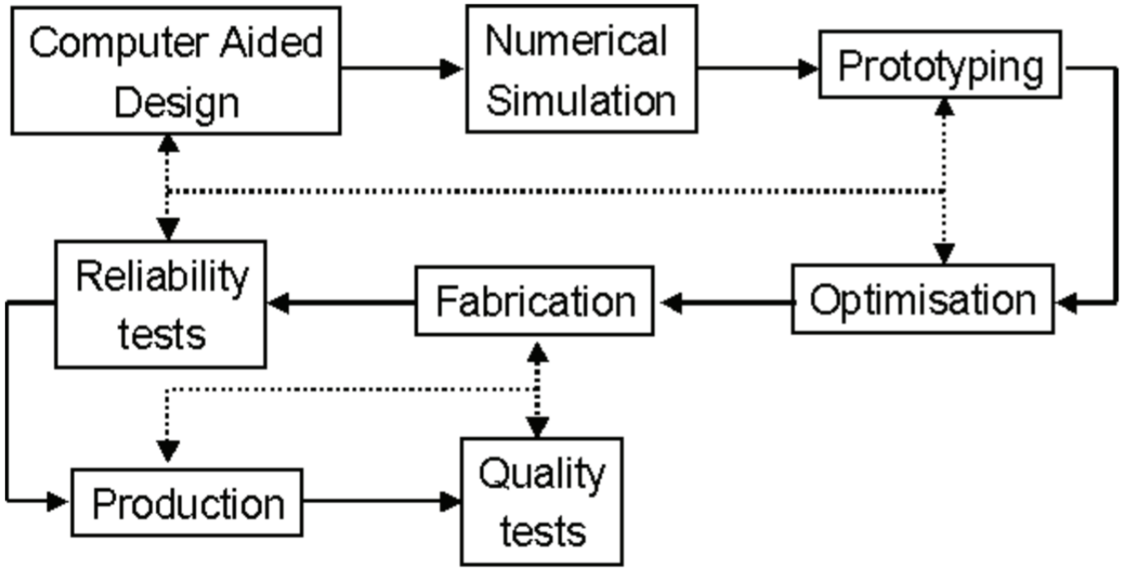
FABRICATION

Today's lecture

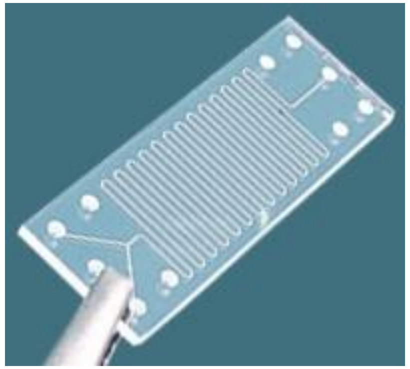




https://ws.lib.ttu.ee/publikatsioonid/Publ/Item/7653bd4e-c740-44e7-af38-3b7c5595fd48

FABRICATION TECHNIQUES FOR POLYMERS

- Why polymers?
  - **Cheap (max. 1-2 EUR per chip)**
  - Easy to machine
  - Optically transparent (if needed)
  - Good thermal and electrical properties
  - High aspect-ratio for microstructures
  - Biocompatible (if needed)
  - Recyclable options available



https://syntecoptics.com/polymer-optics-microfluidics/polymer-microfluidic-devices

https://en.wikipedia.org/wiki/HCG_pregnancy_strip_test

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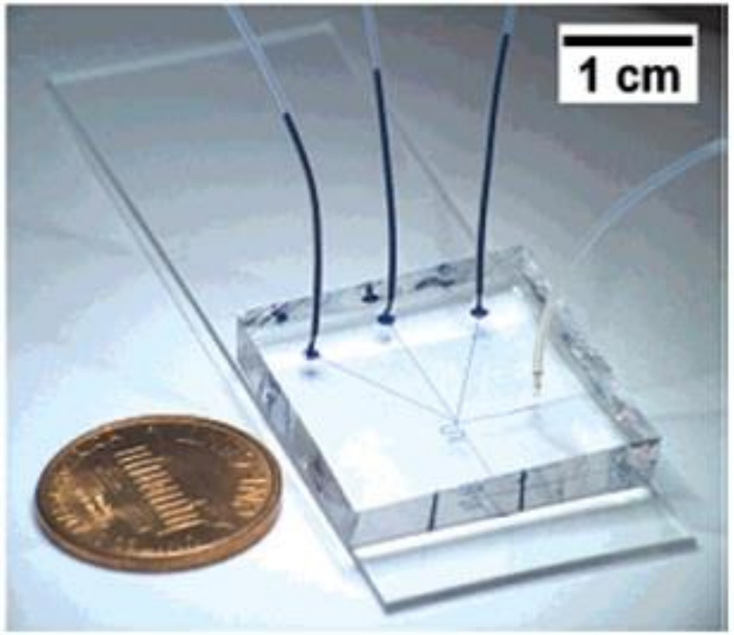
FABRICATION TECHNIQUES FOR POLYMERS

- **NB!** The chip is typically in the cm^2 range, but channels are sub-millimetre
- Polymers:
  - PDMS (polydimethylsiloxane)
  - **Plastics (COC, PC, PMMA)**
- Fabrication techniques:

1. Soft-lithography (PDMS only)
2. Milling (machining)
3. *Hot embossing (next lecture)*
4. *Injection moulding (next lecture)*



http://2010.igem.org/wiki/images/e/eb/ESBS-Strasbourg-fluidfig1.jpg

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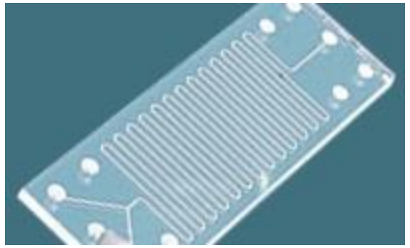
LAYER STRUCTURE OF POLYMER CHIPS

"Monolithic"

All features formed directly in the substrate.

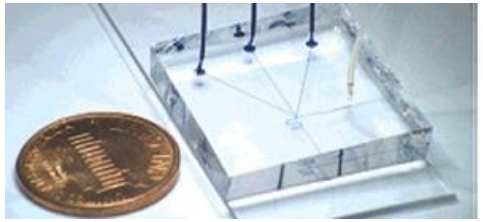
Possible by additive manufacturing (e.g. 3D printing). Difficult to implement en masse…



"Multi-layer"

The substrate is patterned to form channels & I/O features, and an unpatterned sealing layer is attached.

Most common approach.



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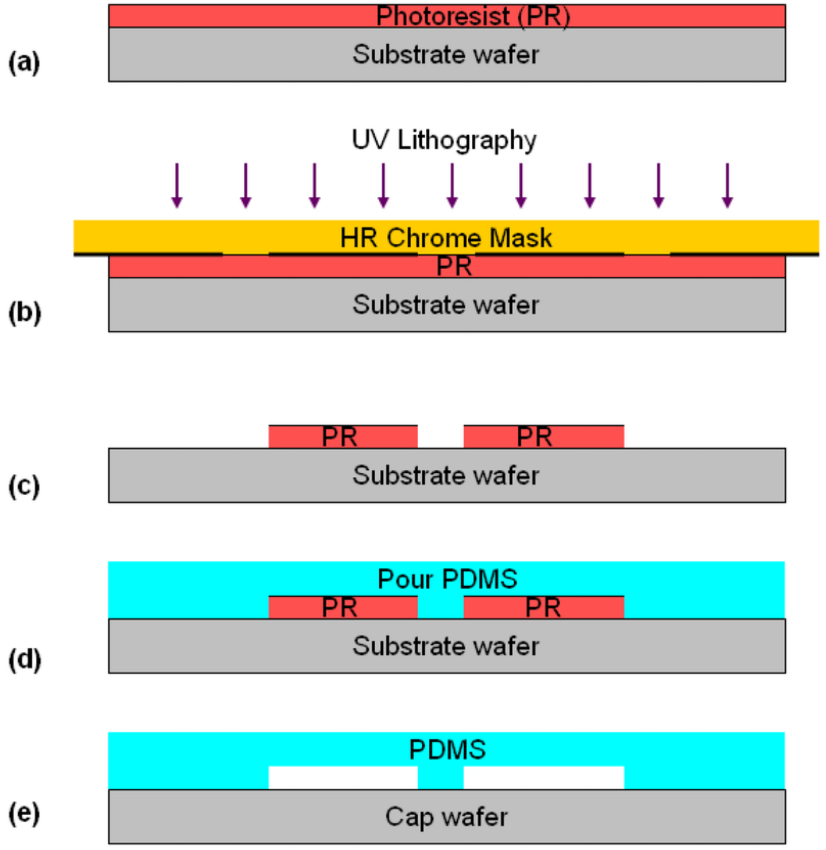
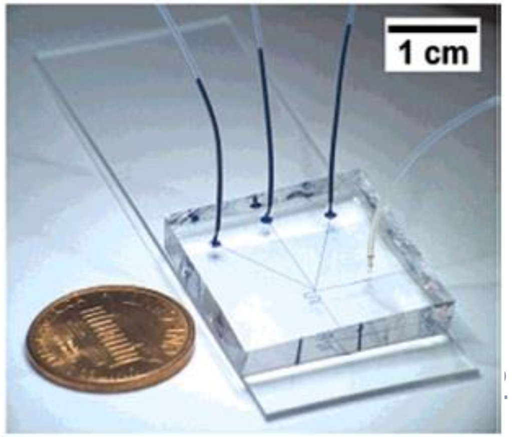
FABRICATION TECHNIQUES: SOFT LITHOGRAPHY

- Soft lithography: replicating microstructures using elastomeric stamps, moulds and conformable photomasks
- PDMS is a pure, soft material (elastomer) that conforms very well to microstructures (down to nanoscale)
- Process:

1. Master mould fabrication (a-c)
2. Mix PDMS elastomer and curing agent
3. Pour on mould (d)
4. Dry
5. Tear off
6. Activate glass surface
7. Apply PDMS (e)



Fast ways to make masks:
- Milling
- 3D printing
- *Hot embossing*



https://www.researchgate.net/figure/Fabrication-Process-of-PDMS-devices-by-soft-lithography-a-Spin-coating-of-photoresist_fig1_51496619

FABRICATION TECHNIQUES: MILLING

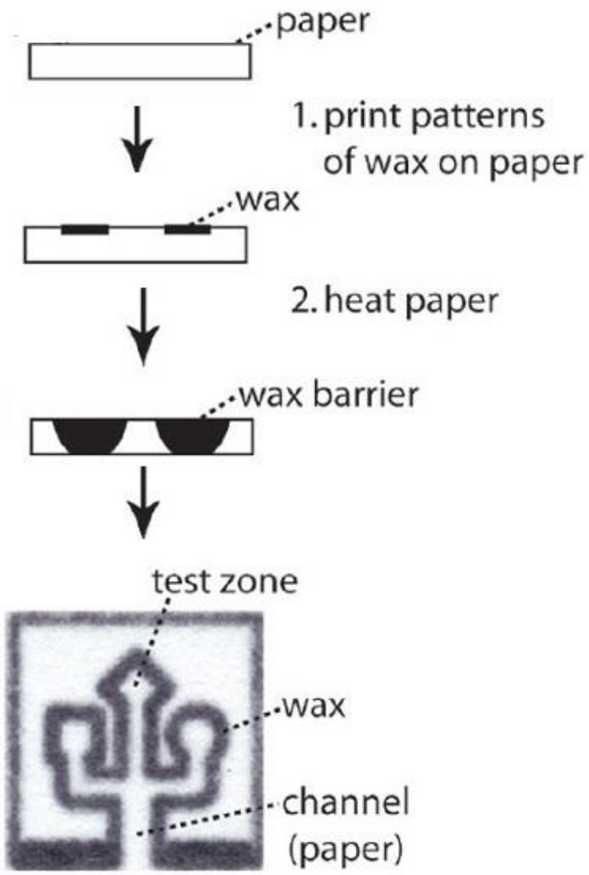
- Milling (machining): process of removing material by rotary cutters in a direction at an angle with the tool's axis.
- CNC (computer numerical control) milling machines are computer-controlled vertical mills with typically 3 normal axes (XYZ).
- Video: https://youtu.be/VCExAr17yU4?t=22
- In simple terms, it's a mechanical drill hung on a 3-axis frame ☺
- Maximum resolution is determined by:
  - Precision of stepper motor
  - Size of drill bit
  - Substrate material properties (e.g. tensile strength)
- Input: CAD file + substrate
  Output: micromachined structure

PAPER MICROFLUIDICS

- Why use paper?
  - Extremely cheap (few cents per chip)
  - Easy to manufacture
  - Good disposability
- But it’s not a tried-and-true method **yet**
- Typical production method:

1. Porous (e.g. filter) paper
2. Screen print wax barriers
3. Bake in wax barriers
4. Screen print electrodes (optional)

- Video: https://youtu.be/J5LwNGm0tbw?t=102



http://www.elveflow.com/wp-content/uploads/2017/01/MICROFLUIDIC-PAPER-BASED-ANALYTICAL-DEVICES-Microfluidic-paper-based-devices-Wax-Printing1.jpg

PAPER MICROFLUIDICS

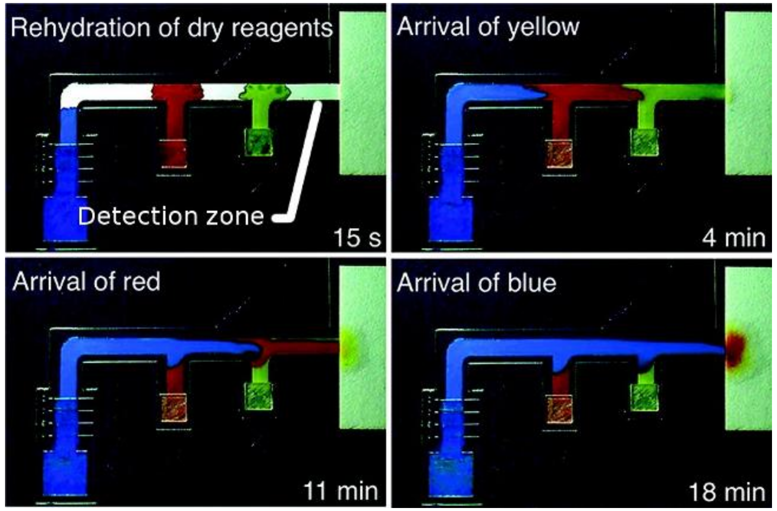
- Typical production method:
  1. Porous (e.g. filter) paper
  2. Screen print wax barriers
  3. Bake in wax barriers

How does this work in Lab-on-a-Chip?

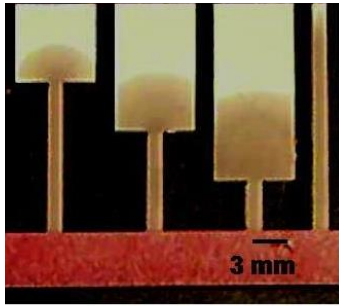
2DPN = 2-dimensional paper network

Similar methodology to pregnancy tests. Reagents are fixed on a paper substrate and liquids passing through the paper network will dissolve them.

Flow rates are possible to regulate through channel width.



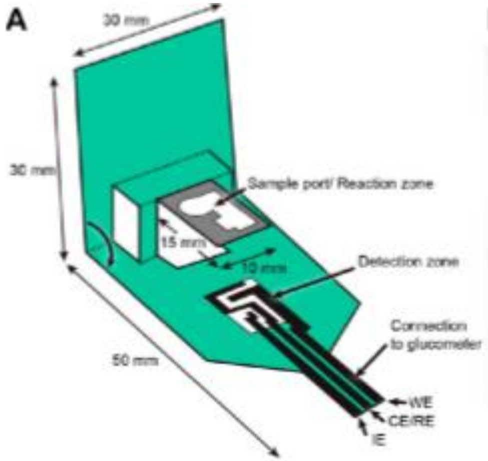
http://mf20.org/sites/default/files/2dpn_color.png

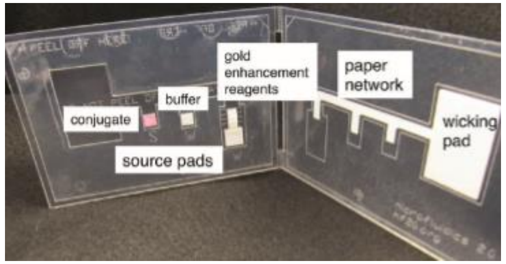


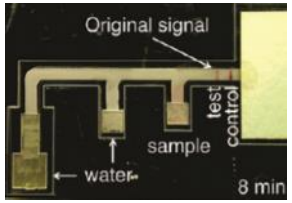
http://mf20.org/sites/default/files/styles/large/public/Fig1-mod_0.jpg?itok=qPkY7pPI

PAPER MICROFLUIDICS

- So, what can you do with this?
- Mostly immunoassays: detecting antibodies produced by the immune system for specific biological targets (antigens)
- Examples:
  - ePad: the cartridge is readable by a regular glucometer
  - Malaria test 2DPN







http://pubs.acs.org/doi/pdf/10.1021/ac300689s

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Paper-Based Microfluidic Devices: Emerging Themes and Applications, Yuanyuan Yang, Eka Noviana, Michael P. Nguyen, Brian J. Geiss, David S. Dandy, and Charles S. Henry, *Analytical Chemistry* **2017** *89* (1), 71-91, DOI: 10.1021/acs.analchem.6b04581

RAPID PROTOTYPING: "CHEAPO"

Sharpie microfluidics

- Procedure:
  - Take a 25 mm * 75 mm glass microscope slide
  - Use a permanent marker or a Sharpie to make walls that will guide the water
  - The ink is hydrophobic, but the glass is hydrophilic, so water will stick to the glass and not wet the walls

Scotch tape PDMS moulding

- Procedure:
  - Take a glass microscope slide
  - Lay tracks of Scotch tape on them – make them as thin as possible and cut the rest with a scalpel
  - Make a moulding well from aluminium foil and pour PDMS on your glass "master mould"
  - Leave in the open for a night or bake at 60 C for 30 minutes to dry (will cause air bubbles)
  - Remove PDMS
  - Apply plasma treatment to another fresh glass slide and attach PDMS
  - Punch input/output holes

https://www.youtube.com/watch?v=eAnittk0sac&ab_channel=SusannBeier

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http://singularityhub.com/wp-content/uploads/2009/04/jeswin_john_img_0521-300x225.jpg
https://www.youtube.com/results?search_query=ashens+poundland+special

RAPID PROTOTYPING

- Polymers - PDMS
- Milling
- Paper and screen printing

13.01.2022

3D PRINTING

- Fused deposition modelling
- Stereolithography
- Laser sintering

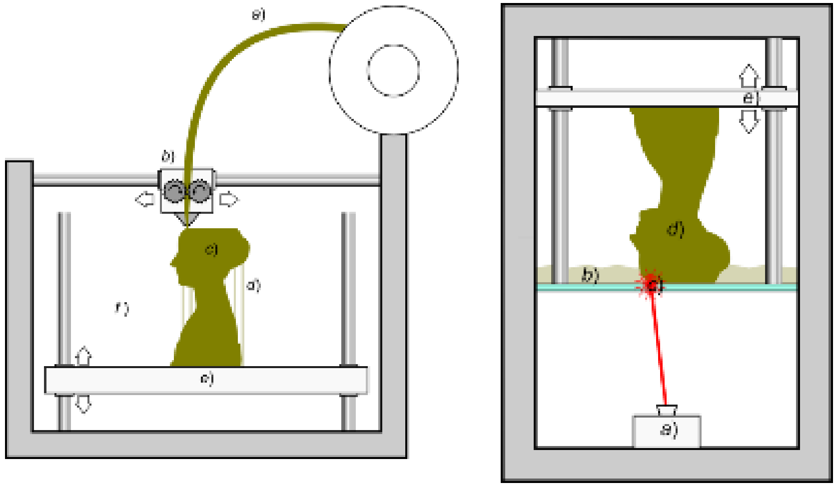
RAPID PROTOTYPING

- Rapid prototyping: techniques to quickly fabricate a scale model or physical prototype using CAD (computer-aided design) models.

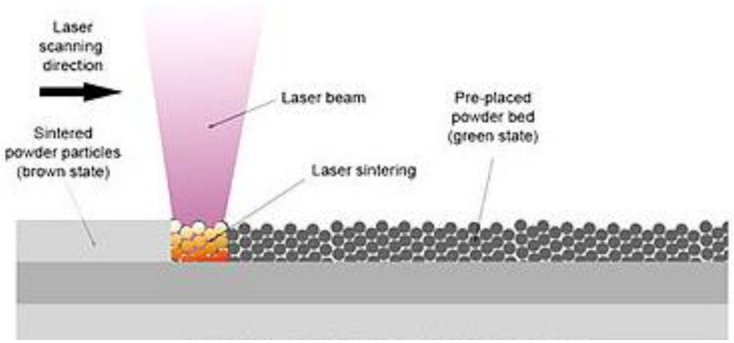
- 3D printing (additive manufacturing) is the most common rapid prototyping method.

1. Fused deposition modelling (FDM)
2. Stereolithography (SLA) or digital light processing (DLP)
3. Selective laser sintering (SLS)

- Voxel = 3D dot ☺



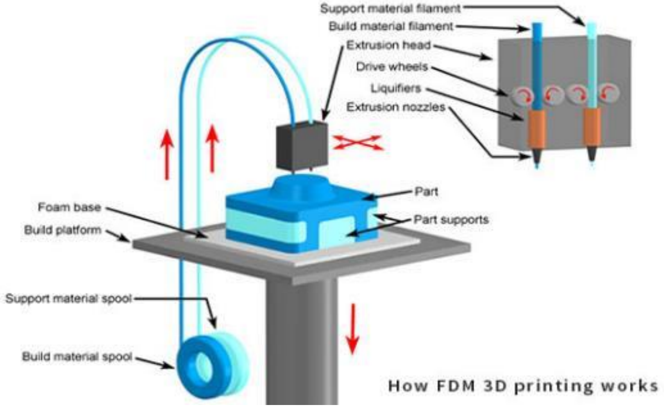
https://en.wikipedia.org/wiki/3D_printing



https://upload.wikimedia.org/wikipedia/commons/thumb/3/33/Selective_laser_melting_system_schematic.jpg/780px-Selective_laser_melting_system_schematic.jpg

RAPID PROTOTYPING

- Fused deposition modelling (FDM): a heated filament is deposited from a nozzle moved in x-y axes, on a platform (z axis)
- Why FDM?
  - It's cheap (1200 EUR for a printer)
  - The material is cheap (30-50 EUR per spool)
  - It's good for larger structures (mm resolution)
- Why not FDM?
  - Simpler models mandate structural supports inside (no holes, channels etc.)
  - Resolution is worse than SLA, SLS

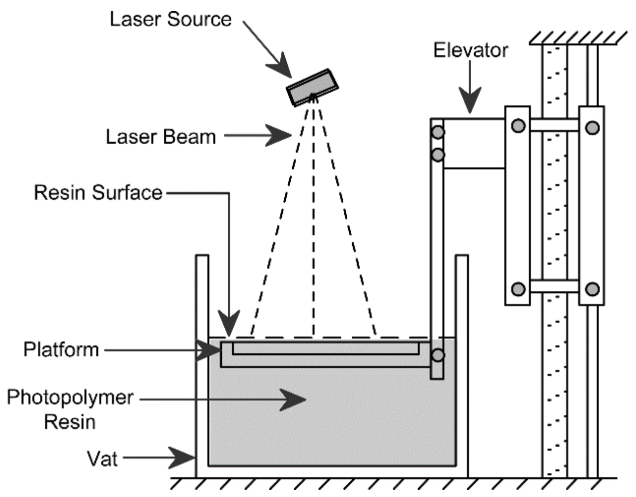


http://www.kul3d.com/wp-content/uploads/2014/08/LearnFDM.jpg

https://i.pinimg.com/736x/25/3b/b9/253bb9b42ac9e194c18d130f85de71ec--diy-d-printer-desktop-d-printer.jpg

RAPID PROTOTYPING

- Stereolithography (SLA) or digital light processing (DLP): a resin monomer is polymerized by a directed light on a glass platform (only z axis)
- Why SLA/DLP?
  - Good resolution (50 µm voxel size)
  - Good printing speed (hours to a day)
  - Good prototype strength (but typically quite brittle)
  - Wide variety of plastics available
- Why not SLA/DLP?
  - High cost for printer (15k-250k EUR)
  - High cost for resin (500-800 EUR per bottle)
  - Typically limited part size (~50x50x60 [cm])

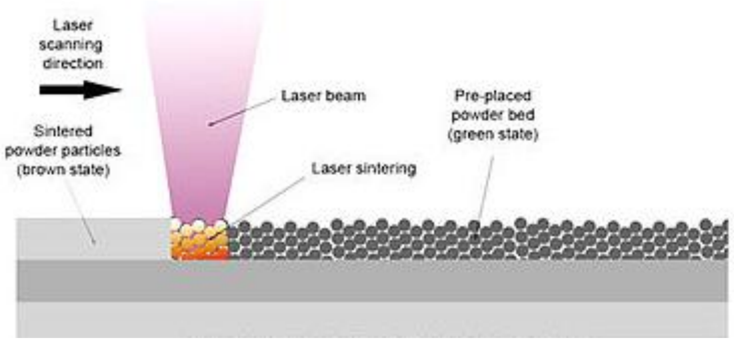


http://www.mkstechgroup.com/wp-content/uploads/2017/03/stereo-lith.png

https://cdn-reichelt.de/bilder/web/xxl_ws/E400/FORMLABS_FORM2_01.png

RAPID PROTOTYPING

- Selective laser sintering (SLS): a directed light sinters powder particles into layers
- Why SLS?
  - Good resolution
  - Fastest 3D printer
  - Complex geometries can be built in a single process without supports
  - Various finishing possibilities (metal, powder coating etc.)
  - Excellent mechanical properties
- Why not SLA/DLP?
  - Highest cost for printer and powders
  - Material porosity



https://en.wikipedia.org/wiki/3D_printing

http://hexus.net/media/uploaded/2013/11/660c800f-6a81-44e6-8977-2ddac339e7b6.jpg

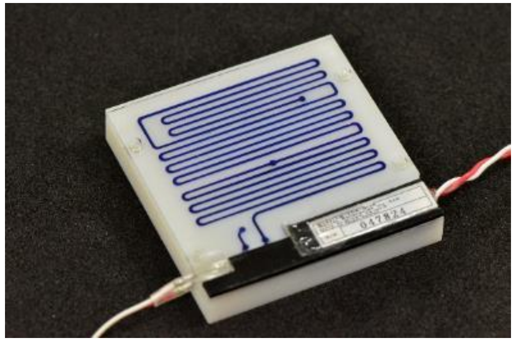
3D PRINTING: COMPARISON

	FDM	SLA	SLS
Printer cost (min.)	~150€	~3.5k€	~12k€
Material cost	~30€	~300€	$$$
Resolution	😃 -> 😃	😃😃 -> 😃😃😃	😃😃😃
Internal supports	Needed	Not needed	Not needed
Best for	Large structures e.g. housing	Small parts e.g. chips	Anything

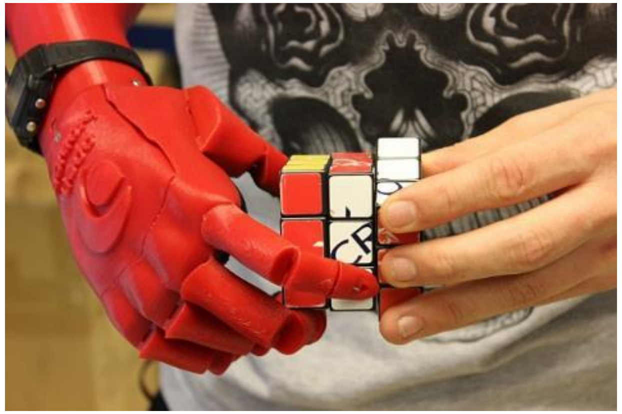
https://all3dp.com/1/best-resin-dlp-sla-3d-printer-kit-stereolithography/
https://formlabs.com/3d-printers/fuse-1/

3D PRINTING: WHY THE HYPE?

- 3D printing helps to
  - produce individual prototypes
  - upscale to production
- In Lab-on-a-Chip
  - SLA/SLS prototypes have working fluidics and some can house reactions too
- In general, 3D printing:
  - Can bring advanced tools to a wider audience via open-source design repositories
  - Decrease logistics costs in manufacturing
  - Produce customized hardware



http://microfluidics.jp/en/wp-content/uploads/2015/01/DSC1467.jpg



https://goo.gl/images/cGroro

3D PRINTING: WHERE DO I BEGIN?

- You can get yourself a DIY 3D printer for ~150 EUR!
- Bear in mind however, that there’s a steep learning curve.
- Here’s a nice summary of the best DIY 3D printers:
- https://all3dp.com/1/best-cheap-diy-3d-printer-kit/

Prusa i3, the best DIY printer (also most expensive). Buy hey, it’s designed and built in the EU ☺

https://www.prusaprinters.org/prusa-i3/

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RAPID PROTOTYPING AT TJS ELIN

- **1. Milling**
  - Available equipment: DATRON M7 HP
  - Minimum feature size 0.1 mm
  - Production time: few hours
  - CAD file input format: STEP

- **2. 3D printing**
  - Available equipment: Envisiontec Perfactory 4
  - Minimum feature size: 0.025 – 0.05 mm
  - Production time: few hours – a day
  - CAD file input format: STL

https://envisiontec.com/wp-content/uploads/2016/09/PerFactory-rebrand2.png

3D PRINTING

- Fused deposition modelling
- Stereolithography
- Laser sintering

IEE1860 BIOMEMS

Contact: tamas.pardy@taltech.ee

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BIOMEMS

self diagnostics

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