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MICROSENSORS FOR BIOMEDICAL APPLICATIONS

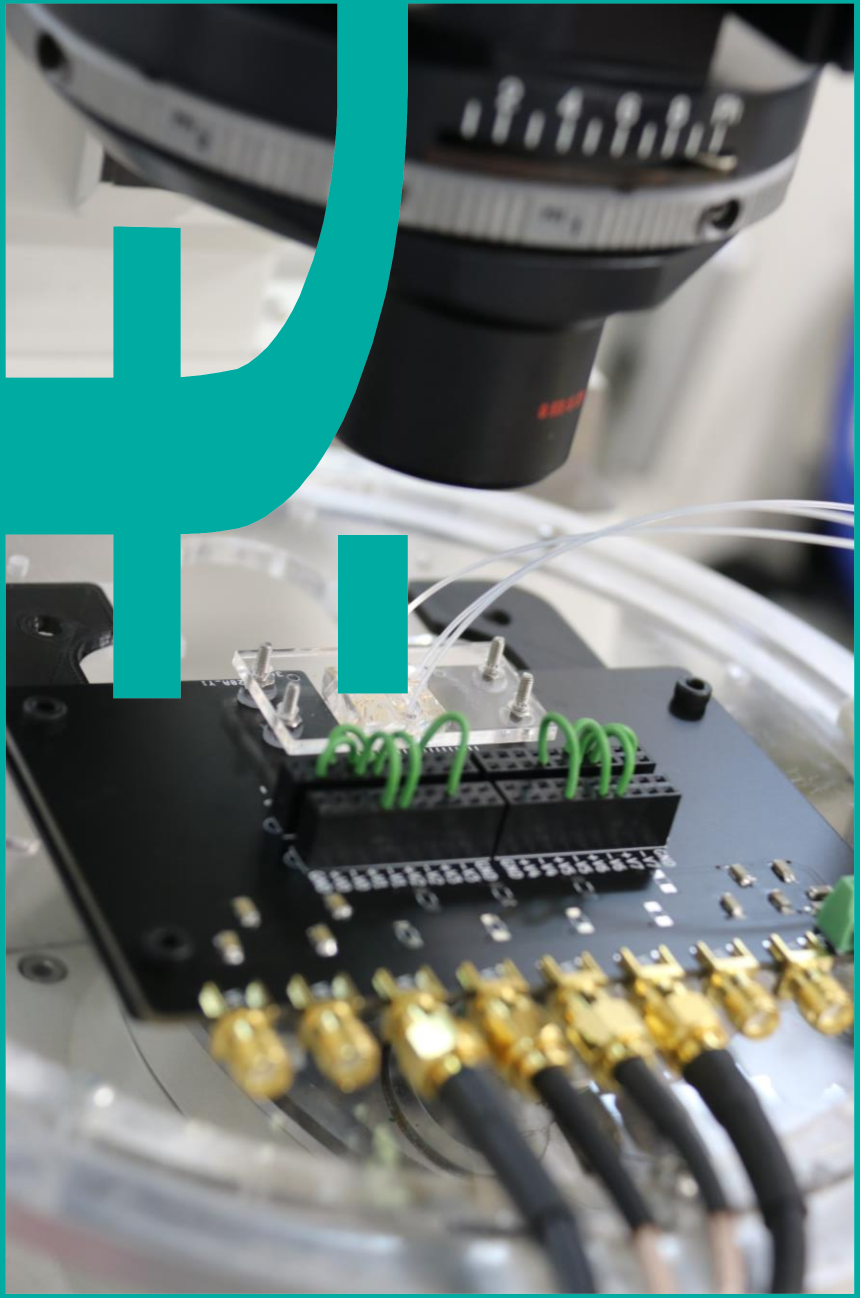
Thérèse Leblois

Université de Franche-Comté

Institut FEMTO-ST

Besançon France

SNOSCELLS



FEMTO-ST RESEARCH INSTITUTE

750 MEMBERS
7 SCIENTIFIC DEPARTMENTS (AS2M, DISC, ENERGIE, DMA, **MN2S**, OPTIQUE, TF)
1 MICRO-NANO- FABRICATION CENTER (MIMENTO, CLEAN ROOM FACILITIES) AND 9 TECHNOLOGICAL CENTERS
1 R&D BUSINESS UNIT FOR TECHNOLOGY MATURITY GROWTH TOWARD THE INDUSTRY: FEMTO-ENGINEERING

From fundamental research to industrial applications
Thematic fields: optics, acoustics, micro nanosciences, microsystems, time-frequency, automatic, microrobotics, computer science, mechatronics, as well as mechanics, materials and electrical engineering

Activities→ social economic impact: Energy and transport, healthcare, optics and phononic telecommunications and the space industry, instrumentation and metrology, watch making industry

Locations: Besançon, Montbéliard and Belfort

BIOMICRODEVICES TEAM

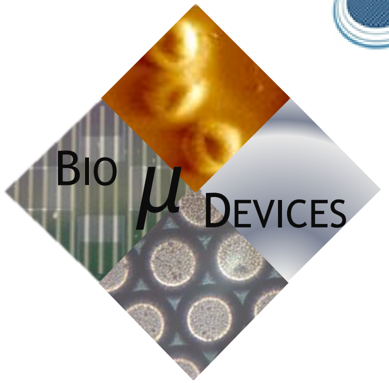
The team BioMicroDevices

- 14 permanent staff
- Pluridisciplinary team: bio-engineering, physico-chemistry of surfaces - interfaces, nanobio-characterization, microfluids, microfabrication, biosensors, lab-on-chips; organ-on-chips
- Field of applications: health, agrofood
- Close collaboration with health actors

femto-st SCIENCES & TECHNOLOGIES

Micro-Nano science and system

RENATECH French national nanofabrication network



CHRU Besançon centre hospitalier régional universitaire

Objective: Detection, characterization and quantification of biomolecules, cells in fluids, nanobiocharacterization for a better knowledge of biological, agrifood and environmental mechanisms

BIOSENSING TECHNOLOGIES?

Two widely used techniques, inexpensive, easy to use:

- lateral flow assays (LFA)

Analysis time~minutes / LOD~0.1µM / low cost / low volume

-Enzyme-linked immunosorbent assays (ELISAs)

Analysis time~1 hour / LOD~1pM / volume (100µL)

→ Objective of Biosensors developement:

- Analysis time~minutes / LOD <1pM
- Portable, miniaturized, real-time, inexpensive, easy to use

CONTENTS

BIOSENSOR INTRODUCTION

Definition and characteristics of biosensor

Biosensor = Analytical device that is able to convert a biological response into an electrical signal.

The "golden" biosensor must be:
- highly specific
- Highly sensitive
- Able to reach a low LOD
- Independent of physical parameters (e.g., pH, temperature, etc.)
- Reliable
- Reusable
- Low cost

Historical background

- 1956: Measurement of the concentration of oxygen dissolved in blood by Clark [Clark1]
- 1962: First amperometric enzyme electrode for the detection of glucose by Leland Clark and Lyons [Clark2].
- 1969: First potentiometric sensor to detect urea by Guilbault and Montalvo [Guilb].
- 1975: First commercial biosensor developed by Yellow Spring Instruments (YSI): glucose in diluted whole blood by use of an enzyme-based biosensor [Yoo].
- 1983: First surface plasmon resonance (SPR) immunosensor by Liedberg et al. [Liedberg].
- …

[Clark1] Clark, L. J. *Trans Am Soc Artif Intern Organs* 1956, 2, 41-48
[Clark2] Clark, L. C.; Lyons, C. *Ann. N. Y. Acad. Sci.* 1962, 102, 29-45
[Guil] Guilbault, G. G.; Montalvo, J. G., Jr. *J. Am. Chem. Soc*. 1969, 91(8), 2164-2165.
[Yoo] Yoo, E.H., Sensors 2010:4558-4576
[Liedberg] Liedberg, B, *Sens. Actuators* 1983;4:299-304

BIOSENSOR INTRODUCTION

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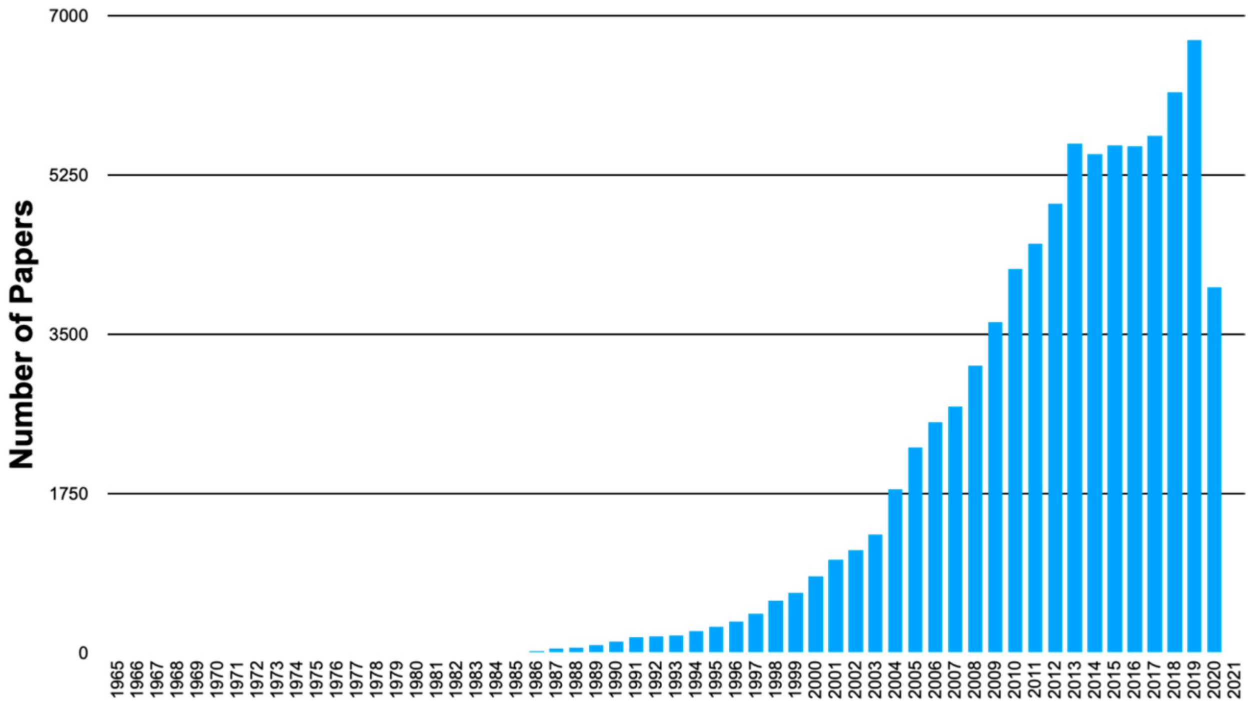


Number of published papers mentioning "biosensors" derived from statistics provided by the Web of Science [Singh]

→ Rapid developments in miniaturization and microfabrication both at research and product developement

Singh et al., *Alexandria Engineering Journal* (2023) 67 673-691

BIOSENSOR INTRODUCTION

4 Fields of applications

Biosensors

Health
Diagnosis – therapy - bioproduction
Drug discovery
Process monitoring
in vivo implantable biosensor

Environment
Water quality management
Detergents, pesticides, heavy metals
Bacteria and pathogens detection
Environemental monitoring

Bioterrorism
Toxic substances detection
Germs, pathogens and toxins detection
Chemical weapons
Explosives

Agrofood
Chemical contaminants detection
Foodborne pathogens detection
Food product production
Food quality monitoring

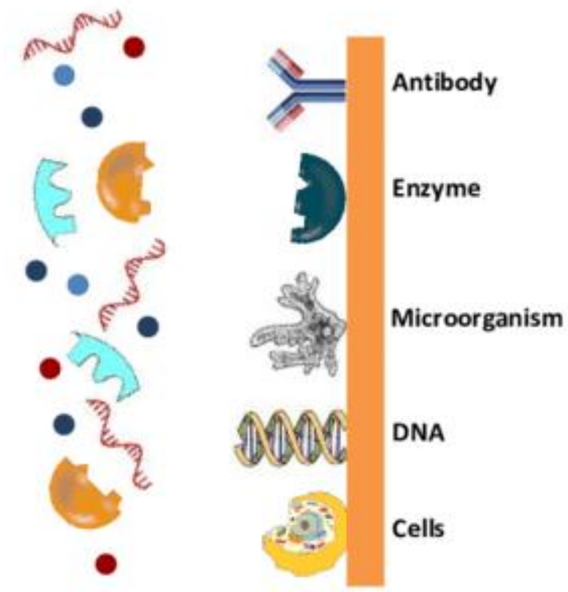
Mehrotra *J Oral Biol Craniofac Res*. (2016) 6(2) 153–159.

BIOSENSOR INTRODUCTION

Definition

Analyte
Sample matrix

Biorecognition
elements



Transducers

Electrochemical
Optical
Thermal
Mass sensitive
Mechanical

Electronics

Signal processing (amplification, noise reduction …)

Display

BIOSENSOR INTRODUCTION

Combinaison of Biology and Physics

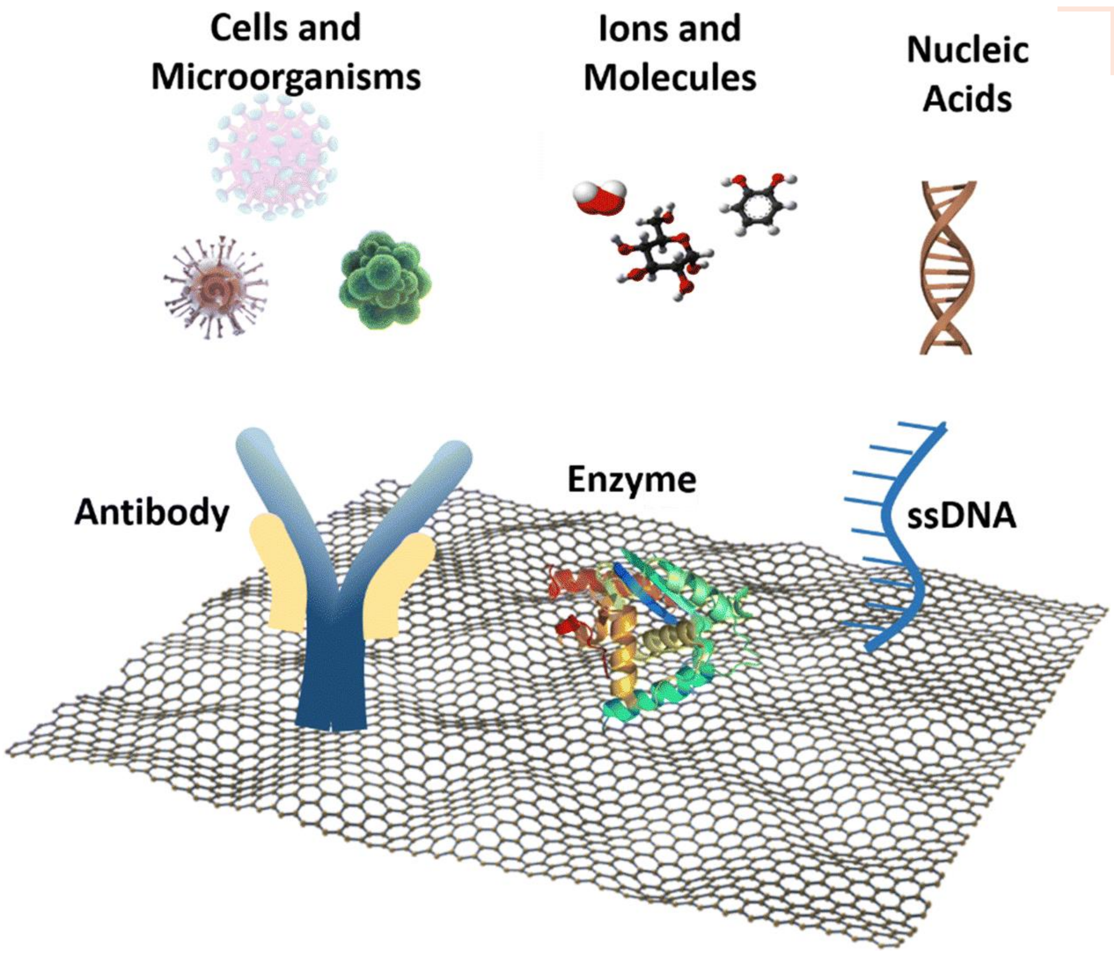
What analyte?

Analyte:
Ions, molecules, nucleic acids, cells

Two main components to design a biosensor

Bioreceptor:
DNA, Antibody, Enzyme

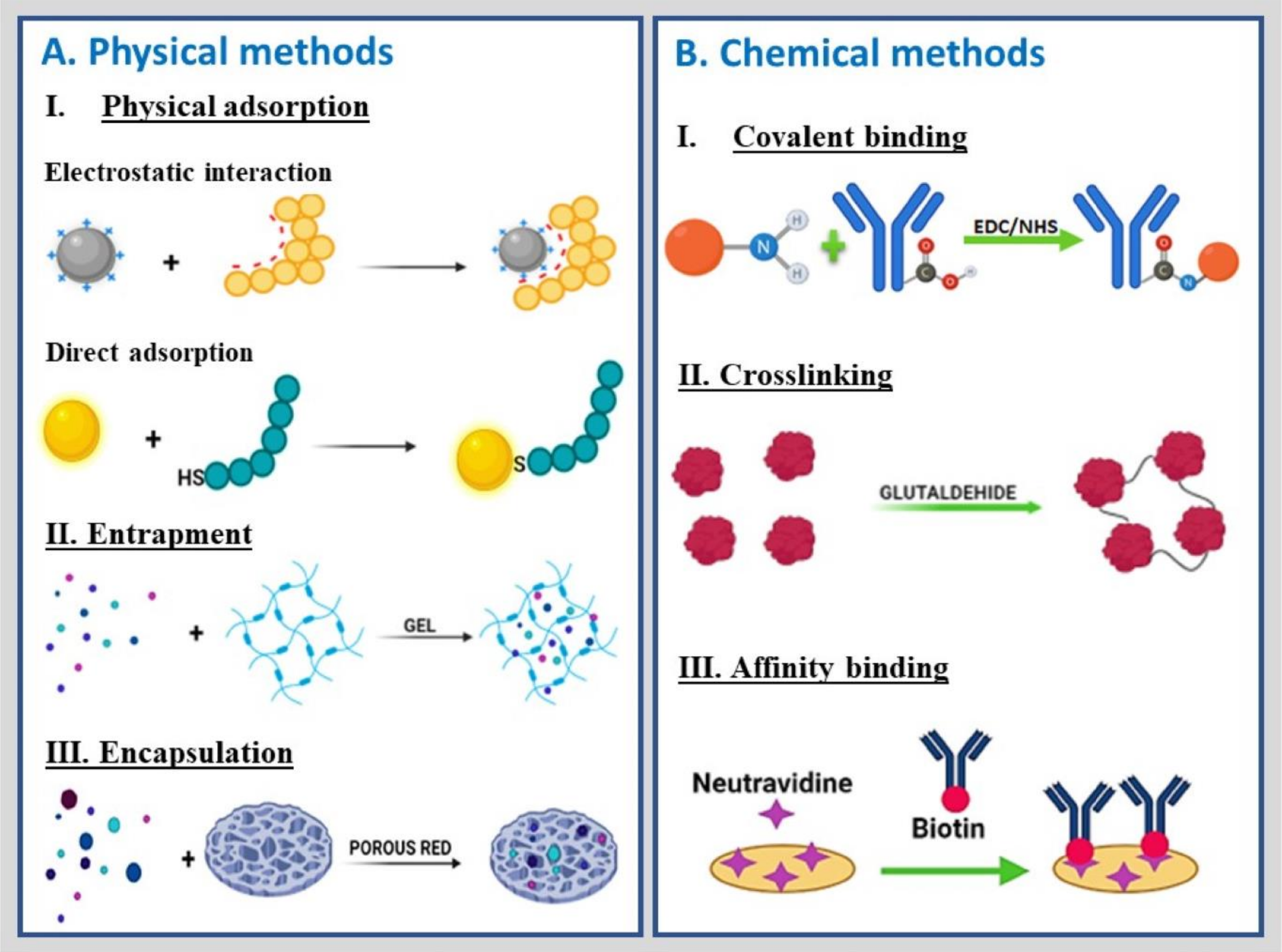
Transducer:
Electrochemical, Optical, Thermal, Piezoelectrical



[Mont] Montrose A. PhD thesis Univ. Toulouse III, march 2013

BIORECOGNITION ELEMENTS

Methods of immobilisation



Physical methods:
AI- Easy, no need for chemical compounds, not very stable, low cost, **reversible**
AII- AIII- not versatile, high selectivity, high sensitivity, high cost, **irreversible**

Chemical methods:
BI- high stability, strong binding, high cost, **irreversible**
BII- high stability, strong binding, cross-linking with or without inert protein, high cost, **irreversible**
BIII- high selectivity, high sensitivity, labelling, high cost, **reversible**

Asal et al. *Sensor review* (2018) 84

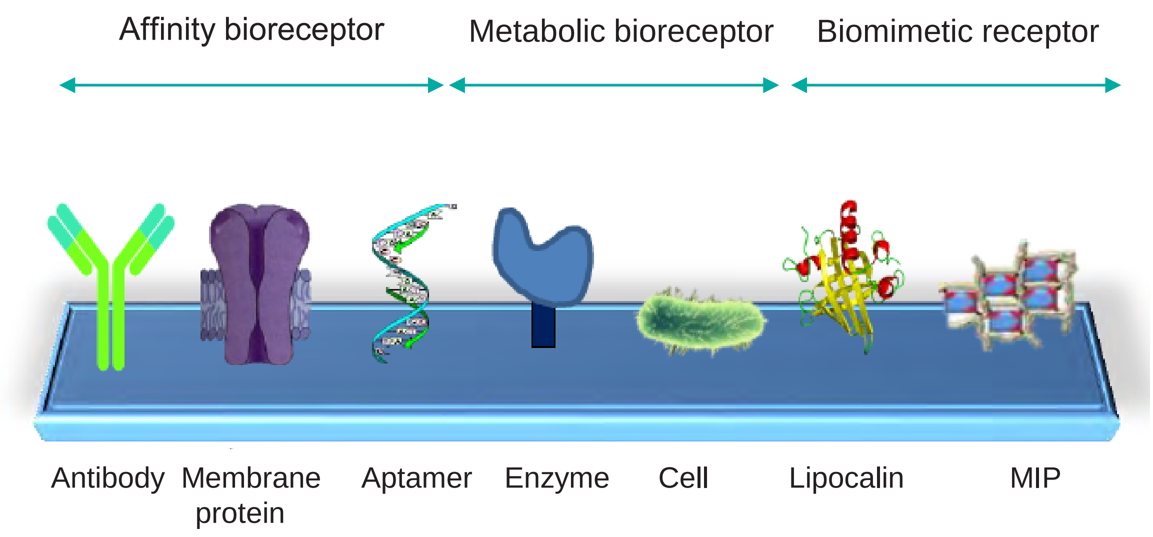
BIORECOGNITION ELEMENTS

- **Bioreceptors → specificity of the biosensor**
- **Type of bioreceptors**

- Classification into 5 types of bioreceptors
  - Enzymes, nucleic acids and antibodies bioreceptors: the most widely used
  - Cells and bacteriophages

- 3 major categories of bioreceptors:
  - Bioreceptors binding the analyte without modification
  - Bioreceptors with catalytic activity
  - Biomimetic receptors

→ The recognition step can thus result either in a static state (affinity bioreceptors) or in a dynamic event (metabolic bioreceptors)



Different types of bioreceptors [Soto]

[Mont] Montrose PhD thesis Univ. Toulouse III, march 2013
[Soto] Soto D., *molecules* 2022 27:3841

TRANSDUCER

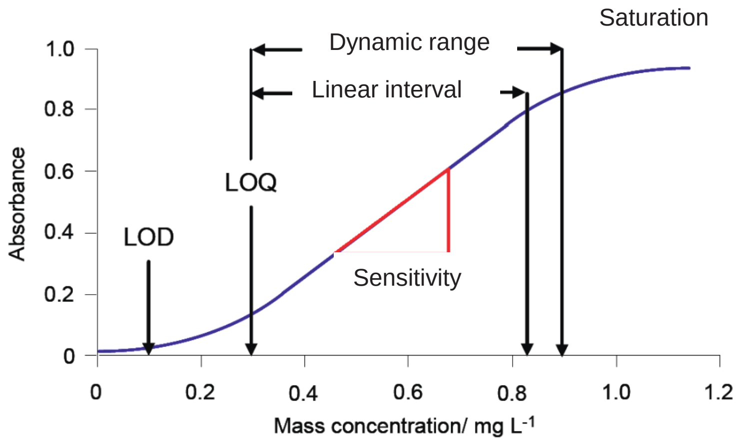
Definition

The transducer converts the received physicochemical reaction signal into measurable signal. The measured signal can indirectly reflect the concentration of the target.

Five types of transducers are commonly used for biosensor design:

A/ Electrochemical: electrical properties, production of redox species,
B/ Thermal: temperature accompanying a reaction,
C/ Optical: optical absorption, refractive index, fluorescence,
D/ Piezoelectric: gravimetry, physical and physicochemical parameters,
E/ Mechanical: constraints, forces.

Main characteristics: Dynamic range, sensitivity, linearity, accuracy, limit of detection (S/3N), drift, reliability, Repeatability, reproductibility



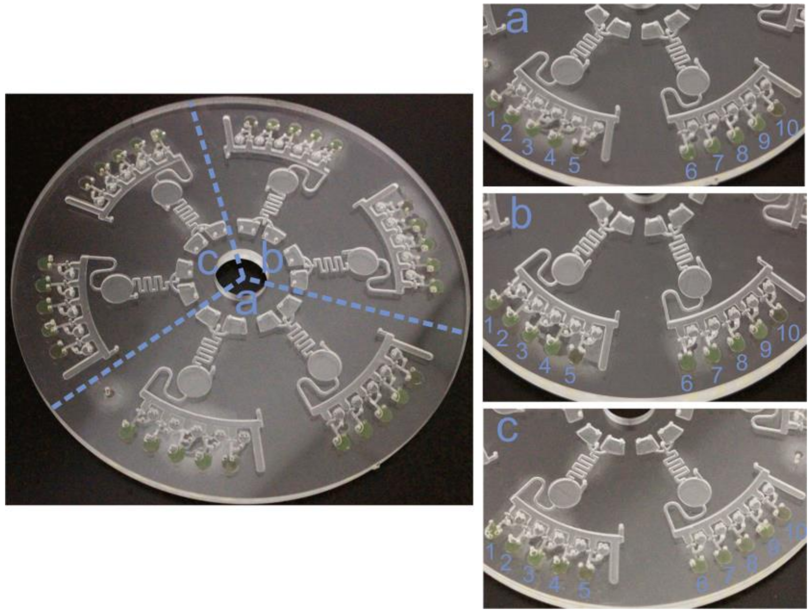
OPTICAL TRANSDUCER (1/7)

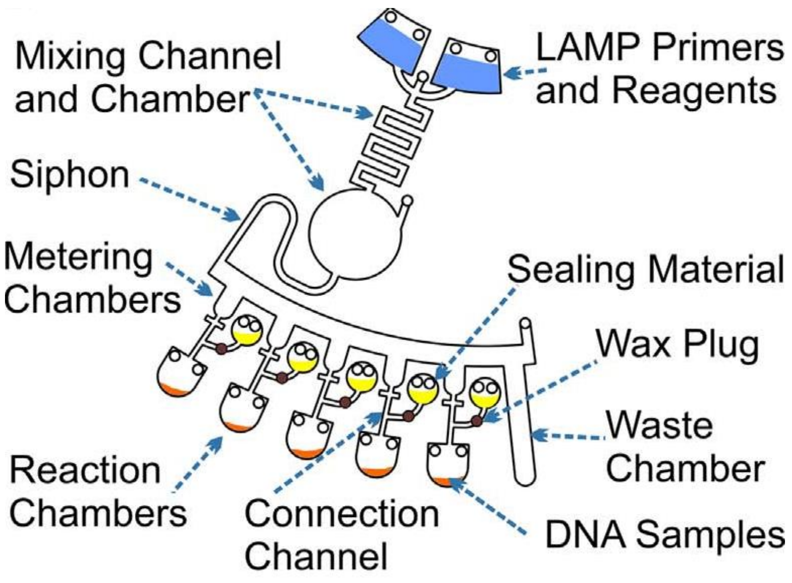
Colorimetric sensing

Colorimetry is a scientific technique that is used to determine the concentration of colored compounds in solutions by the application of the Beer–Lambert law, which states that the concentration of a solute is proportional to the absorbance.

Not label-free method (calcein)

Limit of detection: 3×10^{-5} ng μL^{-1}





Agrofood application: detection of bacteria

[Sayad] Sayad et al. *Biosensors and Bioelectronics* 100 (2018) 96–104

OPTICAL TRANSDUCER (2/7)

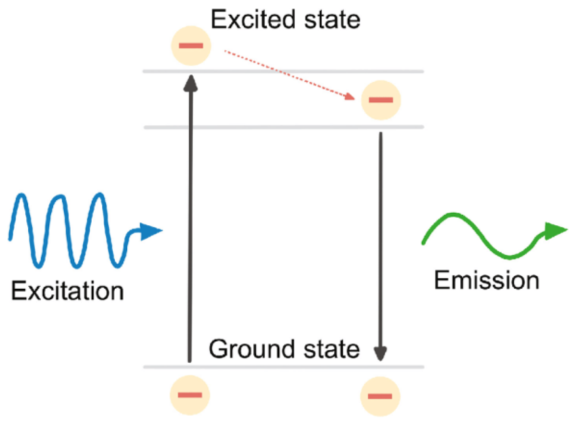
Fluorescence sensing

- Fluorescence
  - Principle: Association of the target molecule with a fluorescent molecule called fluorescent marker. Affinity between fluorochrome and molecule of interest
    Quantification of the presence of molecules of interest in an indirect way

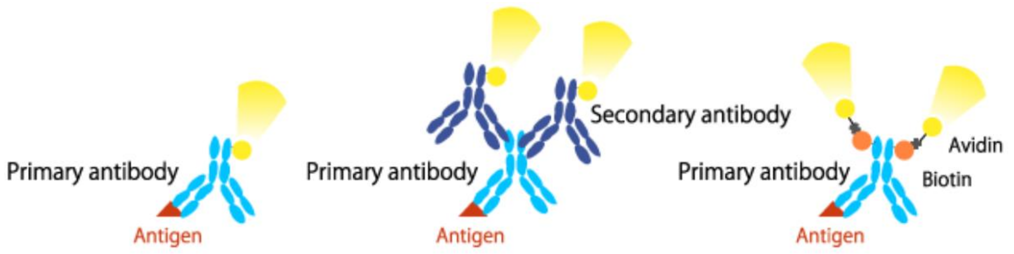
→ One of the numerous labelling techniques

- Characteristics:
  - Limit of detection: a few fg/mL
  - Expensive microscope
  - Addition of fluorochrome / denaturation
  - Decrease of fluorescence in time

- Example of detection:
  - Direct
  - Indirect
  - Amplification



Principle of fluorochrome

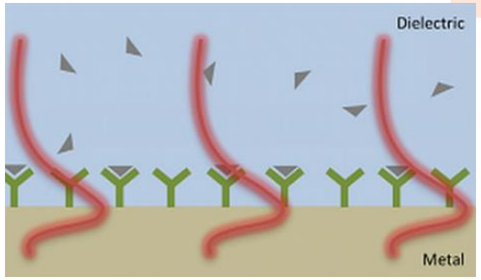


Principle of detection

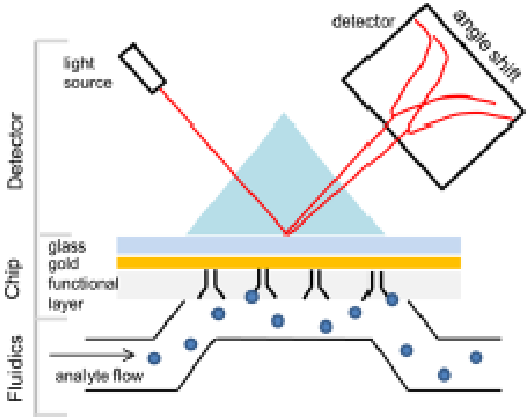
OPTICAL TRANSDUCER (3/7)

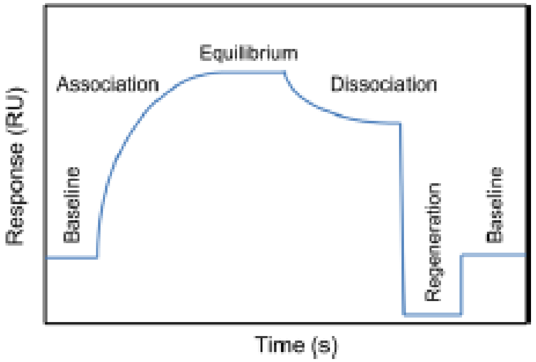
Surface Plasmon Resonance (SPR) / SPR imaging

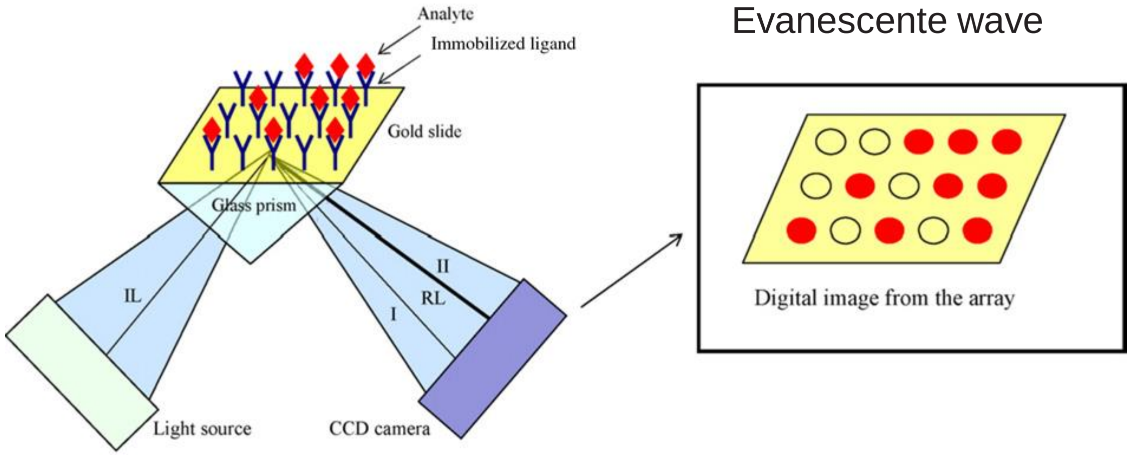
- Principle: shift in the position of the plasmon resonance angle due to the modification of the medium refringence $\Delta\theta=0.1° \Leftrightarrow 1ng/mm^2$
- Label-free method
- Limit of detection $1pg/mm^2$ SPR et $5pg/mm^2$ SPRi
- Depth penetration: 50 to 100nm



Evanescente wave





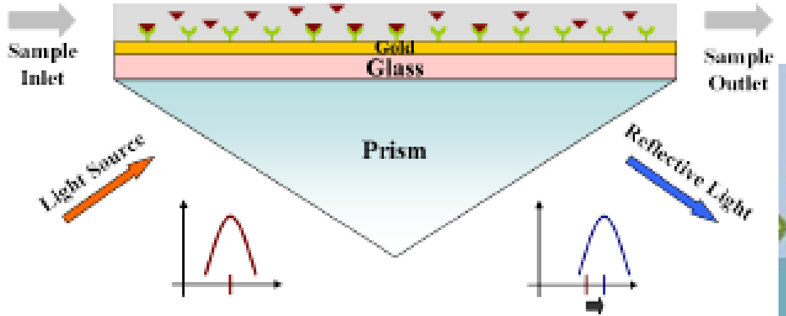


Damborsky P. Essays in biochemistry (2016) 60 91-100

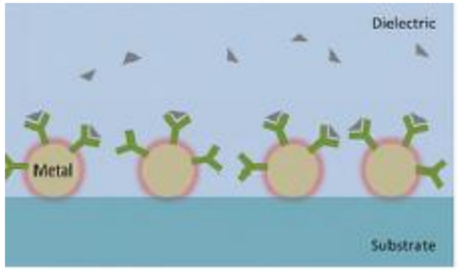
OPTICAL TRANSDUCER (4/7)

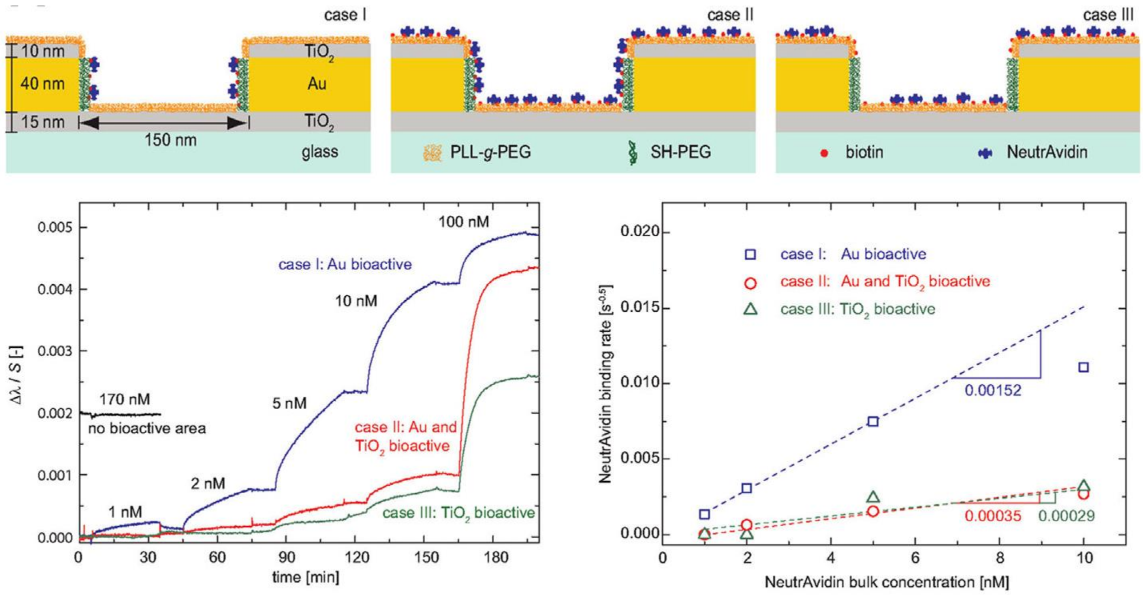
Localized surface plasmon resonance (LSPR)

- Principle: based on metallic nanostructures MNPs (Au, Ag…)
- Interaction of incident light with MNPs→ localized plasmon resonance on the structures
- Laser power: 0.5 → 1 mW



SPR image from angle and wavelength shift





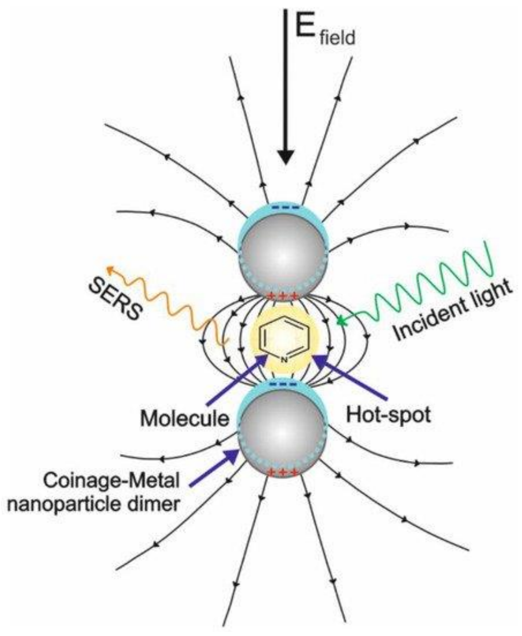
- Application for diagnosis: more sensitive than SPR, lower limit of detection, miniaturization, less bioreceptors, multiplex

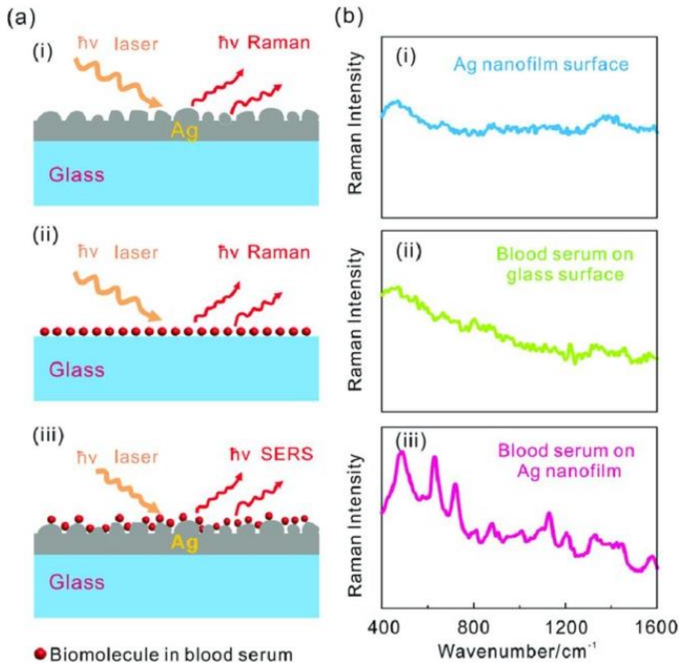
Estevez et al, Analytica Chimica Acta 806 (2014) 55-73

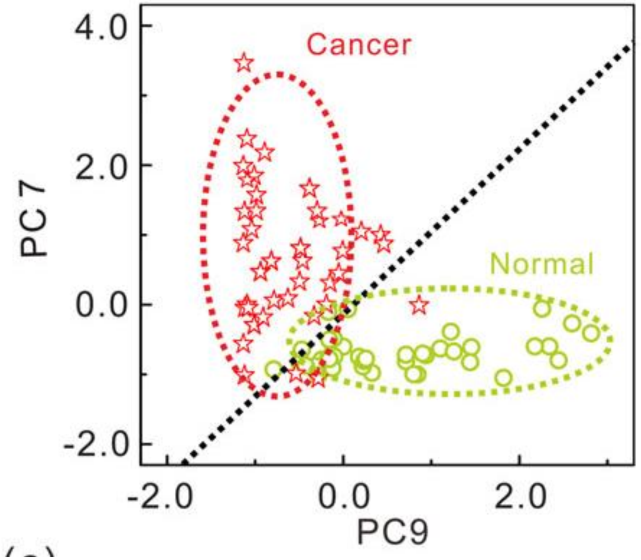
OPTICAL TRANSDUCER (5/7)

Surface enhanced Raman Scattering (SERS)

- Principle: based on the amplification of the Raman response (incident light = laser) of an analyte interacting with the surface plasmon of metals such as Au, Ag, or Cu
- Label free method, non invasive, rapid
- Higher-efficiency than normal Raman spectroscopy
- Diagnosis: diagnostic specificity 97%







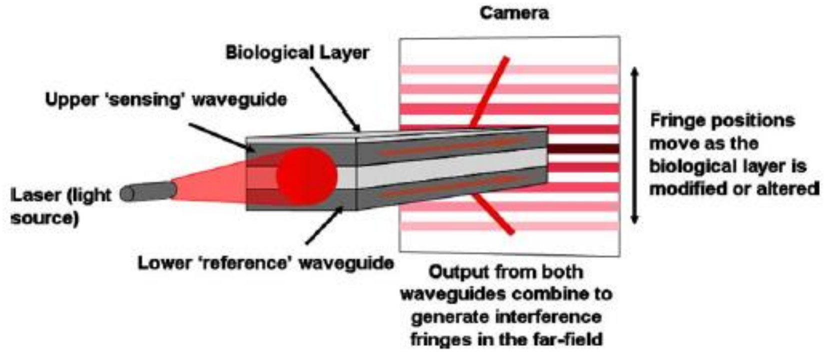
Successfull differentiation of the liver cancers from the normal subjects with high-diagnostic sensitivity of 95.0% and diagnostic specificity of 97.6%

[Liu] Liu et al 2018

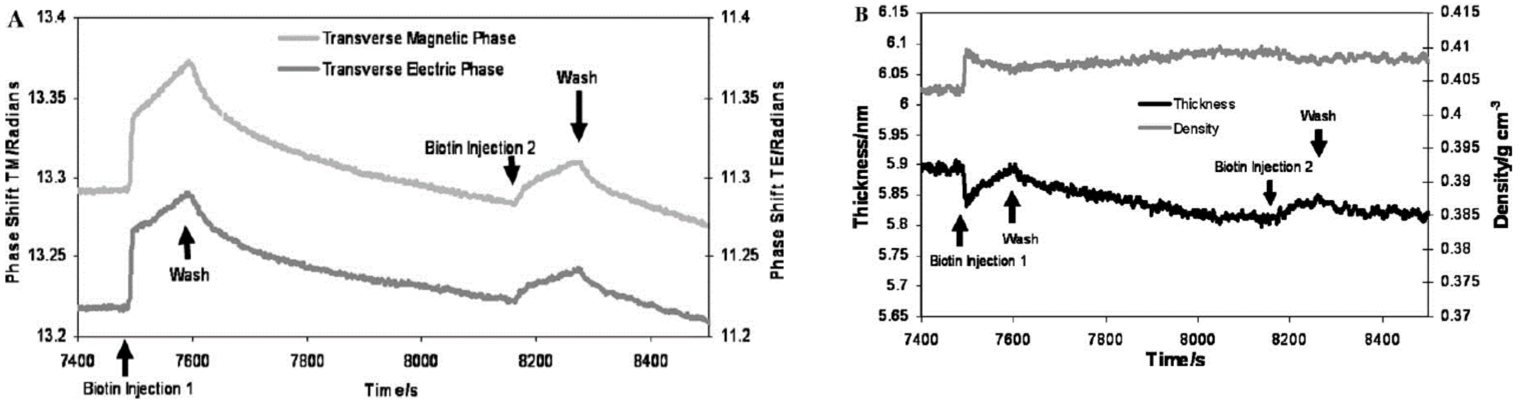
OPTICAL TRANSDUCER (6/7)

Interferometry

- Interoferometric method (« Dual Polarization Interferometry TM et TE» (DPI) Interference generated by two guides → Fringes
  - Principle: the immobilization of biomolecules on the surface of one waveguide modifies the effective index of the guided mode and induces Δϕ between two polarizations



Laser He-Ne / polarizer/2 optical waveguides/camera



Thickness and density of Streptavidin binding free D-Biotin

- Real time measurements
- LOD: a few pg/mm^2

Swann et al,Analytical Biochemistry, vol.329, pp. 190-198, (2004),
D. Johnson BSc,PhD thesis, “Molecular level investigation of coiled-oil proteins”University of Nottingham, (2005).

OPTICAL TRANSDUCER (7/7)

Comparison of performances

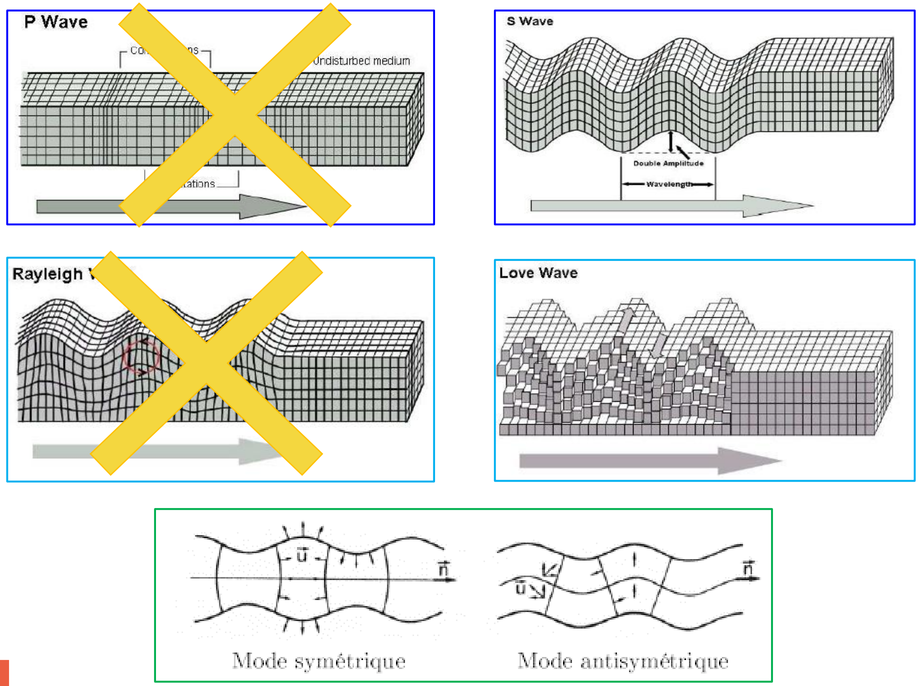
Biosensor	Multiplexing	Commercialization	Label-free?	Selected biological applications
SPR	+ +	+ + +	Yes	Kinetic analysis of biointeractions Antigens in clinical samples Proteins in biological samples Xenobiotics and toxins in food Carbohydrate-specific interactions
SPRi	+ + +	+ + +	Yes	Screening of biomarkers and therapeutic targets Screening of drug–target protein interactions
LSPR	+ +	+	Yes	Detection of DNA hybridization Screening of antigen–antibody interactions Cancer biomarker detection Toxin detection
Evanescent wave fluorescence	+ + +	+ + +	No	Clinical diagnostics, biodefence, food testing Clinical biomarkers Toxin screening
Bioluminescent optical fibre	+ +	+	No*	Response of cells to genotoxic agents Multidetection of genotoxins by live cell array
Waveguide interferometric	+ +	+	Yes	Study of cellular responses and processes Virus detection
Ellipsometric	+ +	+	Yes	Characterizing viral receptor profiles Detection of serum tumour biomarker
RIfS	+ +	+ +	Yes	Xenobiotics in food Detection of circulating tumour cells
SERS	+	+	Yes	Detection of cancer proteins Protein biomarker in environment

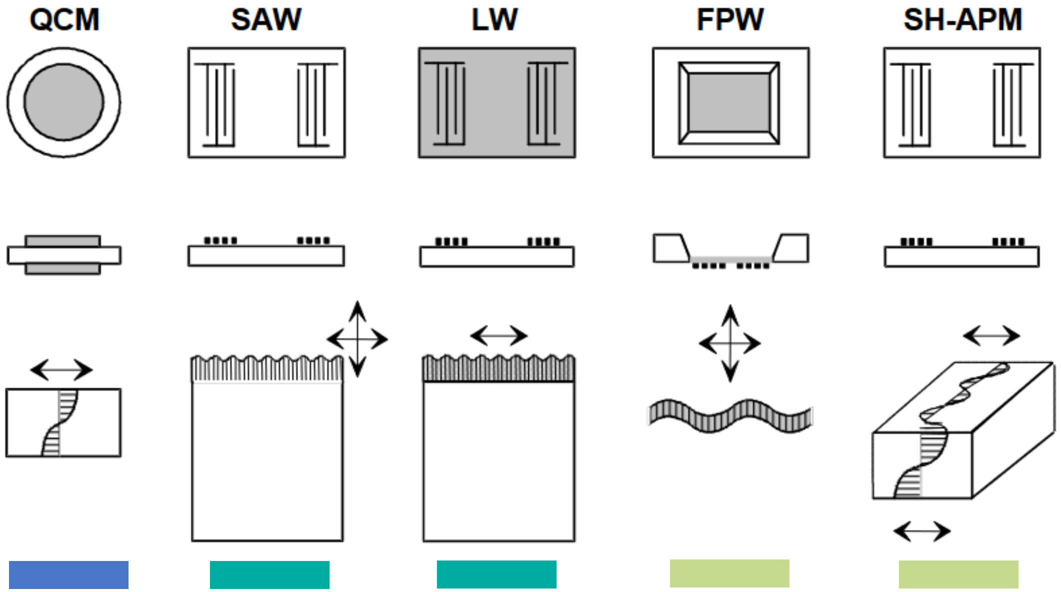
Damborsky P. Essays in biochemistry (2016) 60 91-100

ACOUSTIC TRANSDUCER (1/7)

Acoustic waves: Propagative perturbation of the equilibrium of a medium or a material.

- Elastic regime
- Longitudinal/ transverse propagation
- **Bulk acoustic wave**, **surface acoustic wave**, **plate wave**





- Piezoelectric materials: quartz, ZnO , AlN, $LiNbO_3$, $LiTaO_3$, $KNTiO_3$, $SrTiO_3$, $BiFeO_3$ and $BaTiO_3$

ACOUSTIC TRANSDUCER (2/7)

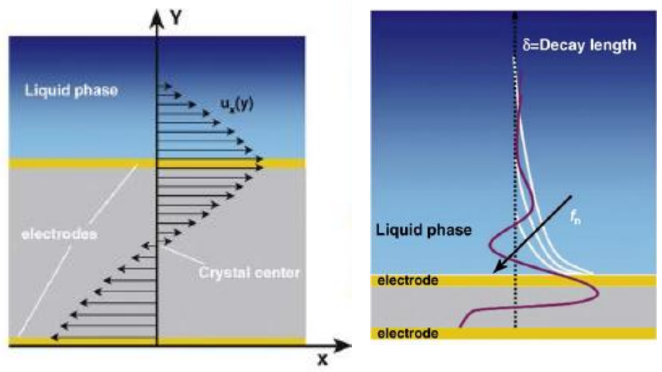
BAW: Quartz Crystal Microbalance (QCM)

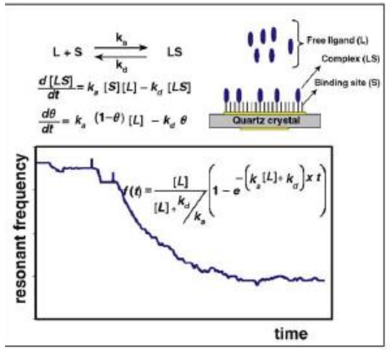
Principle: Piezoelectric effect → resonance of the device → shift in frequency Δf and change in resonance magnitude due to a change in mass

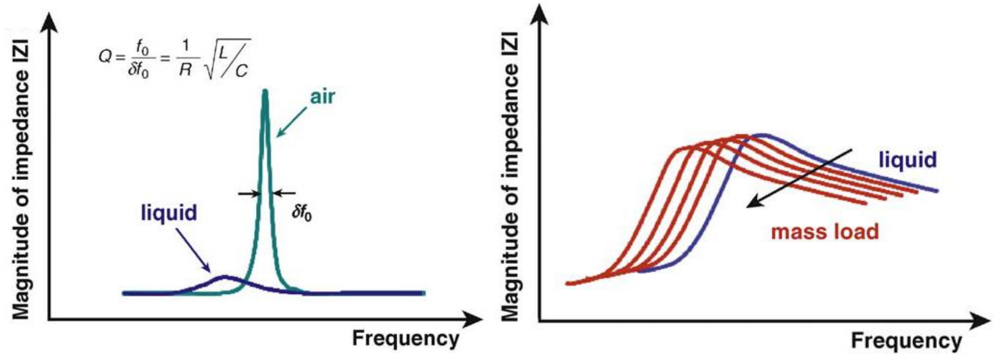
- Generation of shear waves
- Shift in resonance frequency Δf due to Δm and to liquid

$$\Delta f = \Delta f_m + \Delta f_L = -\frac{2 f_0^2}{n(C_{66}\rho_q)^{1/2}}\left[\frac{\Delta m}{A} + \left(\frac{\rho_L \eta_L}{4\pi . f_0}\right)^{1/2}\right]$$

- Penetration depth : 250nm for f_0=5MHz, depending on the resonance frequency







- Sensitivity: : less than 1ng/cm^2
- Good accurancy, reliability,
- Easy microfabrication, low power consumption

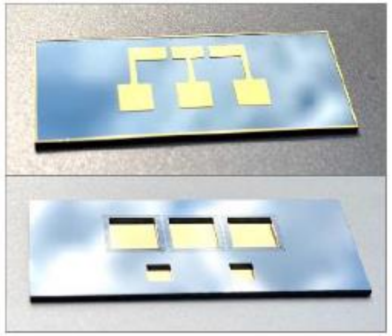
Ferreira G, Trends in Biotechnology, 27(12) 2009

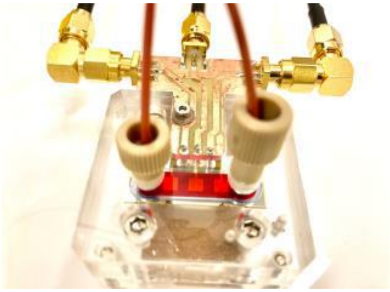
ACOUSTIC TRANSDUCER (2/6)

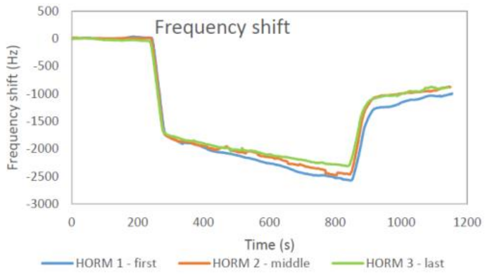
Comparaison between Quartz crytal Microbalance and SPR

	LOD: (mass/area)	LOD_M: (total mass)	Kinetics Analysis Capability	Multiple Channels	Sample Volume	Chips
SPR	0.1 ng/cm^2	~1 fg	Excellent	Easy	10 to 100uL	Au on Glass
QCM	1 ng/cm^2	~1 fg	Difficult	Difficult	~50 to 200 uL	Au on Quartz

→ Miniaturization and multiplex measurements





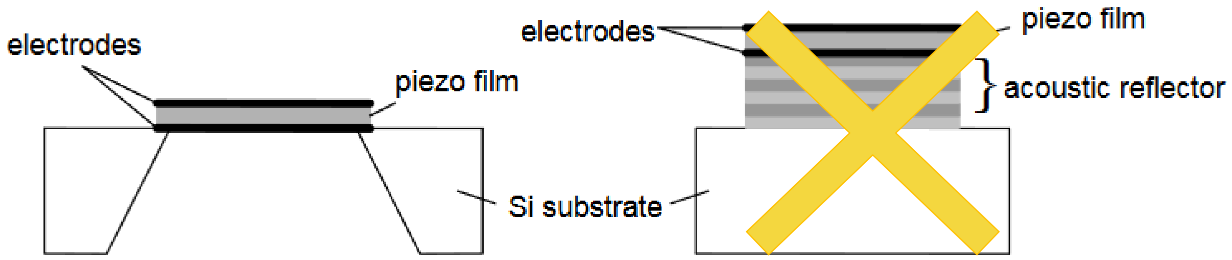


ACOUSTIC TRANSDUCER (3/6)

BAW FBAR: Thin-film bulk acoustic resonator

Principle: device consisting of a piezoelectric material manufactured by thin film methods between two conductive – typically metallic – electrodes and acoustically isolated from the surrounding medium.

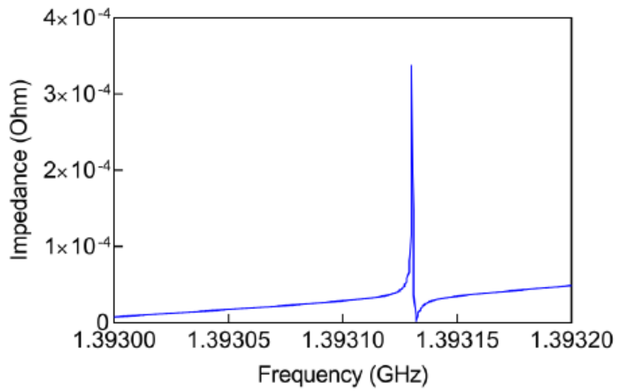
- Two types of structures: membrane / SMR
- High resonance frequency: 200 MHz to 10 GHz
- Rather complex manufacturing
- More sensitive than QCM / Fragile / not often used in liquid

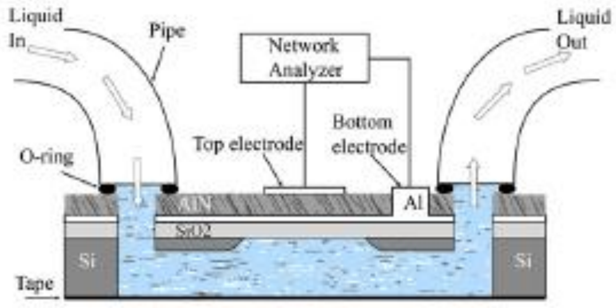


- In Newtonian liquid $$\Delta f_N = -f_R^{3/2}\sqrt{\frac{\rho_l \eta_l}{\rho_0 \mu_0 \pi}}$$
- In non Newtonian liquid $$\Delta f_M = \Delta f_N + \frac{f_R \Delta D}{2}$$

$$\Delta D \approx -2 f_R^{1/2}\sqrt{\frac{\rho_l \eta_l}{\rho_0 \mu_0 \pi}}$$

With ΔD = dissipation





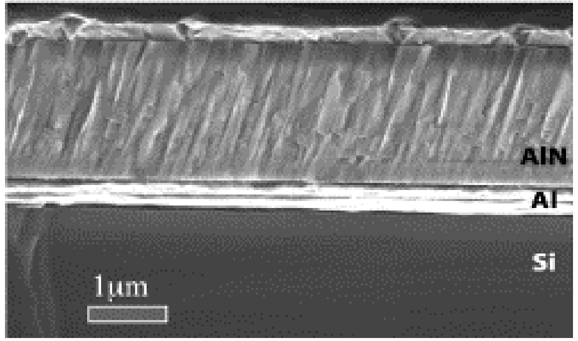
Fu et al, Progress in materials science 89 (2017) 31-91
Wingqvist et al, surface & coating technology 205 (2010) 1279-1286
Patel R. et al, Materials today proc. 4 (2017) 10377–10382

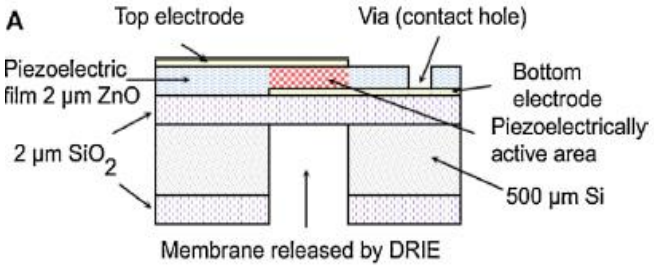
ACOUSTIC TRANSDUCER (3/6)

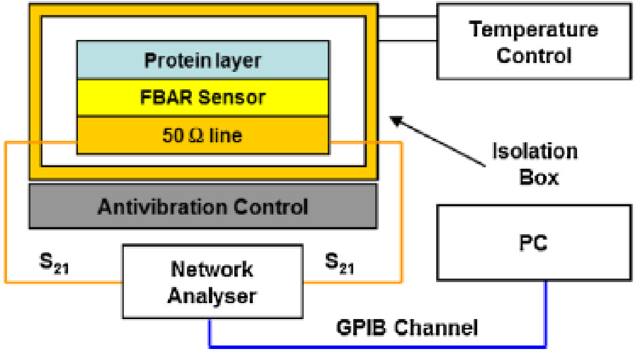
BAW FBAR

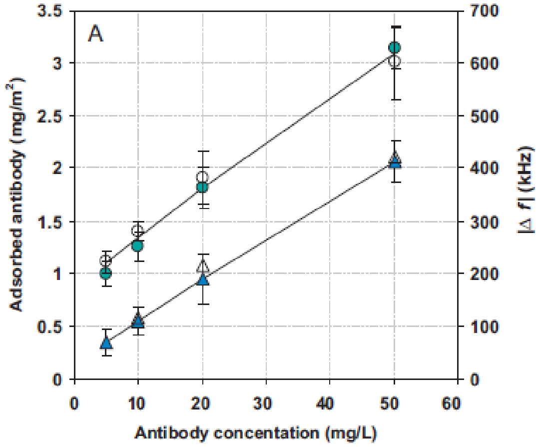
Application for diagnosis: detection of hPSA

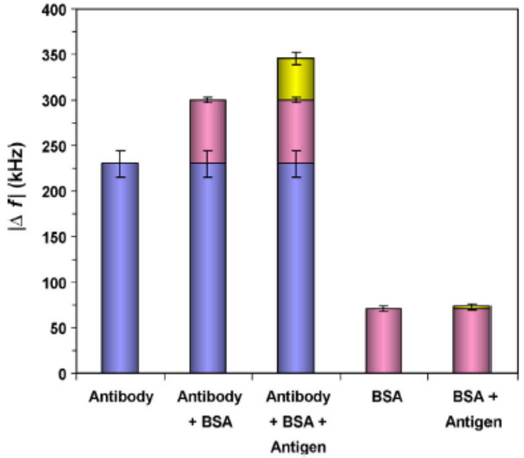
- Resonance frequency: 1.5 GHz
- Structure Si/SiO_2/ZnO/Cr-Au
- Sensitivity in mass: 0.5ng/cm^2 - corrélation with ellipsometry











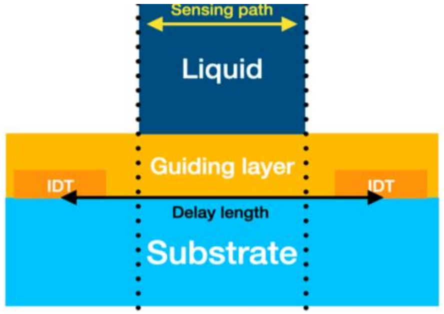
- Low cost, label free, possibility of integration
- Sensitivity FBAR> Sensitivity QCM
- Limit of detection FBAR < Limit of detection QCM

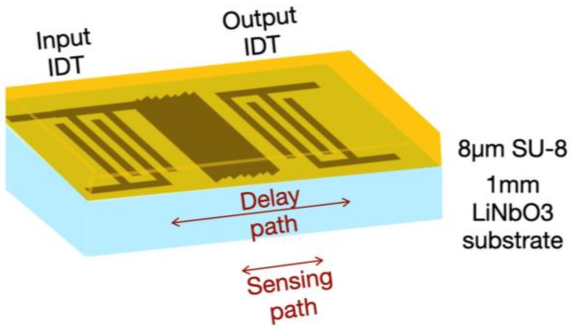
Zhao, Sensors and Actuators,B190(2014) 946-953

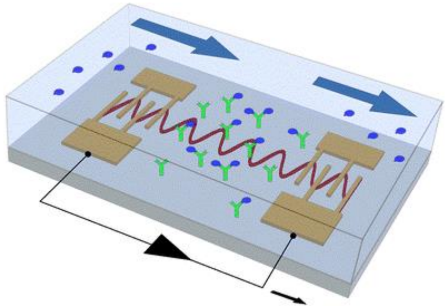
ACOUSTIC TRANSDUCER (4/6)

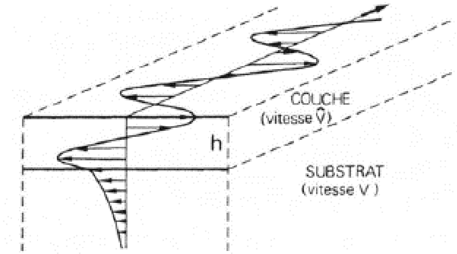
SAW: Love wave → Shear waves generated by two IDTs

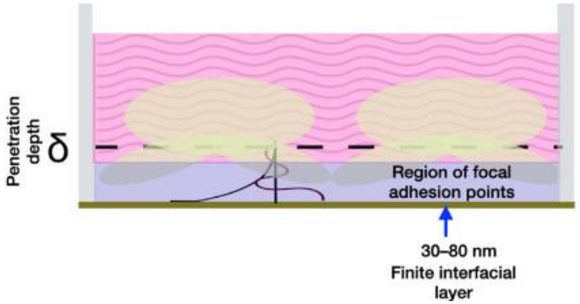
- Three different materials: substrate rigid solid, a viscoelastic guiding layer, and the sensitive layer; a Newtonian liquid as the top layer
- Parameters: thickness, density, dielectric constants, piezo constants, elastic constants, viscosity
- Guided wave in a guiding layer, electric isolation of the IDTs

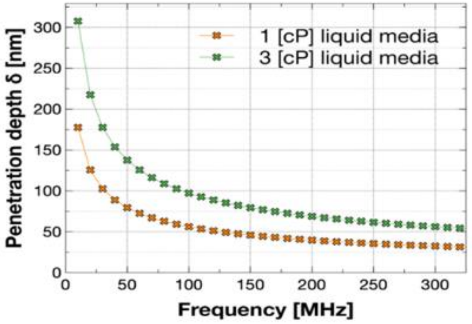


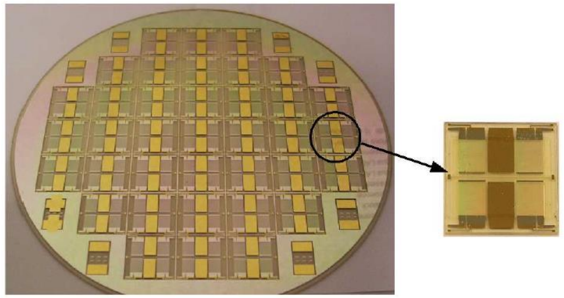












- Penetration depth depending on the resonance frequency and the viscosity

El Fissi L. PhD thesis UFC, December 2009
Chavez et al. *Biosensors 2022, 12(2), 61*

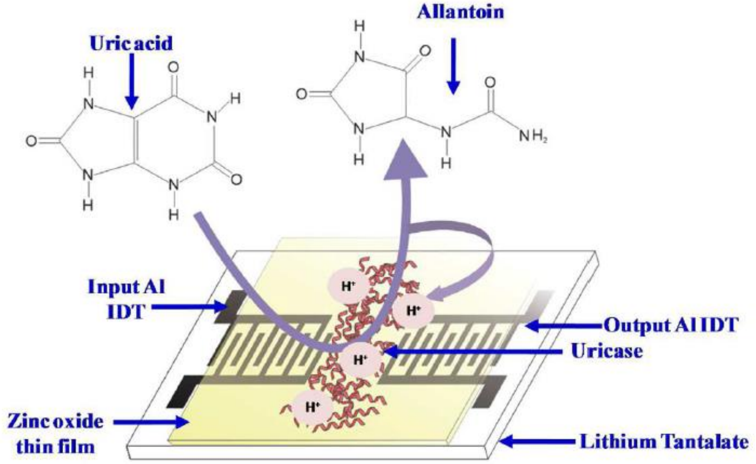
ACOUSTIC TRANSDUCER (4/6)

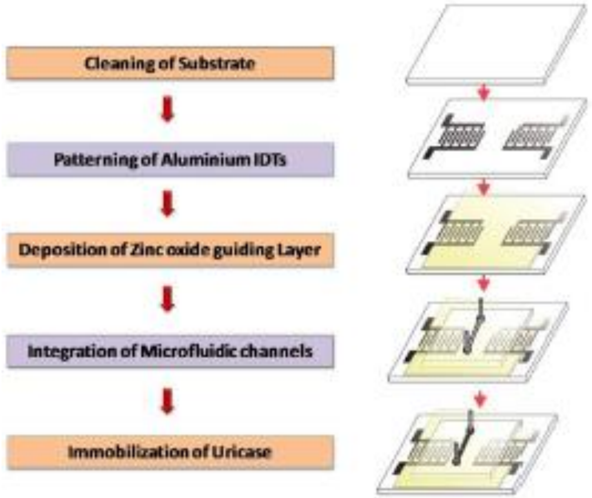
SAW: Love wave transducer

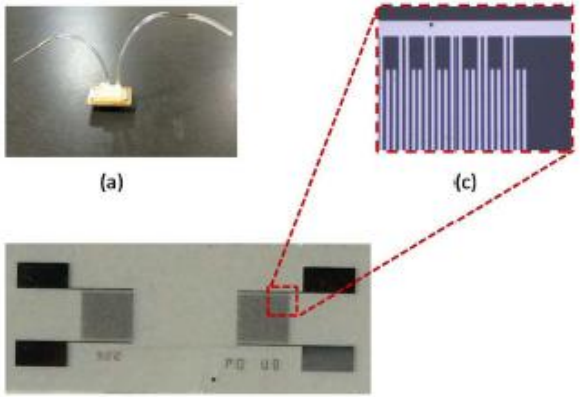
Application : uri acid measurement

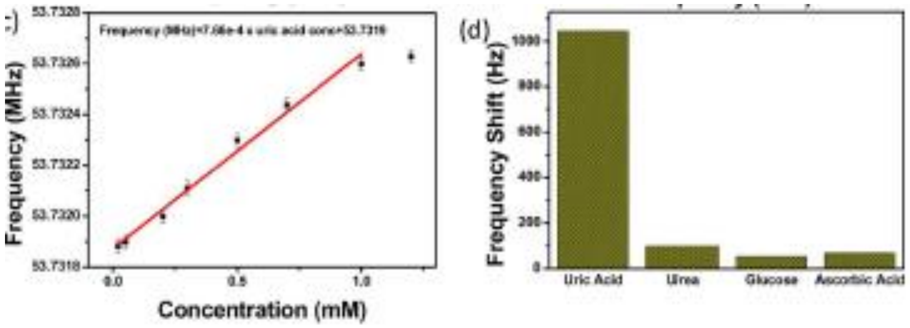
- $LiTaO_3$ and ZnO device
- Resonance frequency: f=53MHz
- chemical reaction:

$$Uricacid + O_2 + H_2O \xrightarrow{Uricase} Allantoin + H_2O_2 + CO_2$$









- High sensitivity: 766Hz/mM
- LOD: 5µM
- Mechanically robust device

Rana et al, Sensors and actuators B 261 (2018)169-177

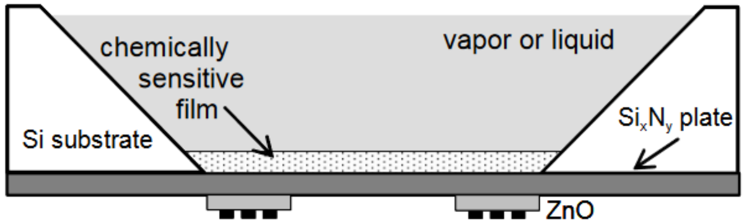
ACOUSTIC TRANSDUCER (5/6)

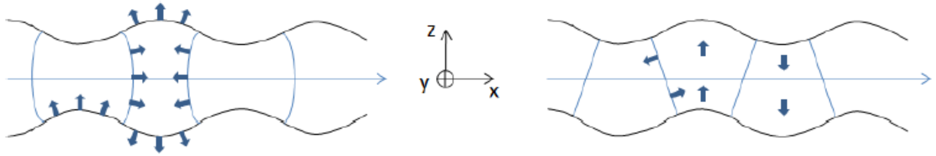
Plate waves - Lamb waves

- Wavelength λ> plate thickness → membrane
- Resonance frequency fr depending on the phase velocity and the geometry of the device
- Waves propagate laterally

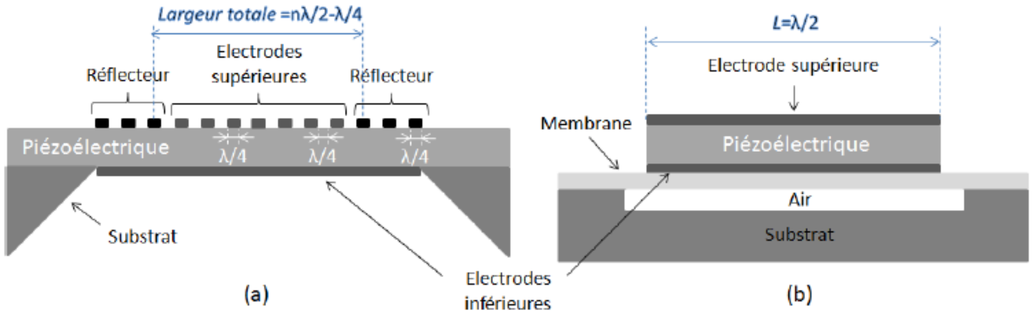
$$f_r = \frac{n v_\varphi}{2L}$$

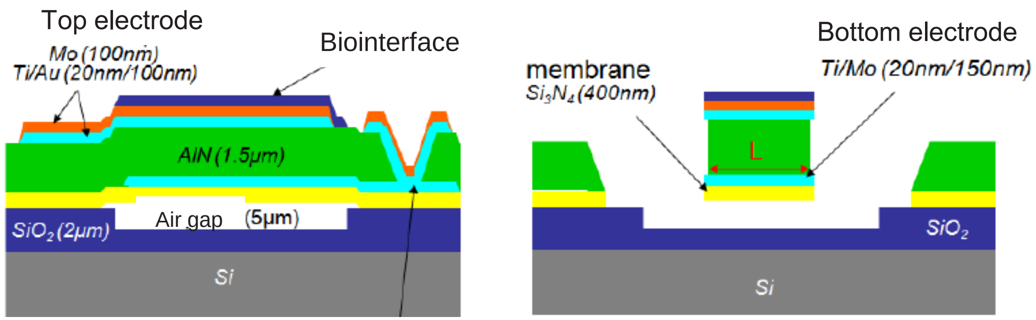
- Two types of geometries
- With reflectors / Plates free on one side





Symmetric mode   Antisymmetric mode





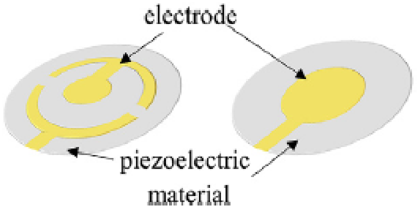
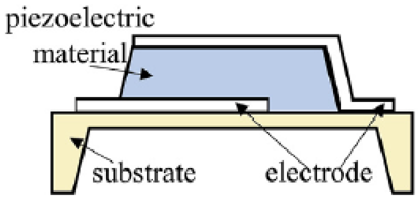
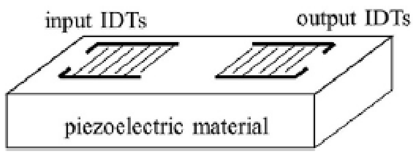
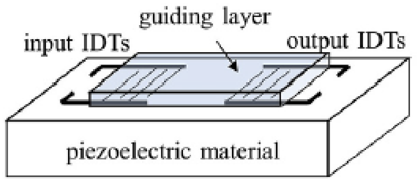
- Small radiation loss in the testing liquid
- High sensitivity
- Short response time
- Low fabrication yield (<10%)
- High insertion loss (>−50 dB)

Matthieu Desvergne, PhD thesis Univ Bordeaux, October 2007

ACOUSTIC TRANSDUCERS (6/6)

Comparison between several acoustic wave biosensors

Key parameters of typical acoustic wave biosensors used for disease-related biomarker detection.

Biosensors	Structure	Piezoelectric substrate	Resonant frequency (MHz)	Sensitivity (Hz. cm²/MHz/µg)	Advantages	Problems
QCM		AT-cut quartz , $LiNbO_3$	5-170	12-70	➢Easy to manufacture ➢Cheap ➢Long-term stability	➢Low detection resolution ➢Large size
FBAR		ZnO, Si_3N_4, AlN	1000 -5.2×10^3	740 -1.425×10^5	➢Very high sensitivity ➢Small size and light weight ➢Low power consumption ➢Compatible with CMOS	➢Large signal to noise ratio ➢Hard to signal control and measurement ➢Not good anti-interference ability ➢Fragile membrane
SH-SAW		$LiNbO_3$, $LiTaO_3$, AT-cut quartz, $KNbO_3$, AlN, ZnO	30-500	70-180	➢Low power consumption ➢Cheap ➢Wireless control	➢The excited wave is usually impure which causes energy loss
LW-SAW		$LiNbO_3$, $LiTaO_3$, AT/ST-cut quartz, ZnO/ SiO2/Si, AlN	80 -1.586×10^3	41.62−950	➢High sensitivity and corrosion resistance among SAW sensors because of the wave guiding layer	➢Guiding layer effect ➢The higher the thickness of guiding layer, the worse the insertion loss

Zhang et al., *Analytica Chimica Acta* 1164 (2021) 338321

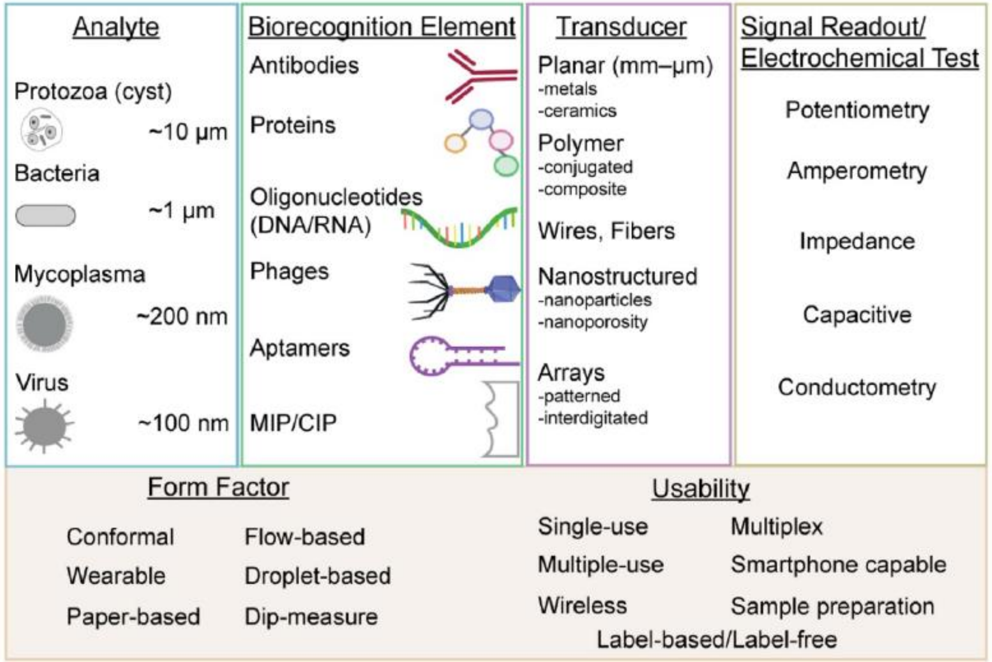
ELECTROCHEMICAL TRANSDUCER (1/6)

Analyte binding → redox reaction/ electrical conductivity change at the interface

- some of the most used biosensors in the market, mainly due to glucose monitoring

- easily miniaturised, inherently inexpensive and require simple electronics for conditioning and read-out, making them ideal for point-of-care applications

- 5 types of transducers



Components and measurement formats associated with electrochemical biosensors [Cesewski]

[Cesewski] Cesewski et al., *Biosensors and bioelectronics* 159 (2020) 112214

ELECTROCHEMICAL TRANSDUCER (1/6)

Types of electrochemical transducers

Measurement type	Transducer	Transducer analyte
1. *Potentiometric*	ion-selective electrode (ISE) glass electrode gas electrode metal electrode	K^+, Cl^-, Ca^{2+}, F^- H^+, Na^+... CO_2, NH_3 redox species
2. *Amperometric*	metal or carbon electrode chemically modified electrodes (CME)	O_2, sugars, alcohols... sugars, alcohols, phenols, oligonucleotides...
3. *Conductometric, impedimetric*	interdigitated electrodes, metal electrode	urea, charged species, oligonucleotides...
4. *Ion charge or field effect*	ion-sensitive field effect transistor (ISFET), enzyme FET (ENFET)	H^+, K^+...

Type of electrochemical transducers for classified type of measurements, with corresponding analytes to be measured [Thevenot]

[Thevenot] Thevenot et al., *Biosensors and bioelectronics* 16 (2001) 121– 131

ELECTROCHEMICAL TRANSDUCER (2/6)

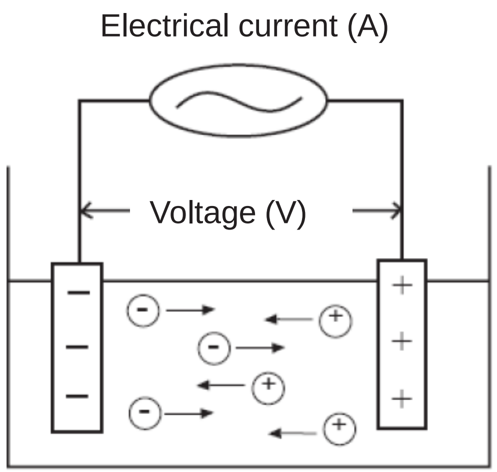
Conductometry

- **Conductivity change in the solution via the production or consumption of charged species**
    - Principle: Generation of an alternative voltage (fixed voltage) between two electrodes. Measurement with an impedance meter, Z= voltage/current ratio.
    - Measurement: variations (consumption or production) of charged species during enzymatic reactions.
    - Conductance G : $G = \gamma A / \lambda$

      γ (S.cm-1): conductance or specific conductivity of the product;

      A (cm): geometrical constant of the cell

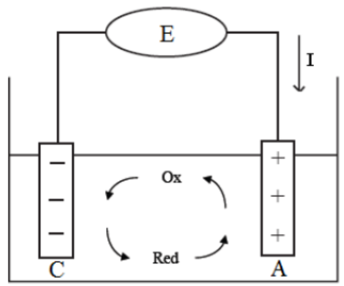
    - High sensitivity
    - Miniaturization (only 2 electrodes)
    - Differential measurement (with and without enzyme)



ELECTROCHEMICAL TRANSDUCER (3/6)

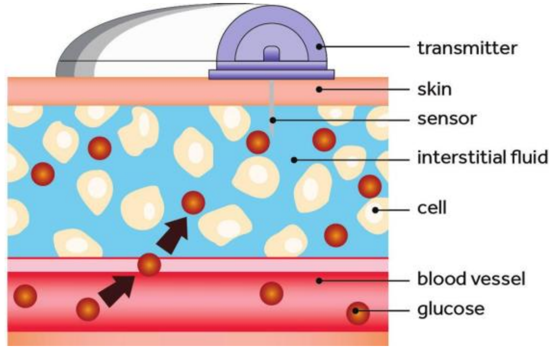
Amperometry

- **Current change due to a redox reaction in the solution pA < I < nA**
  - Principle: measuring currents due to the oxidation or reduction of electroactive species occurring locally in contact with a working electrode. Consumption of one of the products of the reaction.
  - Selectivity governed by the redox potential of the electroactive species present in the solution
  - fast, more sensitive, more accurate and more precise than potentiometric biosensors
  - Example: Glucose
    - Amperometric measurement of H_2O_2



$$\beta\text{-}D\text{-Glucose} + O_2 \xrightarrow{\text{Glucose-Oxydase}} D\text{-gluconic acide} + H_2O_2$$

$$H_2O_2 + 2H_2O \longrightarrow 2H_3O^+ + O_2 + 2\,e^-$$



ELECTROCHEMICAL TRANSDUCER (4/6)

Potentiometry

- Principle: measuring variations in open circuit potential, of which biologically sensitive field-effect transistors Voltage is a special type
- Potential change between an ionosensitive electrode (transducer) and a reference electrode Cal or Ag/AgCl
  - Local equilibrium at the transducer surface → potential proportional to the logarithm of the concentration of the sample according to Nernst's law :

$$E = E^0 + 2,3\frac{RT}{nF}\lg\frac{a_{Ox}}{a_{Red}}$$

E : potential redox couple

E^0: normal potential redox couple

R: constant ideal gaz

a_{Ox}/a_{Red}: ratio of species activity dominating the potential in oxidized and reduced states

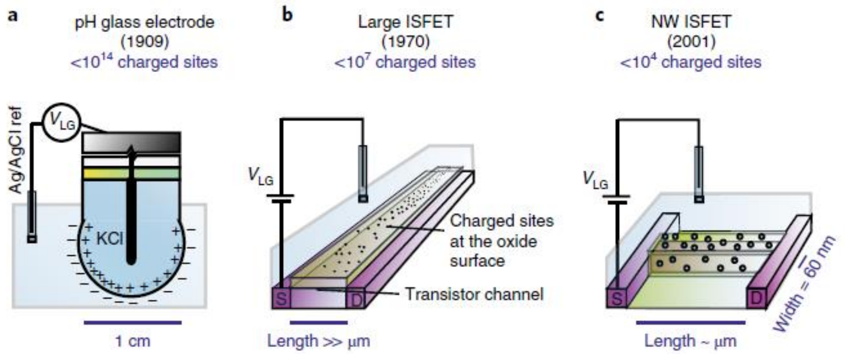
T: Temperature in Kelvin

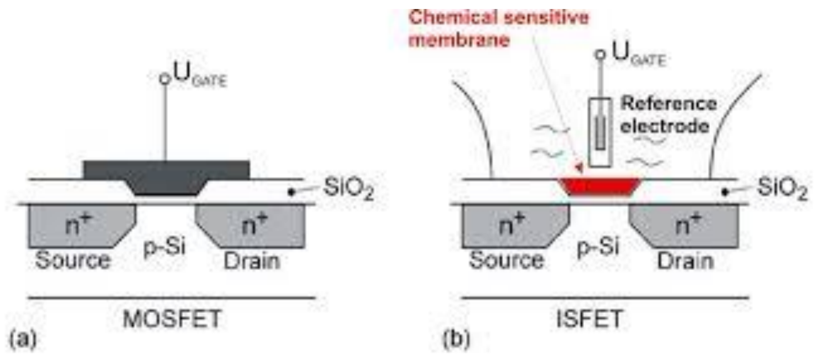
  - Two methods: ISE (Ion Sensitive Electrodes: metallic electrode)/ ISFET (H^+, K^+, Na^+, Ag^+, F^-, Br^-, I^-, Ca^{2+}, NO_3^-)

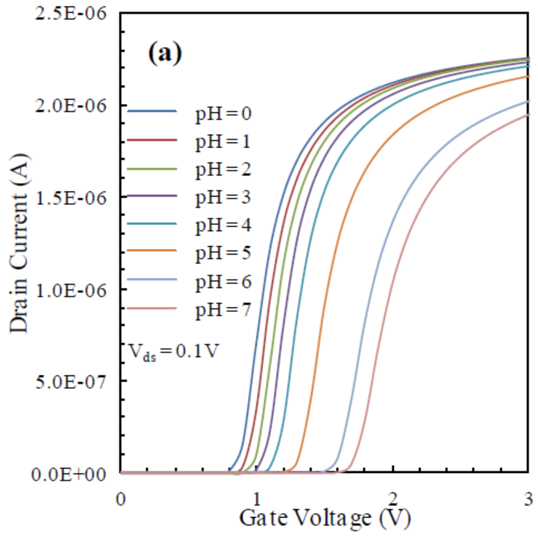
ELECTROCHEMICAL TRANSDUCER (4/6)

- ISE: ion sensitive electrodes (pH or monovalent ions)
  - Macroscopic device, analysis in 30 minutes

- ISFET (Ion sensitive Field Effect Transitor) based on MOSFET principle
  - Miniaturized, analysis in a few minutes, low cost, robust







Miniaturization of ISFET (1), principle MOSFET / ISFET(2) and electrical characteristics (3)

(1) Rsivakumarsamy R. et al, nature materials 17(2018) 464-470
(2) 2) Bergveld P. et al, IEEE Trans. on Biomedical Engin. 17(1970)
(3) Singh A. et al, proc. 3rd Int. Conf. NANOCON, oct 2014

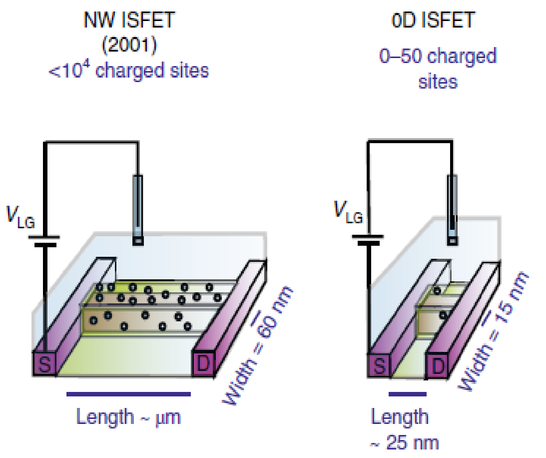
ELECTROCHEMICAL TRANSDUCER (4/6)

0D ISFET: sensor ⇔ Si nanotransistor

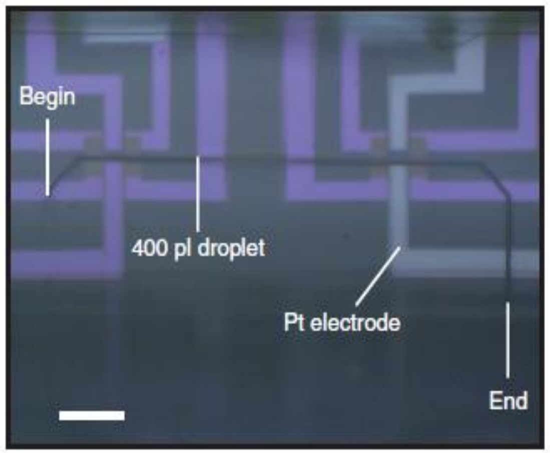
Principle: measurement of ionic effects independent of pH.

- Technological development at nanoscale: nanotransistor Si technology
- No selective coating for ionogram measurements in blood/ independant of pH
- Clinical application: dépistage (for hyperkalemy or renal insufficiency) or therapeutic monitoring

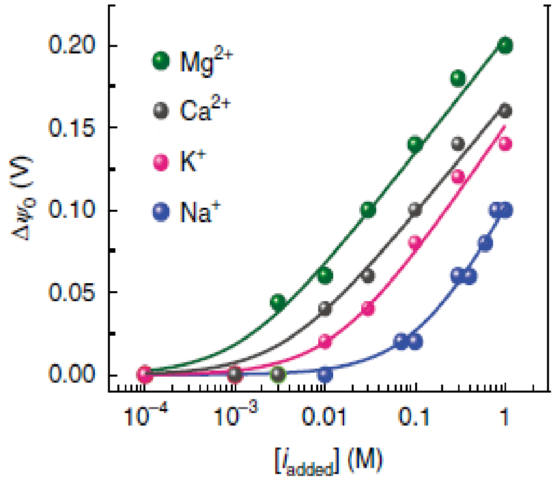
  - Low cost, subnanoliter volume, miniturization, portable, reusable, label-free



Nanowire to 0D ISFET



Subnanolitre sensing and high integration



Sivakumarasamy R., nature materials 17(2018) 464-470

ELECTROCHEMICAL TRANSDUCER (5/6)

Impedimetry

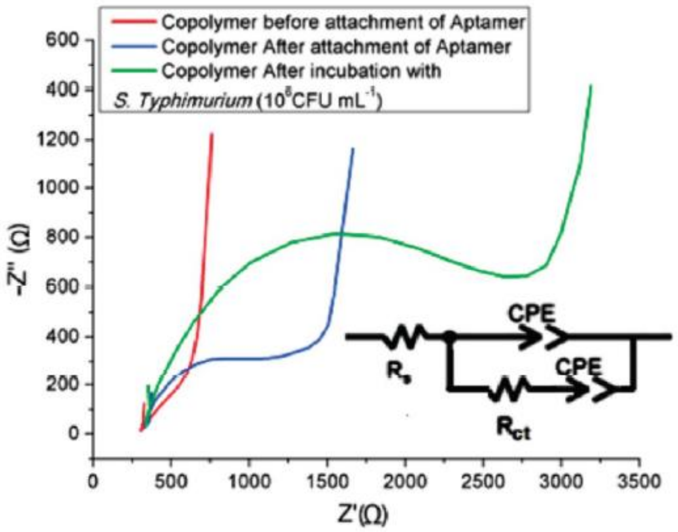
Principle: measuring the ratio: impedance = AC potential / AC current.

- Electrochemical impedance spectroscopy (EIS)
- Impedance is measured over a wide range of AC potential frequencies, typically from 100 kHz to 1 MHz

→ useful information about the physico-chemical changes that take place when an analyte binds

→ Application: detection of cancer and other disease biomarkers, bacteria, polluting agents, toxins

→ **Attomolar concentration**



Detection of S Typhimurium

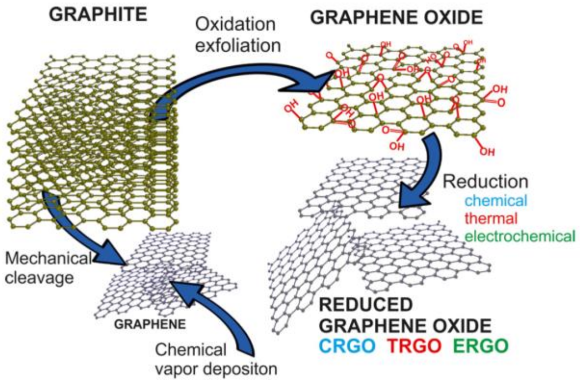
[Cesewski] Cesewski et al., *Biosensors and bioelectronics* 159 (2020) 112214

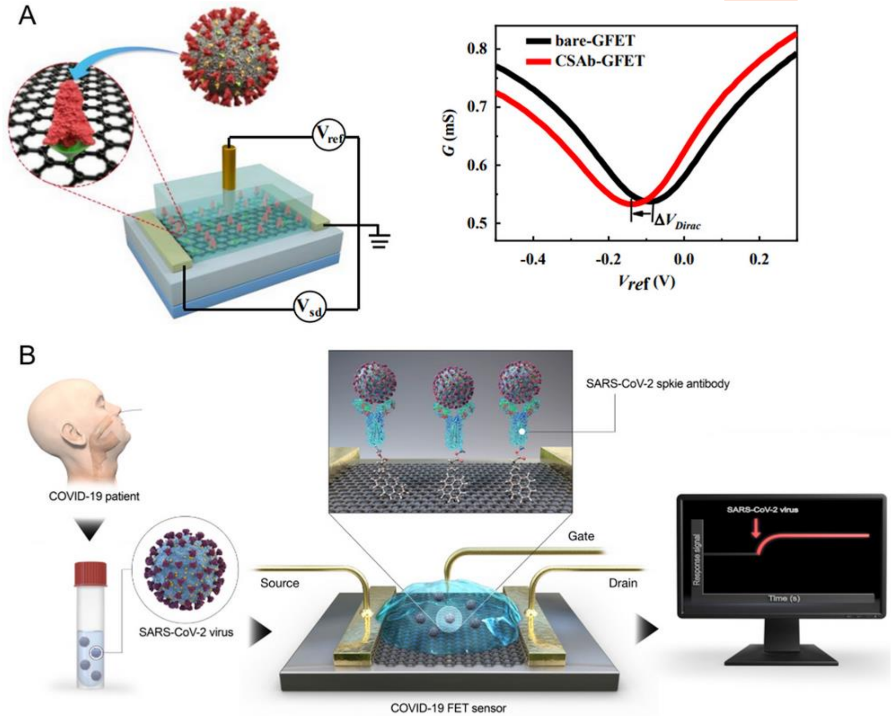
ELECTROCHEMICAL TRANSDUCER (6/6)

Nanomaterial based electrochemical biosensors

Principle: nanomaterial modified electrodes for the construction of biosensors compared with planar electrodes

→ Lowering the limit of detection to unparalleled levels
→ Better accessibility of analyte molecules to reach immobilised biomolecules
→ Direct electronic wiring of redox enzymes allowing direct electron transfer between the modified electrode and active site of the enzyme making such enzymatic biosensors more selective
→ Graphene oxide much cheaper compared with other nanomaterials
→ ultrasensitive affinity-based electrochemical biosensors





New graphene biosensor can detect SARS-CoV-2 in under a minute

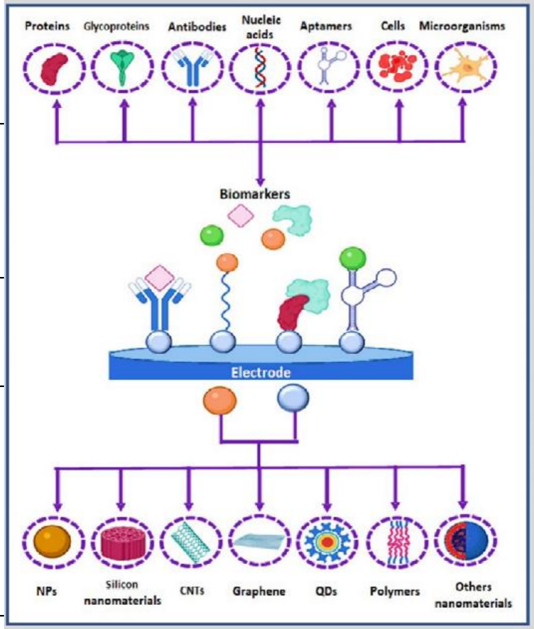
Hammond et al., *Essays in Biochemistry* (2016) **60** 69–80
Xu et al., *Biosensors and Bioelectronics (2020)* **170** 112673

A- Biosensor

ELECTROCHEMICAL TRANSDUCER (6/6)

Nanomaterial based electrochemical biosensors

Nanomaterial	Hybrid [a]	Target [b]	Analytical Characteristics		Comments
			Linear Range	LOD	
Metallic nanostructures	3D hybrid graphene–GNR.	H_2O_2	0 to 50 mM	2.9 µM	Metallic nanostructures have high catalytic activity, easy preparation, and relatively low cost. However, this kind of nanomaterial can change its oxidation state due to variations in conditions of the medium, such as pH, ionic strength, and temperature upon time.
	TiO_2 nanoparticles encapsulated ZIF-8	Glucose	2 to 10 mM	80 nM	
	Nanohybrid of VS_2/AuNP and $CoFe_2O_4$ nanozyme	Kana	1 pM to 1 µM	0.5 pM	
	Ag and hybrid Ag–Fe_3O_4 metallic nanoparticles.	AA	0.2–60 µM	74 nM	
Silicon nanomaterials	$mSiO_2$@MWCNT.	Thrombin	0.0001 nM and 80 nM	50 fM	These nanomaterials have high mechanical resistance, thermal stability, long functional life, and versatility; nonetheless, they require long synthetic processes, and their application is limited to certain analytes.
	MSF/APTES/AgNP	STR	1 to 6.2 ng/mL	0.33 fg/mL	
	Ap–GA–NH_2MCM-41–GCE	hemin and Hb	1.0×10^{-19} to 1.0×10^{-6} M	7.5×10^{-20} M and 6.5×10^{-20} M	
	AuNPs loaded in functionalized MSNPs	CEA	1.0×10^{-3} to 100 ng/mL	9.8×10^{-4} ng/mL	
Carbon nanostructures	MWCNTs and GQDs.	IL-13Rα2	2.7 to 100 ng/mL	0.8 ng/mL	These nanomaterials enjoy thermal stability, large surface area, and a wide range of nanostructures and functional groups. They are the main nanomaterials used in the preparation of electrochemical biosensors.
	GQDs/AuNPs.	P53	0.000592–1.296 pM	0.065 fM	
	CQDs/AuNps	Glucose	0.05 mM to 2.85 mM	17 µM	
	CoCu-ZIF@CDs	B16-F10 cells	1×10^2 to 1×10^5 cells/mL	33 cells/mL	
Polymers	(Chi-Py) mixture, AuNPs, and MWCNT	Escherichia coli	3×10^1 to 3×10^7 cfu/mL	~30 CFU/mL	These have high biocompatibility, high affinity, strong adsorption ability, low molecular permeability, physical rigidity, and chemical inertness in biological processes. However, functionalizing their surface is necessary for the anchorage of bioreceptors, and some polymers oxidize due to changes in medium conditions.
	PANI/active carbon and n-TiO_2	Glucose	0.02 mM to 6.0 mM	18 µM	
	PEG/AuNPs/PANI	alpha-fetoprotein	10^{-14} to 10^{-6} mg/mL	0.007 pg/mL	
Other nanostructured nanomaterials	WSe_2 and AuNPs	Thrombin	0–1 ng/mL	190 fg/mL	Other hybrid nanostructures have a large specific surface area, excellent electrical conductivity, and electrocatalytic properties.
	MoS_2/Ti_3C_2 nanohybrids	miRNA	1 fM to 0.1 nM	0.43 fM	
	AuNPs/Ti_3C_2 MXene 3D	miRNA155	1.0 fM to 10 nM	0.35 fM	



[a] GNR, graphene–gold nanorod; AuNPs, gold nanoparticles; Ap, aptamer; GA, glutaraldehyde; GCE, glassy carbon electrode; MSNPs, mesoporous silica nanoparticles; MWCNTs, multiwalled carbon nanotube; MSF, mesoporous silica thin film; APTES, (3-aminopropyl) triethoxysilane; AgNP, silver nanoparticles; CDs, carbon-dots; Chi-Py, pyrrole branched chitosan; PEG, polyethylene glycols; PANI, polyaniline. [b] AA, ascorbic acid; STR, streptomycin; miRNA; micro-RNA.

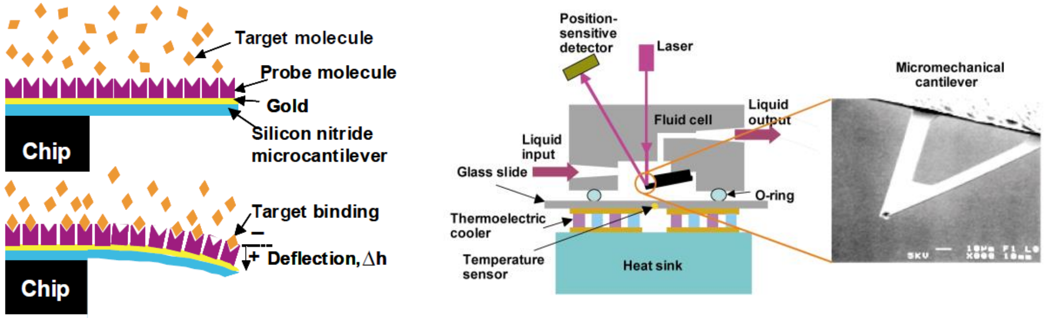
[Soto] Soto et al., *Molecules* (2022) 27, 3841

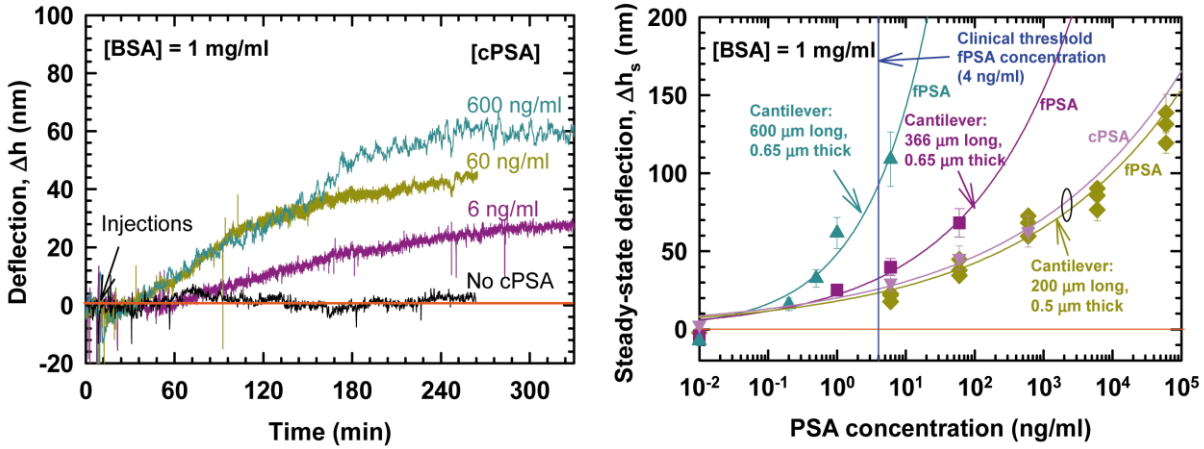
MECHANICAL TRANSDUCER (1/4)

Static cantilever deflection (MC)

Principle: optical detection of displacement linked to the variation of the surface energy: intermolecular bonds in cantilever surface

- Length L=200µm, width l=20µm, thickness d=0.5µm, silicon nitride
- Deflection $\Delta h = 3\sigma(1 - v)/E - (L/d)^2$, σ = surface stress
- Diffusion time $\tau = L^2/2D$





→Multiplex technique, miniaturization, label-free technique, specificity of capture

→Response time to be improved (3-4h) – due to diffusion

→Clinical use

- PSA 0,2 ng/ml → 60 µg/ml in HSA and human plasminogen (1mg/mL)

Wu et al, nature Biotechnol., 2001(19), 856-860

MECHANICAL TRANSDUCER (2/4)

Resonant microdevices (RM)

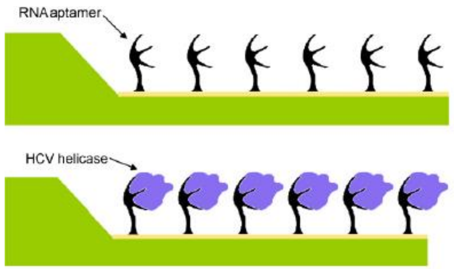
Principle: Dynamic deflection of nanocantilevers linked to stress generated by the interaction between helicase HCV and aptamer ARN → shift in resonance frequency

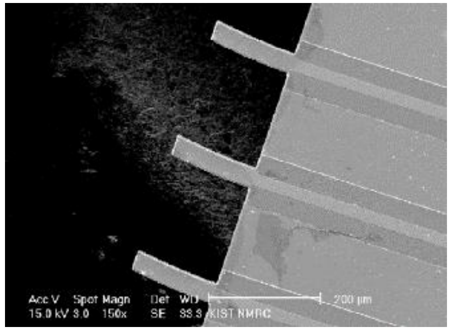
- PZT nanocantilevers Array, length L, fonctionnalized
- Shift in resonance frequency due to added mass negligeable compared to surface stress
- → stress

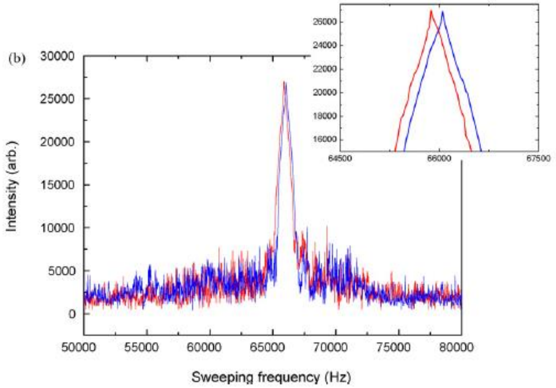
$$\omega_i = \left(\frac{\lambda_i}{L}\right)^2 \sqrt{\frac{\xi}{\mu}}$$

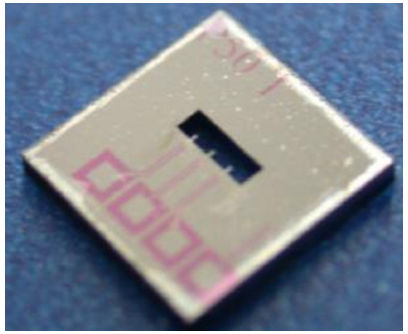
$$\nu_i \equiv \omega_i + \Delta\omega_i = \left(\frac{\lambda_i}{L}\right)^2 \sqrt{\left[\frac{\xi}{\mu + \Delta\mu}\right]\left[1 + \frac{2}{\pi^2}\frac{\tau L^3}{\xi}\right]}$$

$$\tau = \frac{\tau_0}{2}\left[2\left(\frac{\Delta\omega_i}{\omega_i}\right) + \left(\frac{\Delta\omega_i}{\omega_i}\right)^2\right]$$









- Resolution = concentration 100pg/mL in liquid, higher resolution compared to static cantilevers
- Label-free
- Intregration

Hwang et al, Biosensors and Bioelectronics 23 (2007) 459–465

MECHANICAL TRANSDUCER (3/4)

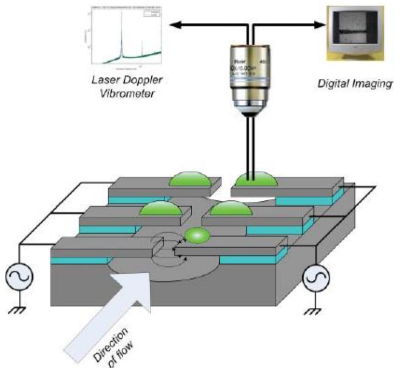
Resonant microdevices (RM): cantilevers (30nm width)

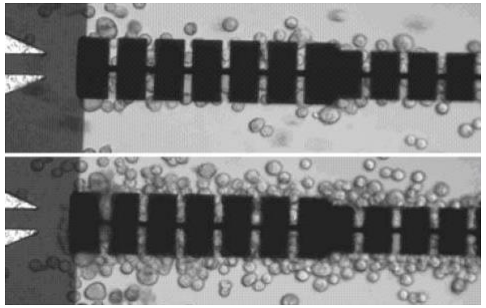
Principle: mass sensing of biological elements in physiological environment → frequency shift

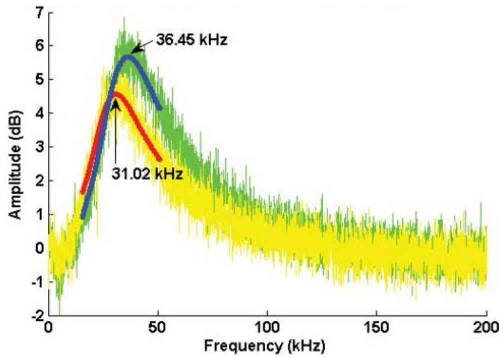
- Poly-L-lysine molecules coated on the surface of cantilever
- Measurements of adherent living cells HeLa: MC + confocal microscope
- Positive dielectrophoresis trapping (6V, 1MHz)→ High speed displacement (0.5 – 1mm/s)
- Change in resonant frequency

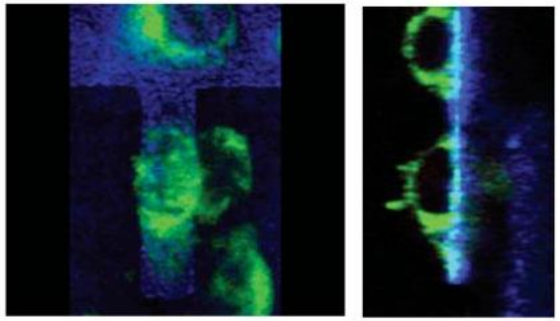
$$f_0 = \frac{3.515}{2\pi}\frac{1}{L^2}\sqrt{\frac{EI}{\rho_c A}}$$

$$\Delta m = \frac{k}{4\pi^2}\left(\frac{1}{f_1^2}-\frac{1}{f_0^2}\right)$$





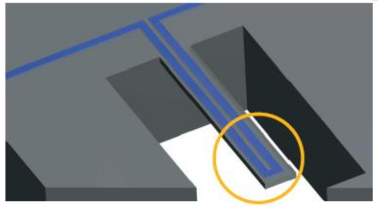




- In physiological environment (measurement at a single cell level)
- In real time, resolution a few ng
- Complementary characterization (microscopy)

Park et al, lab on Chip 2008 (8) 7, 993-1228

MECHANICAL TRANSDUCER (4/4)

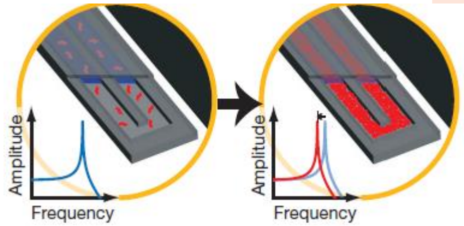


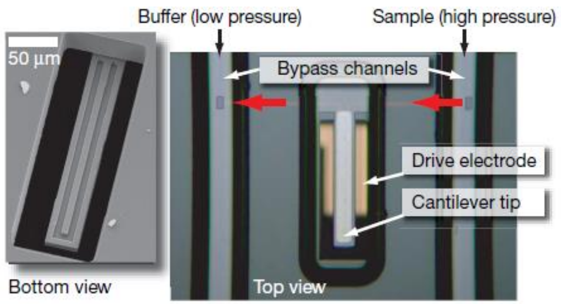
Suspended microchannel resonator (SMR)

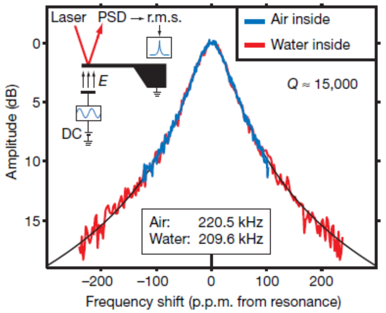
Principle: resonant device out of fluid→ high Q factor (no attenuation due to viscosity)

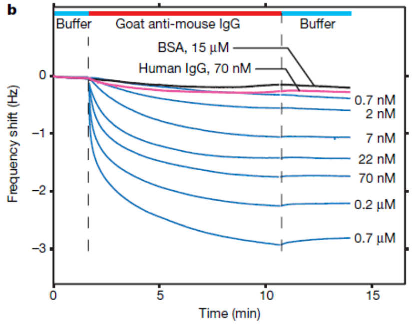
- Electrostatic excitation, optical detection
- microcantilever in a SOI substrate, 200*33*7 µm^3
- Channel with biological sample in the MC 3*8µm^2, by-pass channel 30*100µm^2
- Δm →

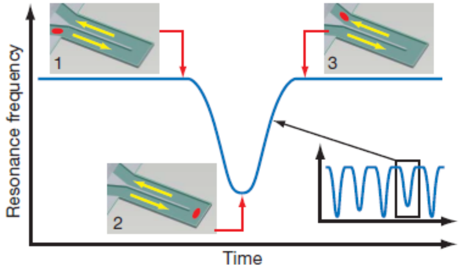
$$f = \frac{1}{2\pi}\sqrt{\frac{k}{m^* + \alpha\,\Delta m}}$$



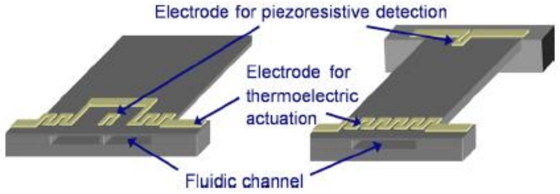






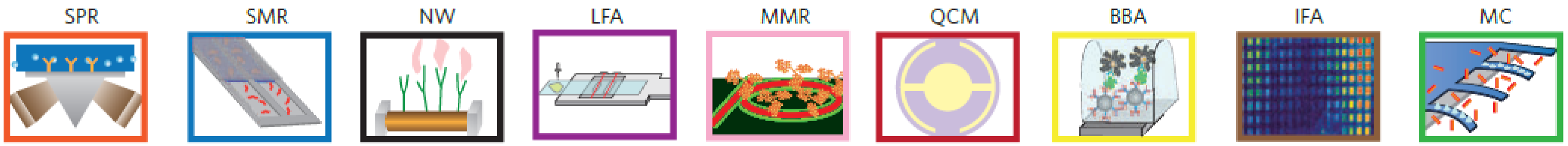


- Limit of detection: 300ag
- Enhanced sensitivity compared to resonant devices in liquid
- In flow
- Small volume of sample



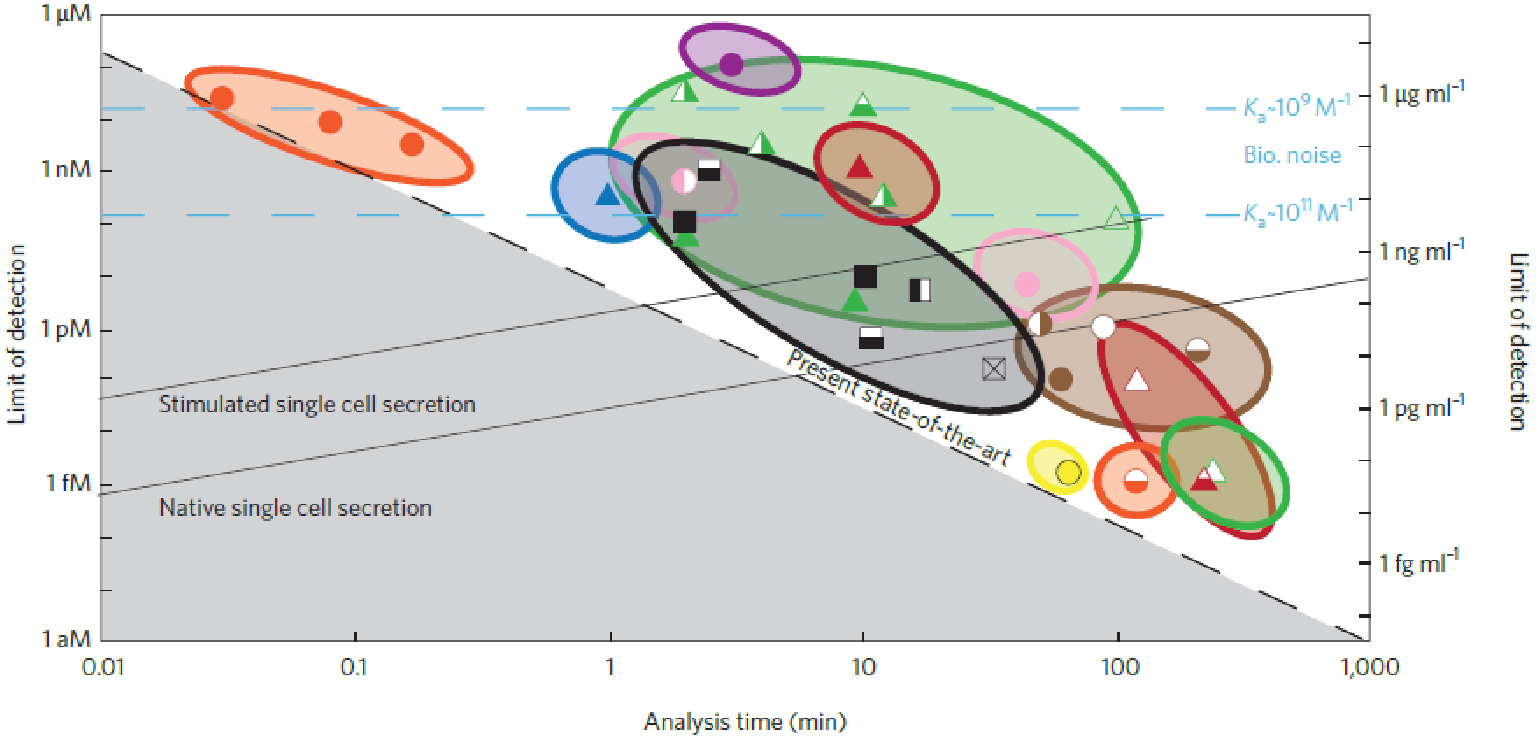
Burg et al, Nature 446 (2007) 1066
Arlett J. et al, Journ. Appl. Phys. 108 (2010) 084701

TRANSDUCERS



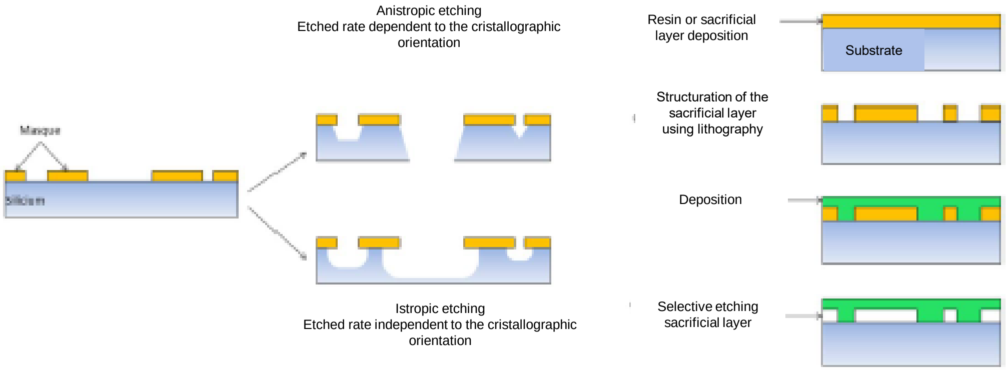
SPR =Surface Plasmon Resonance
SMR = Suspended Mechanical Resonator
NW = Nano Wire
LFA = Lateral Flow Assay
MRR = Micro Ring Resonator
QCM = Quartz Crystal microbalance
BBA = Biobarcode Amplification Assay
IFA = Immunofluorescent Assay
MC = Micro Cantilever

Arlett J. L. et al DOI: 10.1038/nnano.2011.44

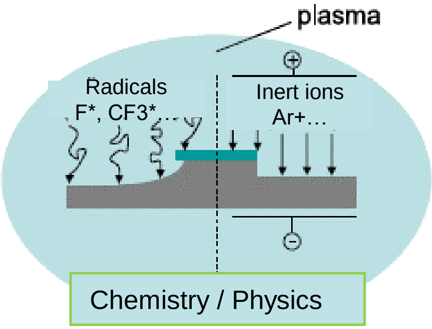


Limit of detection vs analysis time for the quantification of proteins using mechanical biosensors

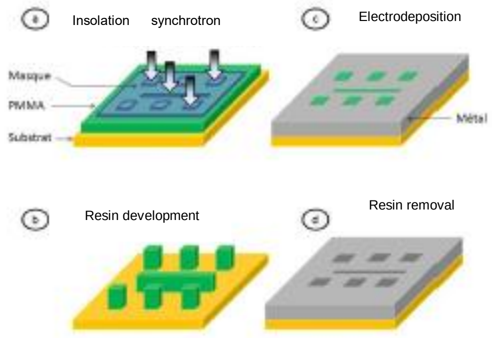
MICROFABRICATION (1/6)



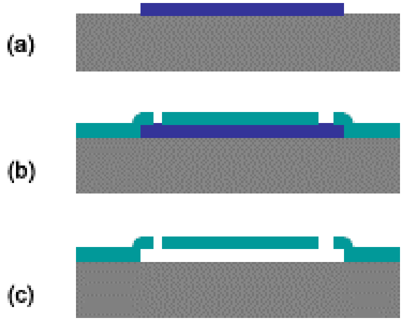
Volume / surface micromachining



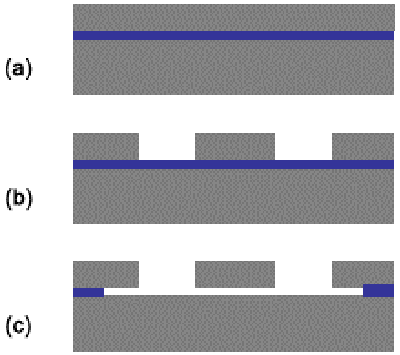
Chemical / physical etching



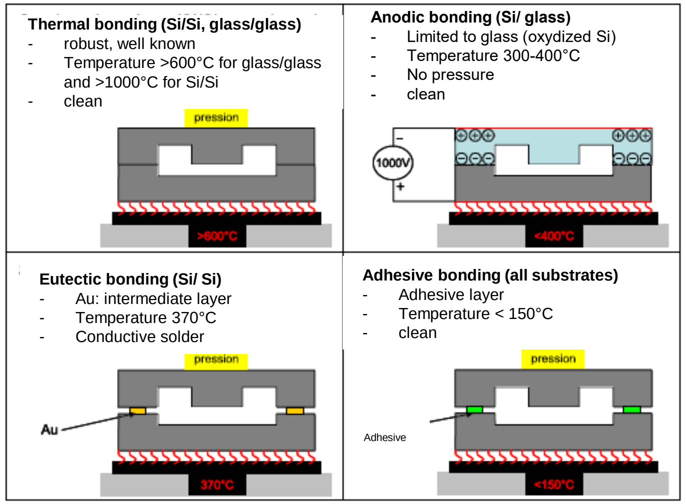
LIGA



Sacrificial layer



SOI etching

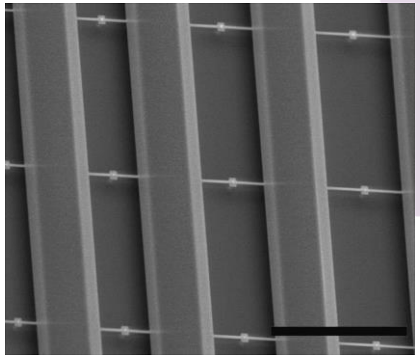


Packaging

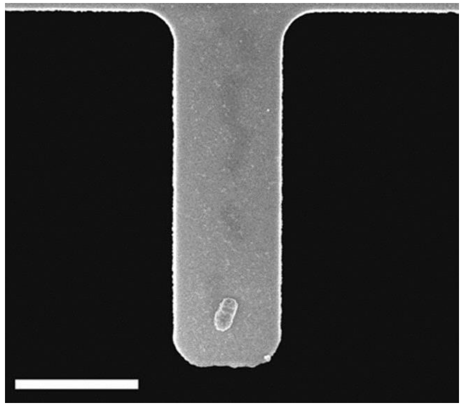
MICROFLUIDICS (2/6)

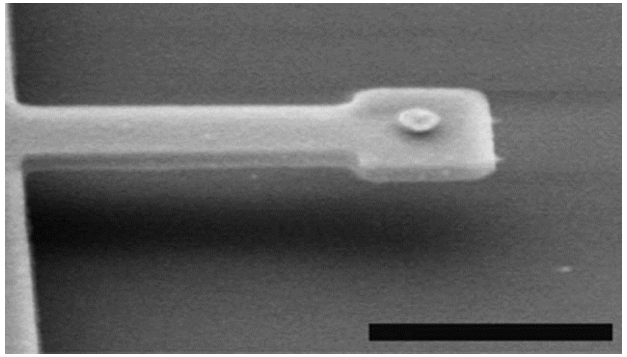
Technology based on Si/ SiO_2/ thin layers (examples SEM images)

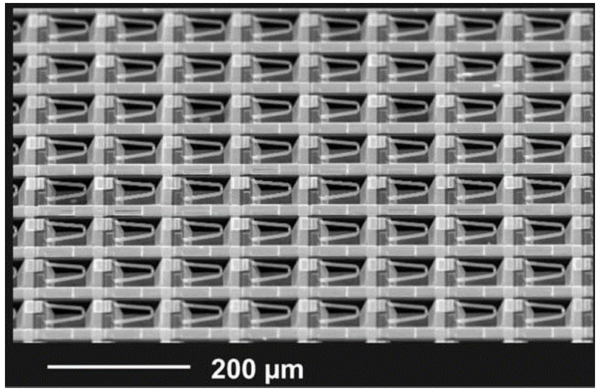
Arrays of bridge oscillators. Scale bar corresponds to 2 µm

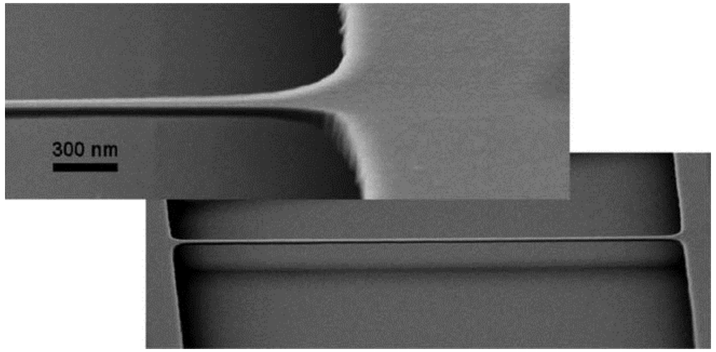


Cantilever with a single E. coli bound near the cantilever tip. Actuated in air, this cantilever measured the mass of a single cell to be 665 fg. Scale bar corresponds to 5 µm









Specialized cantilever fabricated to specifically bind analytes near the tip of the cantilever in order to maximize the effect of added mass. The nanoscale gold dot can be used with thiol-based binding chemistries to localize analyte binding → Detection at attogram quantities. Scale bar represents 2µm.

Several cantilevers in a ''Millipede'' cantilever array, which contains an array of 32 X 32 fully integrated devices. Each cantilever is 50 µm in length

A 15 µm long, doubly-clamped nanomechanical resonator. Electrospun fibers are used as an etching mask in order to define the nanostring resonators.

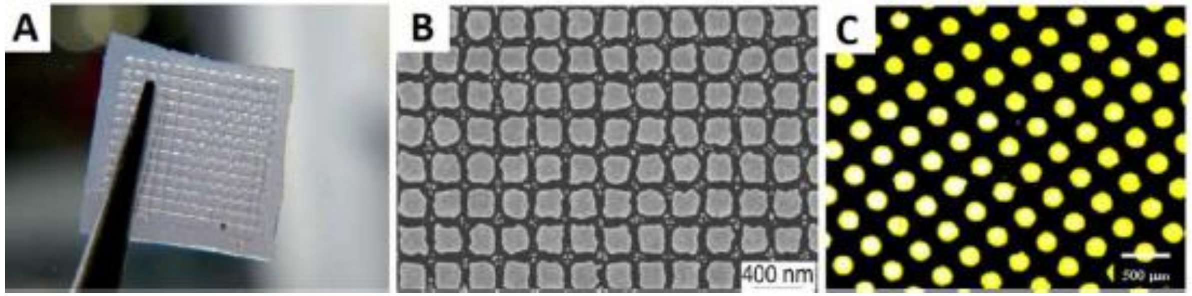
Ilic et al, Journal of Applied Physics **95**, 3694 (2004)
Waggoner et al, Lab Chip, 2007, 7, 1238–1255

MICROFABRICATION (3/6)

Soft technology based on polymers: nanoimprint lithography

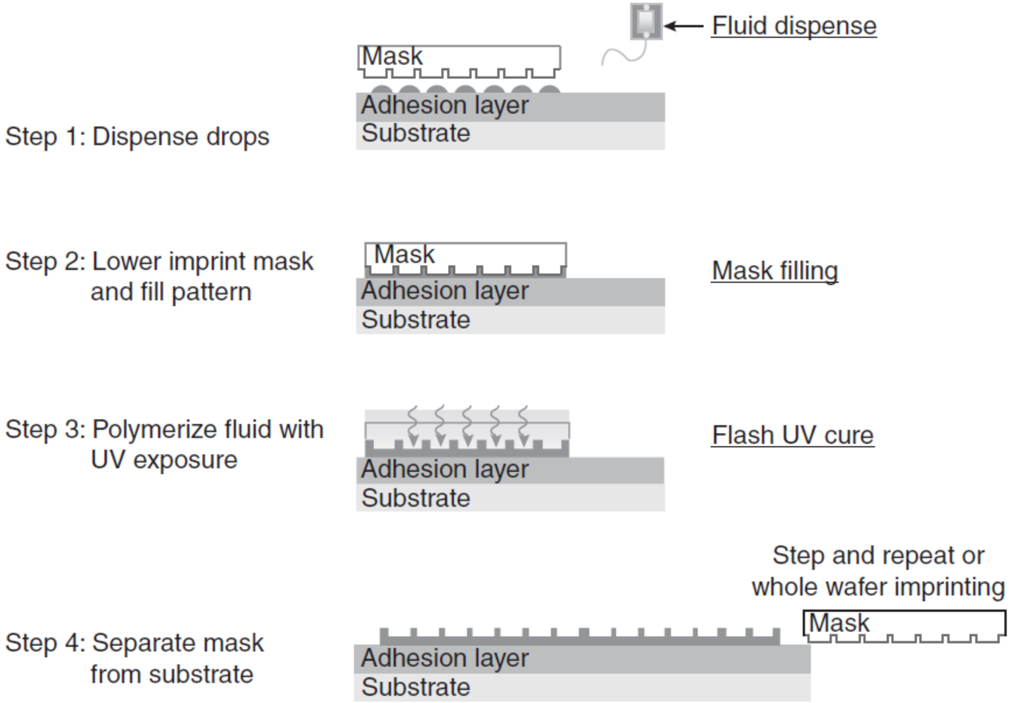
New substrates for flexibility, new features, miniaturized
Polymer is cast in a structured mold

- Common polymers: PDMS, PMMA, etc.
- Moulding materials: SU-8, thick photoresist
- Nanoimprint: pattern micro/nano



Nanoimprint lithography for LSPR sensing

- Advantages of soft lithography:
- 1/ rapid prototyping
- 2/ low cost, biocompatible, disposable



Schematic illustration of the step and flash imprint lithography (S-FIL) process

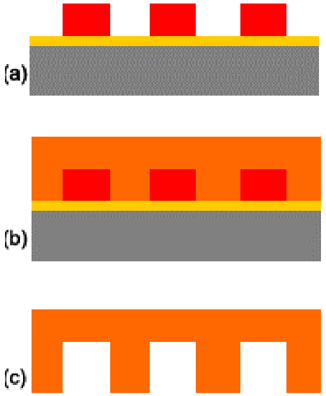
MICROFABRICATION (4/6)

Microstructures obtained by replication

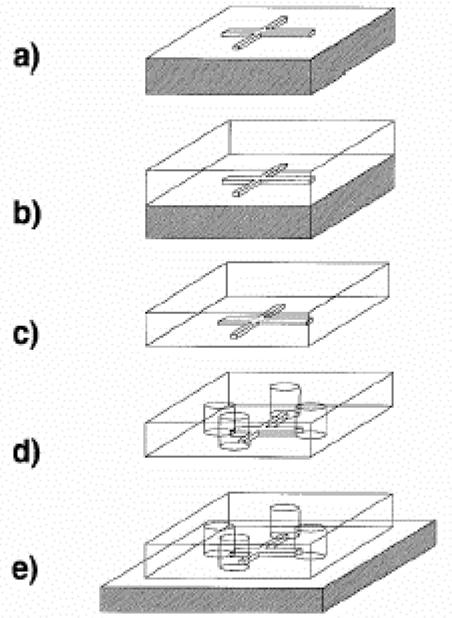
Fabrication of mold
- SI/glass etching
- Electroforming (LIGA / UV-LIGA)
- Thick resin
- Mechanical etching (laser, …)

Replication
- Embossing
- Liquid injection
- thermoforming
- moulding

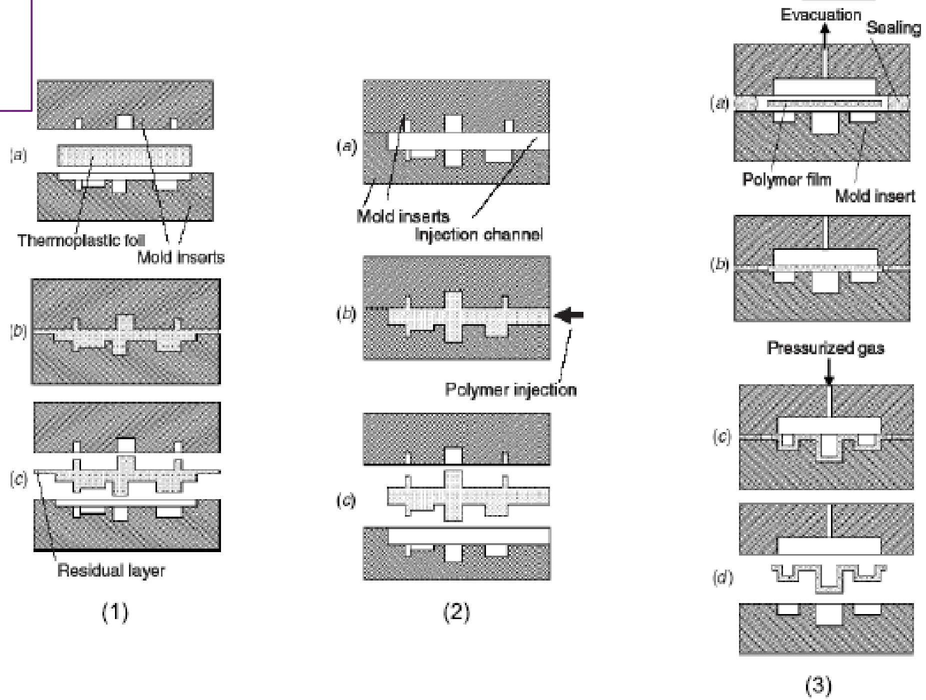
Post treatment
- Metal deposition
- Surface treatment
- Cutting, drilling
- Packaging



Metal mould obtain by electroforming



Moulding



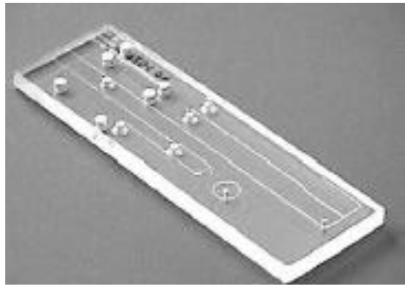
(1) Embossing, (2) liquid injection and (3) thermoforming

Antisticking surface treatment

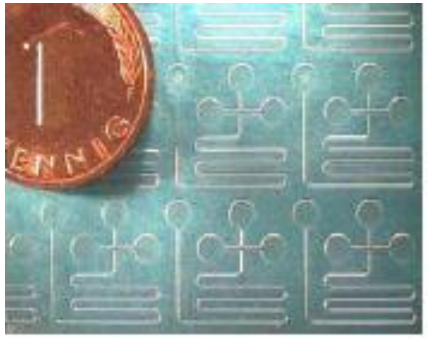
Abgrall P. PhD thesis, Univ Toulouse, Feb. 2006

MICROFABRICATION (5/6)

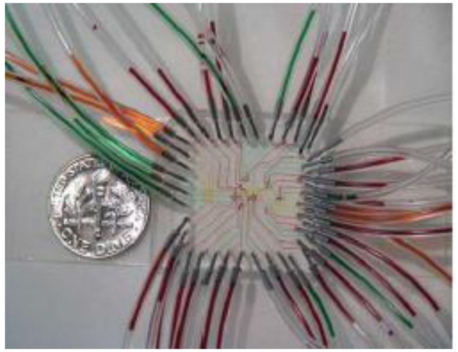
Examples of microfluidic circuits



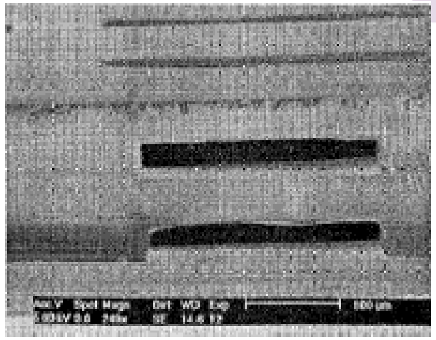
Chip made by hot embossing



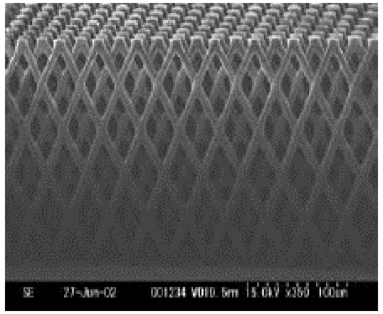
Electrophoresis system by thermoforming



Microfluidic chip in soft lithography (PDMS)

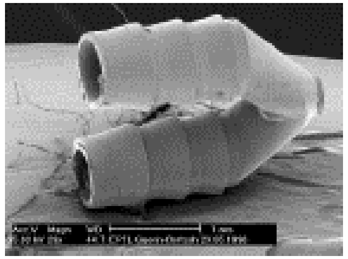


3D Microfluidic in SU8



Filter obtained using tilted lithography

Lab on chip made by injection



Microfluidic connector microsterolithography

Abgrall P. PhD Thesis Univ Toulouse, February. 2006

MICROFABRICATION (6/6)

Sensing systems designed with applying patterning techniques

Patterning Technique	Patterned Material	Pattern Shape	Detected Biomolecule	Detection Methode	Detection Limit	Literature
Soft Lithography	PS/PSMA	Micropillar	Anti-IgG	Fluorescence	0.03 μg.mL^{-1}	Lee et al. (2011a, 2011b)
Stencil Lithography	Sillicon Nitride	Au squar nanodot	Streptavidin	SPR	100 nM	Vazquez-Mena et al. (2011)
Wet Ethcing	ITO	Whell-like	Glucose, Cholin, Lactate	ECL	14, 40, 97 μM	Zhou et al. (2014)
Nanoimprint Lithography	Glass	Au elliptical nano-disc	PSA	SPR	0.0012 ng.mL^{-1}	Lee et al. (2011a, 2011b)
Nanoimprint Lithography	PET	NanoDome	IgG	LSPR	3.4 nM	Endo et al. (2010)
Nanoimprint Lithography	Photonic Crystal	Nanohole	Influenza Virus	Reflectometry	10 pg.mL^{-1}	Choi and Semancik (2013)
Soft Lithography	PEG Hydrogel	pH responsive-Circular	Streptavidin	Fluorescence	–	Lee et al. (2008)
Non-contact Robotic Printer	APTES-coated glass slide	Spot	*Escherichia coli*	Fluorescence	25 bacteria each have 1 nl volume	Melamed et al. (2011)

ECL: Electrochemiluminescence SPR: Surface Plasmon Resonance ITO: Indium-Tin Oxide PSA: Prostate Specific Antigen IgG: Immunoglobulin G PET: Polyethylene Terephthalate PEG: Polyethyleneglycole PS: Polystyrene PSMA: Poly (styrene-alt-maleic anhydride).

- New materials
- New technologies
- Biocompatible
- Low cost
- Disposable

Derkus, Biosensors Bioelectronics, 79(2016) 901-913

MICROFLUIDICS (1/5)

- The main benefits of such a technology consists in:
  - **Reduced volume of reagents**
  - Lower costs
  - Fine control over parameters (size, shape)
    → **Reproduce *in vivo* condition**

- Through miniaturization & automation, microfluidics are a great tool to:
  - Improve the precision of experiments
  - **Lower limits of detection**
  - Confine molecules produced by a cell in a nanometric space for detection purpose
  - Follow the kinetics of chemical reaction
  - **Faster analyses** due to the **shorter reactions** and/or separation times
  - **Run multiple analyses simultaneously**
  - **Manipulate molecules (unique cell scale)** directly and physically
  - Apply local or intense electric or magnetic fields without increasing voltage
  - Design portable devices for point-of-care applications

MICROFLUIDICS (2/5)

Fluid flow and microfluidic chip

Flow equation for microfluidics

F=mɣ incompressibility / Newtionan fluid

$$\frac{D\mathbf{u}}{Dt} = \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u}\nabla)\mathbf{u} = -\frac{1}{\rho}\nabla P + \nu\Delta\mathbf{u}$$

u = velocity
P = pressure

Inertia forces are small in miniaturized devices

$$0 = -\nabla P + \mu\Delta\mathbf{u}$$

Approximation valid for microfluidics

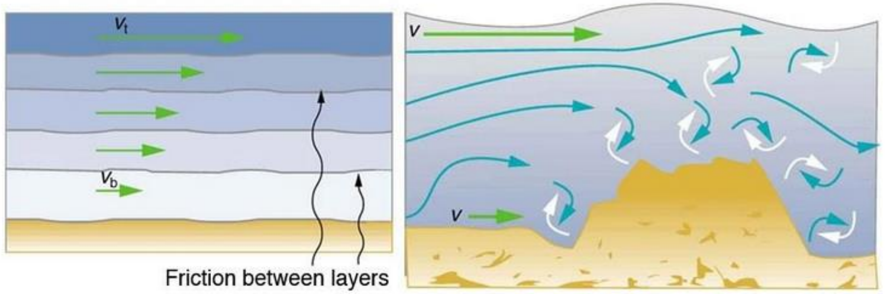
Exceptions : microechangers spotters, inertial microfluidics

Reynolds number Re

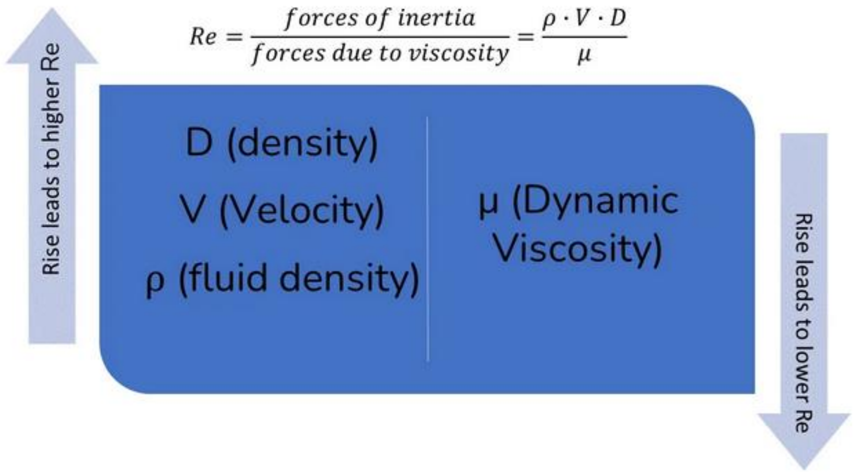
Ratio between the inertial and viscous forces acting on a fluid

→ Indicator of whether fluid flow is turbulent or steady

→ Re<2000 the fluid is considered to exhibit a **laminar flow**



An example of laminar and turbulent flow in the macroscale



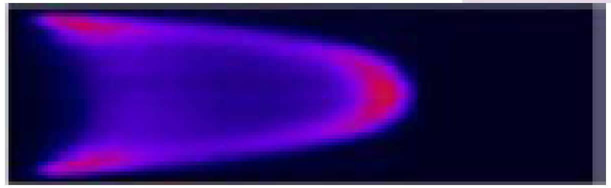
MICROFLUIDICS (3/5)

Case of Re<2000: laminar flow

→ Profil of velocity in a channel (Poiseuil)

→ Diffusion time vs convection time

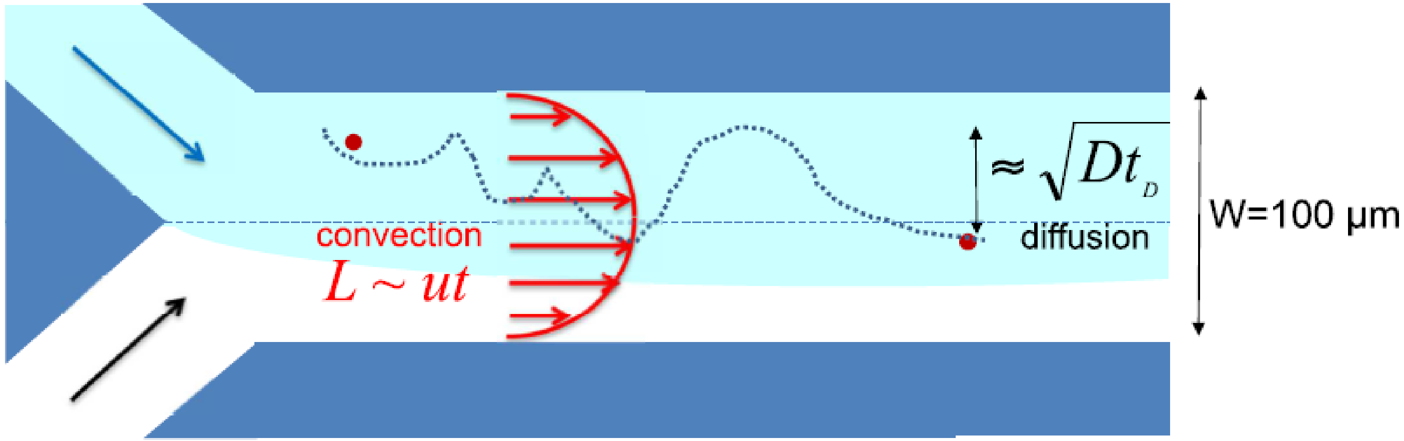
→ Competition between T_C et T_D to reach the surface

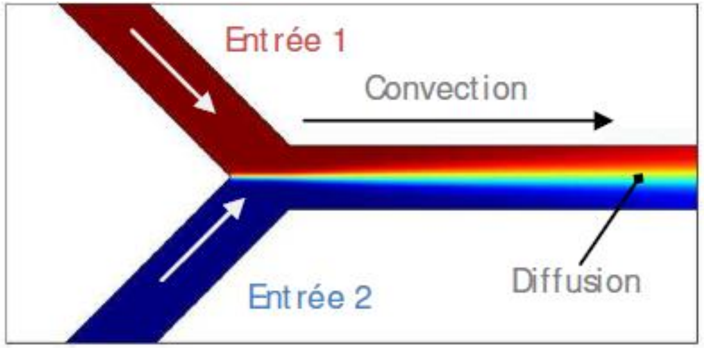


$L_D \approx \sqrt{Dt_D}$ $\quad$ $L_C = ut_C$

Diffusion time $\quad$ Convection time

$t_D \approx L_D^2 / D$ $\quad$ $t_C = L_C / u$





ΔP: Pressure variation / Q= flow rate
L: length, 2R = diameter, η = dynamic viscosity

$$\Delta P = \left(\frac{8\eta L}{\pi R^4}\right) Q$$

MICROFLUIDICS (4/5)

$$\frac{\text{diffusive time}}{\text{convective time}} \sim \frac{H^2/D}{H^2 W_c/Q} \sim \frac{Q}{D W_c} \equiv \mathrm{Pe}_H$$

Example:
D=40µm^2/s,
u=1000µm/s
→ Pe=2500
→ Mixing after 25cm and 4 minutes

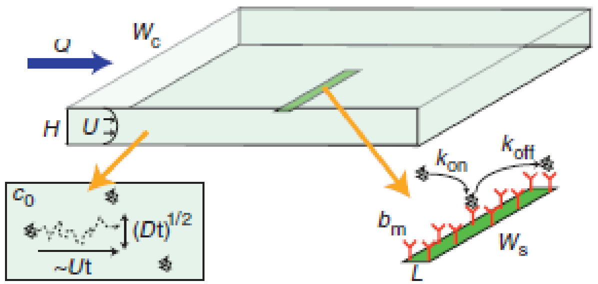
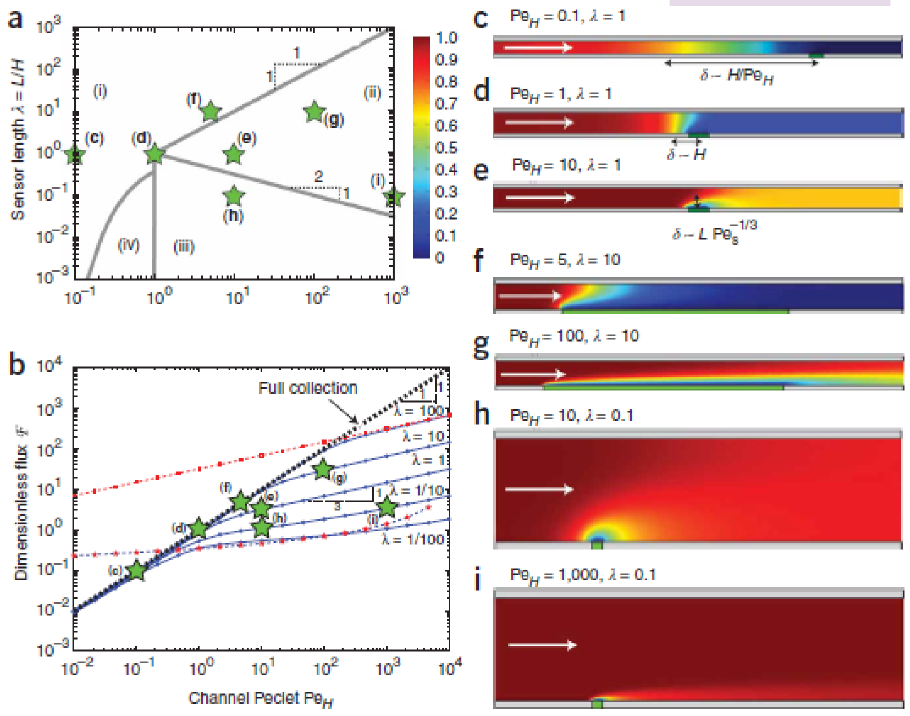


Figure 1 Model system studied here. Solution with target concentration c_0 flows with velocity U and volumetric flow rate $Q \sim HW_cU$ through a channel of height H and width W_c over a sensor of length L and width W_s that is functionalized with b_m receptors per unit area. The kinetic rate constants for the (first-order) binding reaction are k_{on} and k_{off}, and the diffusivity of the target molecules is D.



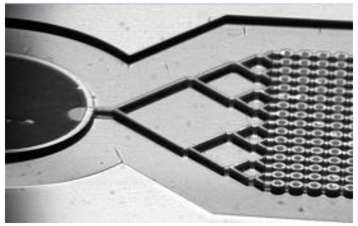
Zone of depletion δ / Comparison with τ=L^2/D
Region i: full collection, diffusion phenomenon prevails
Region ii: depletion zone <H et L
Region iii:depletion zone<H et >L convection phenomenon prevails

Simulation results multiphysics in channel

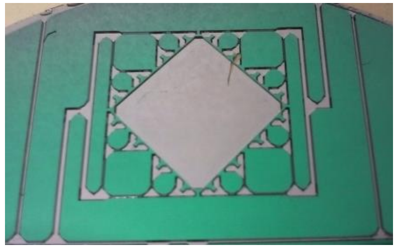
Arlett et al, nature nanotechnology, 44 (2011)
Squires et al, nature biotechnology 26 (2008)

MICROFLUIDICS (5/5)

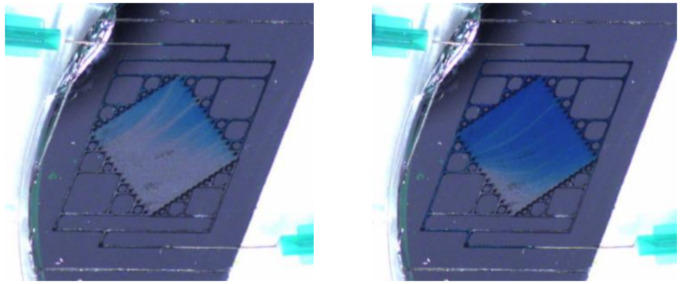
Microfluidic structures (soft matter, silicon, GaAs,…)



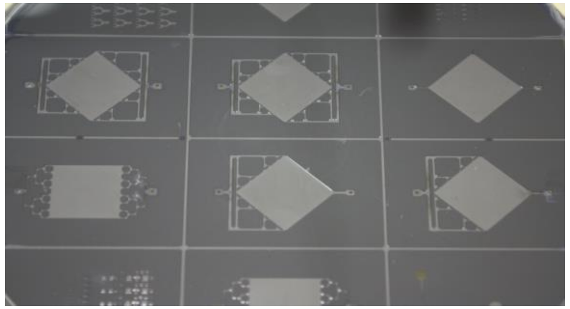
Microfabrication of a microfluidic multiplexer



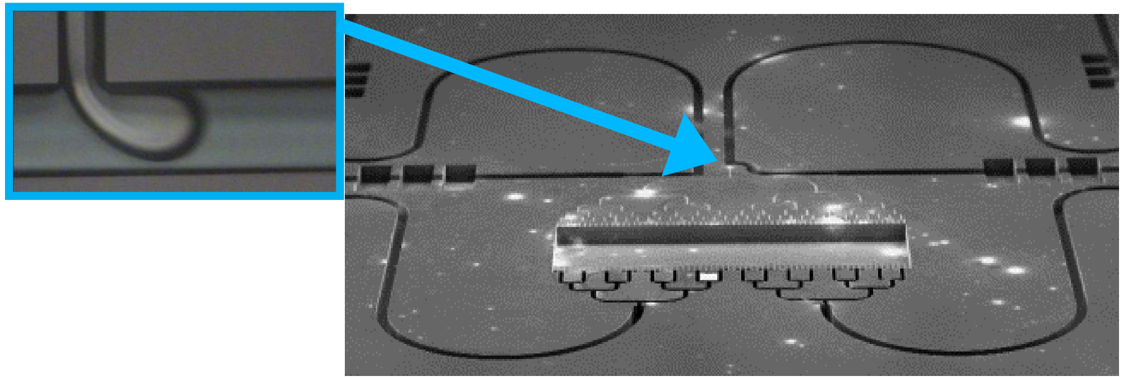
Microfabrication of a microfluidic cell on silicon wafer



microfluidic cell on (110) silicon wafer / GaAs wafer



Microfabrication of microfluidic cells on silicon wafer

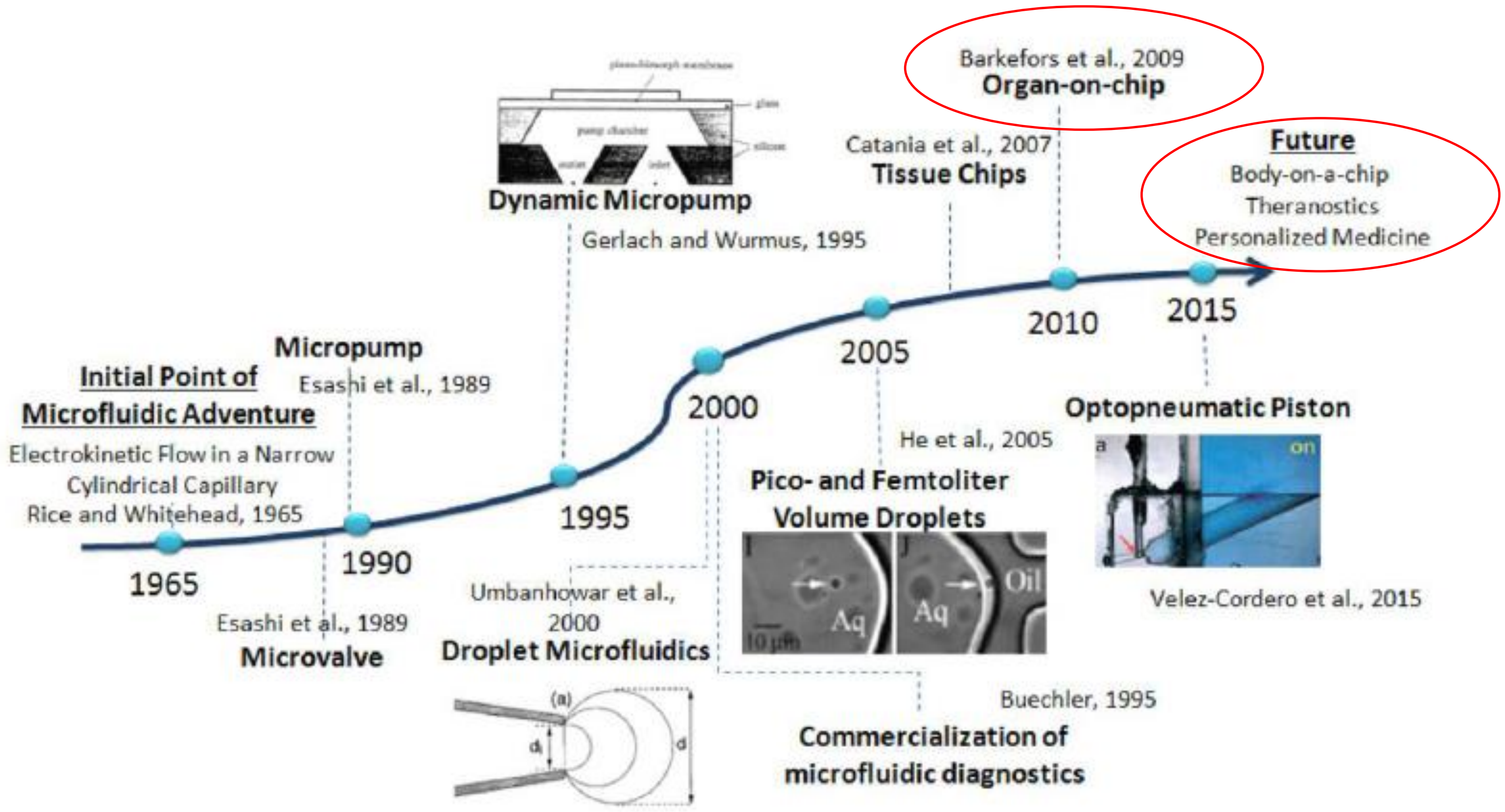


Microfabrication of microfluidic circuit on silicon wafer
T junction to obtain a two-phase mixture

Azzopardi, C.-L et al, Micromachines 8 (2017) : 308

MICROFLUIDIC CHIPS

Timeline on microfludic technology



Derkus, Biosensors Bioelectronics, 79(2016) 901-913

LAB-ON-CHIP ACTUATION (1/3)

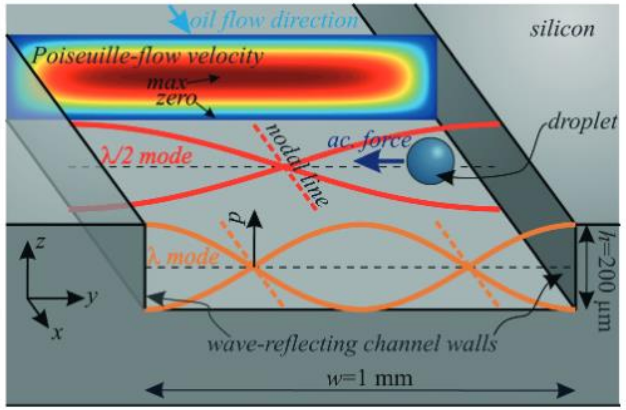
Acoustophoresis: acousto fluidic interaction
Principle of acoustophoresis for particles concentration / sorting

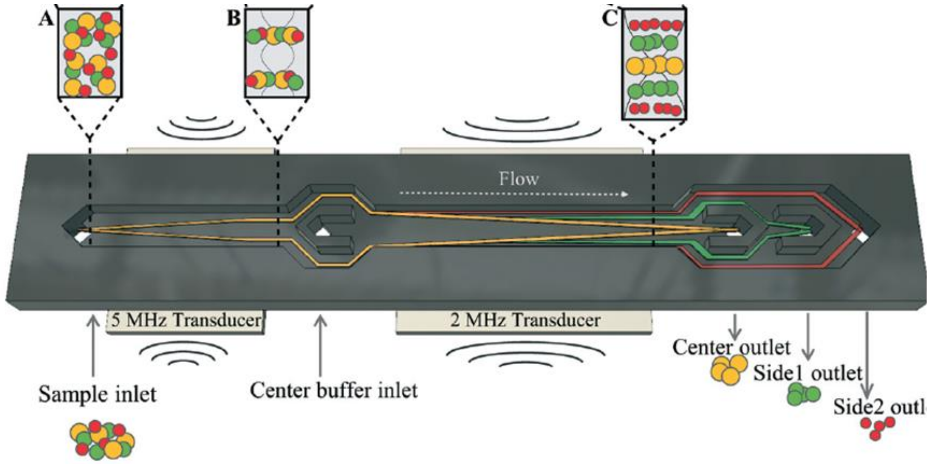
Lab-on-chip:

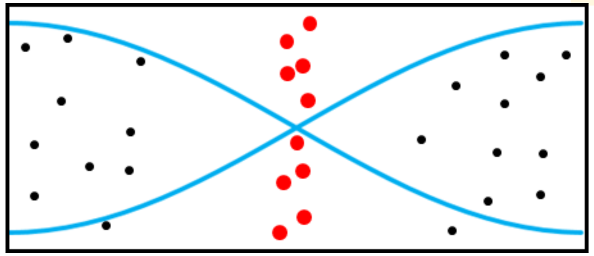
Integration of:
- Microfluidics
- Sensors
- Actuators
- Valve, pump

On a chip

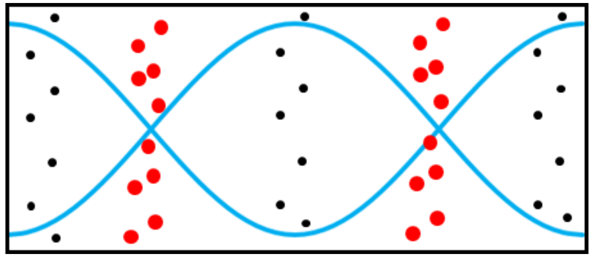
→ **Detection**
→ **Diagnosis**







One acoustic pressure node

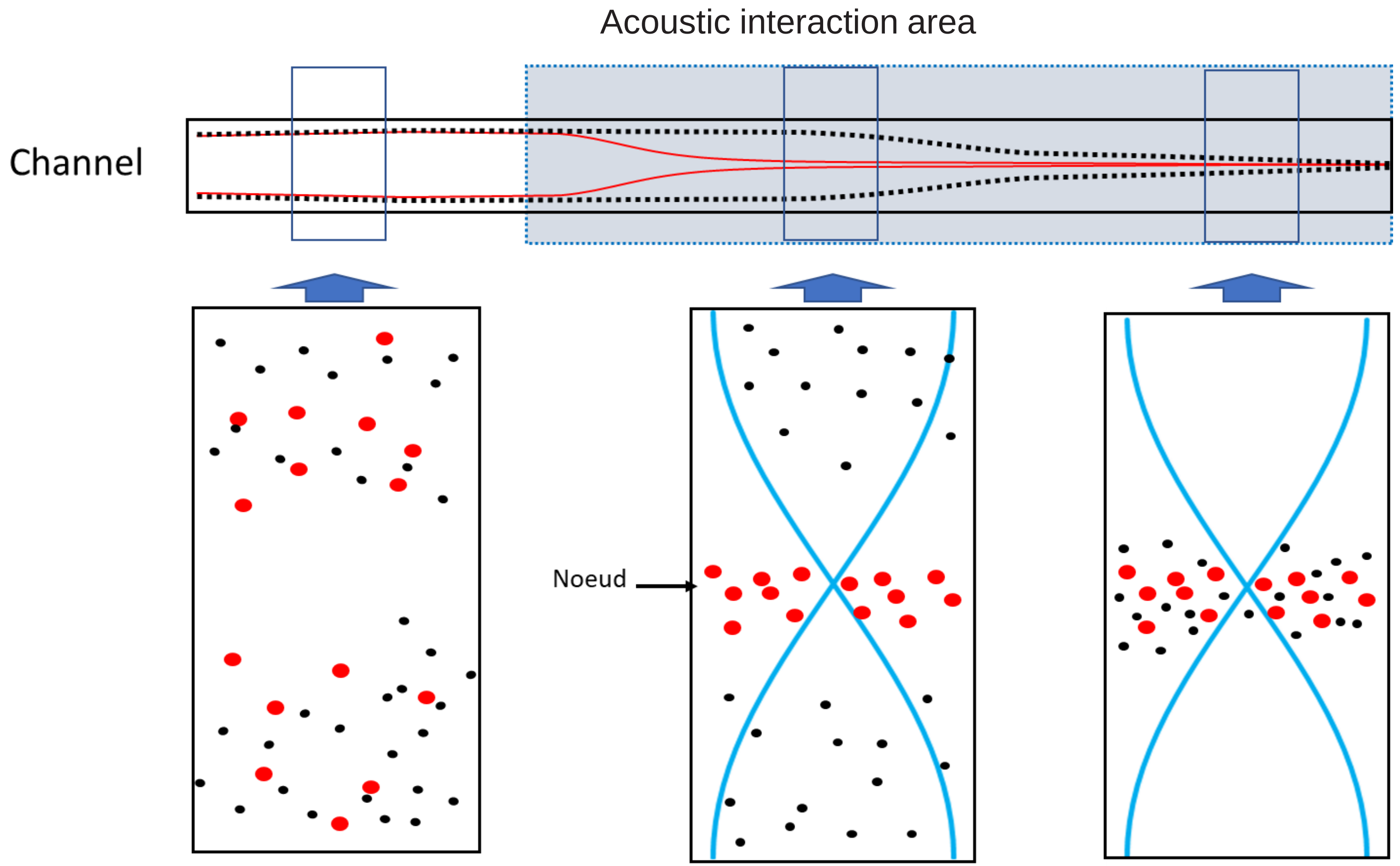


Two acoustic pressure nodes

LAB-ON-CHIP ACTUATION (2/3)

Acoustophoresis

Design of the microdevice developped for acoustic sorting



LAB-ON-CHIP ACTUATION (3/3)

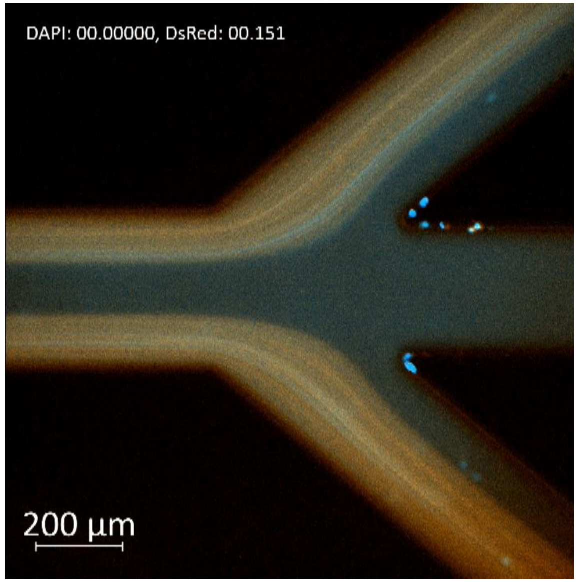
Acoustophoresis: acoustic sorting / separation of biological particles in a channel (w=375µm)

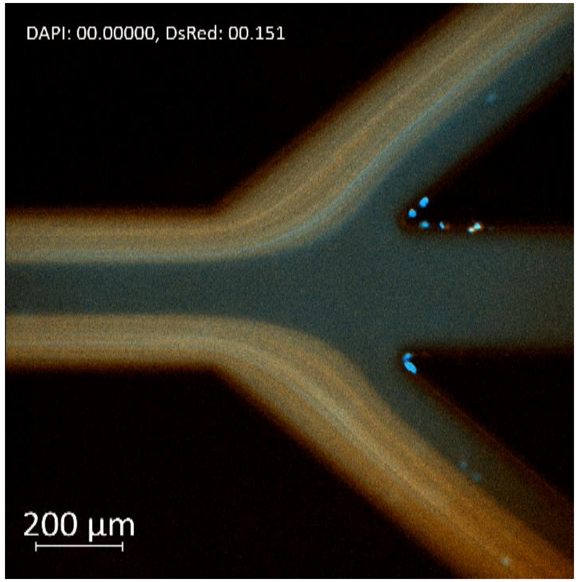
Sample flow rate :
125µL/min ➔ 6 000 Lymphocytes/s

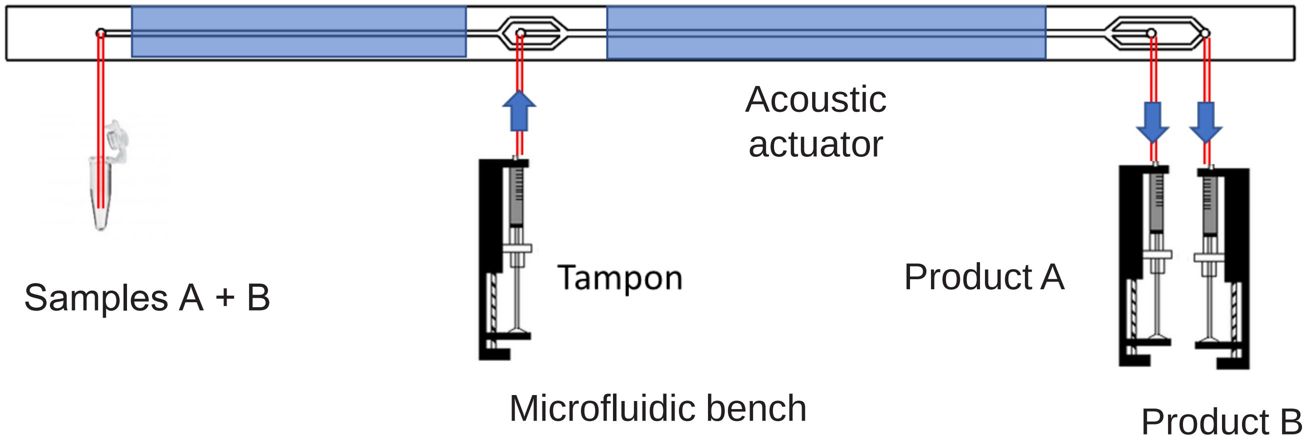
Orange : Platelets 10.10⁶/mL (Anti-CD31-PE)
Blue : Lymphocytes 3.10⁶/mL (Hoechst)

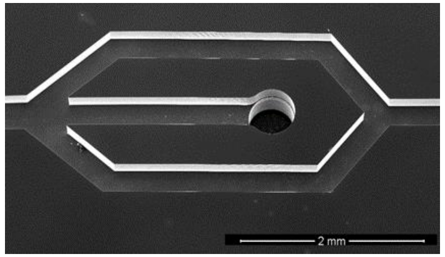
Sample flow rate:
100µL/min

Green : Bacteria 10.10⁶/mL
Blue : Lymphocytes 3.10⁶/mL









device

Performances:

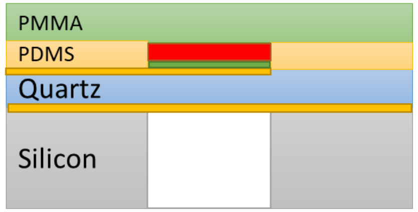
<u>Sorting/separation PBLs/Platelets</u>
150 µL/min
6 000 Lymphocytes/s
87% of lymphocytes were recovered
Platelets depletion (divided by 5)

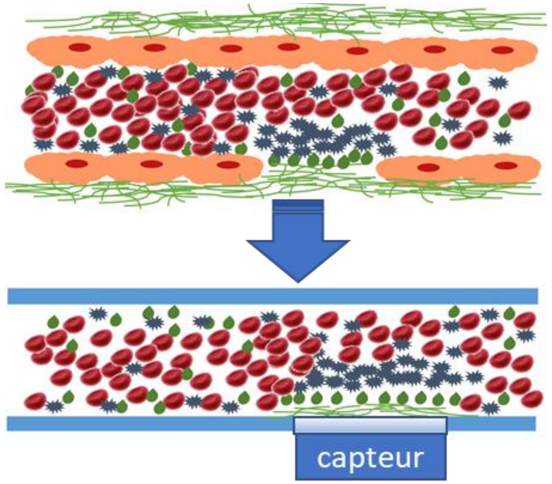
Jouy F. et al., Mimedi Project 2022

LAB-ON-CHIPS DETECTION (1/2)

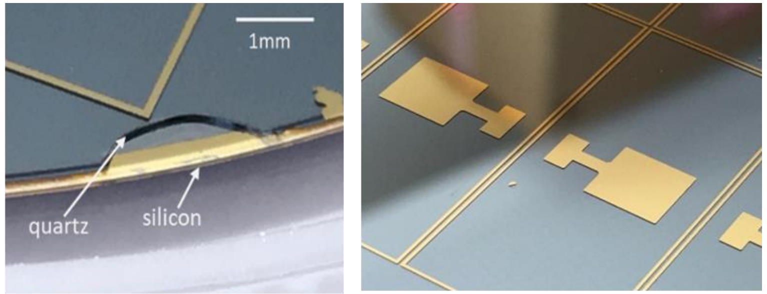
Microdevice for the global assessment of primary haemostasis with flowing whole blood
→ detection of Willbrand's disease

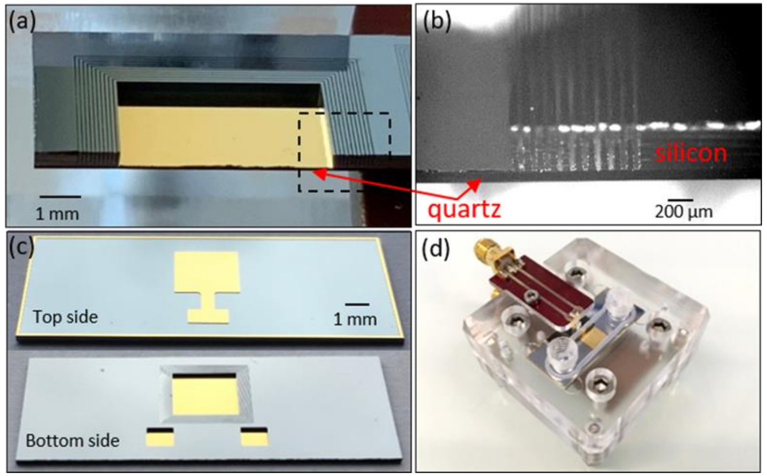
Primary hemostasis = dynamic processus, **in flow**
→ **Mimic *in vivo* conditions**
→ Real time
→ multiplex
→ Low volume of sample





- Rectangular parallel plate perfusion chamber
- Width 5mm / Height 50µm
- Flow rate / Shear rate is in accordance with published recommendations

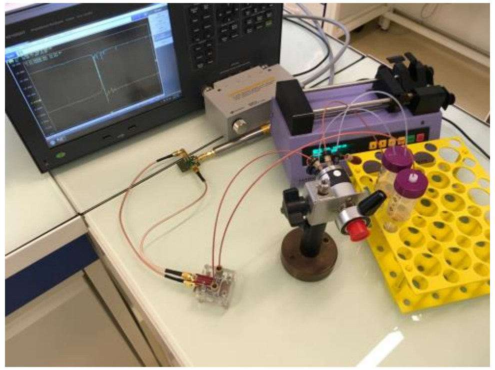




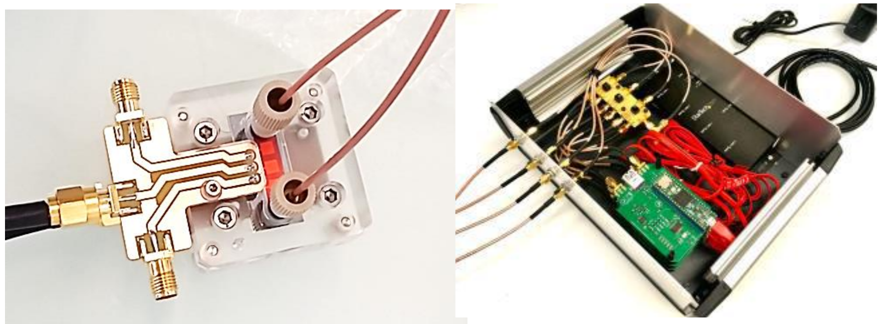
Microfabrication acoustic transducer

Oseev A., *IEEE Transaction on biomedical engineering*, 2020 3031542

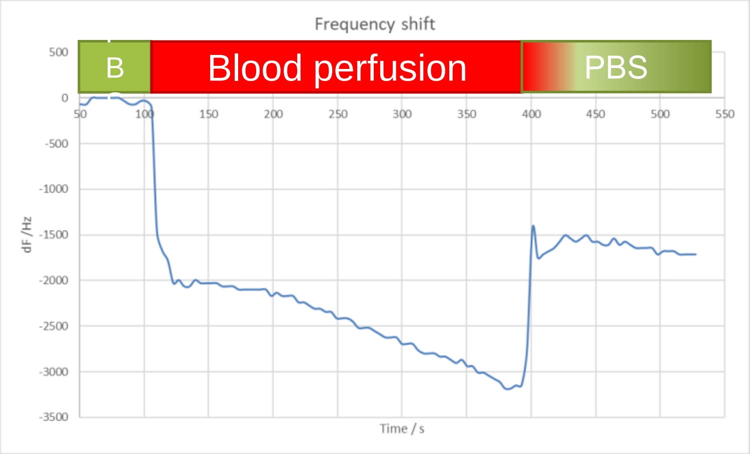
LAB-ON-CHIPS DETECTION (2/2)

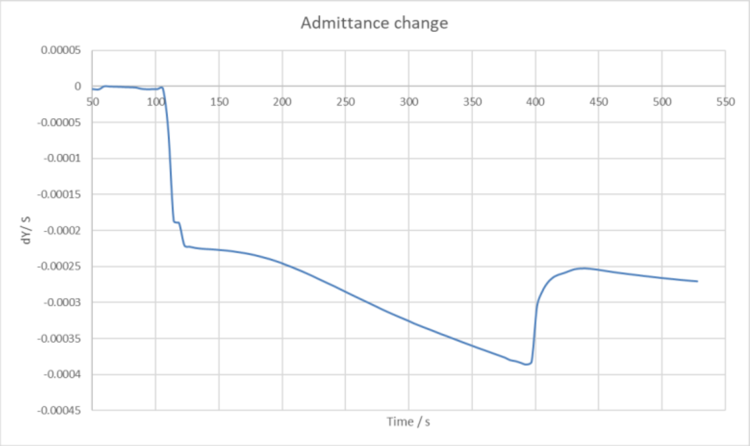


Experimental set up



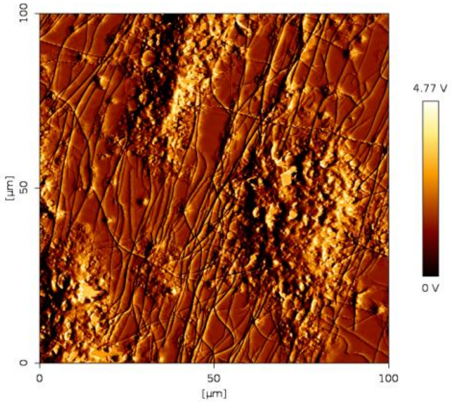
Biosensor / electronics





Biointerface protocol:
Gold surface -> C11C16 -> SE -> <u>HORM collagen 50µg/mL</u>
-> BSA 0.1% -> Ethanolamine

Conditions:
Whole blood
Shear rate: 1500 s^{-1}
Perfusion time: 5min
Real time
Temperature: 23°C ± 1°C

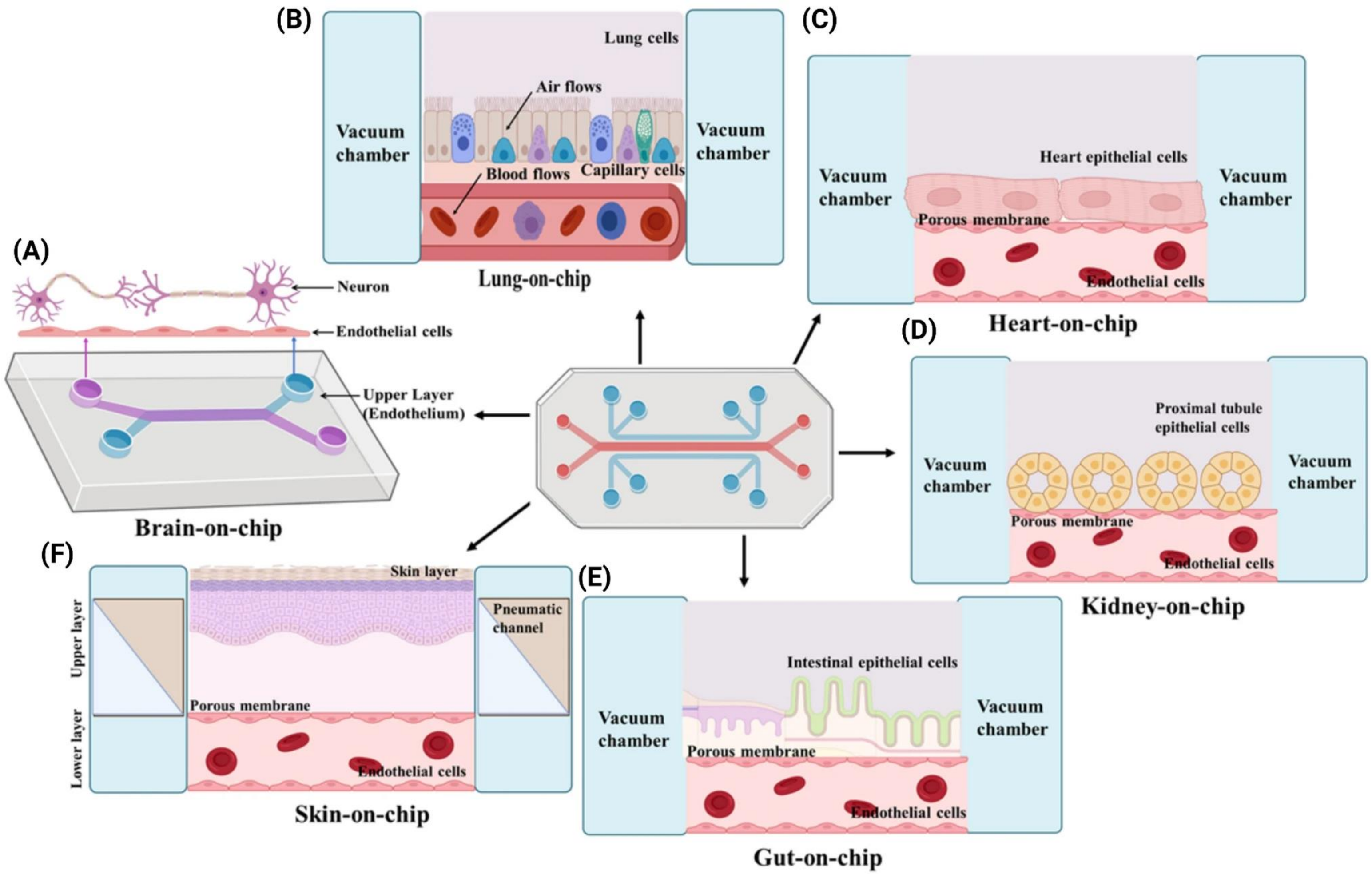


AFM image: collagen and platelets

Oseev et al., *nanomaterials* 2020 10(10), 2079

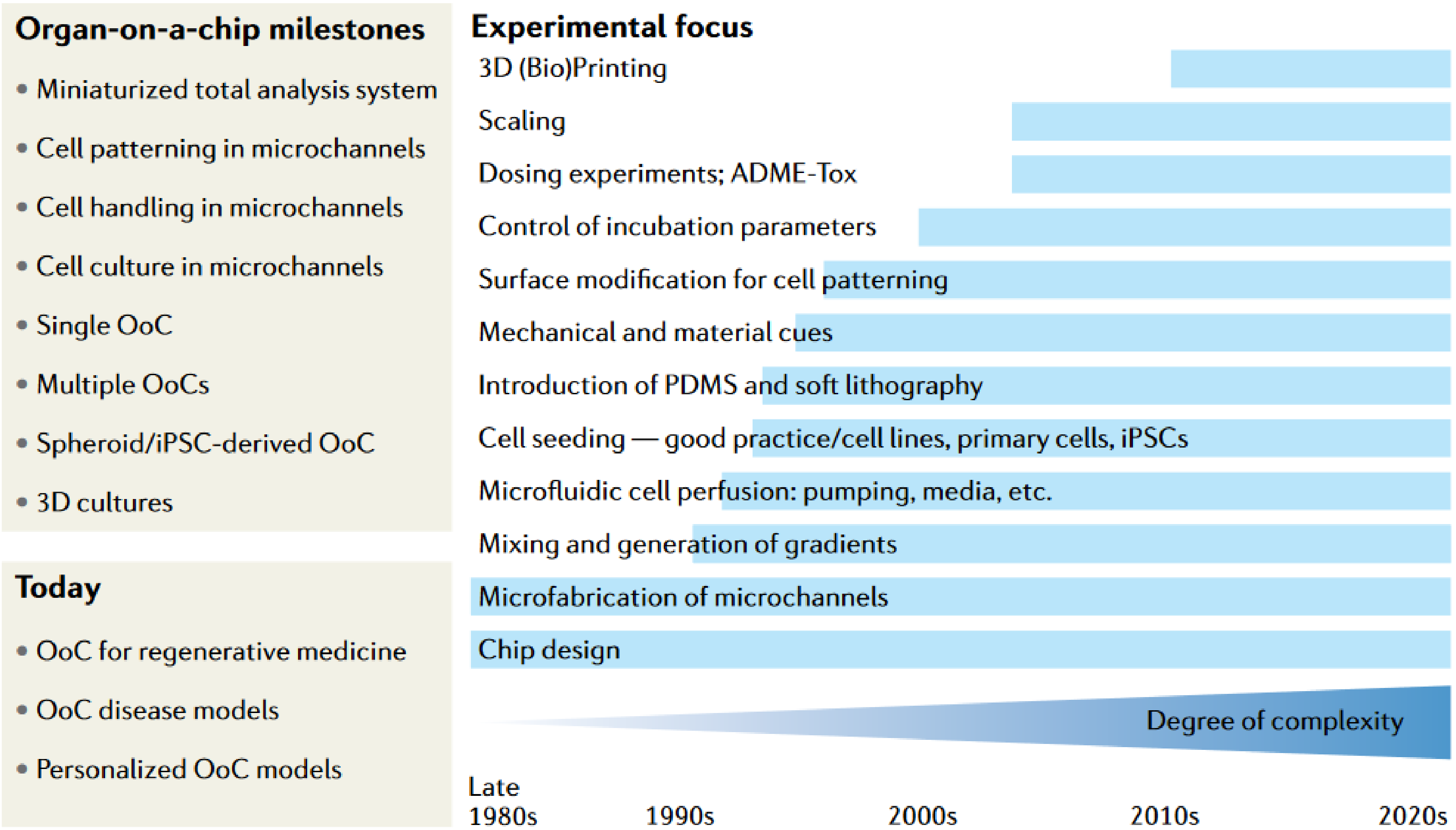
ORGAN-ON-CHIPS (1/6)

Lab-on-chips towards organ-on chips



ORGAN-ON-CHIPS (2/6)

Milestones in the development of organs-on-chips and experimental techniques



ADME-Tox, absorption, distribution, metabolism, excretion and toxicology; iPSC, induced pluripotent stem cell; PDMS, poly(dimethylsiloxane).

Leung *nature review* (2022) 2:33

ORGAN-ON-CHIPS (3/6)

Most common materials used for fabricating OoCs, their advantages and drawbacks and their main purpose in OoC devices

Materials	Advantages	Drawbacks	Experimental model
PDMS[10,315,316]	Gas-permeability Optical transparency Elasticity Biocompatibility	Absorption of small molecules Difficulty in mass production	Disease modelling Mechanical and chemical stimuli Electrode patterning
Thermoplastics[277,317]	Optical transparency Mass production Cost-effective Low absorption	Rigidity Difficulty in producing complex structures Low permeability	Drug screening Large-scale experimentations
3D printing resins[318,319]	High mechanical and thermal properties Low cost Complexity and design freedom	Autofluorescence Opacity Toxicity Low permeability Surface roughness	3D design modelling Rapid prototyping
Glass[320]	Optical transparency Inert Biocompatibility Low autofluorescence	Laborious fabrication Fragile Expensive	Electrode patterning
Silicon[321,322]	Low absorption Generation of high-resolution channels on the nanoscale	Laborious fabrication due to need for clean-room facilities Expensive	On-chip sensors Formation of diffusive barriers

OoC, organ-on-a-chip; PDMS, poly(dimethylsiloxane).

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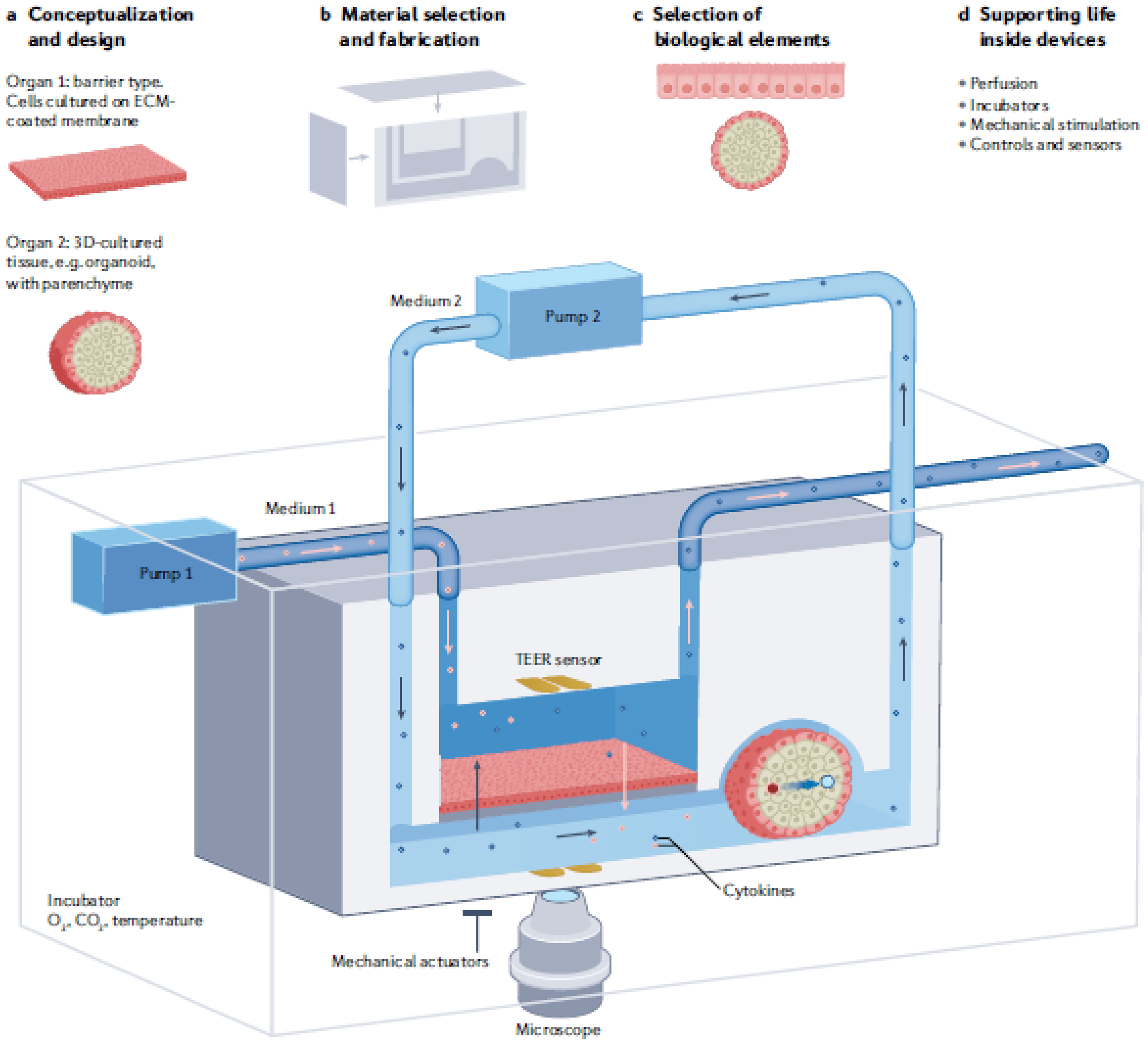
ORGAN-ON-CHIPS (3/6)

Experimental set-up for a generic two-organ system with supporting peripheral equipment



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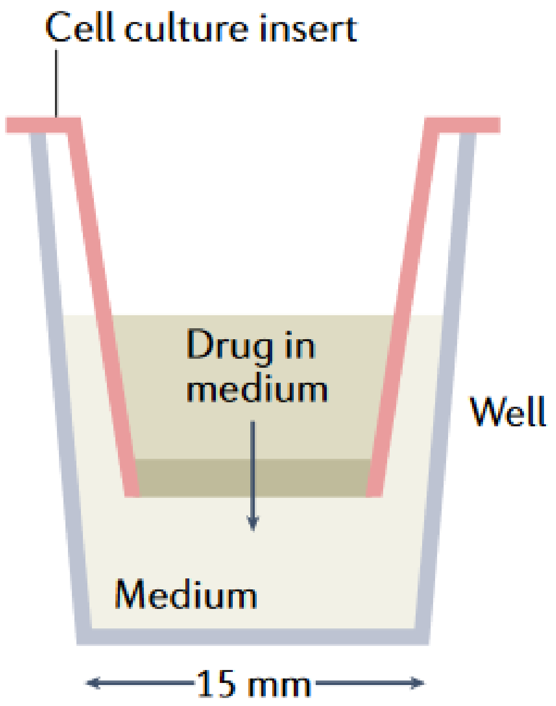
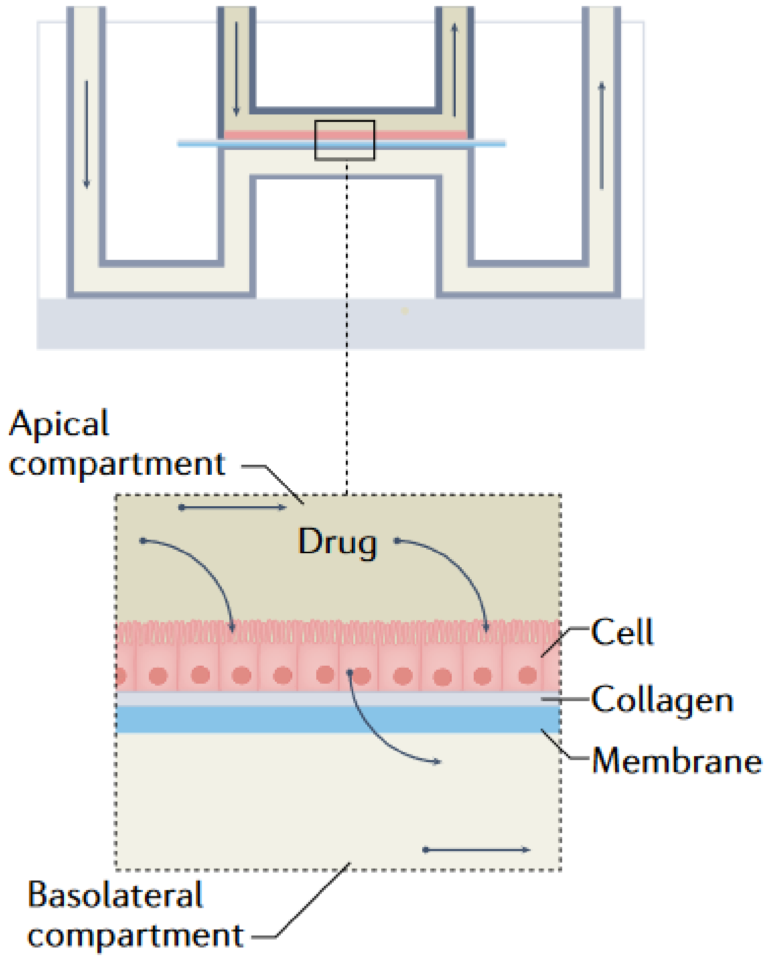
ORGAN-ON-CHIPS (4/6)

Schematic drawings of single-OoCs

Gut-on-chip for drug absorption → transport





Gut-on-a-chip device for drug absorption studies

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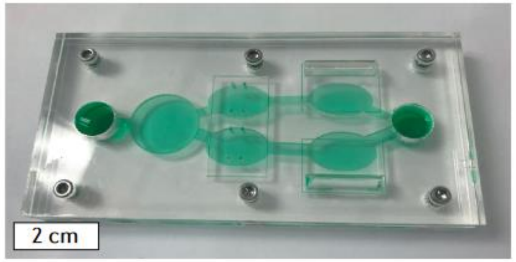
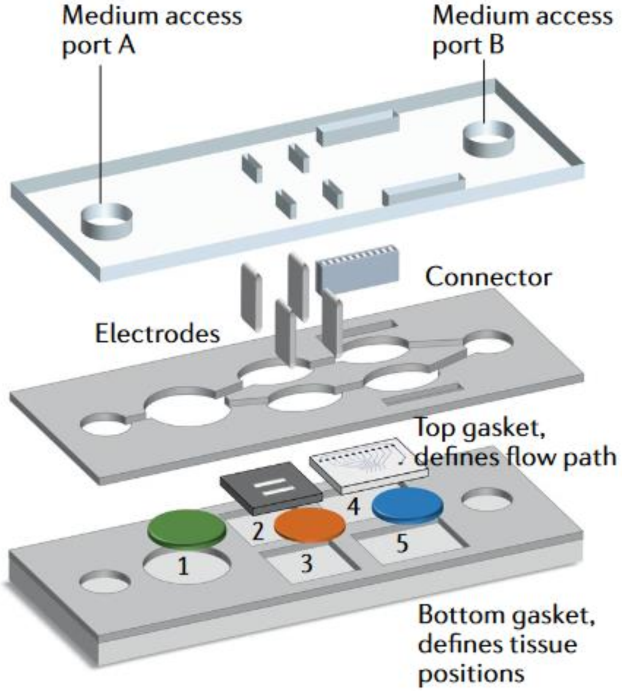
ORGAN-ON-CHIPS (4/6)

Schematic drawings of multiple -OoCs





Multi-OoC developed consisting of
several OoC compartments together in one device

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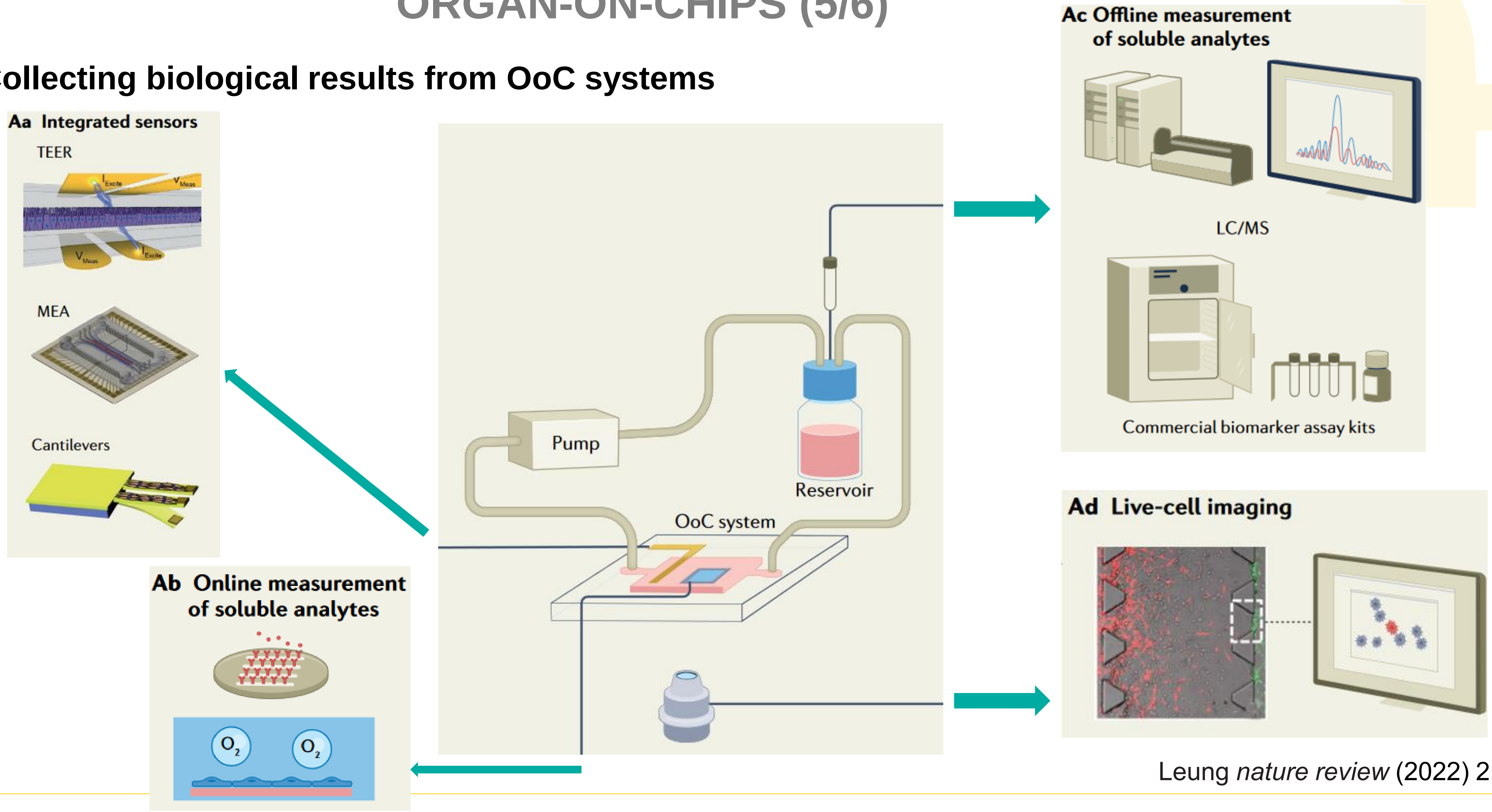
ORGAN-ON-CHIPS (5/6)

Collecting biological results from OoC systems



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ORGAN-ON-CHIPS (6/6)

- OoCs can represent a **single tissue unit or multi-tissue units** linked by microfluidic flow to recapitulate complex physiological functions such as cancer metastasis, inflammation and infection.
- OoCs are able to **approximate one or few organ- level functions**: barrier function of the lung, contractile function of the heart or filtration in the kidney.
- OoC systems that are based on the use of iPSCs and organoids offer an unprecedented opportunity to study **patient diversity** (racial and ethnic background, sex, age, state of health or disease) as a biological variable, and to conduct patient-specific studies of the progression of disease and effects of treatment.
- By using OoCs we can **identify early-stage biomarkers**, monitor disease progression and determine **optimal therapeutic treatment** regimens in a personalized manner.
- OoCs are poised to **become broadly accepted** in biological research, as they offer biologic fidelity along with experimental control in human tissue settings

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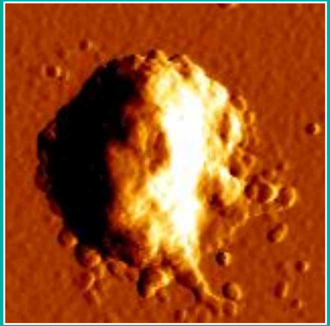

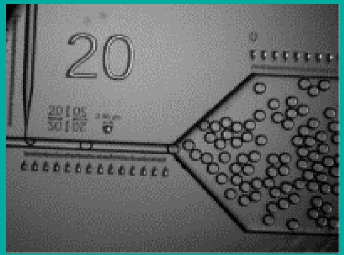

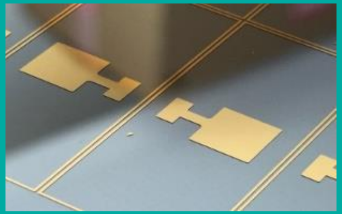

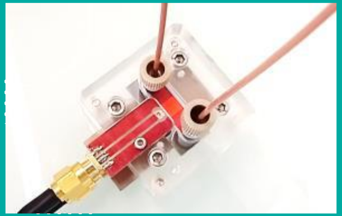

Thank you for your attention!

BioMicroDevices team

Contact: therese.leblois@femto-st.fr

websites: www.femto-st.fr, http://teams.femto-st.fr/BioMicroDevice