# FIELD EFFECT TRANSISTOR BIOSENSORS: OPTIMISATION OF THE INFLUENCE OF SIZE AND GEOMETRY AND FABRICATION METHODS.

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Lead Research Associate

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NANOLITO Summer School - June 29th 2021

LUXEMBOURG INSTITUTE OF SCIENCE AND TECHNOLOGY
LIST

# AT THE HEART OF BUSINESS

# THE NEW RESEARCH AND TECHNOLOGY ORGANISATION

Created in 2015 | Active in 3 fields

ENVIRONMENT

INFORMATICS

MATERIALS

# R&D PROJECTS IN PROGRESS IN 2019

**100**
competitive national projects

**25**
competitive European projects

**63**
collaborative projects & similar

**1**
international competitive project

**7,87%**
main service contracts

**∑ 297**
total of RDI projects & contracts

# SCIENCE AND TRANSFER IN 2019

**230**

scientific articles in 1st quartile journals

**1**

spin-off

**20**

filed patents

**21**

paid licences

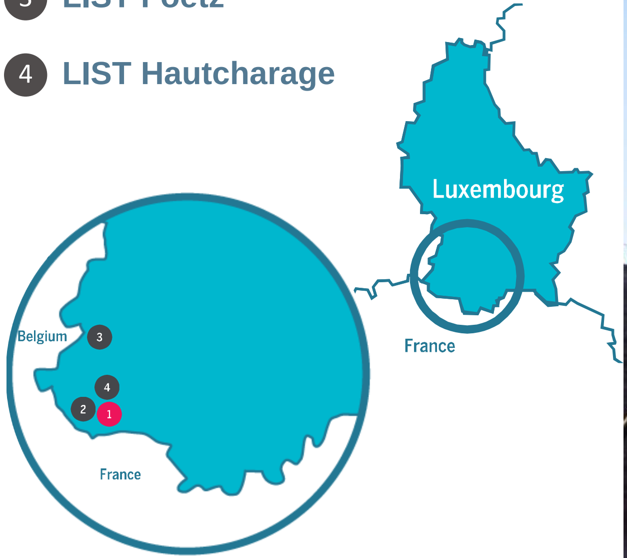
# OUR 4 SITES

1 LIST Belval (Headquarters)

2 LIST Belvaux

3 LIST Foetz

4 LIST Hautcharage




# FIELDS OF ACTIVITY

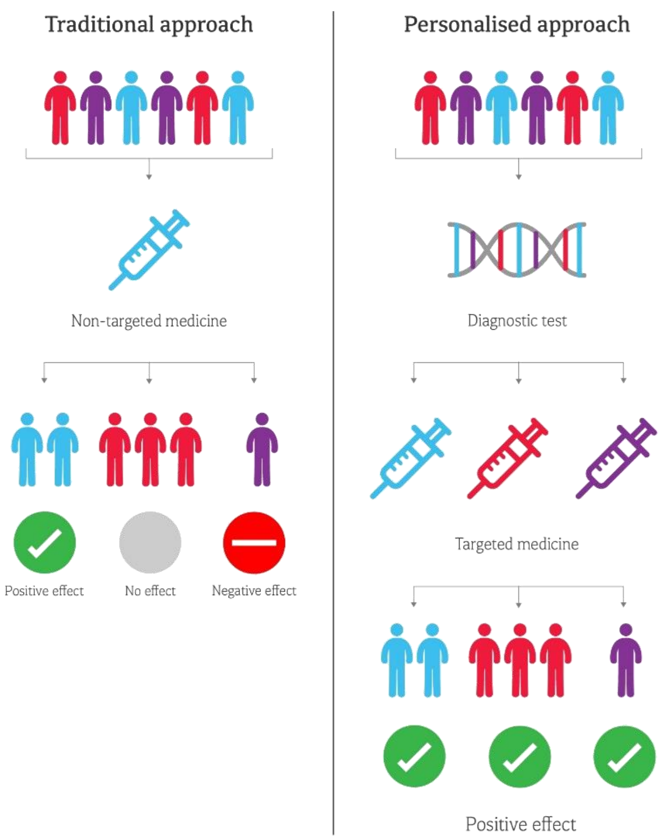
## Working across the entire innovation chain

- Fundamental & applied research
- Incubation & transfer of technologies
- Policy support
- Doctoral & post-doctoral training

# LIST MATERIALS

- Sensors & actuators
- Photocatalysis & energy harvesters
- Fibres/matrices adhesion
- Functional coatings
- Smart nanocomposites
- Structures & multifunctional composites
- Bio-based polymers & composites
- Advanced manufacturing

# PERSONALIZED MEDICINE-CONCEPT




**Improved 4 Ps:**

**- P**rediction and Prevention of disease
- More **P**recise diagnoses
**- P**ersonalised and targeted interventions
-A more **P**articipatory role for patients


Horizon 2020 Future emerging technologies
Project: 862539 — ElectroMed

This project is funded by the European Union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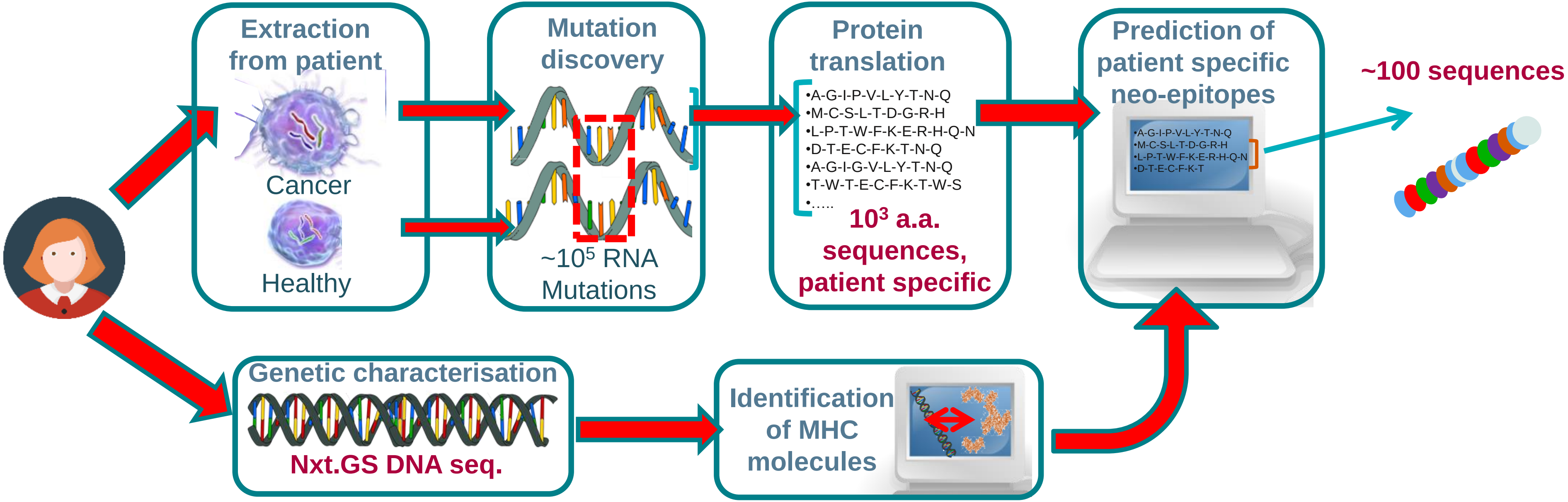
# CURRENT POSSIBILITIES OF PERSONALIZED MEDICINES

## Similar to biontech COVID19 Vaccine

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# FROM WIGNER´S CRYSTALLIZATION TO CANCER

## Beginning studies of fundamental properties of semiconductors with inelastic light scattering

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# BEGINNINGS WITH OPTICAL SPECTROSCOPY

UAM UNIVERSIDAD AUTONOMA DE MADRID

FACULTAD DE CIENCIAS

ELSEVIER

Physica E 12 (2002) 722–725

PHYSICA E

www.elsevier.com/locate/physe

Optical study of the one-dimensional electron gas in cleaved-edge-overgrown semiconductor quantum wires

J. Rub

[a] Departa

[b] Dep

APPLIED PHYSICS LETTERS VOLUME 76, NUMBER 24 12 JUNE 2000

## Carrier and light trapping in graded quantum-well laser structures

G. Aichmayr, M. D. Martín, H. van der Meulen, C. Pascual, L. Viña,[a] and J. M. Calleja
*Departmento de Física de Materiales, Universidad Autónoma, Cantoblanco, E-28049 Madrid, Spain*

F. Schafer, J. P. Reithmaier, and A. Forchel
*Technische Physik, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany*

APPLIED PHYSICS LETTERS VOLUME 77, NUMBER 23 4 DECEMBER 2000

## 1.26 $\mu$m intersubband transitions in $In_{0.3}Ga_{0.7}As/AlAs$ quantum wells

César Pascual Garcia,[a] Andrea De Nardis, Vittorio Pellegrini,[b] Jean Marc Jancu, and Fabio Beltram
*Scuola Normale Superiore and INFM, Piazza dei Cavalieri 7, I-56126 Pisa, Italy*

Bernhard H. Müeller,[c] Lucia Sorba,[d] and Alfonso Franciosi[e]
*Laboratorio Nazionale TASC-INFM, I-34012 Trieste, Italy*

(Received 24 August 2000; accepted for publication 10 October 2000)

We observed room-temperature intersubband transitions at 1.26 $\mu$m in *n*-doped type-II $In_{0.3}Ga_{0.7}As/AlAs$ strained quantum wells. An improved tight-binding model was used to optimize the structure parameters in order to obtain the shortest wavelength intersubband transition ever achieved in a semiconductor system. The corresponding transitions occur between the first confined electronic levels of the well following mid-infrared optical pumping of electrons from the barrier *X*-valley into the well ground state. © *2000 American Institute of Physics.* [S0003-6951(00)02950-8]

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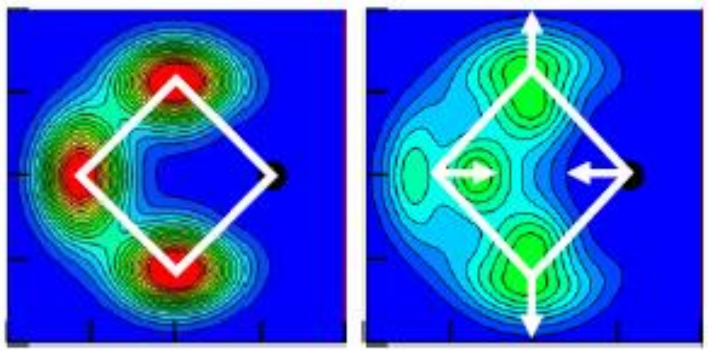
# PhD. at Scuola Normale Superiore

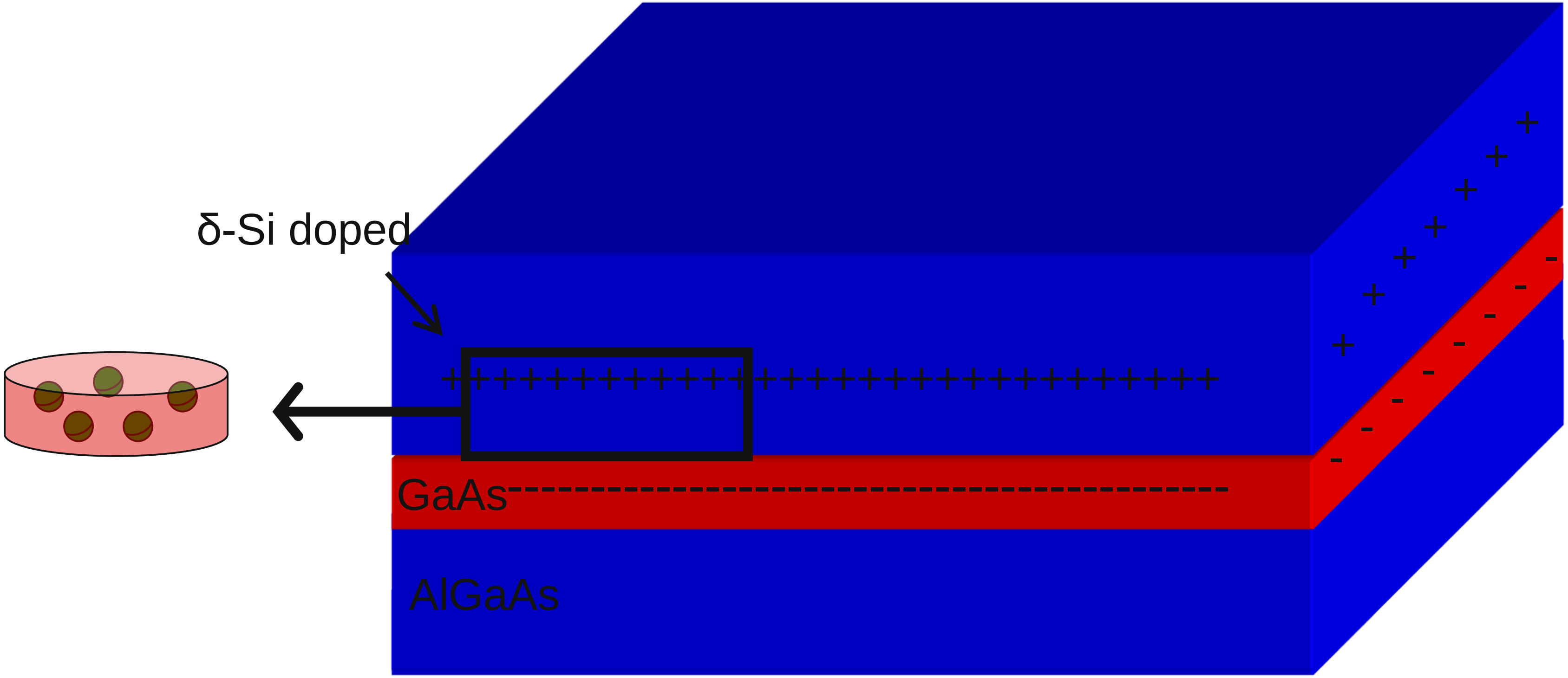
## Wigner molecule

In the localized limit (strong correlation) the excitations of electrons in a QD correspond to the roto-vibrational modes of an electron molecule.

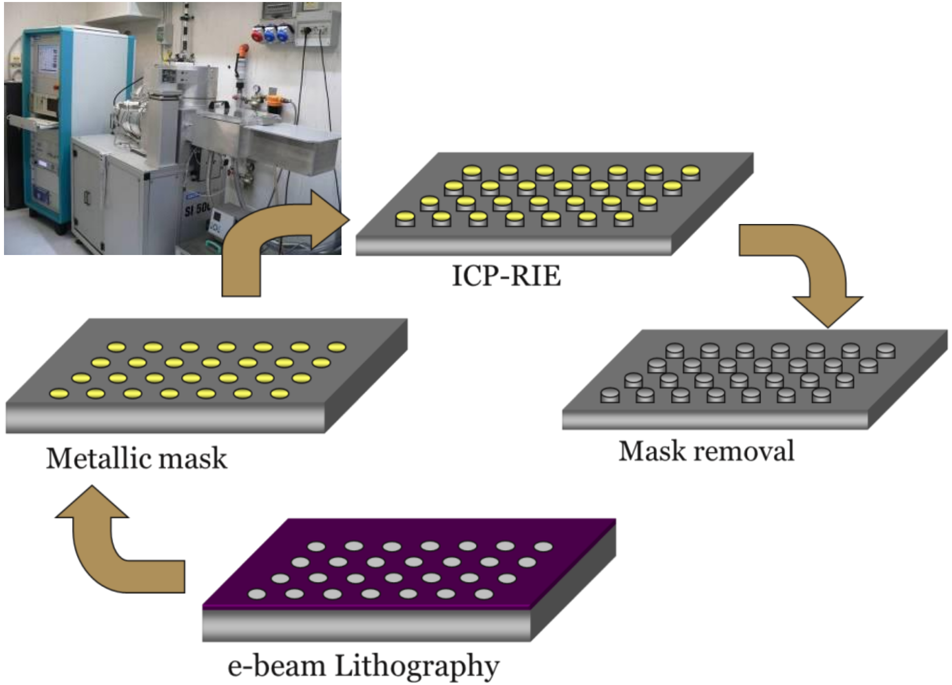


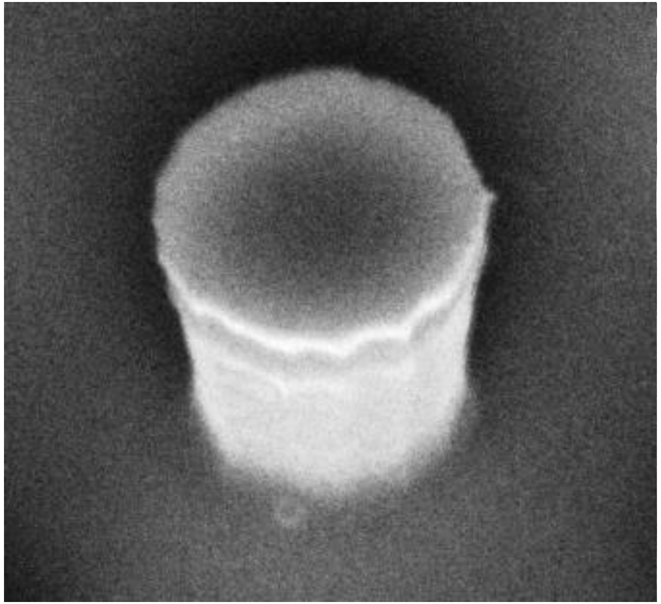
Modulation-doped heterostructure

Modulation-doped quantum dots

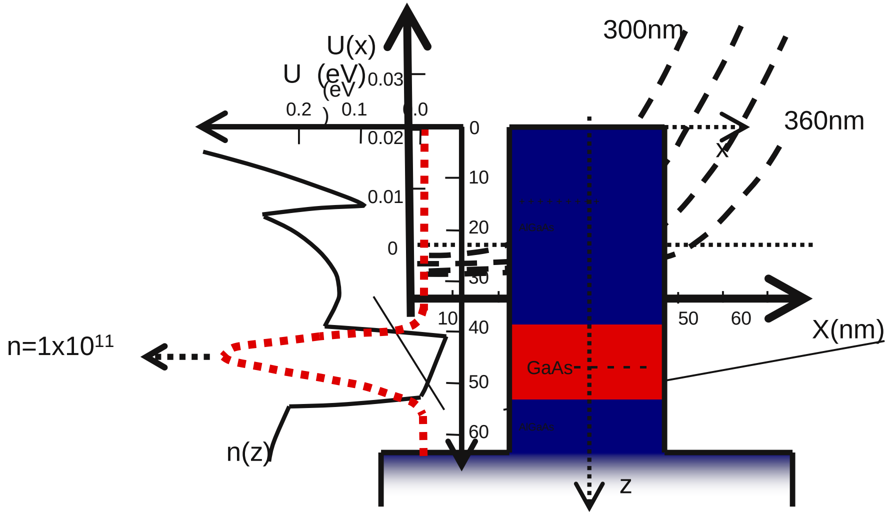


# QUANTUM DOT FABRICATION

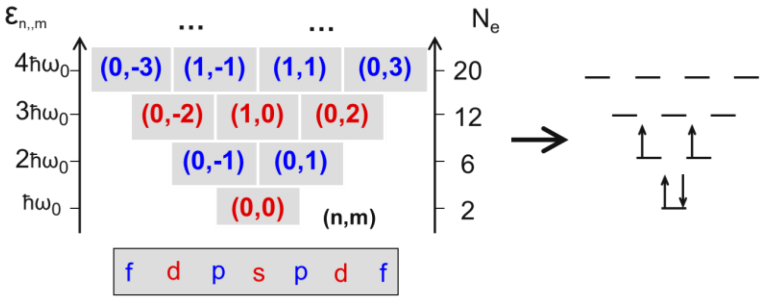


# FOCK-DARWIN ENERGY LEVELS IN A PLANAR QD



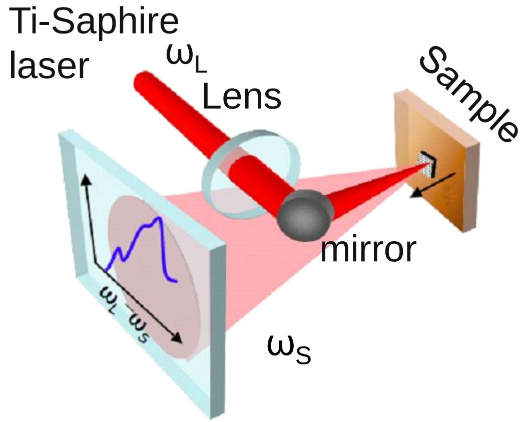

$$\varepsilon_{n,,m} = \hbar\omega_0(2n+|m|+1) = \hbar\omega_0(N)$$

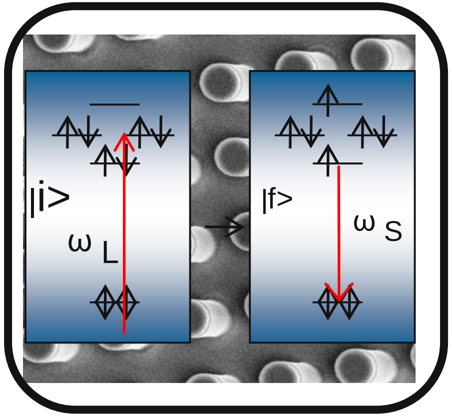


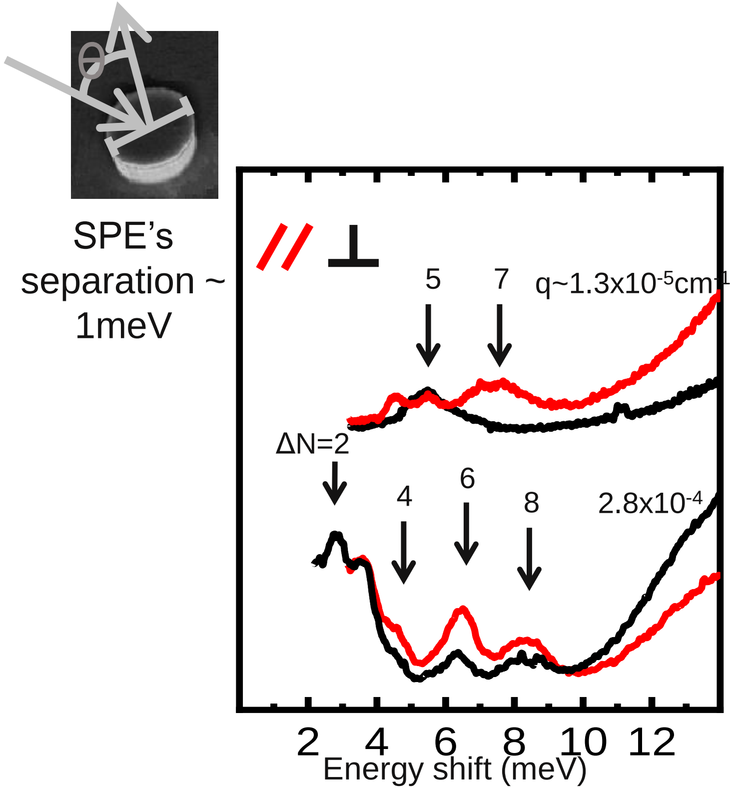
# PROBING COLLECTIVE EXCITATIONS

## Inelasttic light scattering

Inelastic light scattering probes both charge and spin excitations

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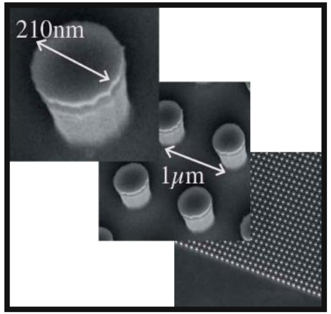
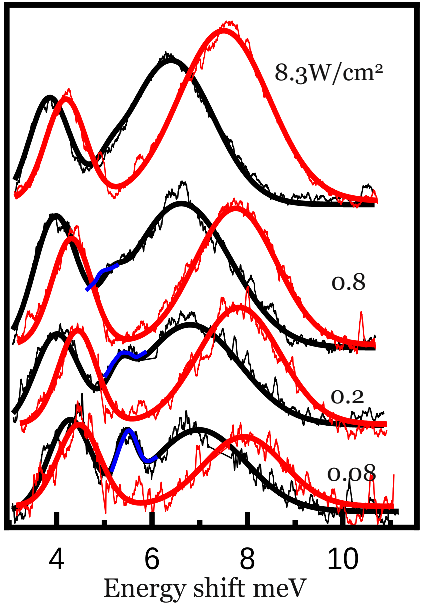
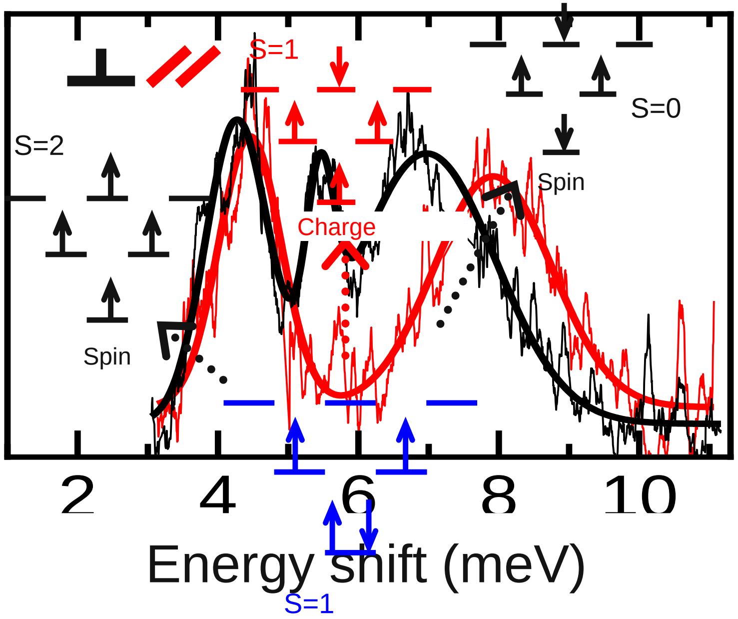
# DICOVERING A NEW EXCITATION

## Four electron quantum dot

PRL **95**, 266806 (2005)



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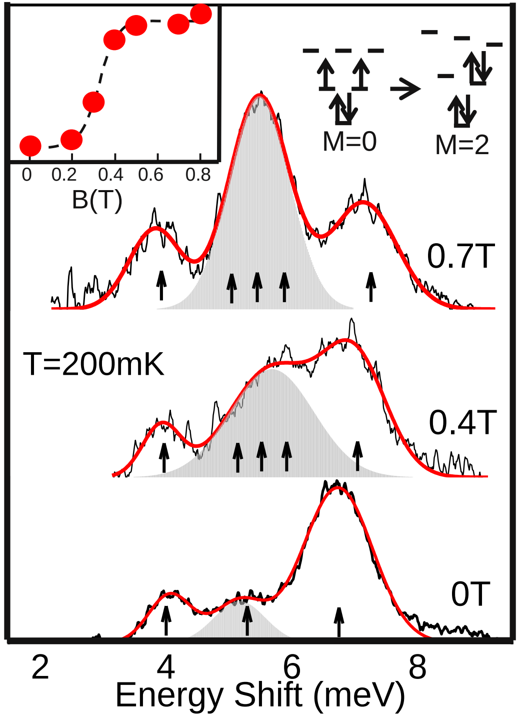
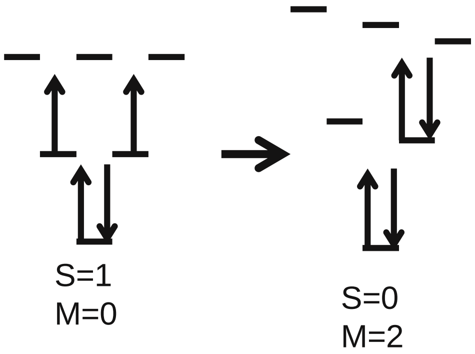
# MOLECULAR WIGNER CRISTALISATION

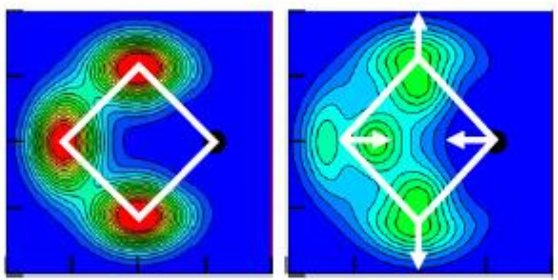



$$\varepsilon_{n,,m} = \hbar\Omega_0(N) - \hbar\omega_c m/2$$

$$\Omega^2 = \omega_0 + \omega_c$$




**In the localized limit (strong correlation) the excitations of electrons in a QD correspond to the roto-vibrational modes of an electron molecule.**



Nature physics 944, 1038 (2008)
PRL 95, 266806 (2005)

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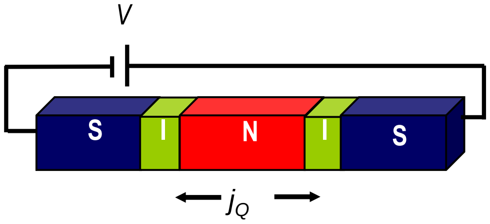
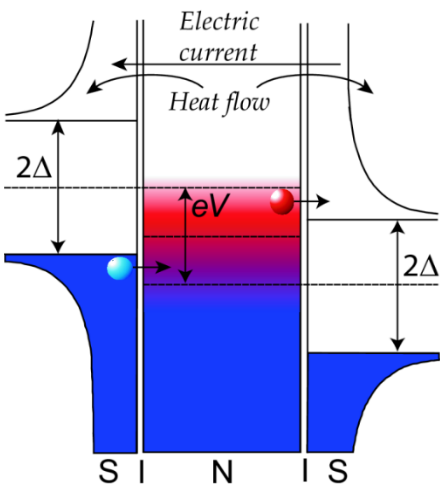
# TRANSIT TO BIOLOGY

## From SNS to JRC

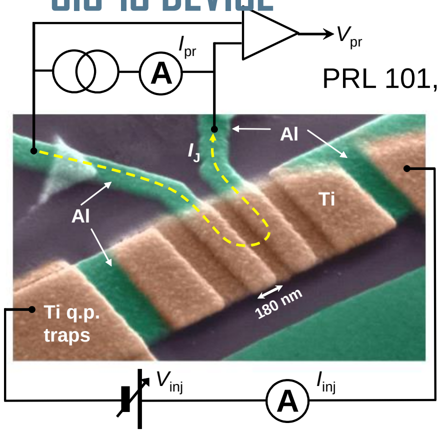
# SUPERCONDUCTOR DEVICES

## SINIS REFRIGERATOR

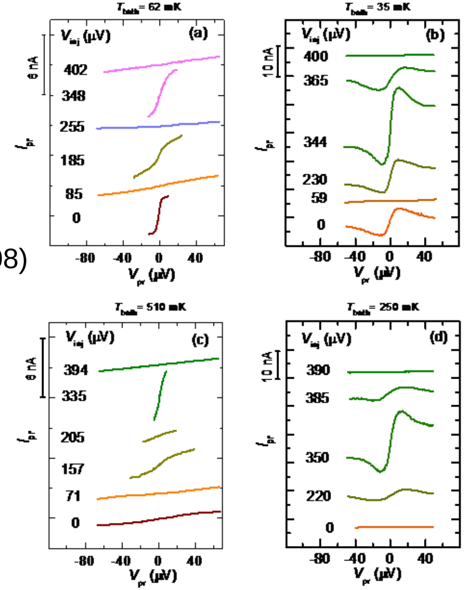



## SIS*IS DEVICE

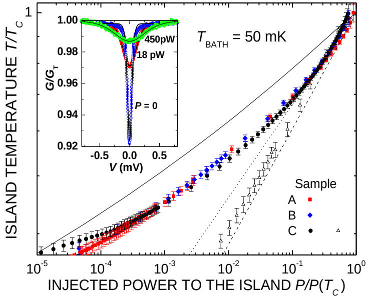


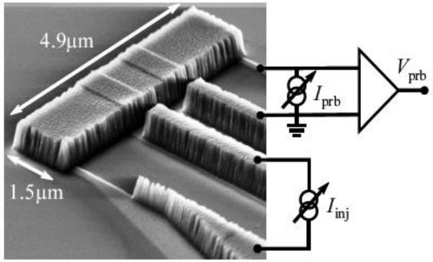

PRL 101, 077004 (2008)




## SISIS DEVICE

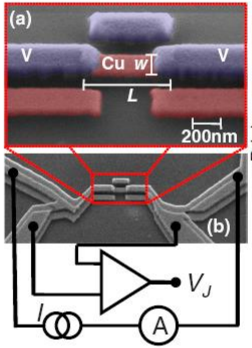
PRL. 102, 017003 (2009)

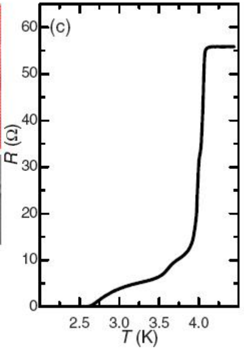


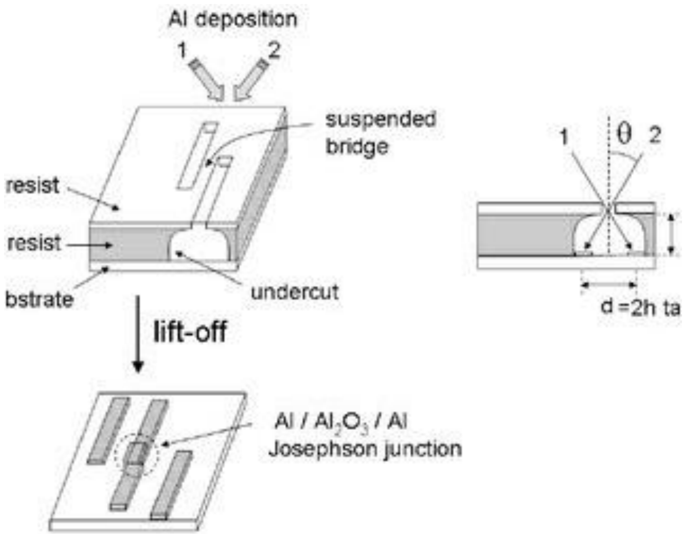

## SNS DEVICE

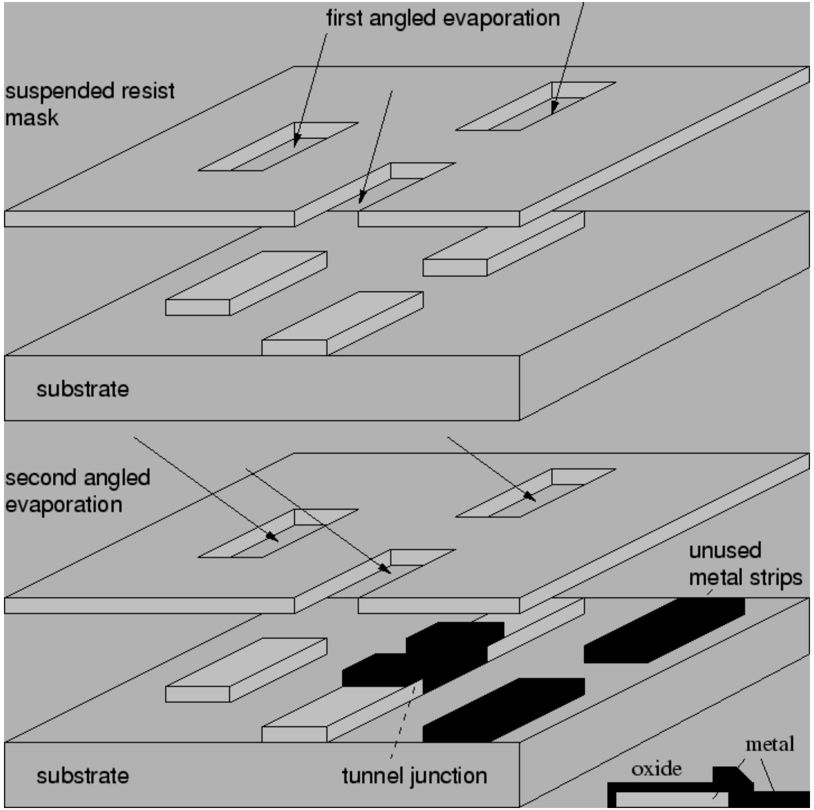
APL94 132508 (2009)



# SHADOW EVAPORATION




Advantages:
- Saves lithography steps
- Possibility to deposit different materials without breaking vacuum
- Usually very good lift-off

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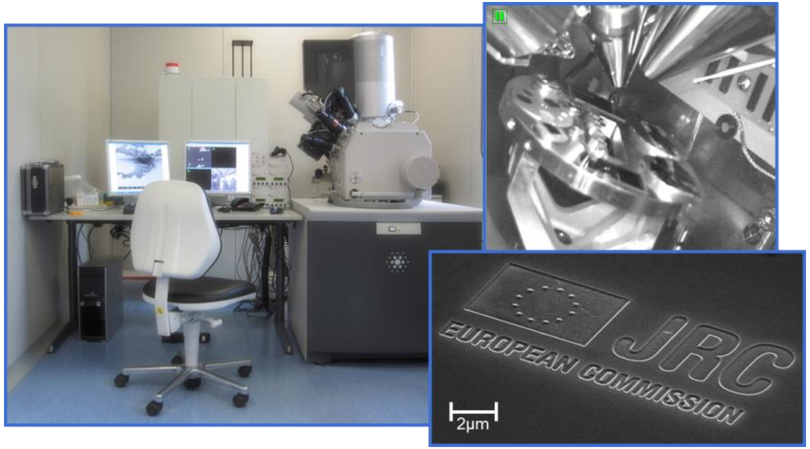
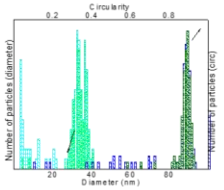
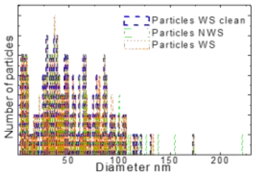
# JOINT RESEARCH CENTRE

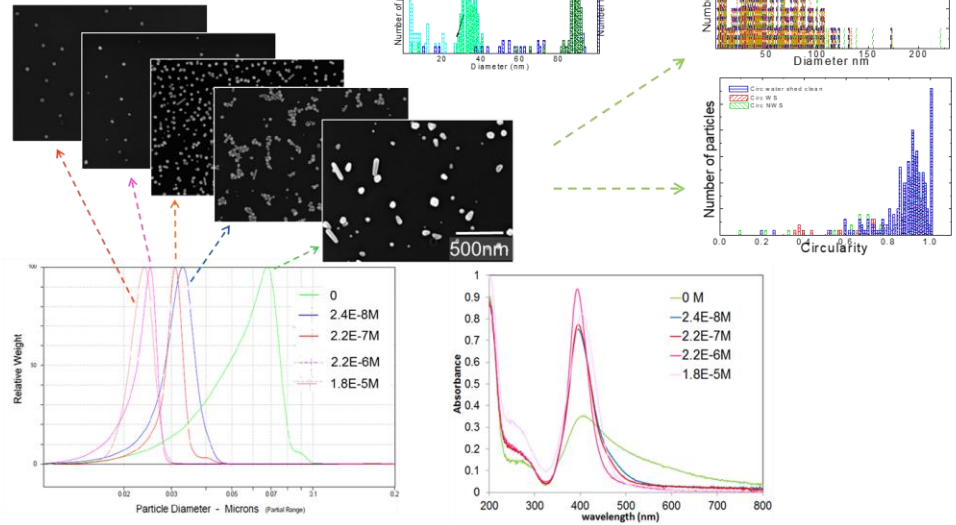
## ELECTRON MICROSCOPY




Ag Nanoparticles grwon with different concentrations of Tannic acid

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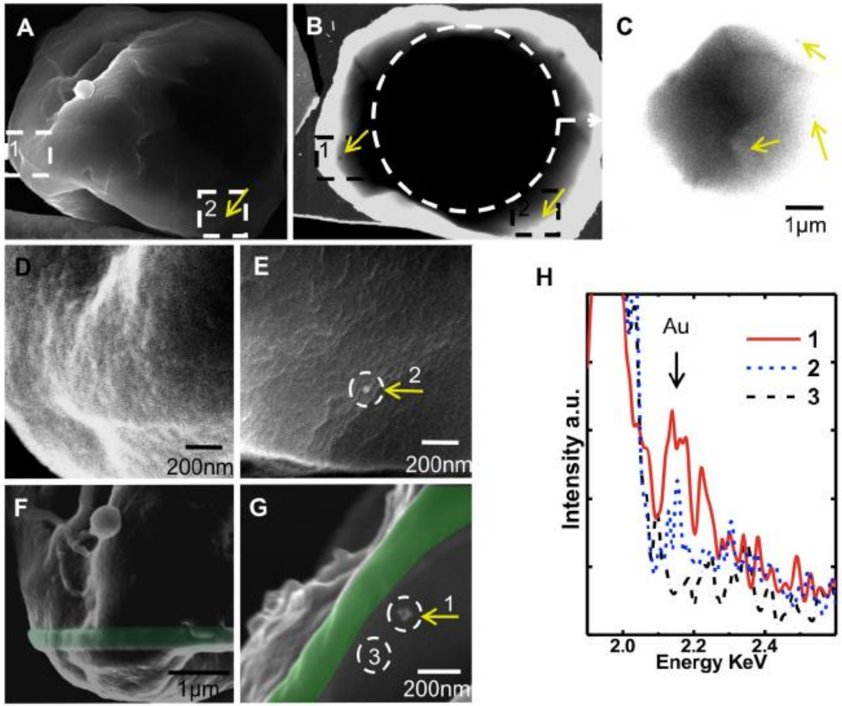
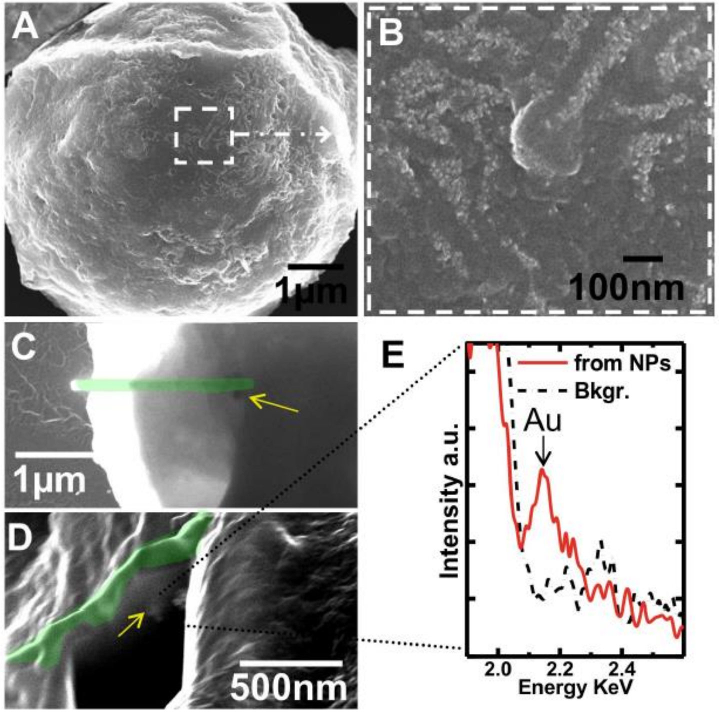
# UPTAKE OF NP'S BY CELLS

## Study by FIB lithography

### 35nm NPs




### 5nm NPs




Small 9, 472 (2013)
SCIENTIFIC REPORTS 3, 1326 (2013)

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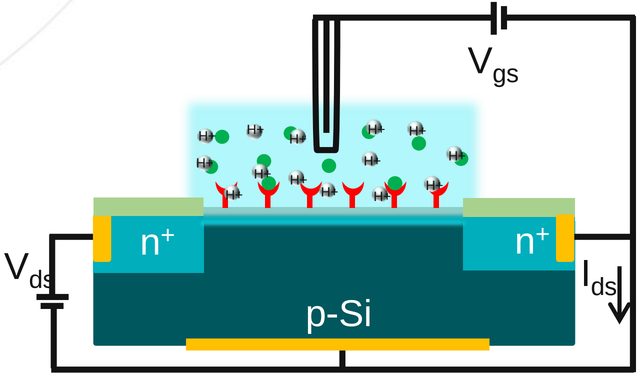
# BIOSENSORS

## UNEXPECTED PROBLMES…

## COMING FROM WINGER CRISTALISATION

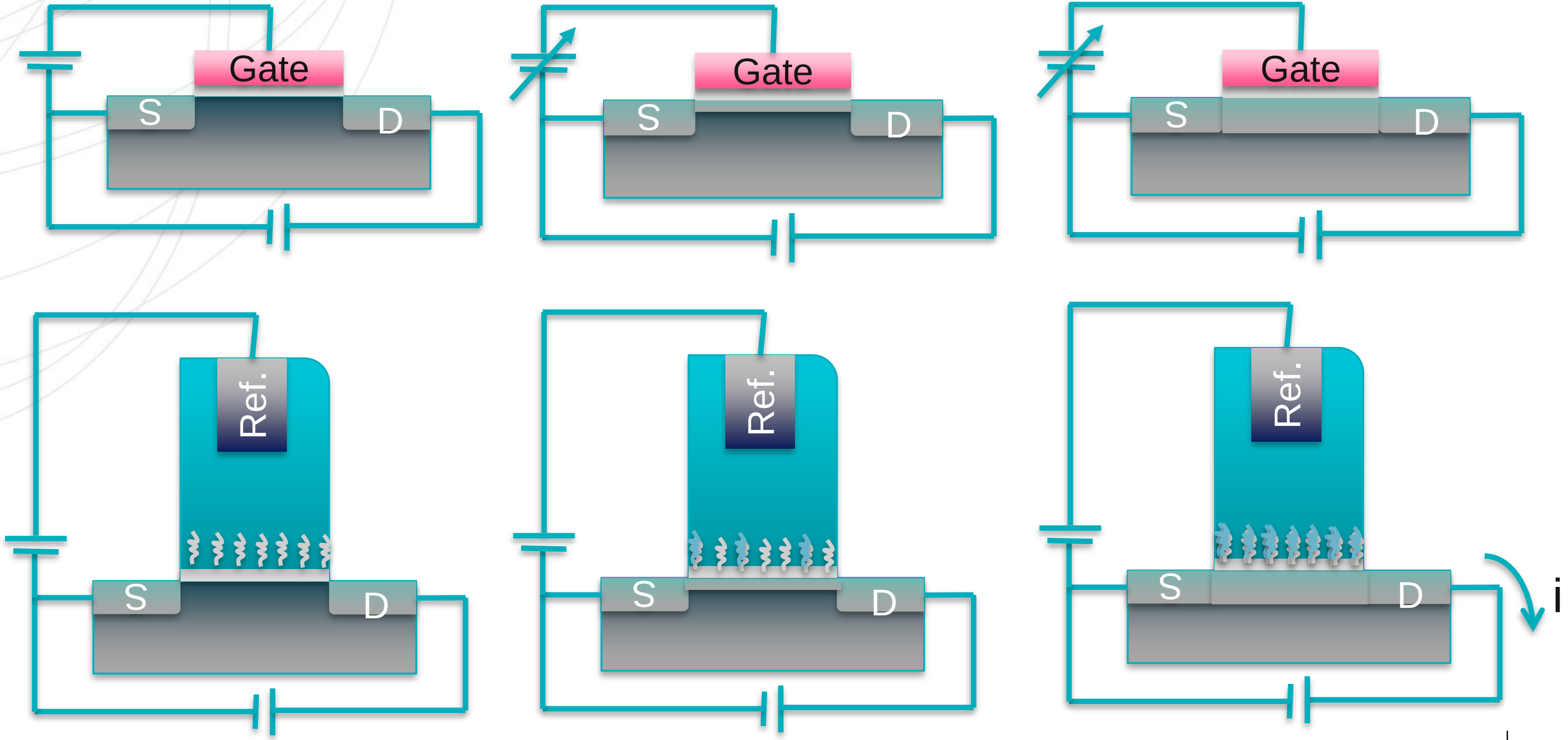
# BIOSENSORS


**A device which combines a biorecognition element with a transducer**




- ✓ Label-free sensing
- ✓ Real time
- ✓ Selectivity
- ✓ Small size
- ✓ Multiplexing
- ✓ Reduce costs
- ✓ Material control

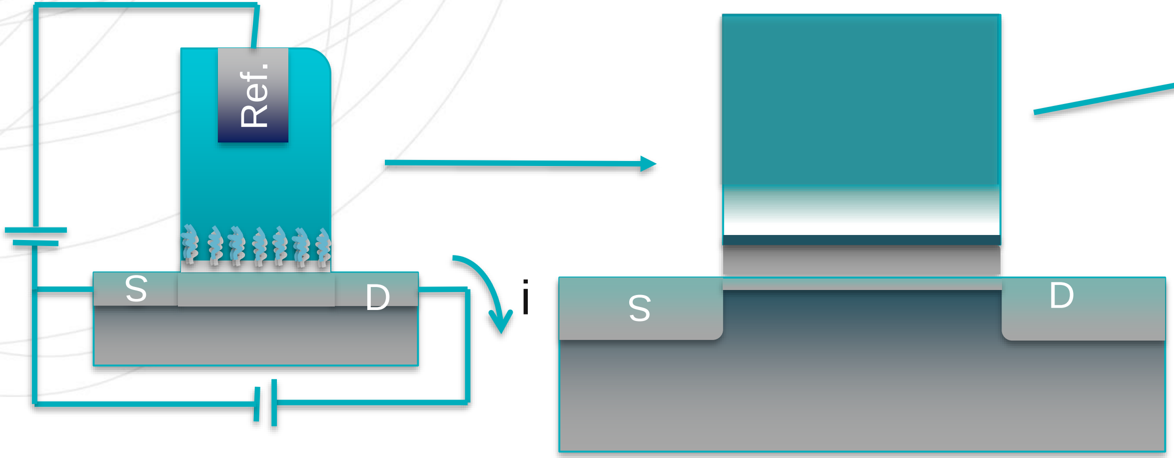
# From MOSFET to Bio-ISFET

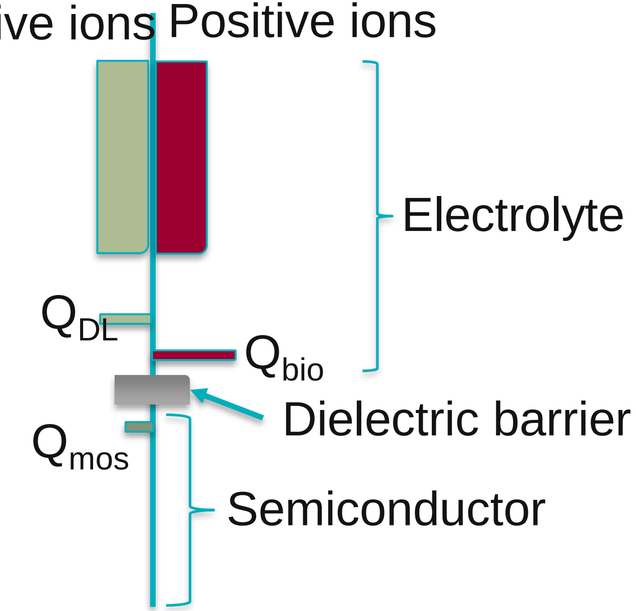



$$i = v \times Q_{MOS} = q\,v \times n \times A$$

# Charge screening

In reality the charges are screened

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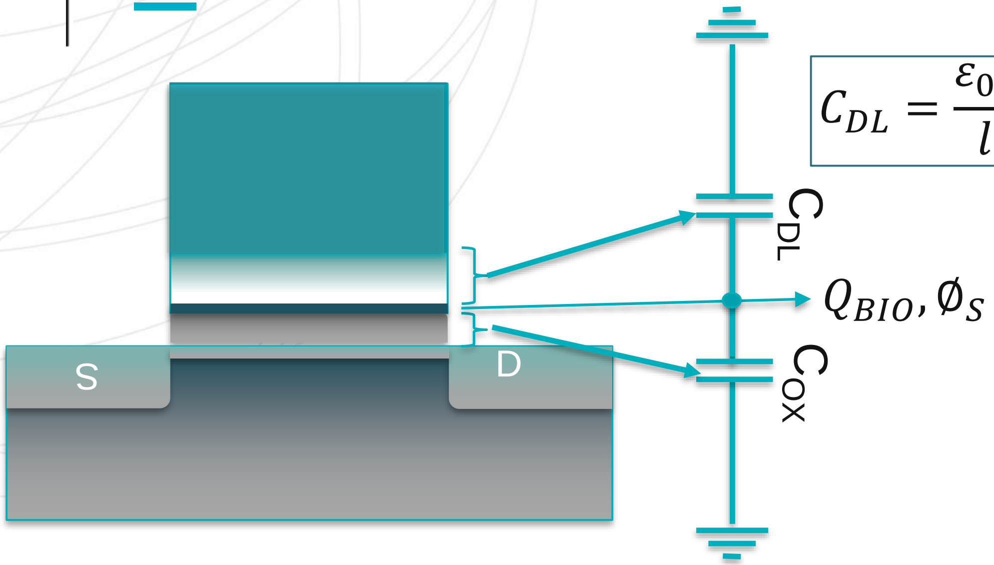
# What is the charge distribution




$$\boxed{C_{DL} = \frac{\varepsilon_0 \varepsilon_r}{l_d} \sim \sqrt{I(M)}}$$


$$Q_{MOS} = \frac{C_{ox}}{C_{ox} + C_{DL}} Q_{BIO}$$

$$= \frac{\varepsilon_{ox}\varepsilon_0 / t_{ox}}{\varepsilon_{ox}\varepsilon_0 / t_{ox} + \varepsilon_r \varepsilon_0 / l_D} Q_{BIO}$$

$$l_d = \sqrt{\frac{\varepsilon_r \varepsilon_0 RT}{2F^2 C_0}} \sim l_d(nm) = \frac{0.304}{\sqrt{I(M)}} \longrightarrow \quad if\ l \sim t_{ox} \rightarrow \quad \boxed{Q_{MOS} \sim \frac{\varepsilon_{ox}}{\varepsilon_r} \frac{l_D}{t_{ox}}}$$

# So what is the real pontential

$$Q_{DL} = C_{DL}\emptyset_0 = \emptyset_0 \frac{\varepsilon_0 \varepsilon_r}{l_d}$$

At low salt concentration

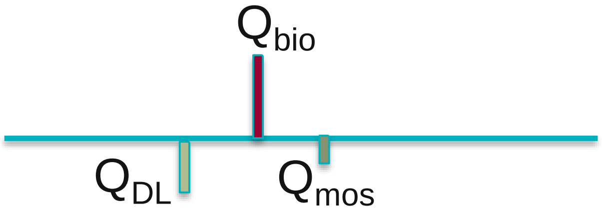
$$Q_{DL} = Q_0 exp\left(\frac{zq\emptyset_0}{2KT}\right)$$

$$Q_0 = \sqrt{\underline{2KT\varepsilon_0\varepsilon_r} N_{avg} I_0}$$

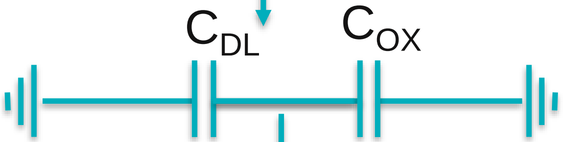
Starting ionic strength

Avogadro number

Other *"constants"*




$$Q_{Bio} = Q_{DL} + Q_{Mos}$$




$$\underline{Q_{Bio} = Q_0 exp\left(\frac{zq\emptyset_0}{2KT}\right) + C_{Ox}\emptyset_0}$$

$$\boxed{\emptyset_0 = \frac{2KT}{zq} ln \frac{Q_{Bio}}{Q_0}}$$

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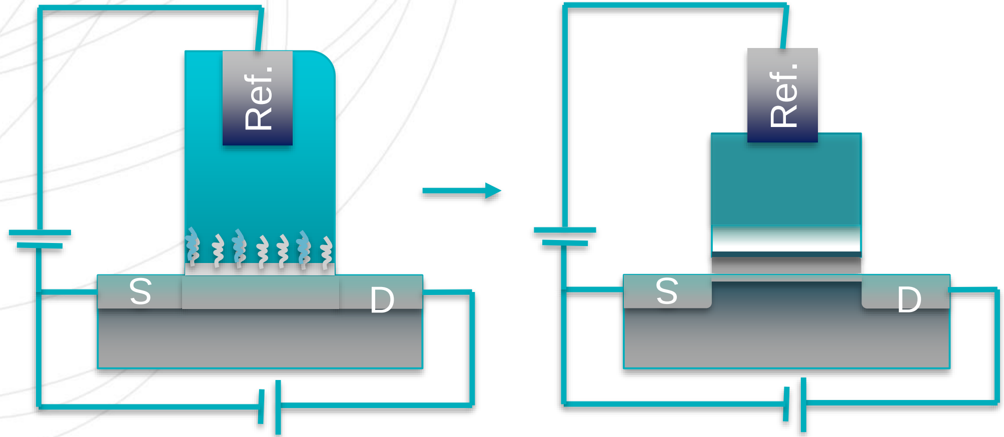
# Difference dependences of the current




$$\boxed{i = v \times Q_{MOS} = q\, v \times n \times A}$$

$$\boxed{\emptyset_0 = \frac{2KT}{zq} ln \frac{Q_{Bio}}{Q_0}}$$

$$Q_{Bio} = Q_0 exp\left(\frac{zq\emptyset_0}{2KT}\right) + C_{Ox}\emptyset_0$$

$$Q_{Mos} = C_{Ox}\emptyset_0 = \frac{\varepsilon_0\varepsilon_{ox}}{T_{ox}}\frac{2KT}{zq} ln \frac{Q_{Bio}}{Q_0}$$

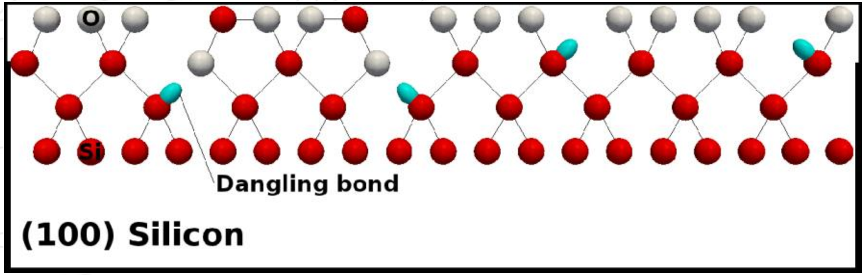
Semiconductor parameters

Charge

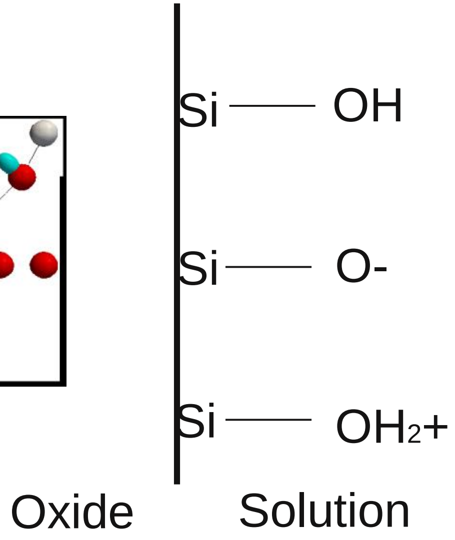
$N_s \rightarrow$ from the analyte but also geometery!

$$Q_{Mos} \sim \frac{\varepsilon_0\varepsilon_{ox}}{T_{ox}}\frac{2KT}{zq} ln \frac{\sigma_T \times k\rho_0 \times t_S^{\left(\frac{3-D_F}{2}\right)}}{Q_0} = \sqrt{2KT\varepsilon_0\varepsilon_r N_{avg} I_0}$$

# Oxide surface as pH sensor




Site Binding Model




Deprotonation

$$Si\text{-}OH \overset{K_b}{\rightleftharpoons} Si\text{-}O^- + H^+$$

Protonation

$$Si\text{-}OH_2^+ \overset{K_a}{\rightleftharpoons} Si\text{-}OH + H^+$$

# Proton equilibrium

$$Q = q\left[[SiOH_2^+][SiO^-]\right]$$

$$k_b = \frac{[SiO^-][H^+]_S}{[SiOH]}$$

$$Q(pH) = qN_0 \frac{\frac{[H^+]_S}{k_a} - \frac{k_b}{[H^+]_S}}{1 + \frac{k_b}{[H^+]_S} + \frac{[H^+]_S}{k_a}}$$

$$k_a = \frac{[SiOH][H^+]_S}{[SiOH_2^+]}$$

Point of zero charge $Q(pH) = 0$

$$\downarrow$$

$$k_a k_b = \left[[H^+]_S^2\right] = \left[[H^+]_B^2\right]$$

$$\downarrow$$

$$pzc = \frac{pk_a + pk_b}{2} = \frac{6 + (-2)}{2} = 2$$

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# NERST lIMIT

$$Q(pH) = qN_0 \frac{\frac{[H^+]_S}{k_a} - \frac{k_b}{[H^+]_S}}{1 + \frac{k_b}{[H^+]_S} + \frac{[H^+]_S}{k_a}}$$

$$\emptyset_0 = \frac{2KT}{zq} ln \frac{Q}{Q_0}$$

Self consistent problem

$$Q_{DL} = Q_0 exp\left(\frac{zq\emptyset_0}{2KT}\right)$$

$$[H^+]_S = [H^+]_B exp\left(\frac{q\emptyset_0}{2KT}\right)$$

$$\frac{\delta Q}{\delta pH_s} \equiv -q\beta_{int}$$

Intrinsic buffer capacity

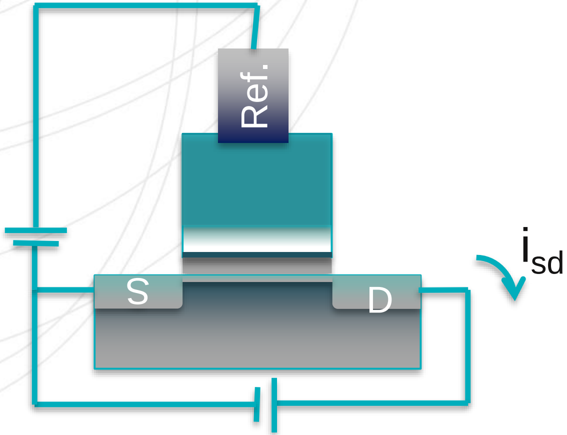
Nerst equation $pH_S = pH_B + \frac{q\emptyset_0}{2.3\ KT}$

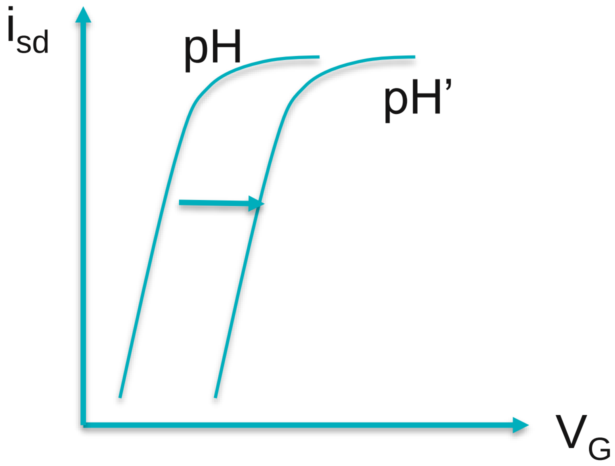
$$\frac{\delta\emptyset_0}{\delta pH_s} = \frac{\delta\emptyset_0}{\delta Q} \times \frac{\delta Q}{\delta(pH_s)} = \frac{1}{C_{DL}} \times (-q\beta_{int})$$

$$\frac{\delta\emptyset_0}{\delta pH_B} = -2.3\frac{KT}{q}\left(1 + \frac{2.3KTC_{DL}}{q^2\beta_{int}}\right)^{-1}$$

$$\Delta V_G \approx 2.03\left(\frac{KT}{q}\right)\Delta\text{pH}$$

# pH Transfer characteristics




$$\frac{\delta \emptyset_0}{\delta pH_B} = -2.3\frac{KT}{q}\left(1 + \frac{2.3KTC_{DL}}{q^2\beta_{int}}\right)^{-1}$$

$$\Delta V_G \approx 2.03\left(\frac{KT}{q}\right)\Delta\mathrm{pH}$$

$$\boxed{\frac{\Delta V_G}{\Delta \mathrm{pH}} \approx 59\, mV/pH}$$

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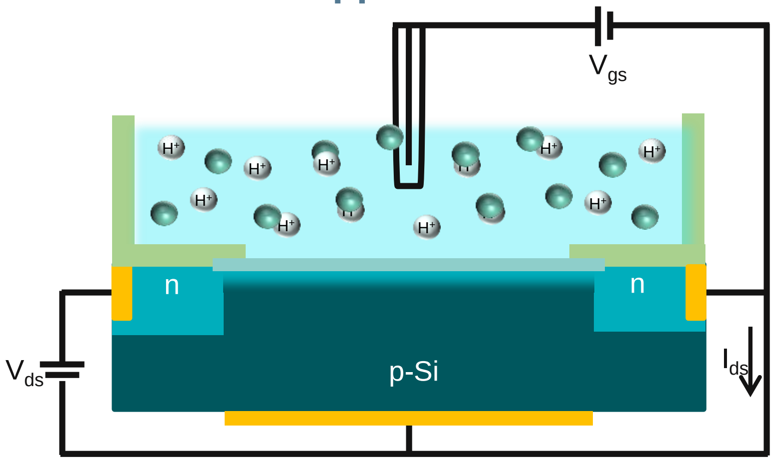
# ION SENSITIVE FIELD EFFECT TRANSISTOR


**ISFET**

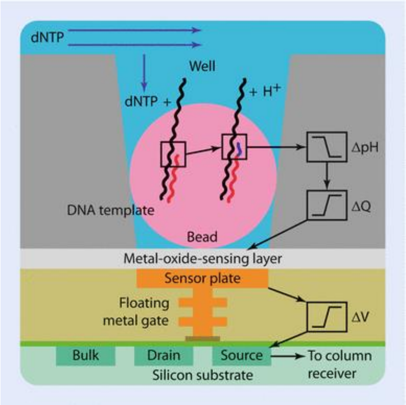
**– 1970 Piet Bergveld –**

**– 2020 the most extended pH sensor for precision applications**

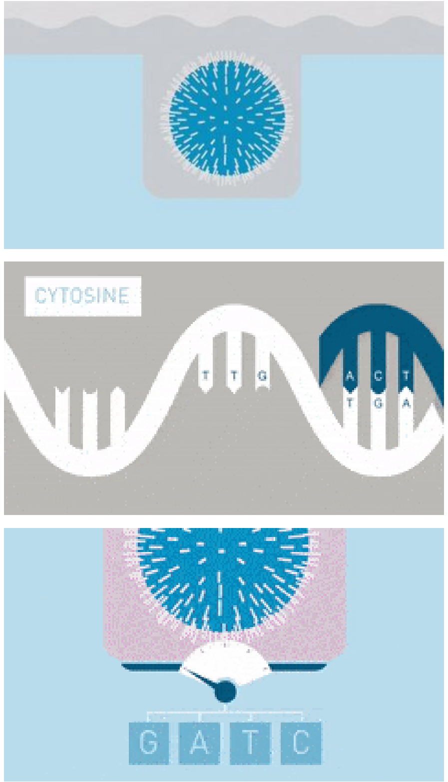


# STATE OF THE ART IN CLINICAL ISFET TECHNOLOGY

## Ion torrent technology

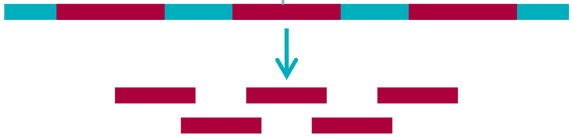







## Amplicon Sequencing

- Sequencing of a dedicated panel of genes/hotspots




Mostly Ion Torrent technology
~**15% market share**

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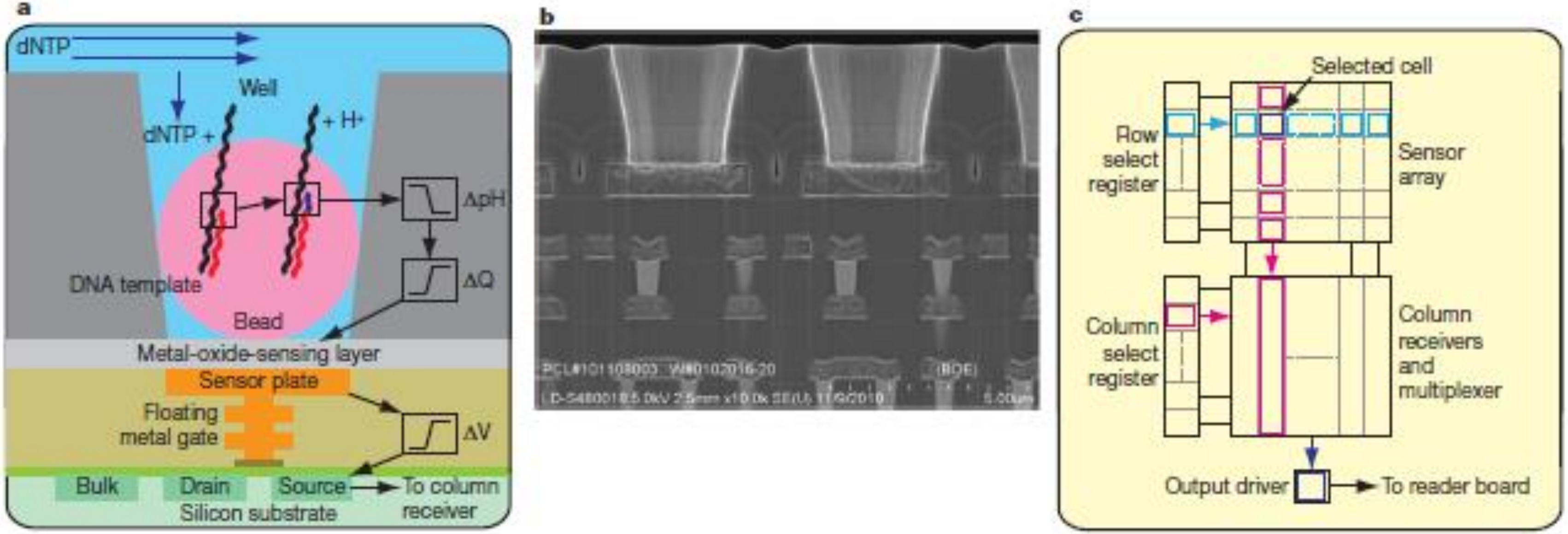
# pH ISFET for NGS




Rothberg et. al.
3 4 8 | N AT U R E | V O L 4 7 5 | 2 1 J U LY 2 0 1 1
doi:10.1038/nature10242

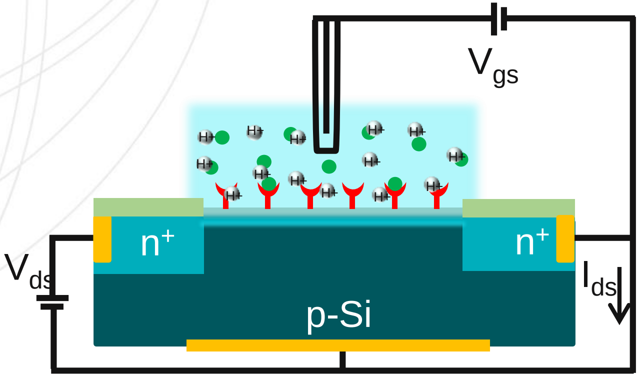
# NANO-BIOSENSORS

## AND SUDDENLY…

## MORE PROBLMES

# BIOSENSORS

**A device which combines a biorecognition element with a transducer**


*Bioconjugation* of *target-analyte/receptors* are *transduced* by the *capacitive effect* of a *dielectric/semiconductor junction in contact with the electrolyte*.

- ✓ Label-free sensing
- ✓ Real time
- ✓ Selectivity
- ✓ Small size
- ✓ Multiplexing
- ✓ Reduce costs
- ✓ Material control

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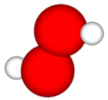
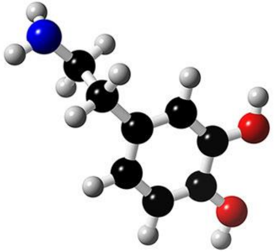
# Biosensing

**Objectives:**

- Detect the presence/no presence of something
- Quantify

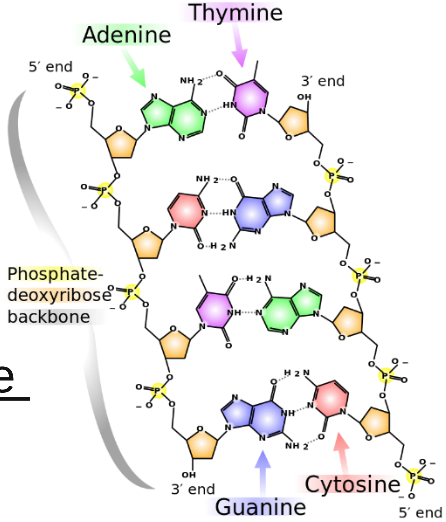




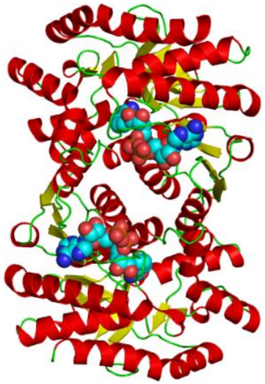
**What:**

- Small molecules: Oxygen, Peroxides, NO, Neurotransmisors (dopamine…)
- DNA:
- Proteins
- Sugars
- Lipids
- Hormones, enzyme

…







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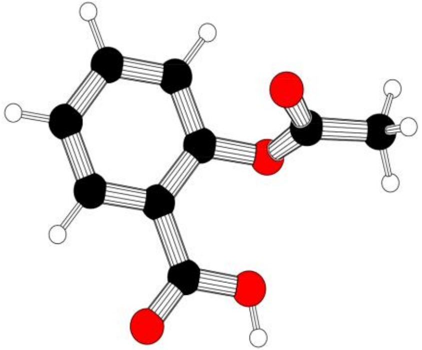
# concentrations

$C_9H_8O_4$ →180.157 g/mol

Solubility 1mg/mL

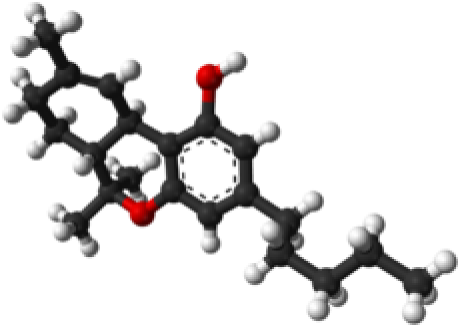
650 mg in 6 L → ~3 mM



$C_{21}H_{30}O_2$ →314.45 g/mol

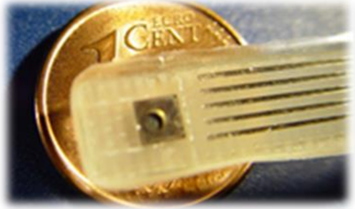
Solubility 2.8mg/mL

130 mg in 6 L → ~0.4 mM

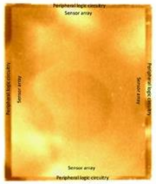


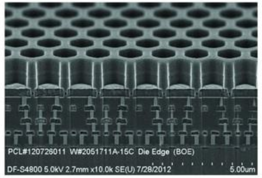
# ISFET TECHNOLOGIES

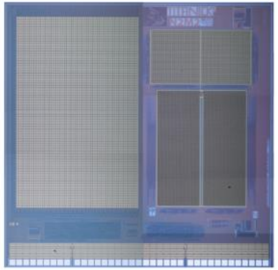
## 01 Traditional planar sensors

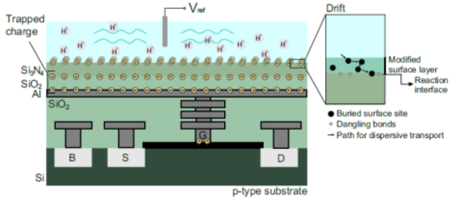


## 02 Extended gates

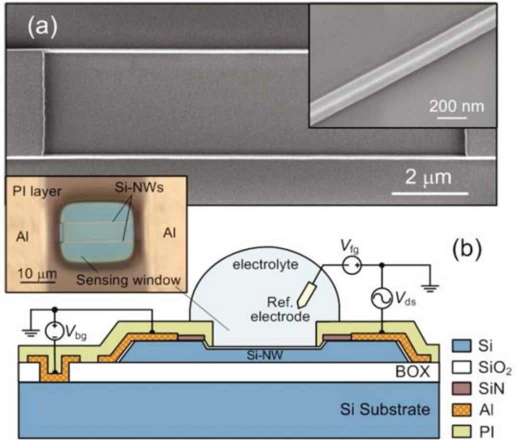








## 03 Nanowires

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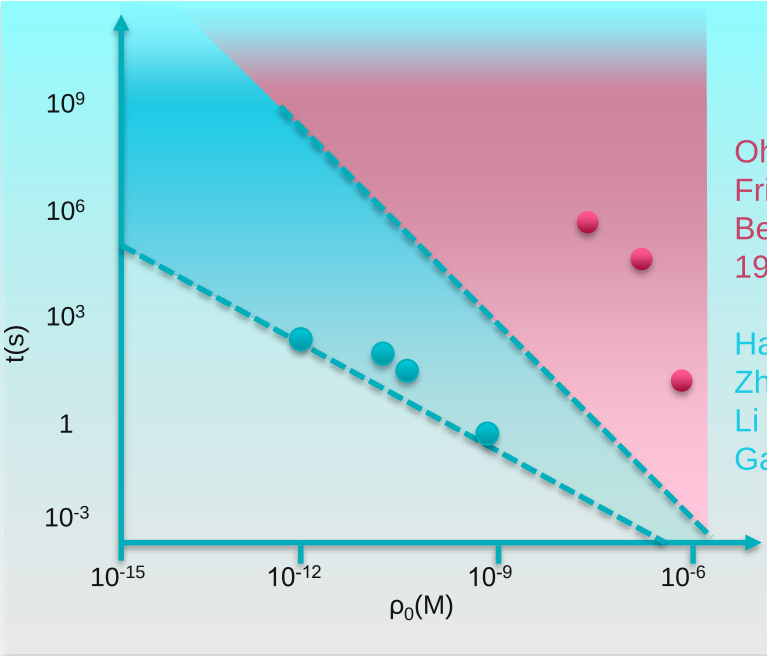
# Traditional FET vs nano-wires

## Why so sensitive?

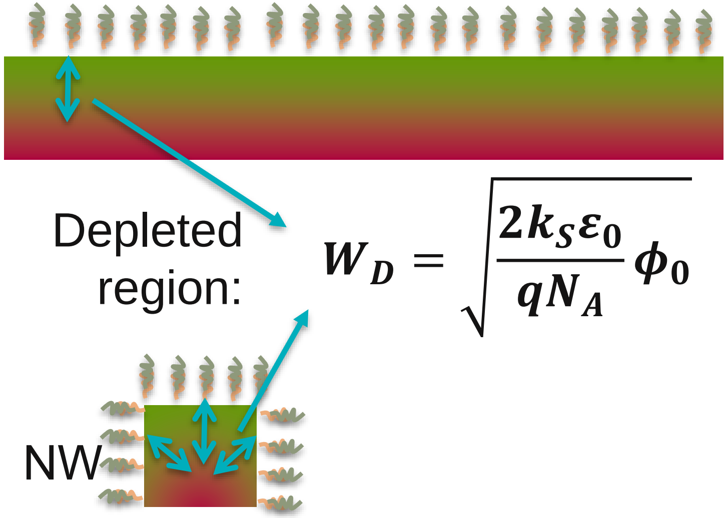



Ohtake et. al. 2004
Fritz et. al. 2002
Bergveld et. al. 1991

Hahm et.al. 2004
Zheng et al. 2005
Li et. al. 2005
Gao et. al. 2007

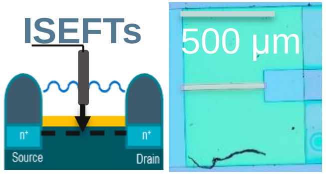
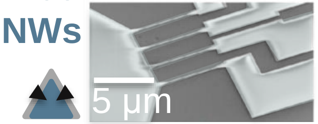
## Surface area?

Planar sensor

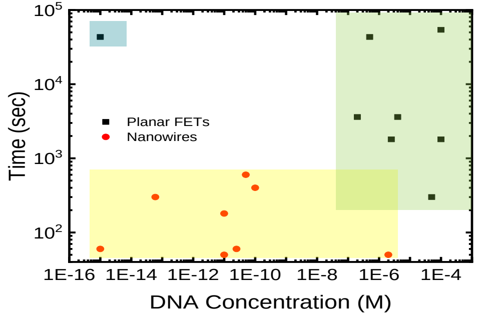


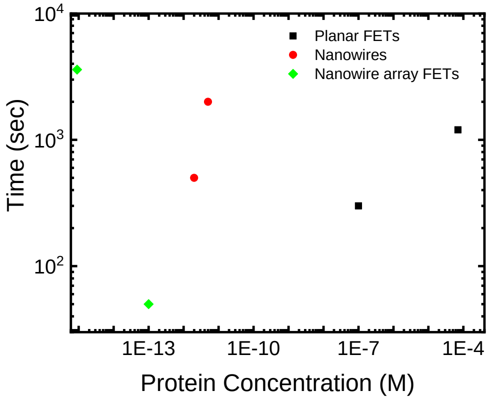

$$W_D = \sqrt{\frac{2k_S\varepsilon_0}{qN_A}\phi_0}$$

# FET LABEL FREE SENSING

| | Gating | Defect Propag. | Signal/ noise | Footprint | Diffusion | Materials | Reliability |
|---|---|---|---|---|---|---|---|
| ISEFTs   Sensitivity = 50µM to 20mM | Single | Less sensitive to local defects | OK | Tens of µm² | Diffusion limited (1D) | High K Dielectrics/ Surface chemistry | High |
| Silicon NWs   Sensitivity = 10fM to 25pM | 2D | Sensitive to local defects | Low (improved with arrays) | Few µm² to tens of µm² (arrays) | 2D single<br>1D array | High K Dielectrics/ Surface chemistry | Low |

# Comparison of detection limit, Response time for different configurations of BioFETs




| Sensor type | | Analyte type | | | | References |
|---|---|---|---|---|---|---|
| | | DNA | | Protein | | |
| | | **Limit of Detection (M)** | **Response Time (s)** | **Limit of Detection (M)** | **Response Time (s)** | |
| **NW FETs** | Conventional | 1E-6 to 1E-15 | 50 to 600 | 1E-12 | 500 to 2000 | 9-15, 18-19 |
| | NW arrays | | | 1E-13 to 1E-16 | 50-3600 | 20,21 |
| **Planar FETs** | Conventional | 1E-4 to 1E-7 | 300 to 54000 | 1E-5 to 1E-7 | 300 to 1200 | 3-8, 16-17 |
| | Porous sensing layer WITH HEATING | 1E-15 | 43200 | | | 1 |
| **FinFETs** | | | | | | |

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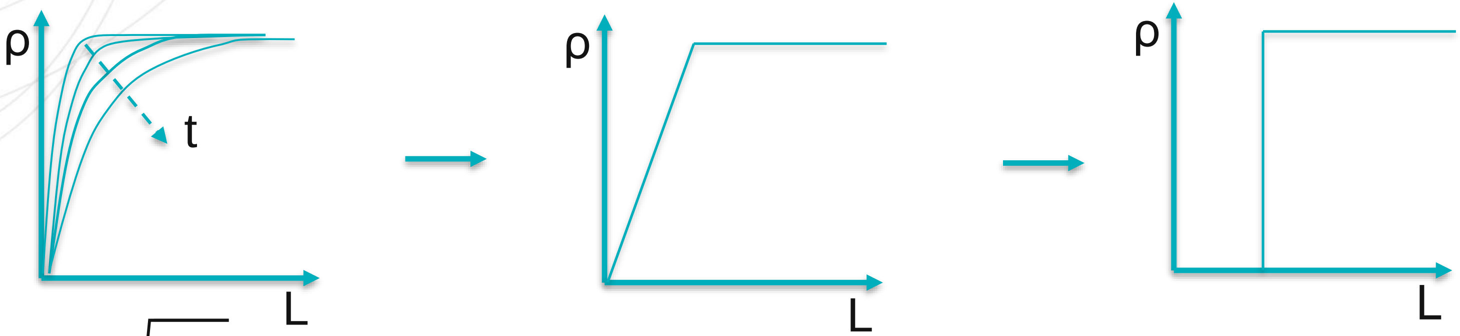
# Mass transport in a planar sensor

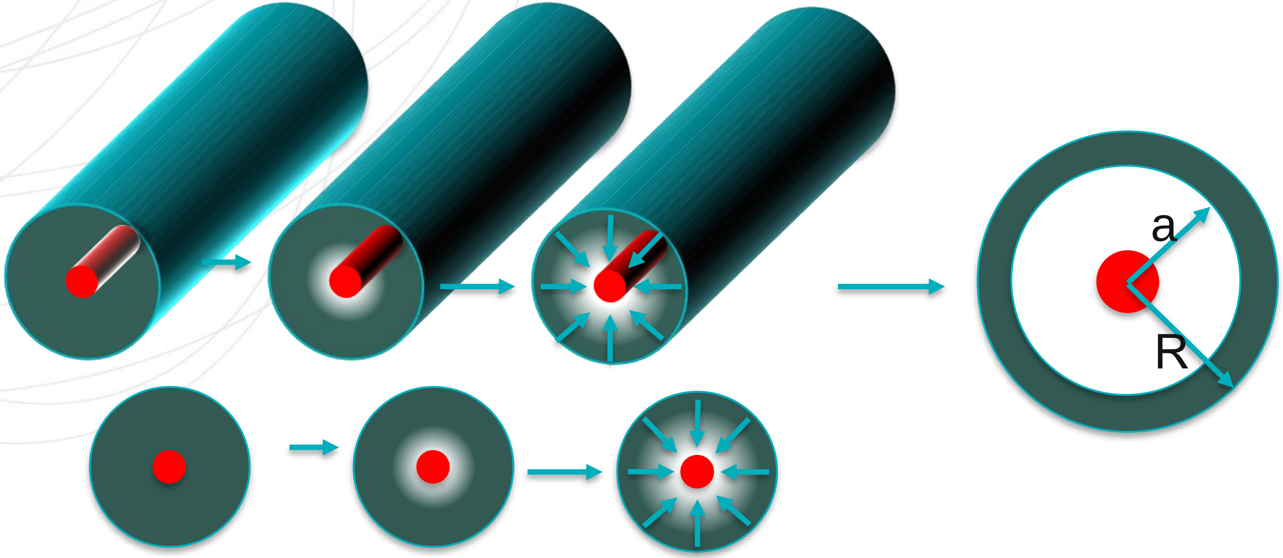
$$N(t) = \int^{S} [\rho_0 - \rho(x,t)]\,dS$$




$$N(t) = \sqrt{4/_{\pi}} \cdot \rho_0 \cdot \sqrt{Dt} \longrightarrow N(t) = 1/2 \cdot \rho_0 \cdot \sqrt{Dt} \longrightarrow N(t) = \rho_0 \cdot \sqrt{Dt}$$

$$\boxed{t_s \sim \frac{N_S^2}{D}\frac{1}{\rho_0^2}}$$

# Mass transport in the case of a NW




$$N(t) \sim \rho_0 \cdot \pi(R^2 - a^2)$$

$$a \sim \sqrt{Dt}$$

$$N(t) \sim \rho_0 \cdot \pi\left(R^2 - \sqrt{Dt}^2\right)$$

$$N(t) \sim \rho_0 \cdot Dt$$

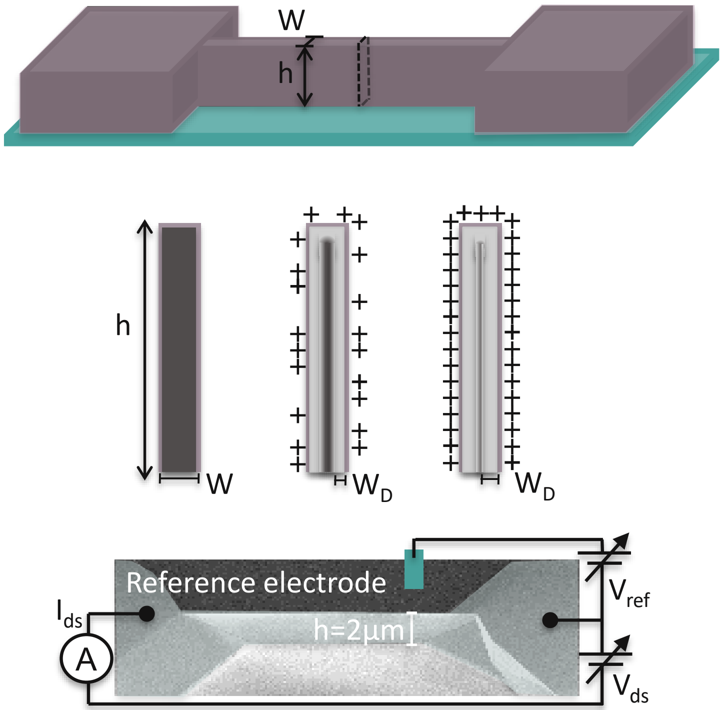
$$\boxed{t_s \sim \frac{N_S}{D}\frac{1}{\rho_0}}$$

Nair P. R. & Alam M. A. (2006). App. Phys. Lett., 88(23), 11–14.

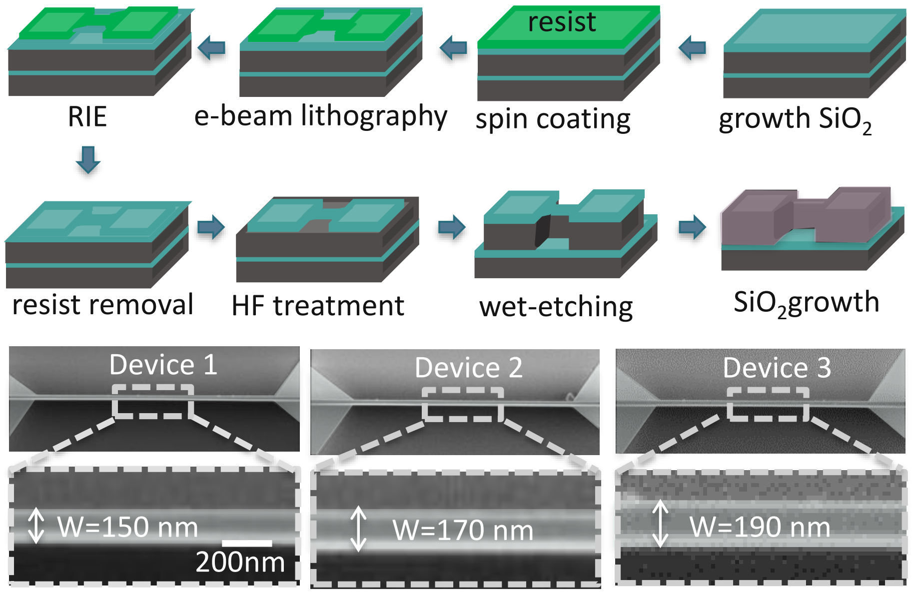
# HIGH ASPECT RATIO FIN-FET

## Our proposal for FETs

# HIGH ASPECT RATIO FINFET




## FABRICATION




**h:W ~1:4**

Rollo S. et.al. (2019). *Sci. Rep. 9*(1).

# UV LITHOGRAPHY
# MLA 150 HEIDELBERG INSTRUMENTS


- **Maskless UV Lithography :**

Direct laser writing lithography system for patterning down to 1µm.

MLA characteristics:
- Substrates size from 5*5mm² to 8'
- Substrates thickness from 0.1 to 6 mm
- Front side alignment (500nm accuracy)
- Back side alignment (1µm accuracy)
- Laser wavelength 375 nm (I line)
- Real time autofocus system

# FLOW CHART

Mask design → Wafer preparation → Dose calibration → File conversion → Alignment → Exposure → Development → Post-baking

**Mask design**

- Sample layout
  - Size
  - Orientation
- Layers
  - Alignment features

**Wafer preparation**

- Sample cleaning
  - Size of writing field
  - Density of features
- Choose resist
  - + /-Resist
  - Single resist (Etching)
  - Double layer (Evaporation)
  - Thickness
- Baking

**Dose calibration**

- Substrate
- Resist (s)
- Layers
- Resolution
- Density of features

**Post-baking**

- Mask hardening

**Development**

- Dilute developer?
- Temperatur e
- Agitation / soniquing
- Time?

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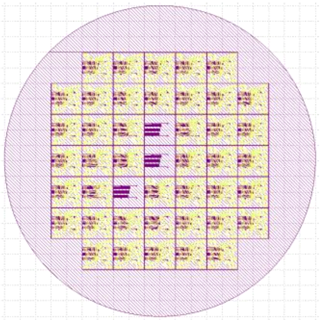
# MASK DESIGN

- Sample layout
  - Size
  - Orientation
- Layers
  - Alignment features

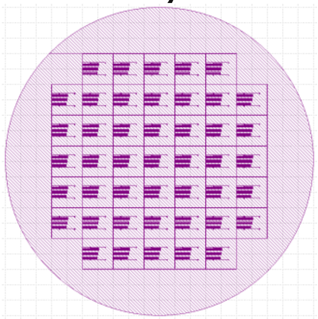
4' wafer



Primary flat

Negative resist (Single resist)

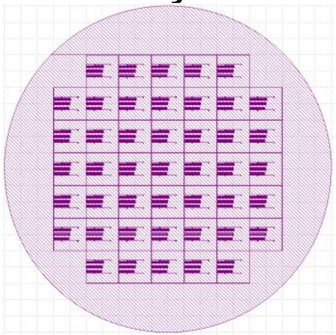
Layer 1



Positive resist for resist mask (RIE)

(Sir sist)

Layer 2

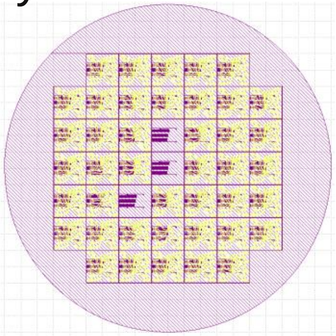


Possitive resist Ohmic

c s

( )

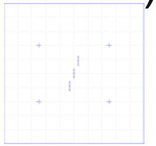
Layer 3

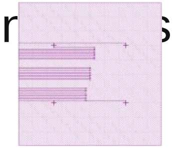


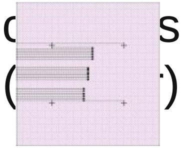
Possitive resist lead contacts

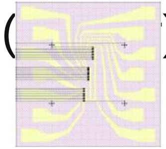
( )

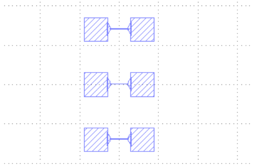
1cm$^2$

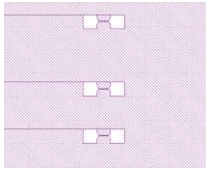


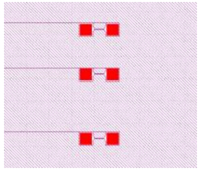


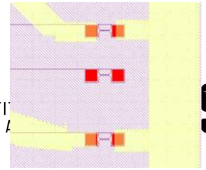








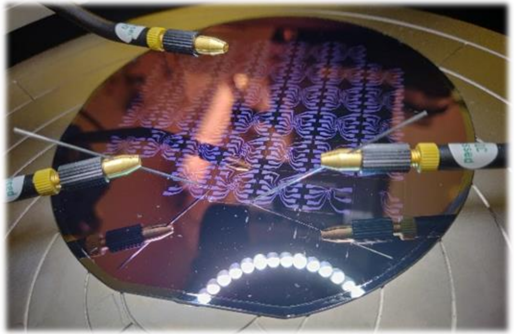




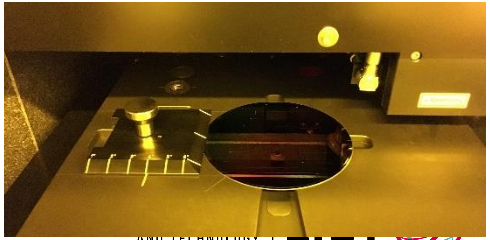
# DOSE CALIBRATION

- Substrate
- Resist (s)
- Layers
- Resolution
- Density of features

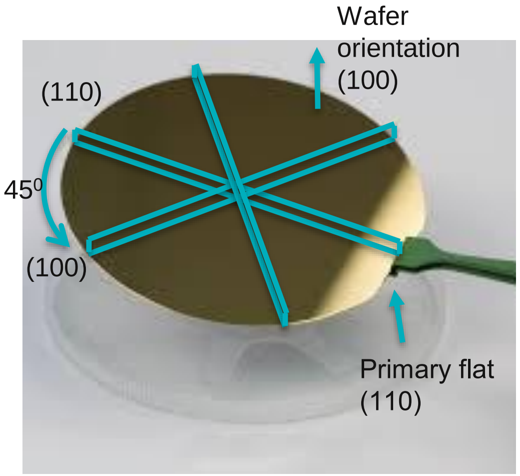
- Dose calibration every time you change resist
- Every time you change substrate refractive index
  - Be aware of transparent layers
  - Every time you have a new deposition
- UV is also sensitive to local changes of refractive index so you may need for each layer.
- Optimise the layer with the material with highest resolution (smallest features)
- Try to do a dose test with similar density of features

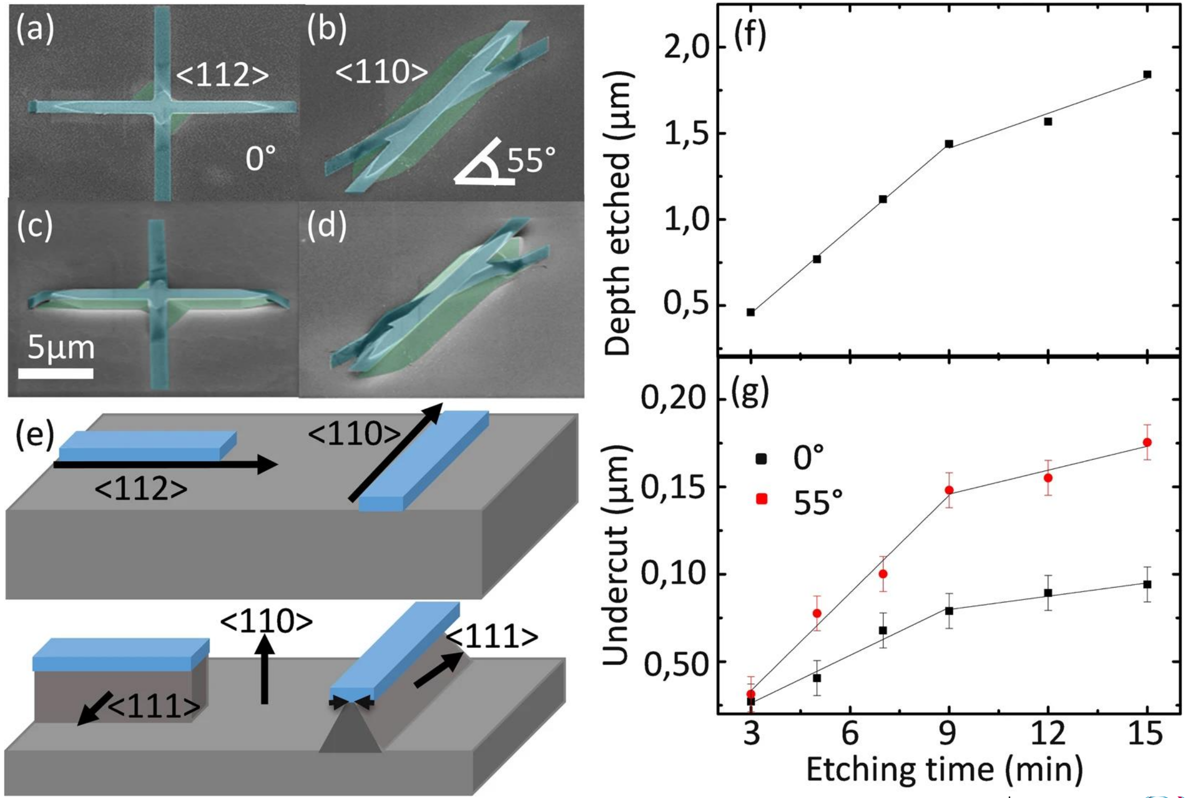


Sample loading ->



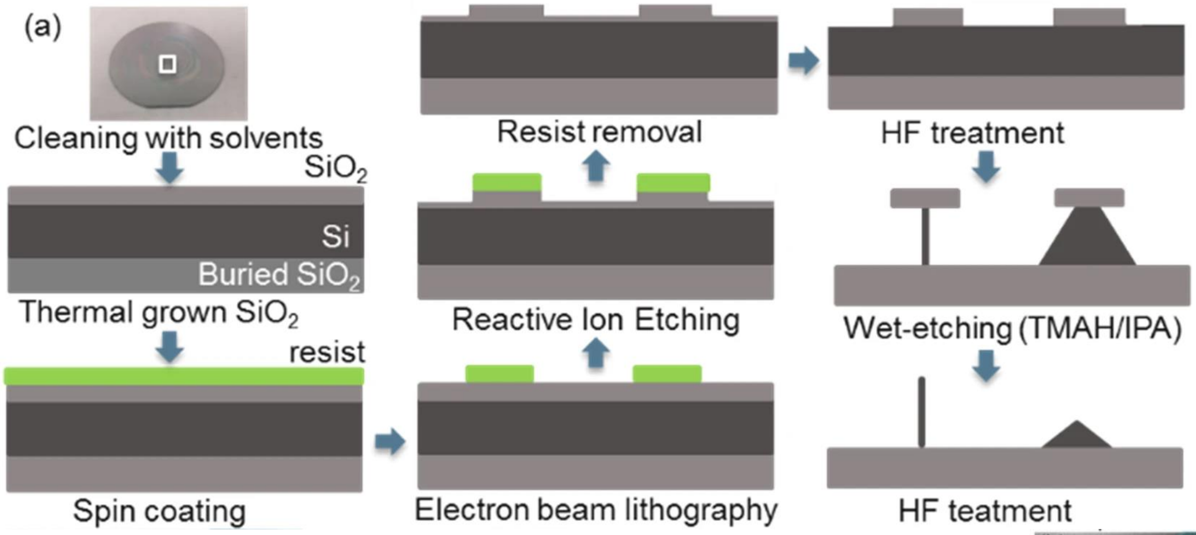
# SI ANISOTROPIC ETCHING



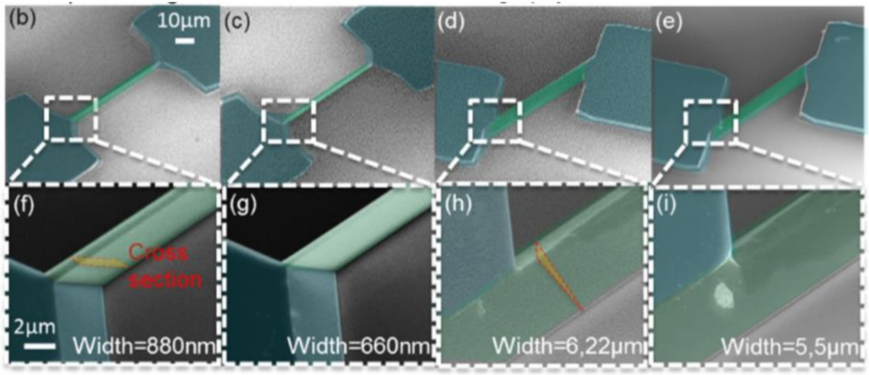




Rollo et.al. Scientific Reports volume 9, Article number: 2835 (2019)

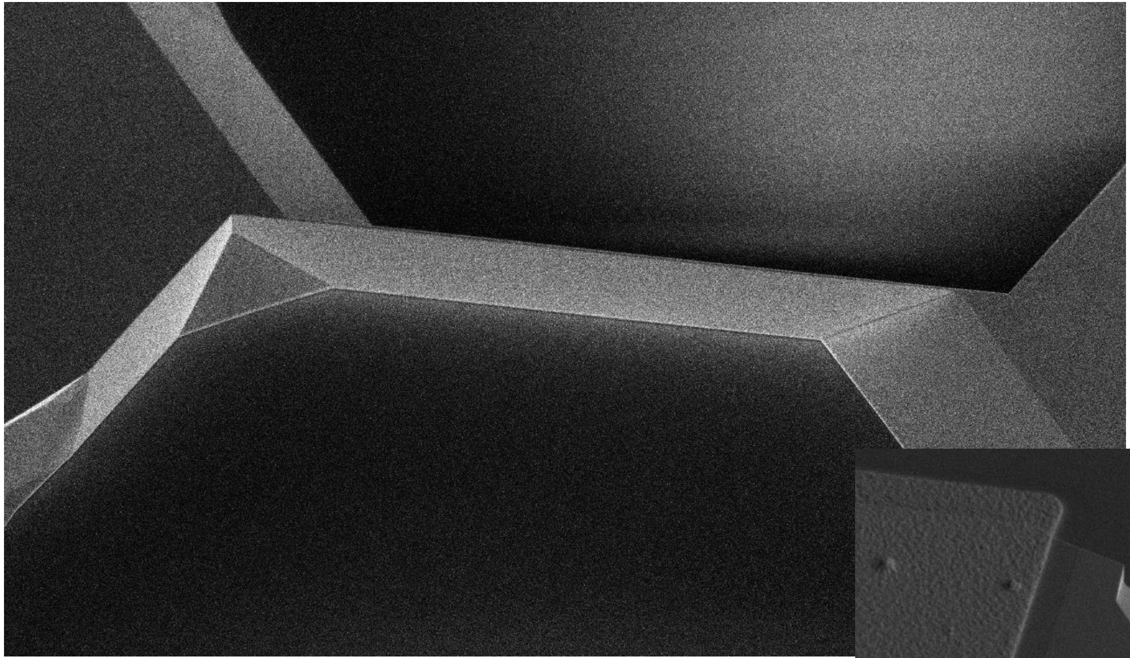
# FLOW FOR WET ETCHING

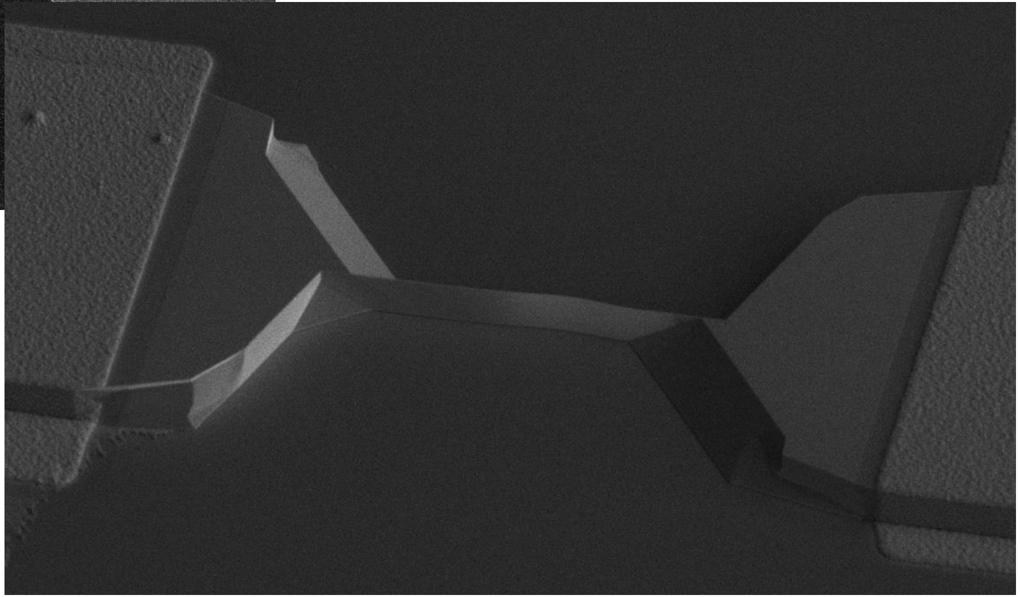



- ✓ Low roughness
- ✓ No ion implantation (or very low)
- ✓ Suitable for prototipying
- ✓ Economical
- ✗ Reproducibility/stability
- ✗ Mass production

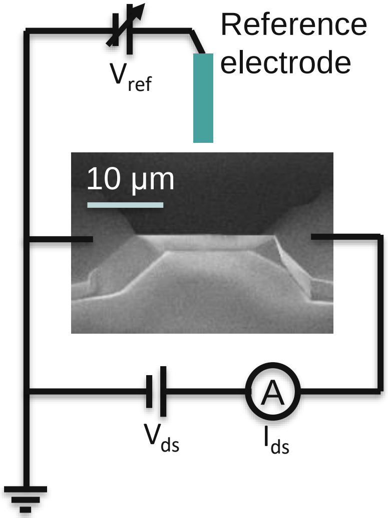


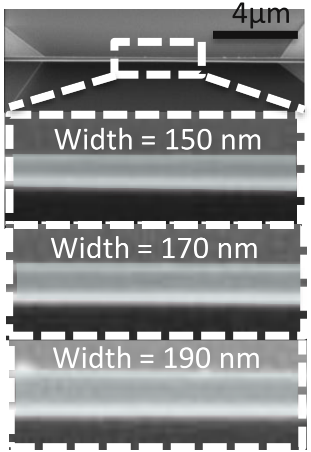

Rollo et.al. Scientific Reports volume 9, Article number: 2835 (2019)

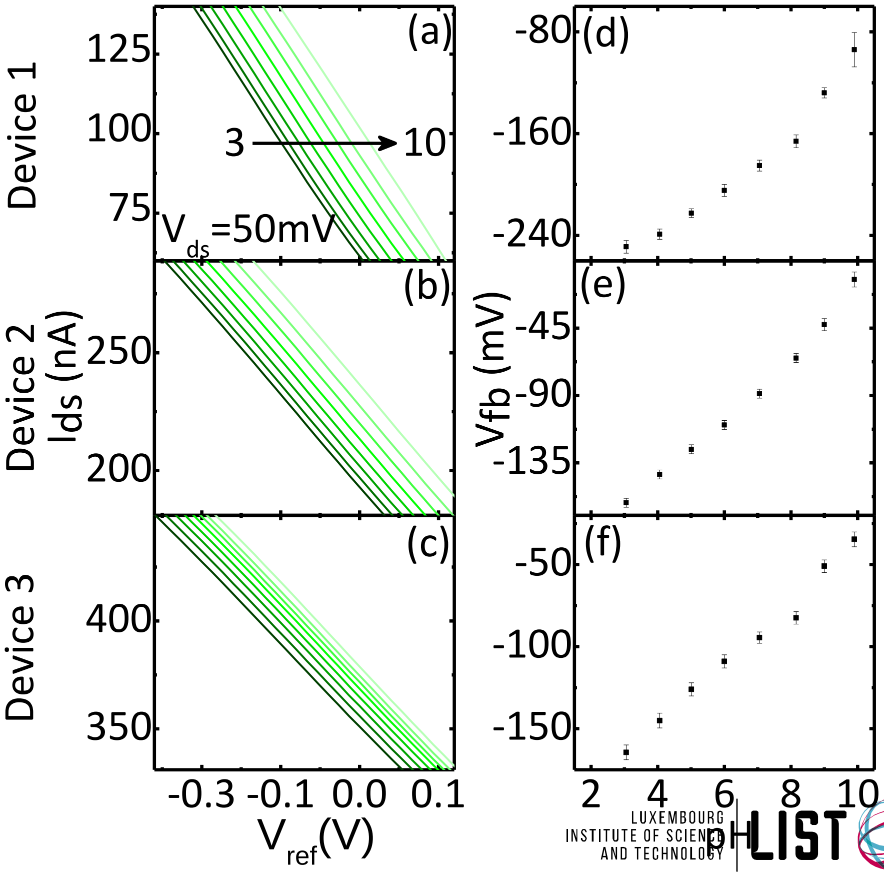




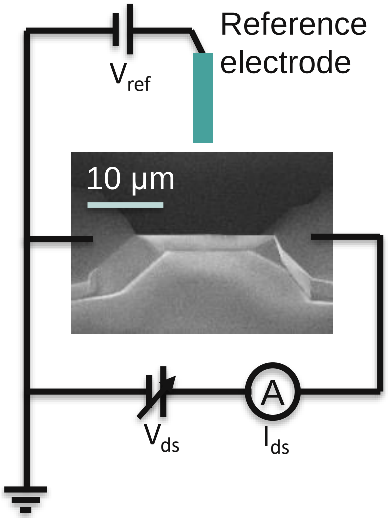
# TRANSFER CHARACTERISTICS

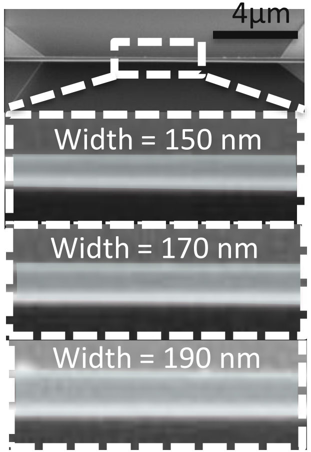


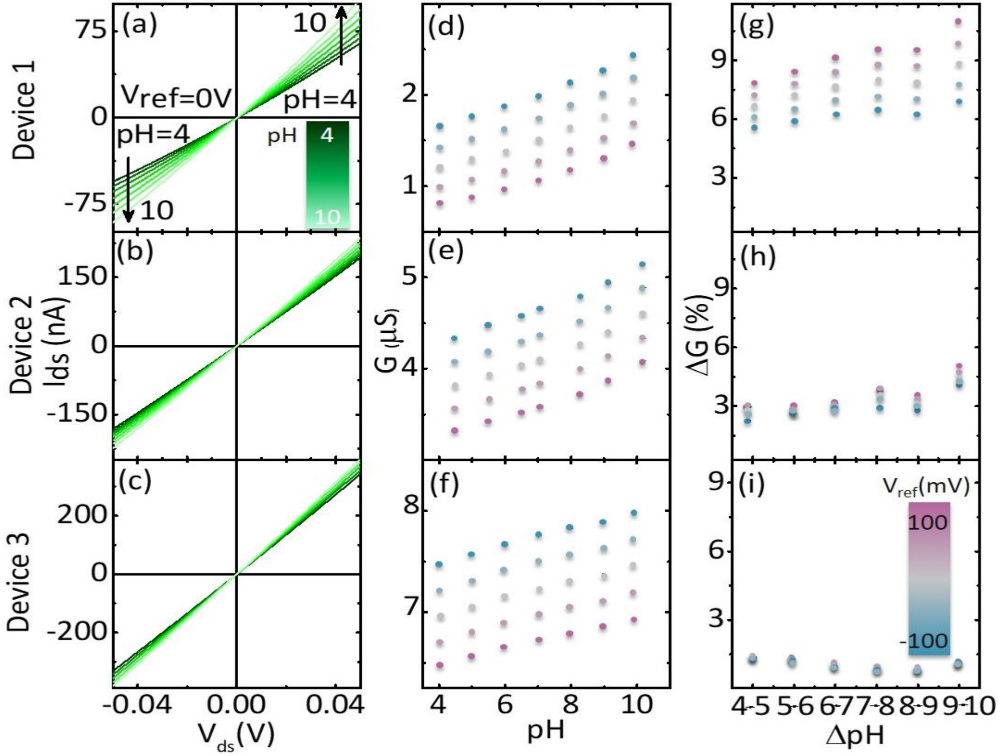



# OUTPUT CHARACTERISTICS

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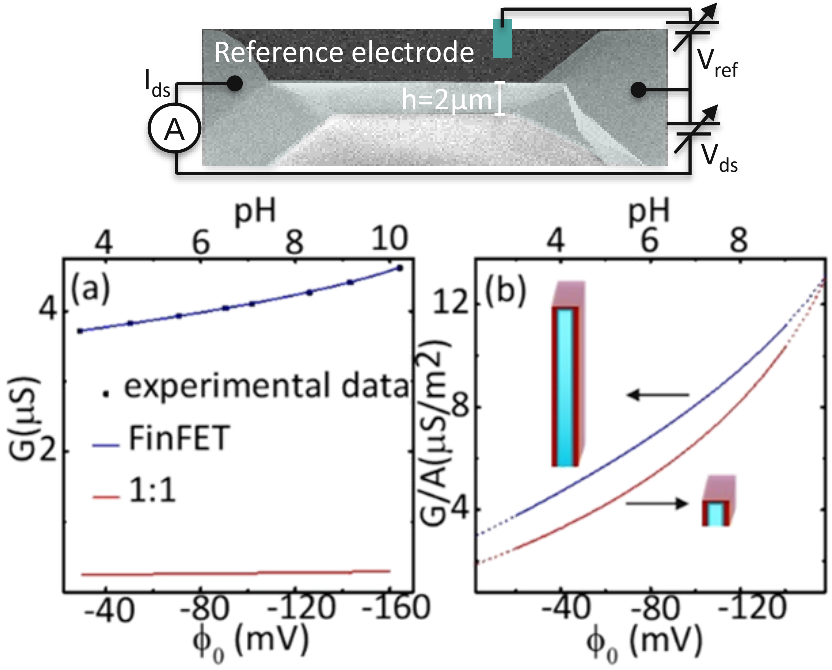
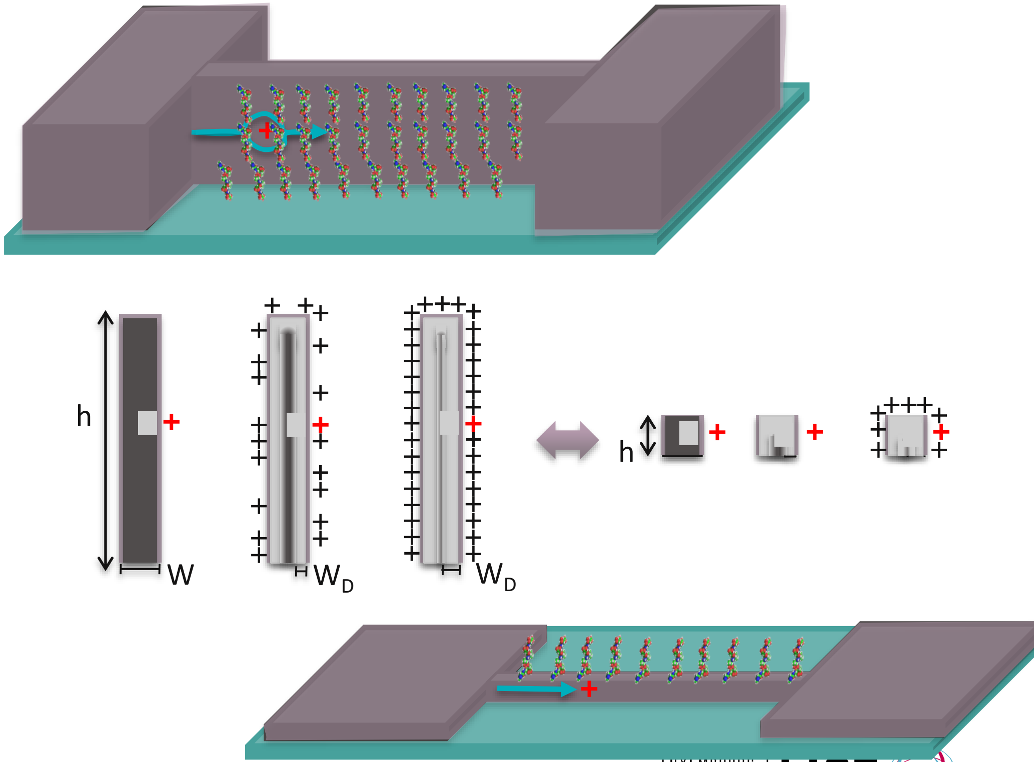
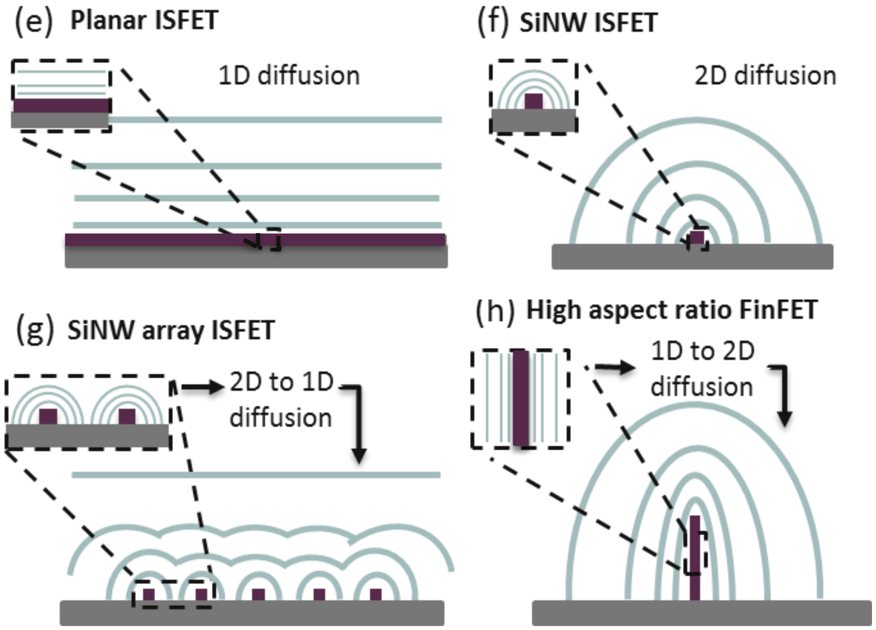
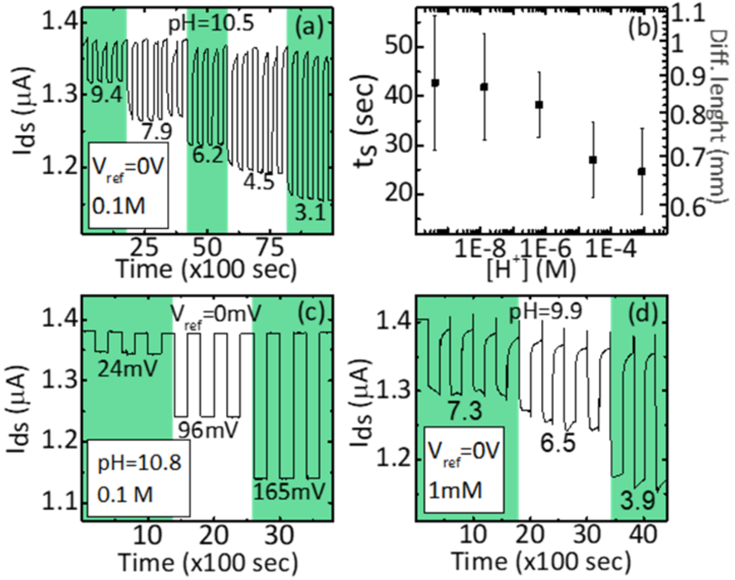
# FINFET ADVANTAGES



# FINFET IMPROVED SENSITIVITY



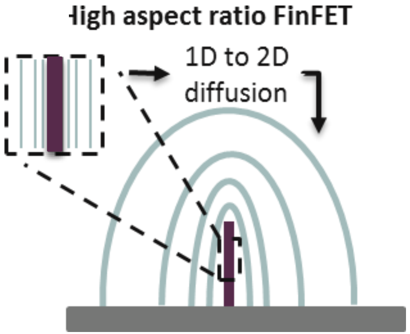



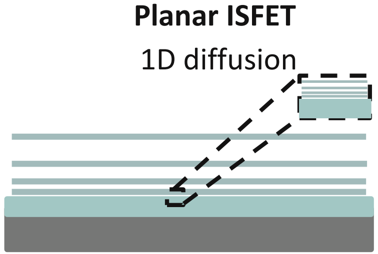
# PROYECTION

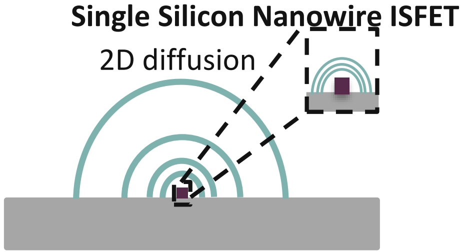
| FinFET | D ($m^2$/sec) | C (M) for 43s | Time (s) For $10^{-10}$M |
|---|---|---|---|
| **Protons** | $9 \cdot 10^{-9}$ | **$4 \cdot 10^{-10}$** | 43 s |
| **Hemoglobin (in water)** | $6.9 \cdot 10^{-11}$ (4) | **$5.1 \cdot 10^{-8}$** | **$2.25 \cdot 10^{4}$** |
| **DNA (in water)** | $5.3 \cdot 10^{-11}$ (5) | **$6.6 \cdot 10^{-8}$** | **$2.92 \cdot 10^{4}$** |

| ISFET | D ($m^2$/sec) | C (M) for 43s | Time (s) For $10^{-10}$ M |
|---|---|---|---|
| **Protons** | $9 \cdot 10^{-9}$ | **$3.74 \cdot 10^{-8}$** | **$2 \cdot 10^{4}$** |
| **Hemoglobin (in water)** | $6.9 \cdot 10^{-11}$ | **$1.48 \cdot 10^{-6}$** | **$2.7 \cdot 10^{6}$** |
| **DNA (in water)** | $5.3 \cdot 10^{-11}$ | **$1.74 \cdot 10^{-6}$** | **$3.4 \cdot 10^{6}$** |

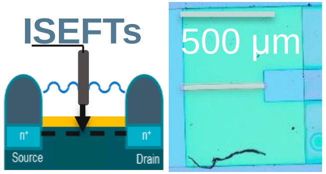
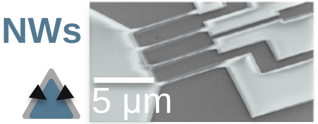
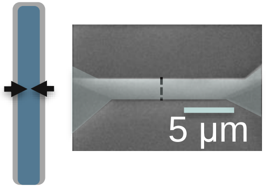
| Nanowires | D ($m^2$/sec) | C (M) for 43s | Time (s) For $10^{-10}$ M |
|---|---|---|---|
| **Protons** | $9 \cdot 10^{-9}$ | **$4.8 \cdot 10^{-11}$** | **21** |
| **Hemoglobin (in water)** | $6.9 \cdot 10^{-11}$ | **$6.36 \cdot 10^{-9}$** | **$2.74 \cdot 10^{3}$** |
| **DNA (in water)** | $5.3 \cdot 10^{-11}$ | **$8.3 \cdot 10^{-9}$** | **$3.6 \cdot 10^{3}$** |



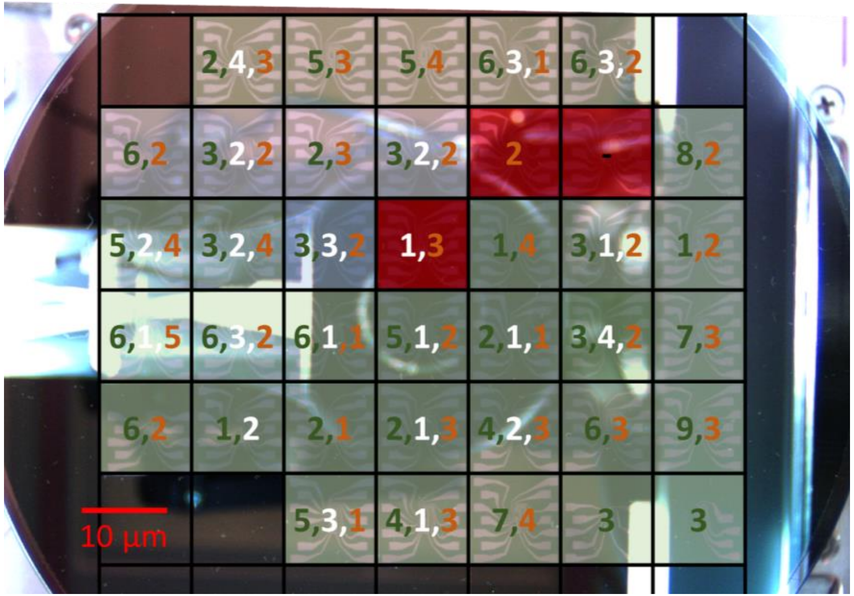



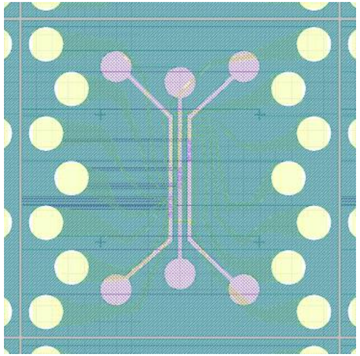
# FET COMPARISON

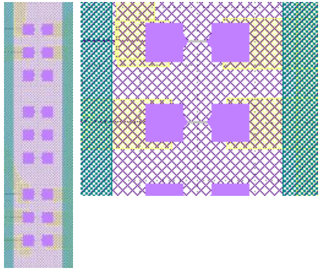
| | Gating | Defect Propag. | Signal/ noise | Footprint | Diffusion | Materials | Reliability |
|---|---|---|---|---|---|---|---|
| **ISEFTs**   **Sensitivity = 50µM to 20mM** | Single | Less sensitive to local defects | OK | Tens of µm² | Diffusion limited (1D) | High K Dielectrics/ Surface chemistry | High |
| **Silicon NWs**   **Sensitivity = 10fM to 25pM** | 2D | Sensitive to local defects | Low (improved with arrays) | Few µm² to tens of µm² (arrays) | 2D single<br>1D array | High K Dielectrics/ Surface chemistry | Low |
| **FinFETs**   | Double | Less sensitive to local defects | OK | Few µm² | 2D at low concentrations | High K Dielectrics/ Surface chemistry | High |

# FinFET sensors- wafer fabrication



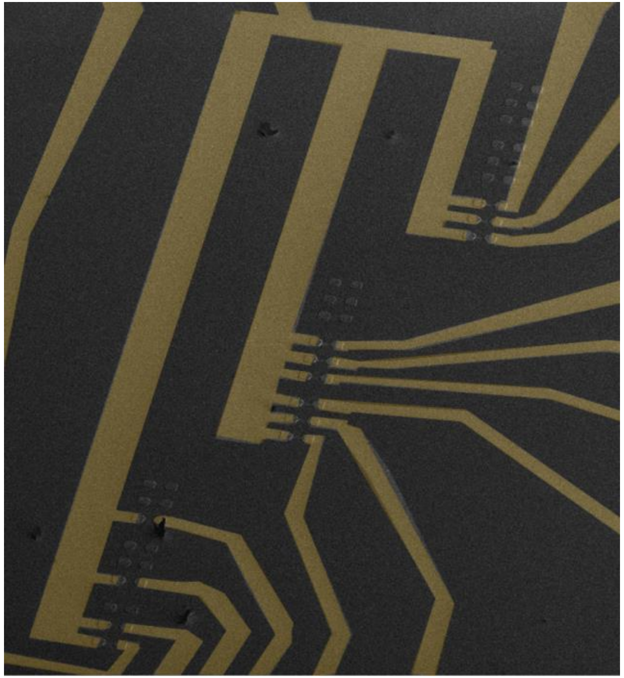

Devices have been tested, they have good ohmic behavior through the wafer

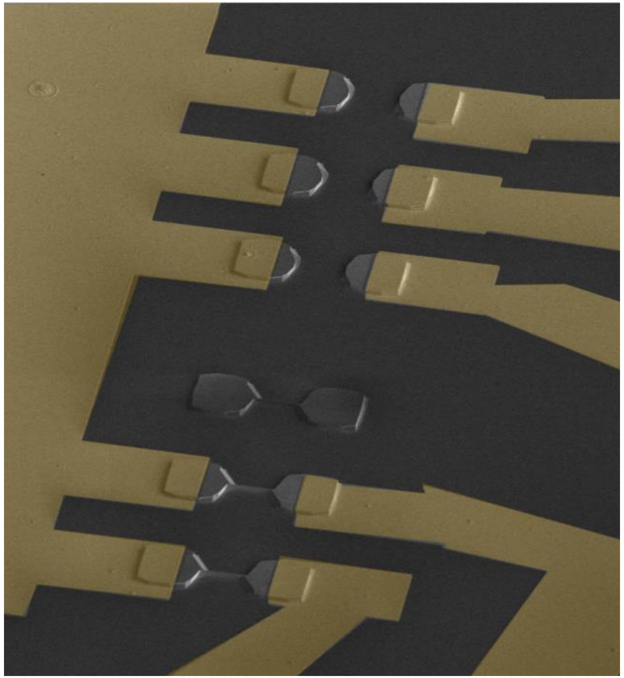


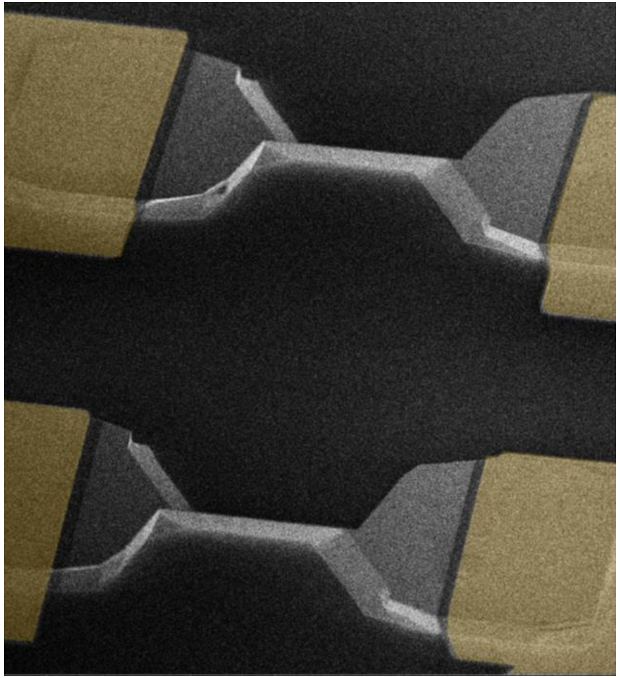


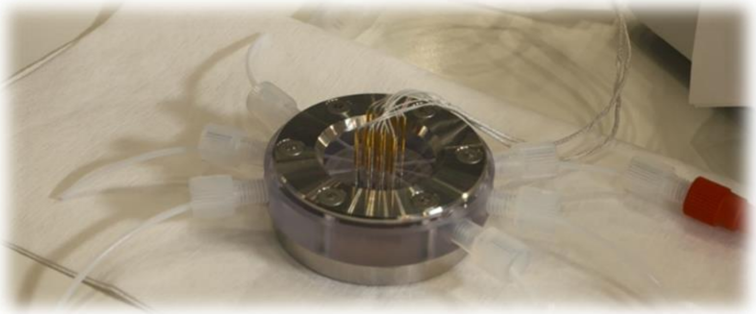
3 epoxy layers

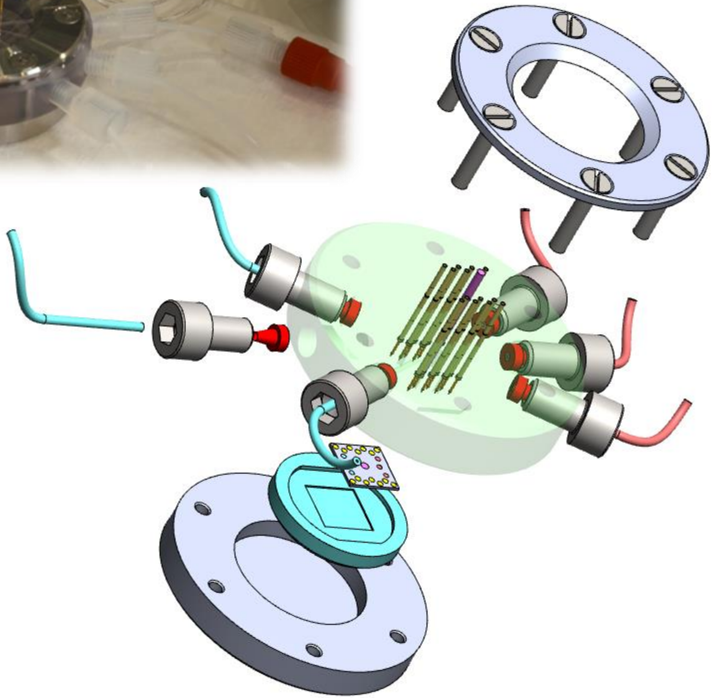
1. Passivation of non-sensing regions (300 nm)
2. Isolation of exposed contacts (8 µm)
3. Integrated microfluidic channels (100 µm)

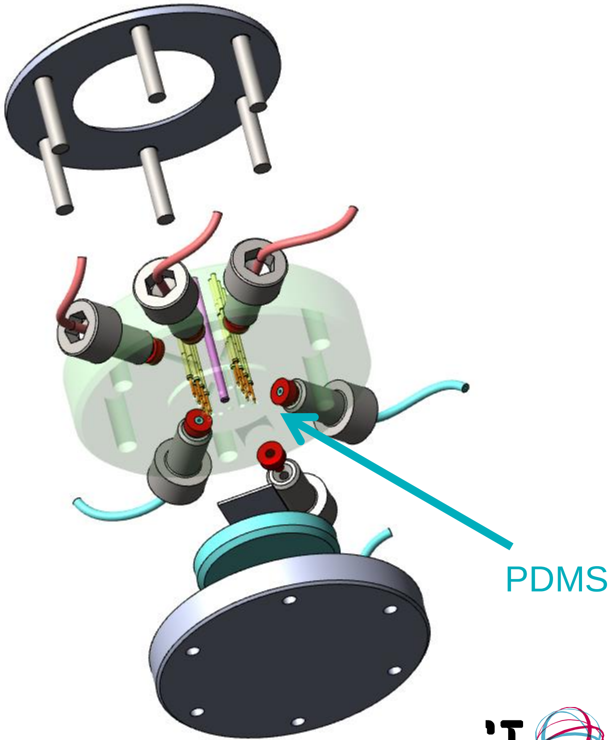


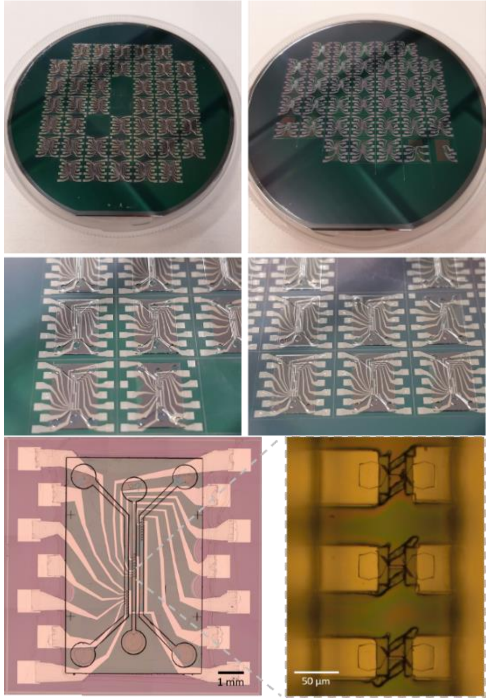


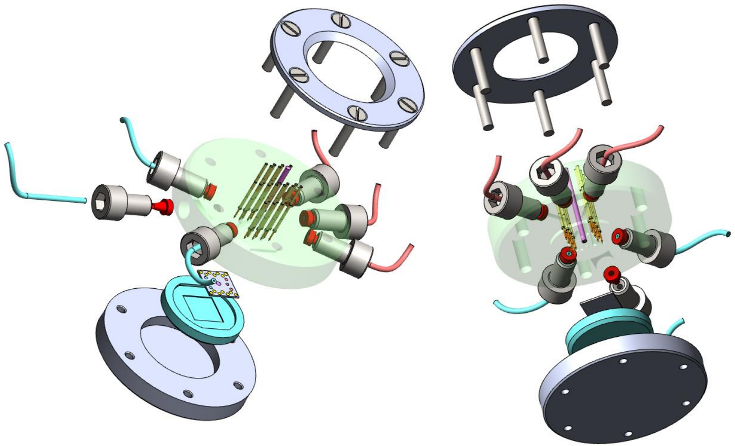


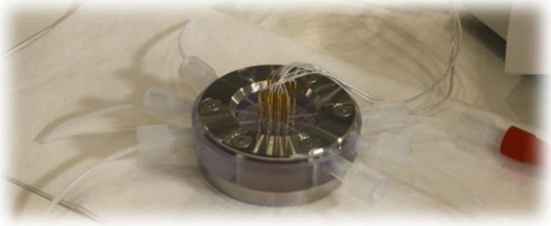





PDMS


1 mm
50 µm





# AND THE PERSONALIZED MEDICINE?

ELECTROMed

This project is funded by
the European Union

Horizon 2020 Future emerging technologies
Project: 862539 — ElectroMed

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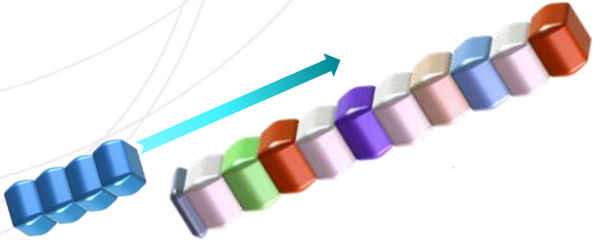
# The Challenge of Combinatorial Chemistry

**The combinatorial challenge:**
n-peptide has $n^{23}$ combinations

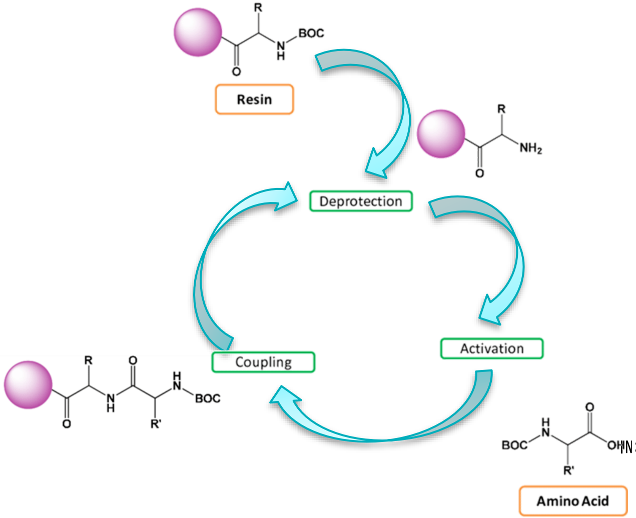


Peptides
(23 Aminoacids) A deca-aminoacid peptide has

**$10^{23}$ combinations**

## There is a need for programmable sensors

## Solid Phase synthesis





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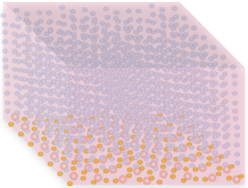
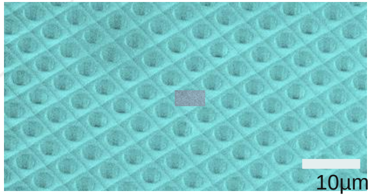
# Our Approach : Miniaturized control of acidity

## CHALLENGES

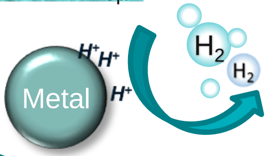
Surface to volume ratio:



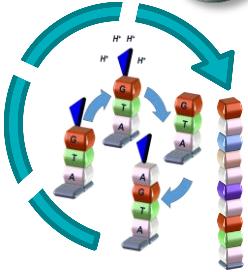
Diffusion:



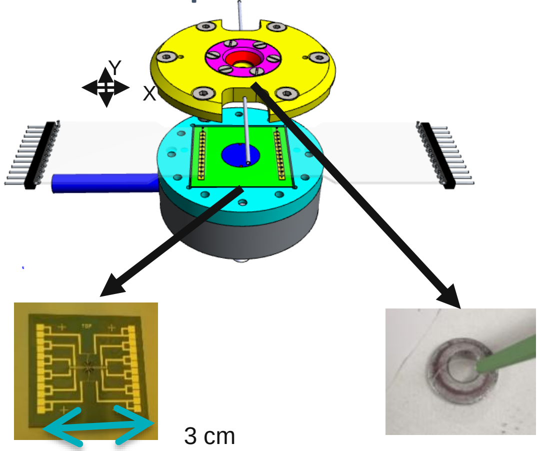

Proton reduction:




Reversibility:

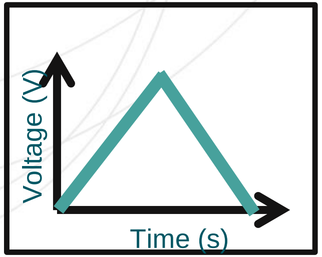


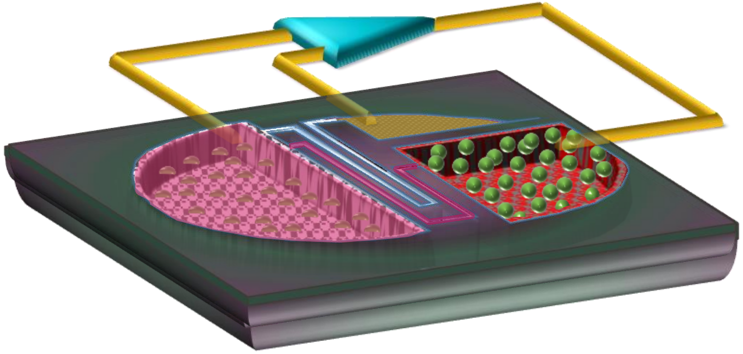
μ-fluidic platform

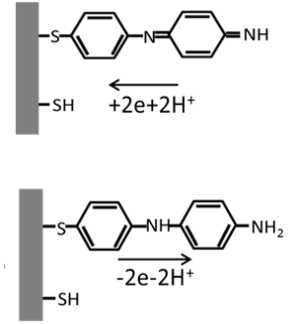


# Our Approach : Miniaturized control of acidity

### Voltage bias

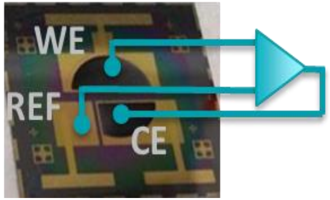


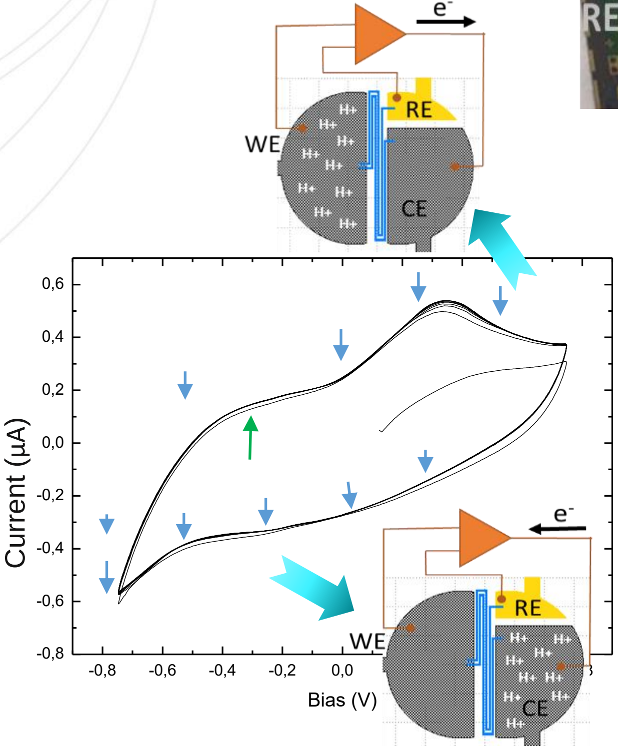





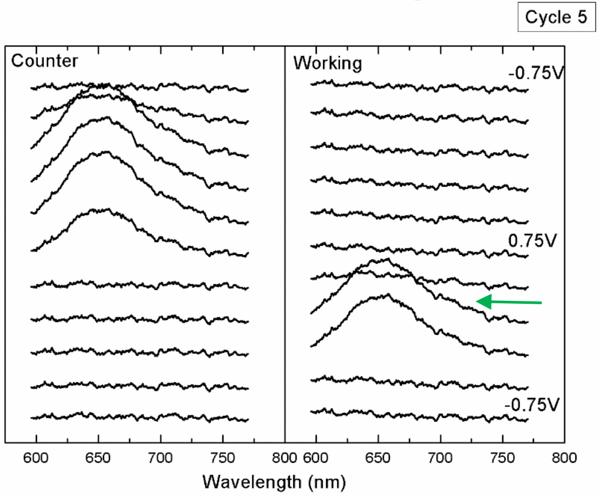

$$pH = -\log\left[\frac{H^+}{V}\right] = -log\left[\frac{I \cdot t}{e \cdot N_A \cdot Vcell}\right] < -\log\left[\frac{S}{h}\right]$$

# pH ACTUATION




## SNARF fluorescence spectra




*Balakrishnan et al. Nano Lett.* 2018, DOI: 10.1021/acs.nanolett.7b05054

*Balakrishnan et al. Proceedings.* 2018, DOI: 10.3390/proceedings2

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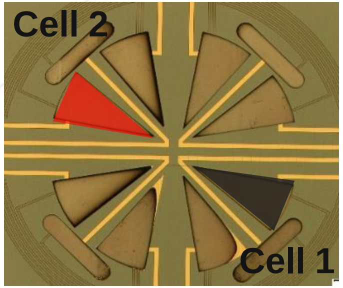
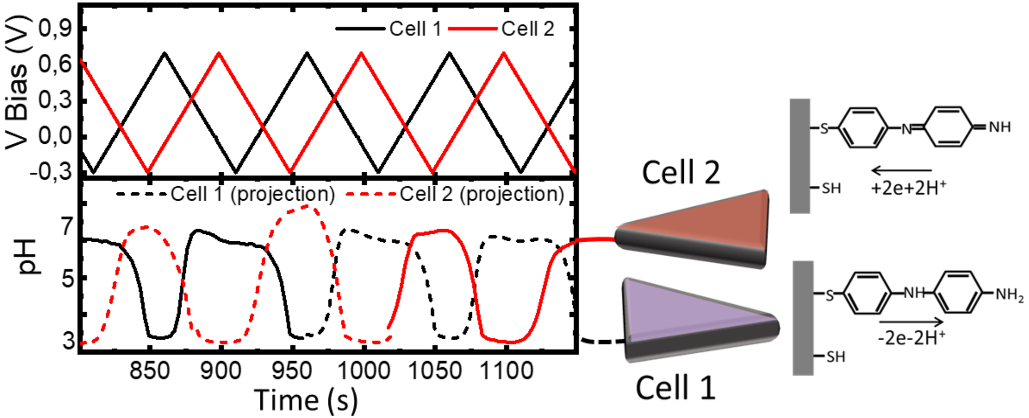
# pH control in Multiplex electrodes

**Multiplexed Control**

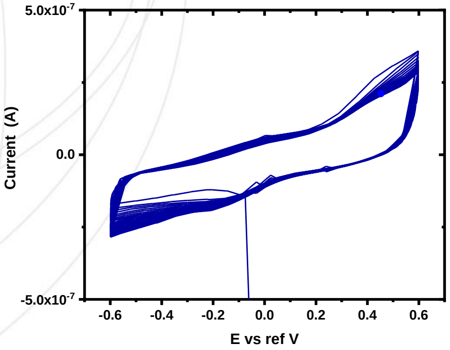


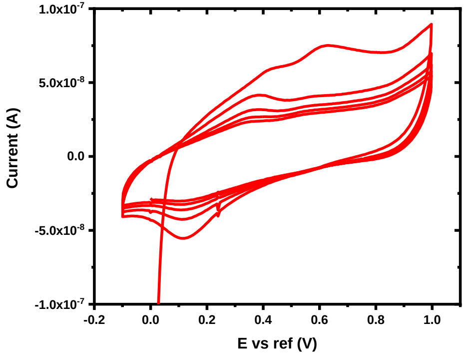



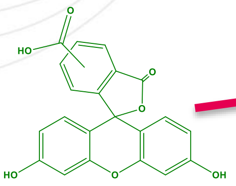

**Stability of proton concentration= 10 min**

*Balakrishnan et.al.*
*arXiv:1908.02465*
*[physics.app-ph] (2019)*

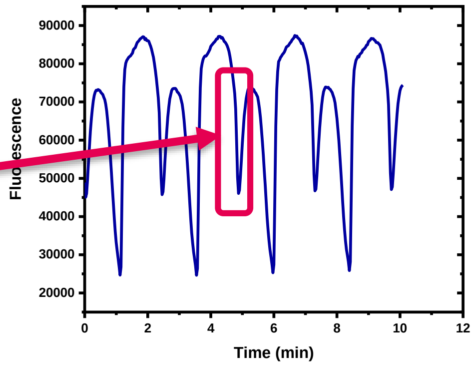
# Acidity generation in Aqueous vs Organic solvent

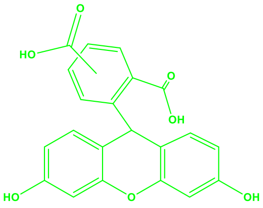


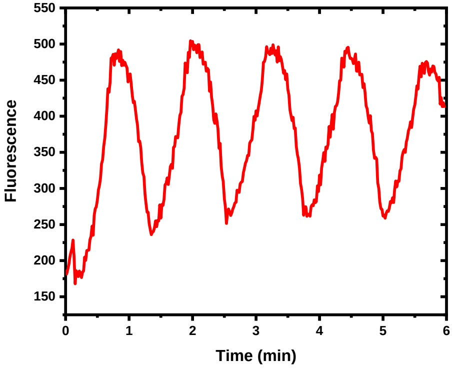




Less fluorescent Tautomer




Fluorescent tautomer




5(6)-Carboxyfluorescein 500uM in KCl 100mM

5(6)-Carboxyfluorescein 500uM in ACN $Bu_4PF_6$ 10mM

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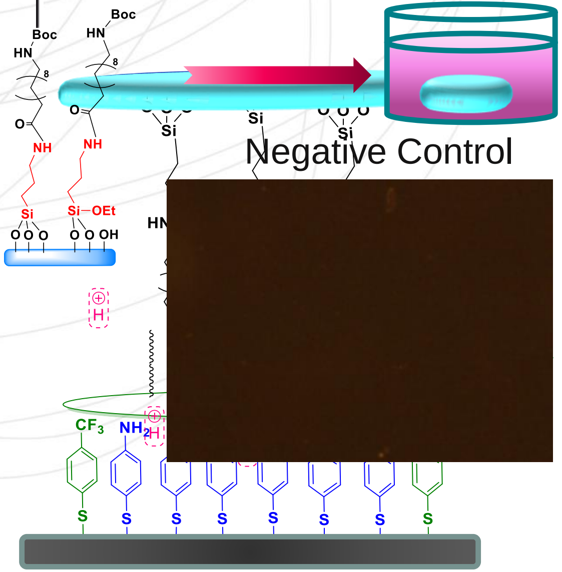
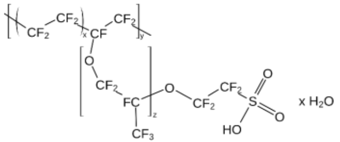
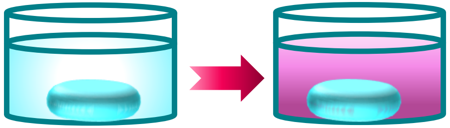
# In situ peptide synthesis. Boc deprotection

## Integration of Teflon- Electrode isolation

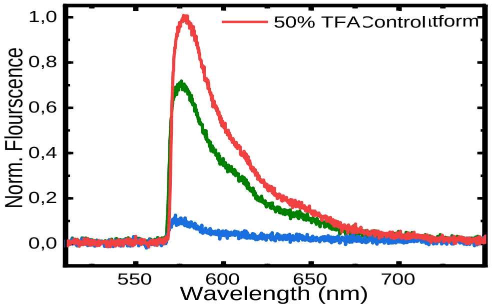


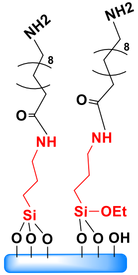

Nafion Coating

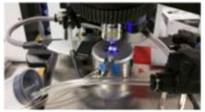


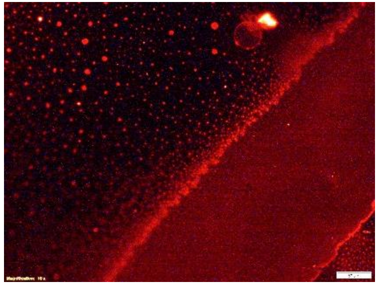
50 % TFA deprotection

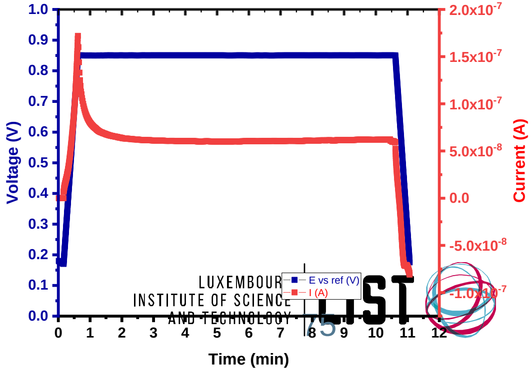



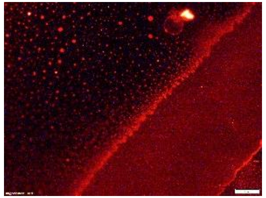
Acidity deprotection on the Platform



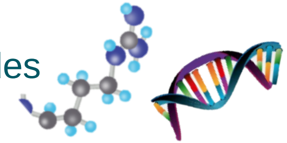


# Conclusions and Perspectives

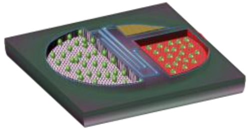
**Production of acidity ~ 50 % TFA**



Peptides and Nucleotides

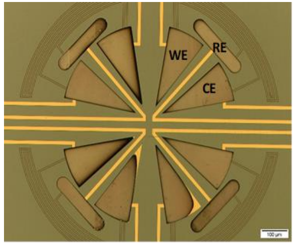


Stability of H+ concentration



Increase the yield = Longer biopolymers

High density devices




10 µm spots = $10^4$ devices /cm$^2$

100 µm spots = $10^6$ devices /cm$^2$

Increased Combinatorial Throughput

# Industrial PhD position in Paris – microfluidic hardware development

ELVESYS
MICROFLUIDICS INNOVATION CENTER

You don't recognize yourself in the academic world?
You want to combine entrepreneurship and a PhD?
You feel ready to work on an interdisciplinary research project?

IMPORTANT: You must not have spent more than 12 months in France during the past 3 years.

- 3 years CDD (PhD)
- 35-45 k€
- Paris, France
- Master (or equivalent), in engineering
- September 2021

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Aruna Singh

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University Of Copenhagen

University of Glassgow-School of Engeneering

Universitat Pompeu Fabra

University of Twente

ELVESYS

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