UNI BASEL

SWISS NANOSCIENCE INSTITUTE
EINE INITIATIVE DER UNIVERSITÄT BASEL UND DES KANTONS AARGAU

Molecular and carbon-based electronic systems

Lecture 11: Sensing

sensors, sensing, transduction & more

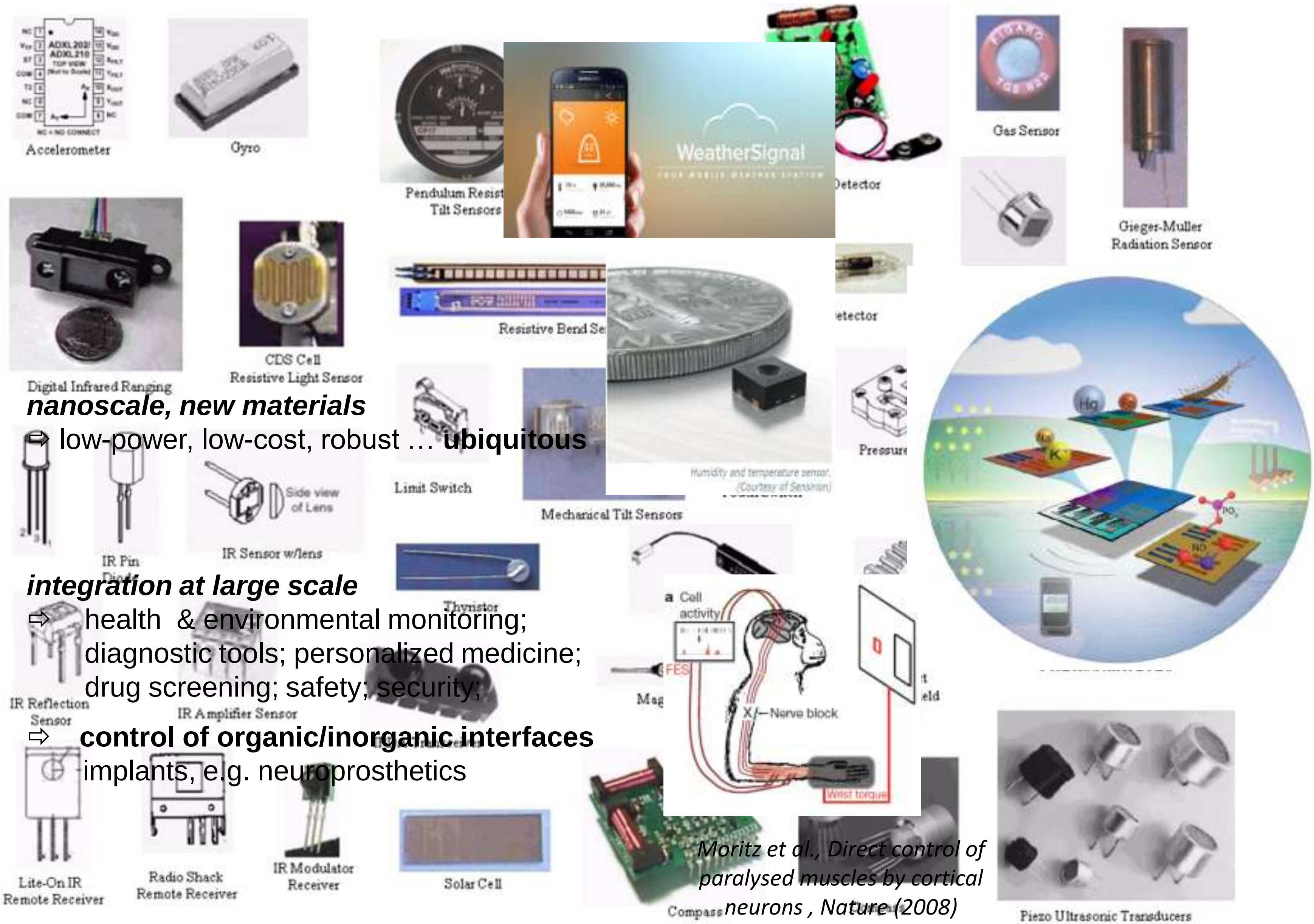
ISFETs & nanopores

Vorlesung Uni Basel, FS2017

sensors


Accelerometer
Gyro
Pendulum Resistive Tilt Sensors
Piezo Bend Sensor
Metal Detector
Gas Sensor
Gieger-Muller Radiation Sensor
Pyroelectric Detector
Digital Infrared Ranging
CDS Cell Resistive Light Sensor
Resistive Bend Sensors
UV Detector
Limit Switch
Mechanical Tilt Sensors
Touch Switch
Pressure Switch
Miniature Polaroid Sensor
IR Pin Diode
Side view of Lens
IR Sensor w/lens
Thyristor
Magnetic Sensor
Hall Effect Magnetic Field Sensors
Polaroid Sensor Board
IR Reflection Sensor
IR Amplifier Sensor
IRDA Transceiver
Magnetic Reed Switch
Lite-On IR Remote Receiver
Radio Shack Remote Receiver
IR Modulator Receiver
Solar Cell
Compass
Compass
Piezo Ultrasonic Transducers

sensors



nanoscale, new materials

⇨ low-power, low-cost, robust … **ubiquitous**

integration at large scale

⇨ health & environmental monitoring; diagnostic tools; personalized medicine; drug screening; safety; security;

⇨ **control of organic/inorganic interfaces** implants, e.g. neuroprosthetics

Moritz et al., Direct control of paralysed muscles by cortical neurons , Nature (2008)

sensors

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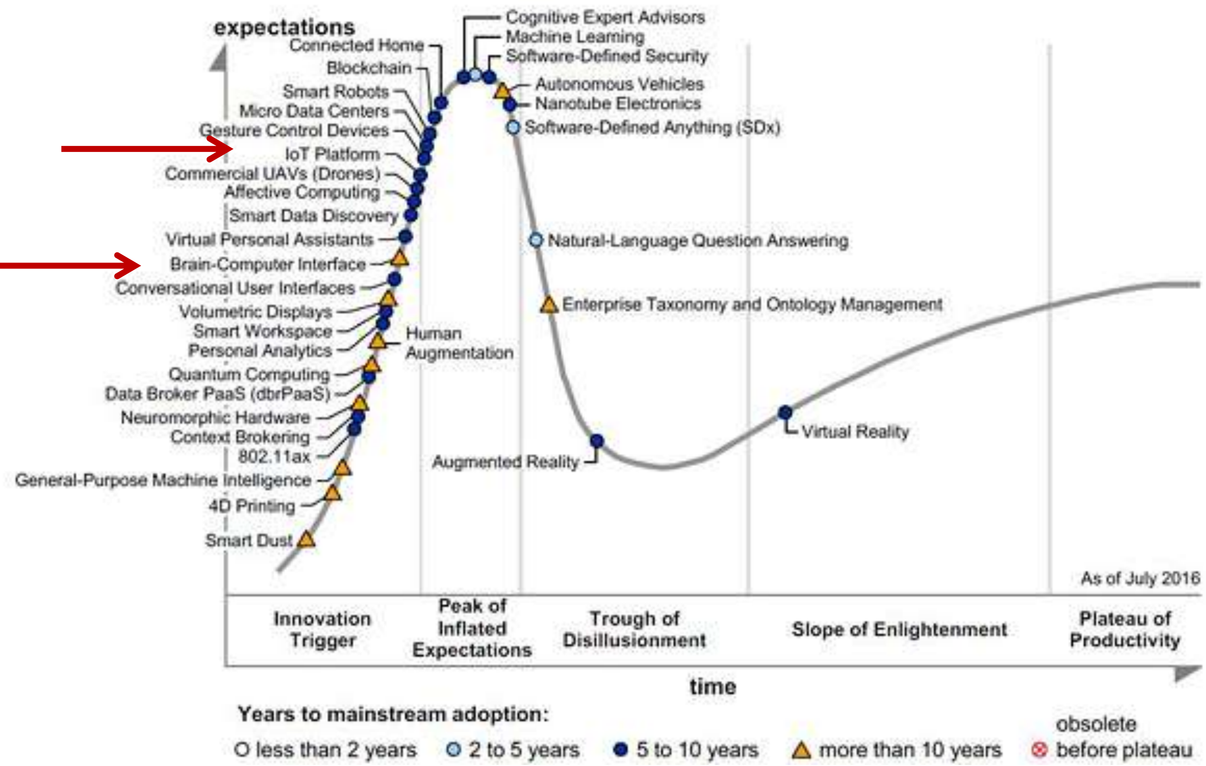


Hype cycle emerging tech. (2016), http://www.gartner.com

sensors

smart…

phone

refrigerator

nanoscale, new materials
⇨ low-power, low-cost,
robust … **ubiquitous**

Internet of Things (IoT)

def.: *Open network of intelligent objects that have the capacity to auto-organize, share information, data and resources, reacting and acting in face of situations and changes in the environment*

Internet 1.0 sharing of data created by people
Internet "2.0" sharing of data created by things

NB: data protection issues…

⇨ **integration of smart objects …**

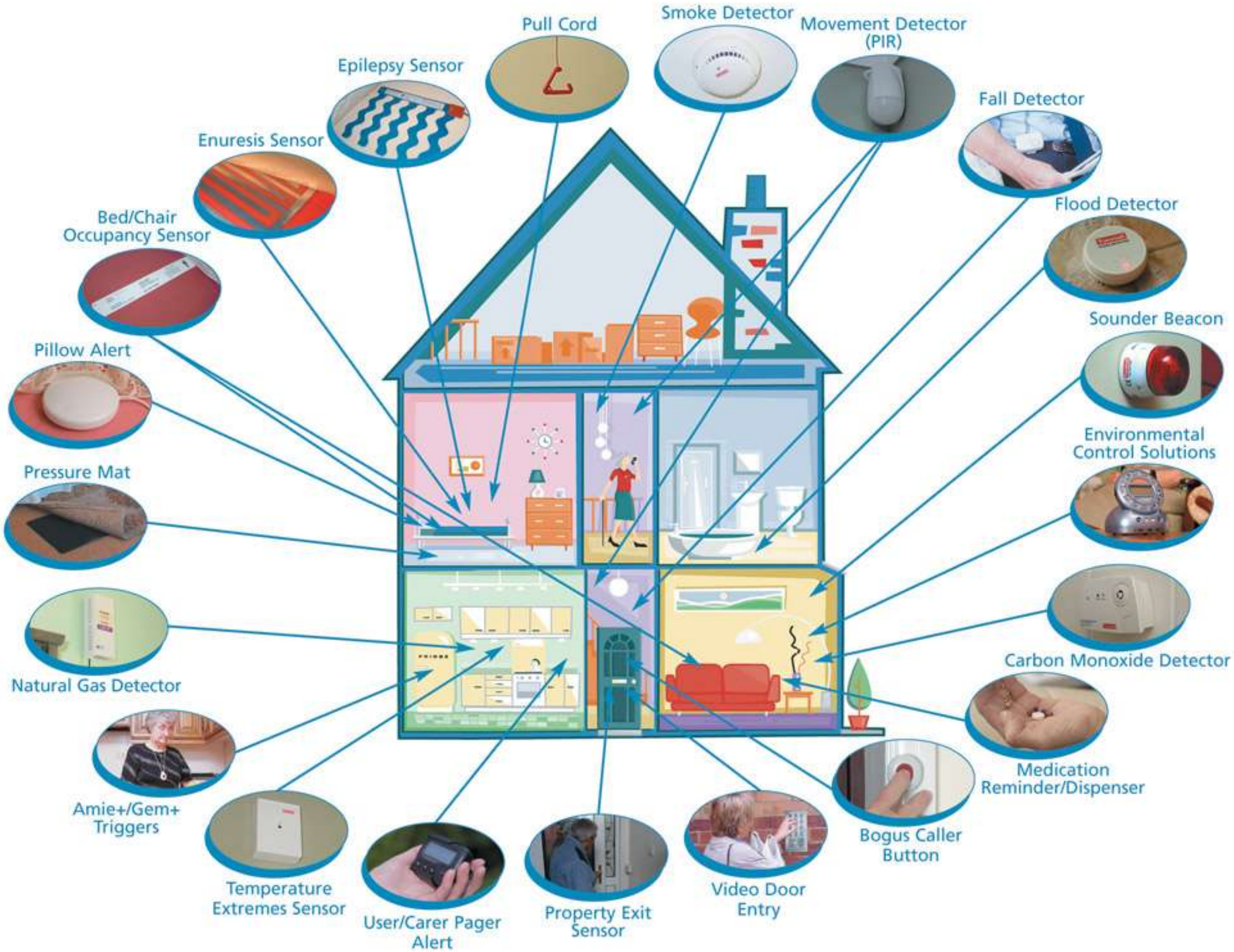
sensors

smart building: the technical side

monitors/integrates conditions of various systems for optimization and alerting, …

smart building: the human side

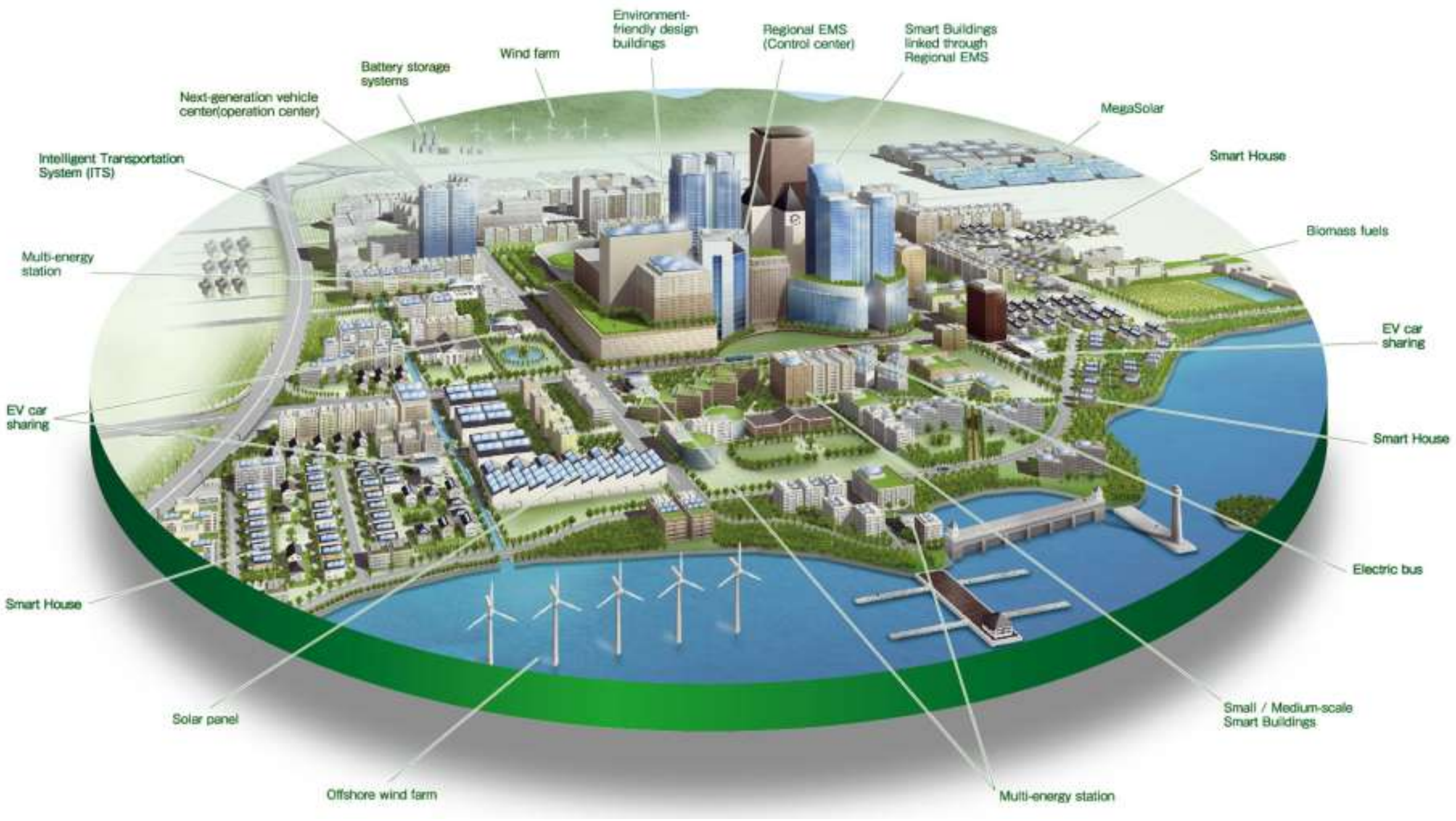
monitors/integrates conditions of various systems for optimization and alerting, …



sensors

smart city

critical infrastructures: energy, water, transportation (avoid congestion, state of bridges), waste management, …



sensors

smart refrigerator

smart building

nanoscale, new materials
⇨ low-power, low-cost, robust … **ubiquitous**

Internet of Things (IoT)

"smart" monitoring for environment, health care, agriculture/farming, logistics

⇨ ***sensors beyond p, T***
detection, quantification and monitoring
of more complex analytes
gases, ions, organic molecules, biomarkers, …
e.g.: ***continuous glucose monitoring*** *(diabetes)*
Dexcom, reading on phone/watch

smart city

- **general aspects on sensing**

  sensitivity, specificity

  overview of transducers

- **field effect transistors (FETs) as charge sensors**

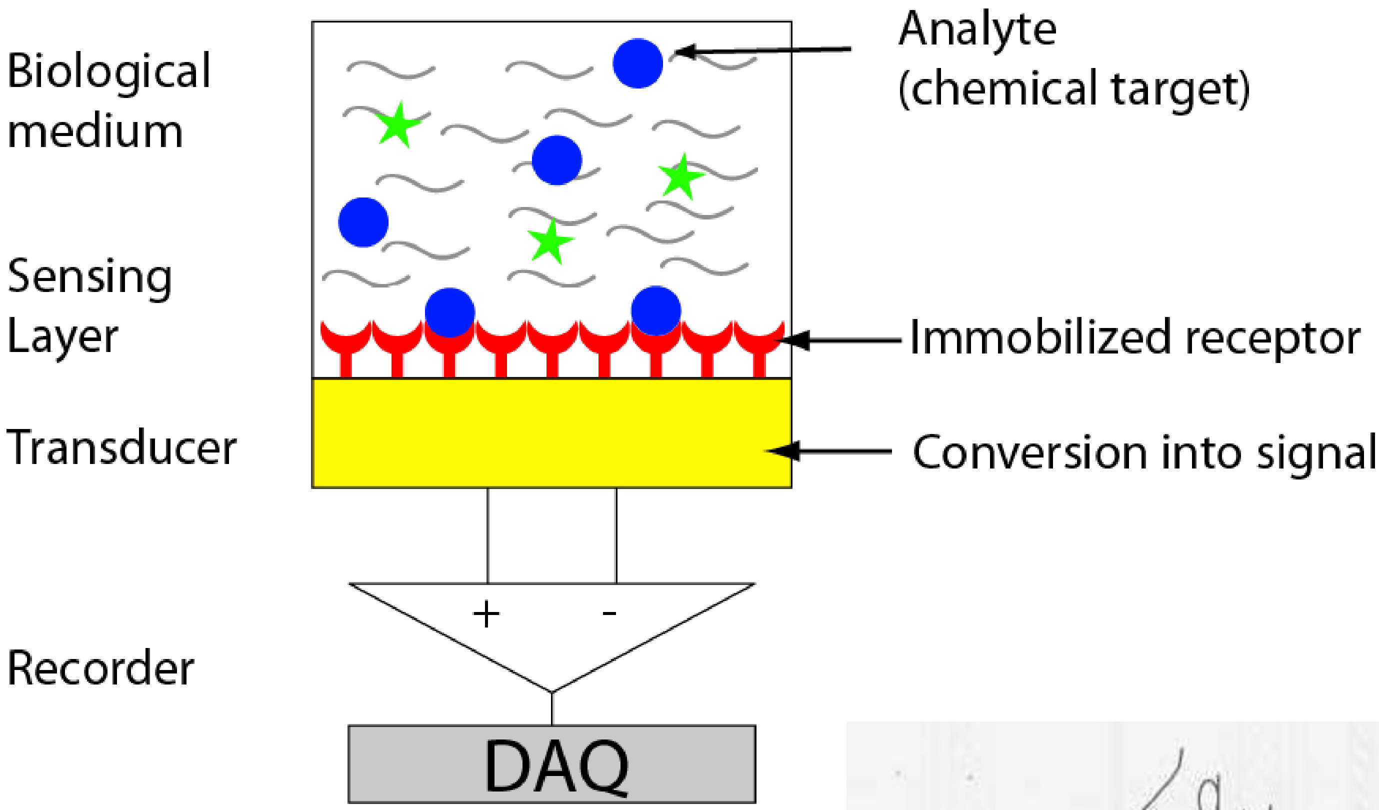
  MOSFET, graphene and GFET

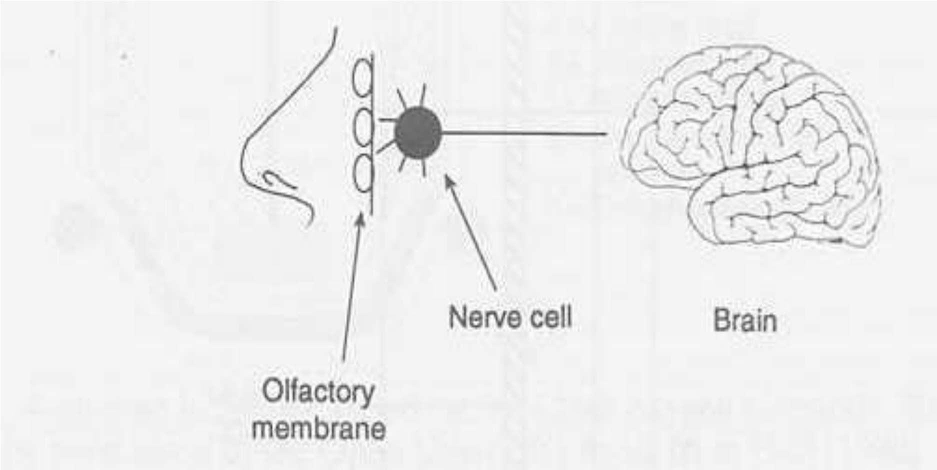
Examples

- Ion sensitive field-effect transistors (ISFETs) for pH, ionic and biochemicals detection

- Nanopores for sequencing

(biochemical-)sensing

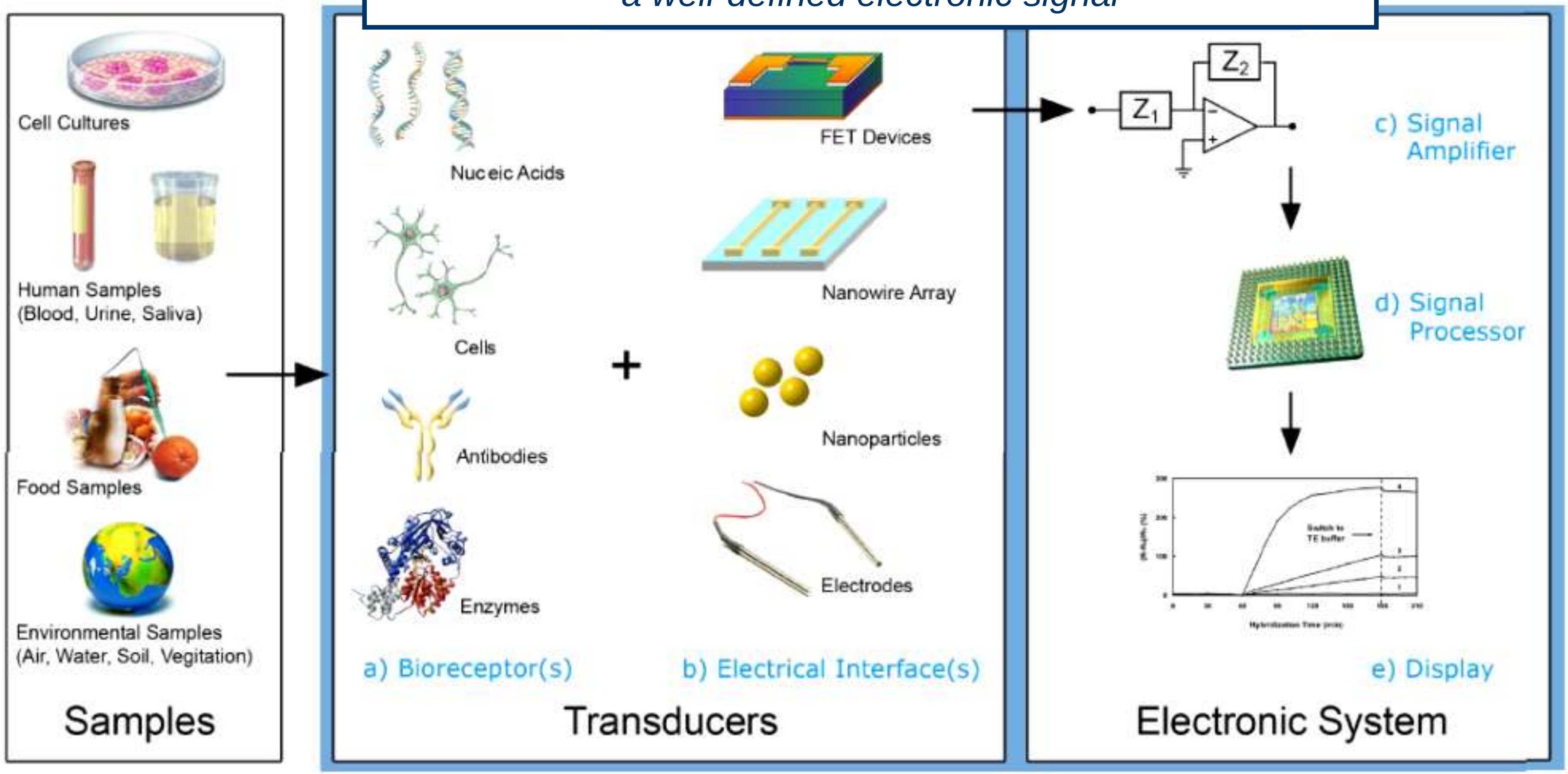




cf e.g. R. Bashir, Nanohub.org

(biochemical-)sensing

challenge: controlled conversion of (bio-)chemical signal into a well-defined electronic signal



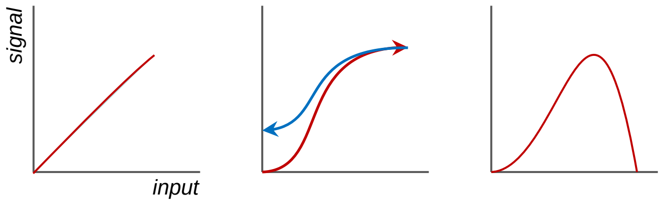
competences ?

See e.g. *Willner et al., Nanoparticles arrarys sensors, ChemPhysChem, 2000*
Lieber et al., Nanowires nanosensors, Mat. Today, 2005

Grieshaber et al., Sensors (2008)

(biochemical-)sensing

Characteristics of a sensor



- **Transfer function**, nonlinearity

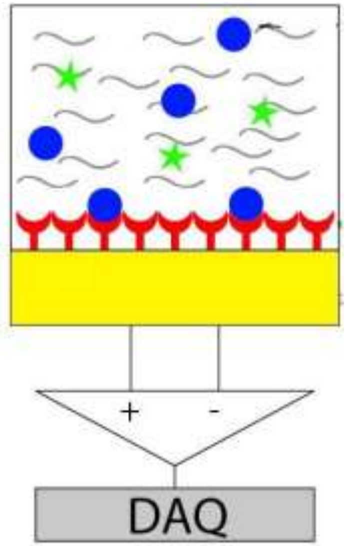
- **Sensitivity**: typ., derivative of transfer function
- **Selectivity**: response exclusively to changes in specific target analyte concentration

- **SNR, low background**: low noise, with ability for correction (differential measurements)
- **Dynamical range**
- **Response dynamics**: rapid response and recovery
- **Hysteresis** : signal (in)dependent of prior history of measurements *(nanoscale devices: nanotubes, graphene, etc: interfacial polarisation effects at contacts)*

- **Long-term Stability:** not subject to fouling, poisoning, or oxide formation that interferes with signal; prolonged stability of biological molecule
- **Simple calibration** (standards)
- **Size, cost, power consumption**
- **Operating conditions** (pH range, temperature, ionic strength), **biocompatibility**

sensing

<u>functional</u> (sensing) layer & signal transduction



biological, chemical medium

molecular interface

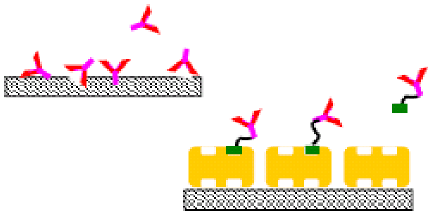
electronic interface

cf e.g. R. Bashir, Nanohub.org

Functionalization & immobilization techniques

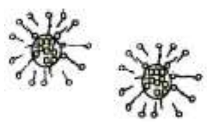
- **adsorption** (non-specific)

  weak bonding; susceptible to pH, temperature, ionic strength, and substrate variations; simple but short lifetime



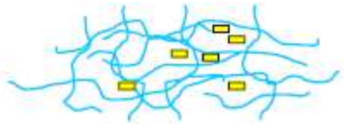
- **encapsulation:** place biomaterial behind a **membrane permeable** to some materials only (e.g. porous graphene membrane)

  limits contamination, relatively stable towards changes in pH, etc..



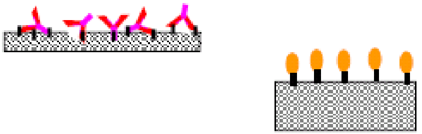
- **embedding** of a the sensing biological component in a **matrix** such as a gel or a polymer film

  stable but may limit diffusion of sample towards biodetector; activity of biomolecule may be limited also due to gel mesh



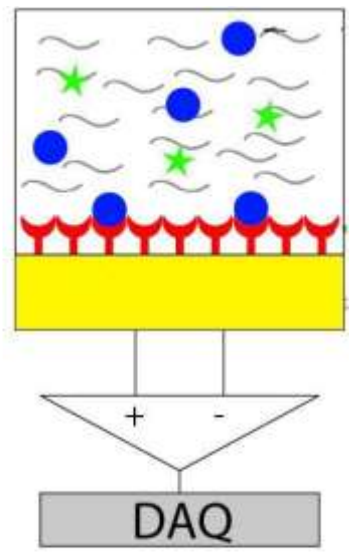
- **covalent** attachment

  direct or zero-length cross-linking, strong binding, can limit activity depending on bonding



sensing

functional
(sensing) layer
& signal
transduction



biological, chemical medium

molecular interface

electronic interface

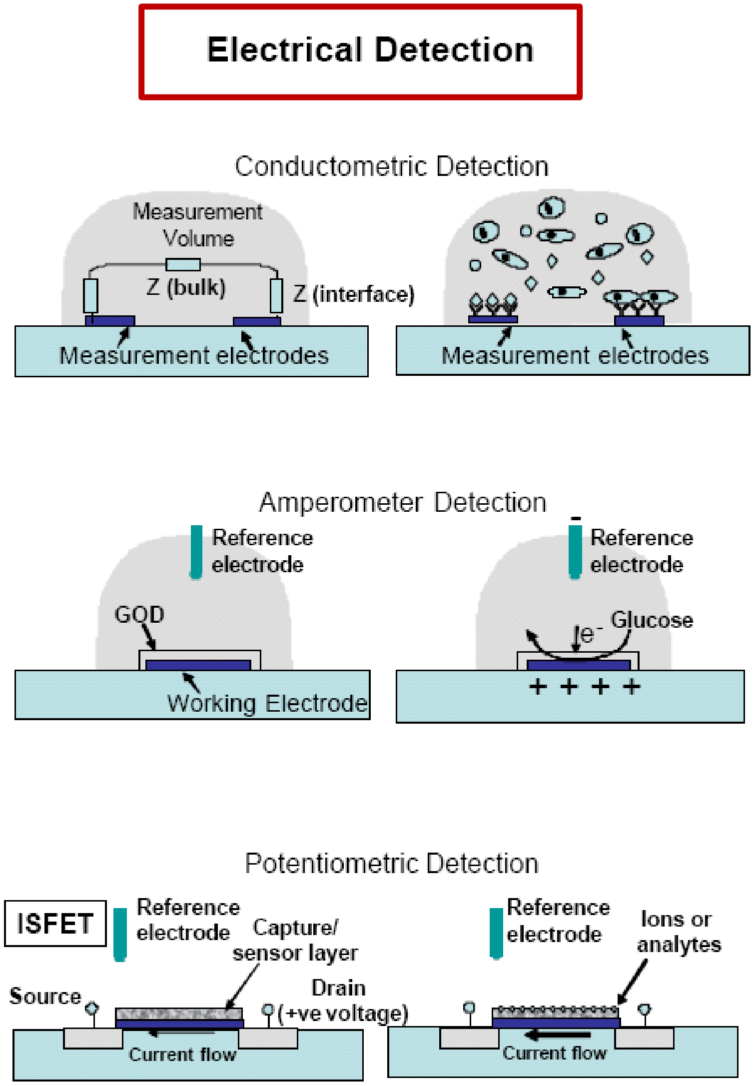
transduction: electrical

Transduction

- **electrical & electrochemical**
  *direct measurement of **current** through a molecule for instance, molecular electronics; current monitoring through device while binding of sample*

  charge detection** – e.g. ions, charge species; pH meter; ionic concentration variation, e.g **ISFETs

  impedance spectroscopy; *voltammetry or amperometry: cycle a potential to an electrochemical cell with an oxidizing substance)*



cf e.g. R. Bashir, Nanohub.org

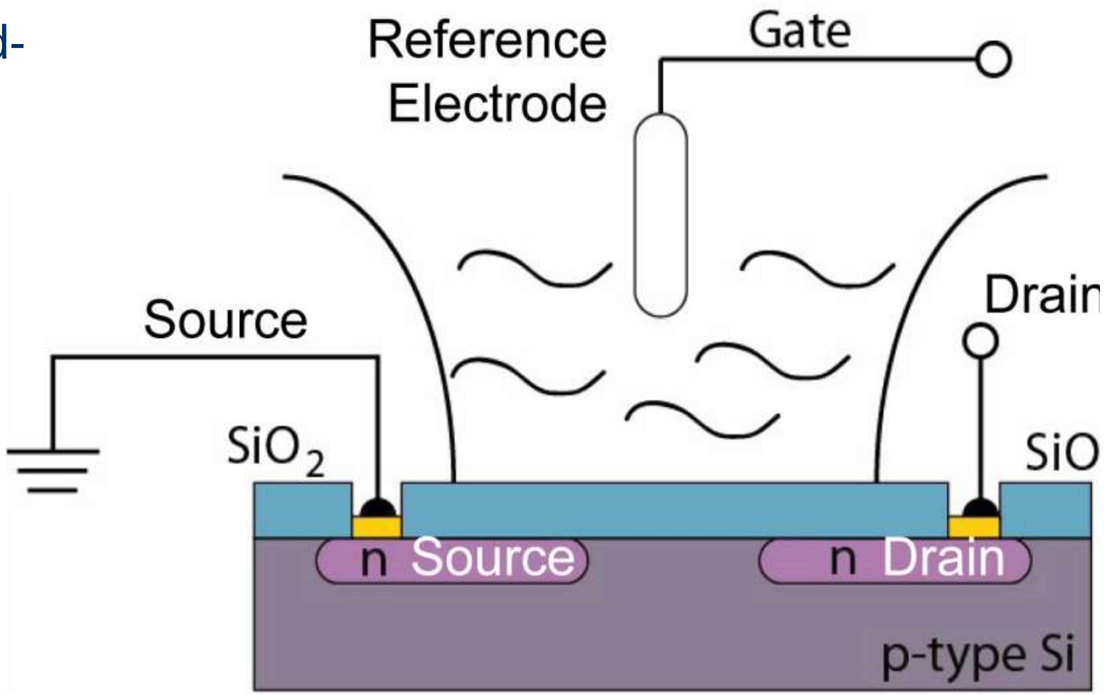
example: ISFETs

ISFETs: ion-sensitive field-effect transistors

concept from the 70's

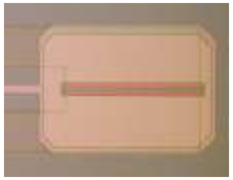
Bergveld, IEEE Trans. Biomed. Eng (1970)

Bergveld, IEEE Sensor Conf. (2003)



pH sensors

Mettler-Toledo



Sentron

Endress+Hauser :CPS441 and CPS441D
with integrated Ag/AgCl reference (needs a KCl reservoir)

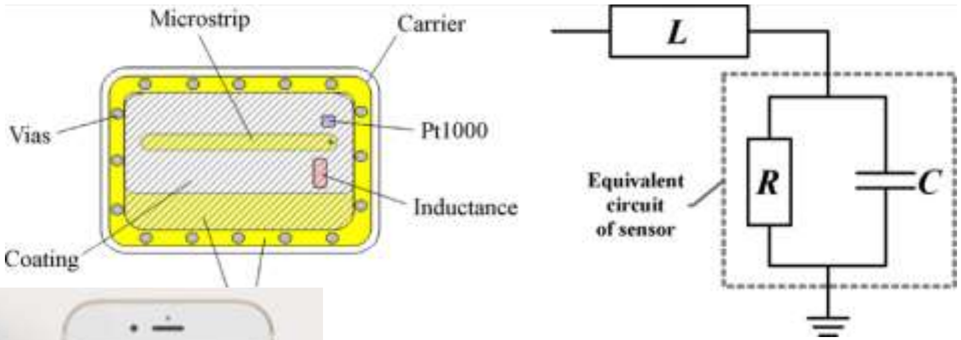
example: conductometric detection

non-invasive glucose monitoring: impedance spectroscopy

- glucose variations affect electrical properties of erythrocytes membranes, and lead to variations of the electrolyte balance (in blood, cells and interstitial fluid)
- changes in interface polarisability of cells (Maxwell-Magner),
- typ. freq. 20-60MHz

GlucoWatch® Monitor

Biovotion
Solianis until 2011



www.dexcom.com

www.gluco-wise.com

Transduction

- **mechanical**
  mass (QCM - piezo, AFM), surface stress (AFM)

- **piezoelectric**
  vibration frequency shifted by mass adorption at surface of device; QCM: at 10MHz, 4ng $cm^{-2}Hz^{-1}$

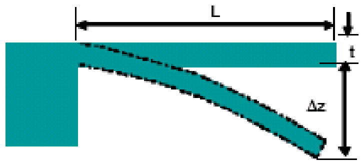
- **calorimetric**
  heat produced or absorbed during biochemical reactions

AFM-based: cf e.g. Ch. Gerber et al.

Kavli Prize 2016 in Nanoscience

Mechanical Detection

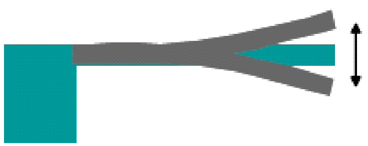
Surface Stress Change Detection



$$\Delta z = 4\left(\frac{l}{t}\right)^2 \frac{(1-\nu)}{E}(\Delta\sigma_1 - \Delta\sigma_2)$$

- Δz = deflection of the free end of the cantilever
- L = cantilever length
- t = cantilever thickness
- E = Young's modulus
- ν = poison's ratio
- $\Delta\sigma_1$ change in surface stress on top surface
- $\Delta\sigma_2$ change in surface stress on bottom surface

Mass Change Detection



$$f = \frac{1}{2\pi}\sqrt{\frac{k}{m}}$$

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

- k = spring constant
- m = mass of cantilever
- *f_0 = unloaded resonant frequency*
- *f_1 = loaded resonant frequency*

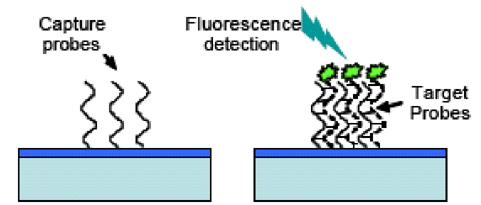
QCM: ***Q-Sense***

cantilever: ***Concentris***

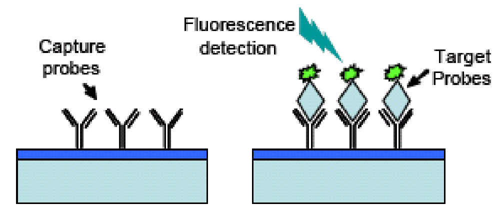
Transduction

- **optical** (absorption-, **fluorescence-**, luminescence-, internal reflection spectroscopy; **surface plasmon resonance** - SPR; light scattering)

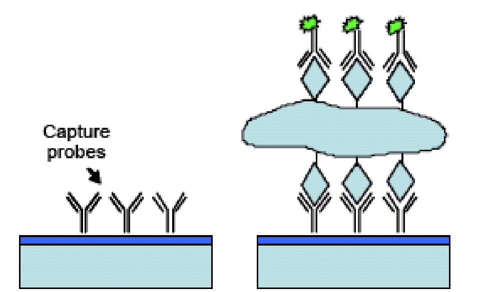
Optical Detection



DNA detection on chip surfaces



Protein detection on chip surfaces



Cell detection on chip surfaces

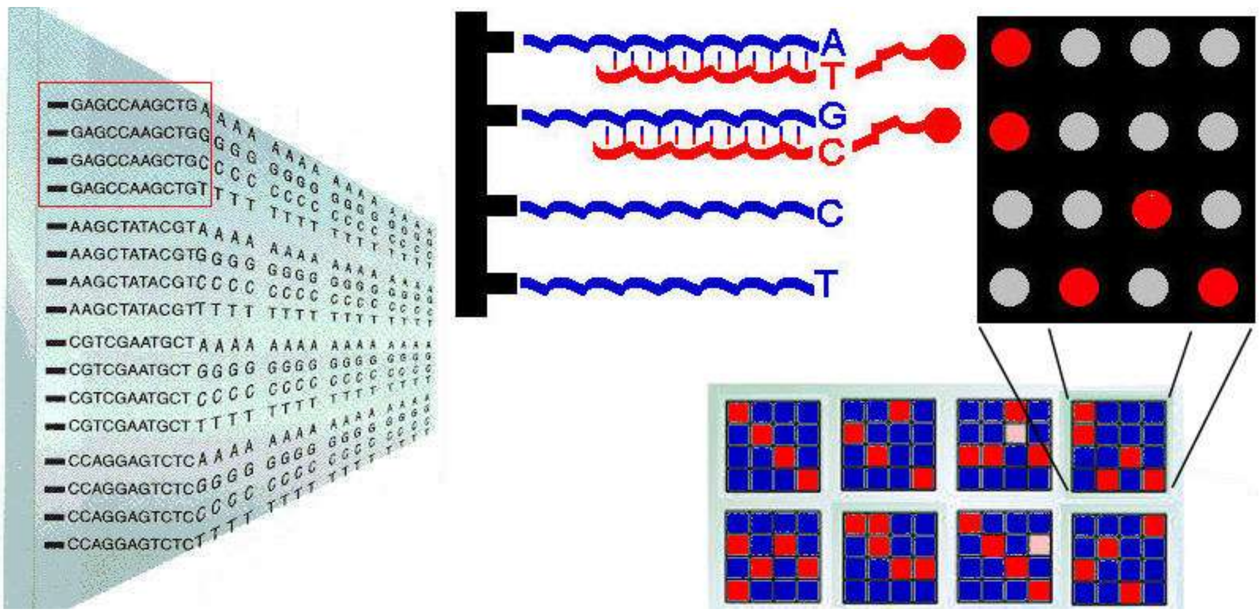
fluorescence: ***Affymetrix***

SPR: ***Biacore***

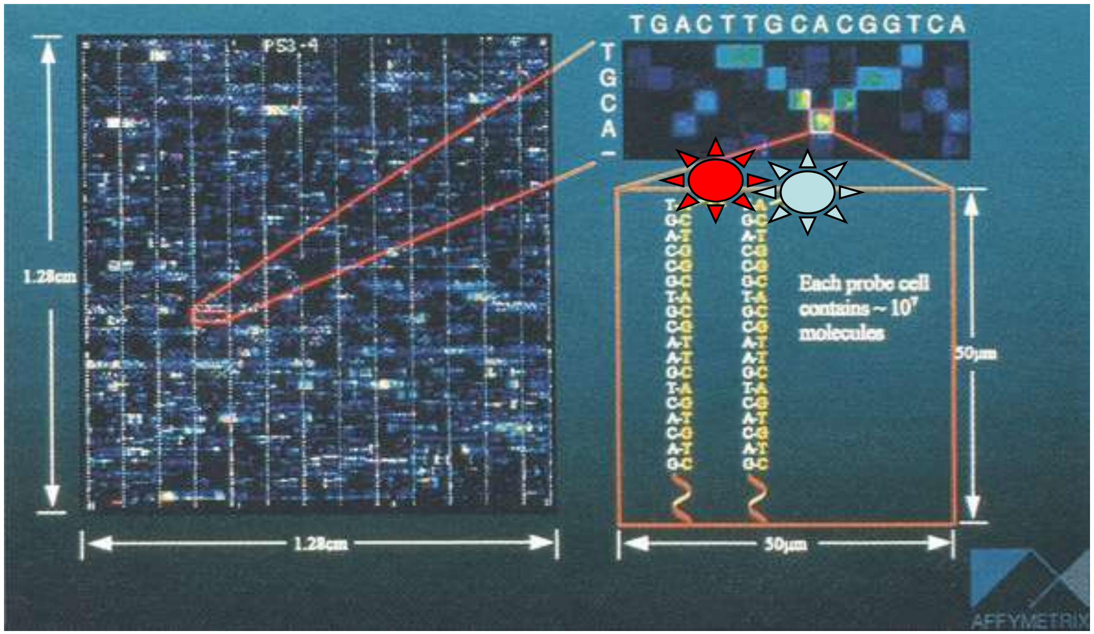
example: fluorescence, DNA microarray

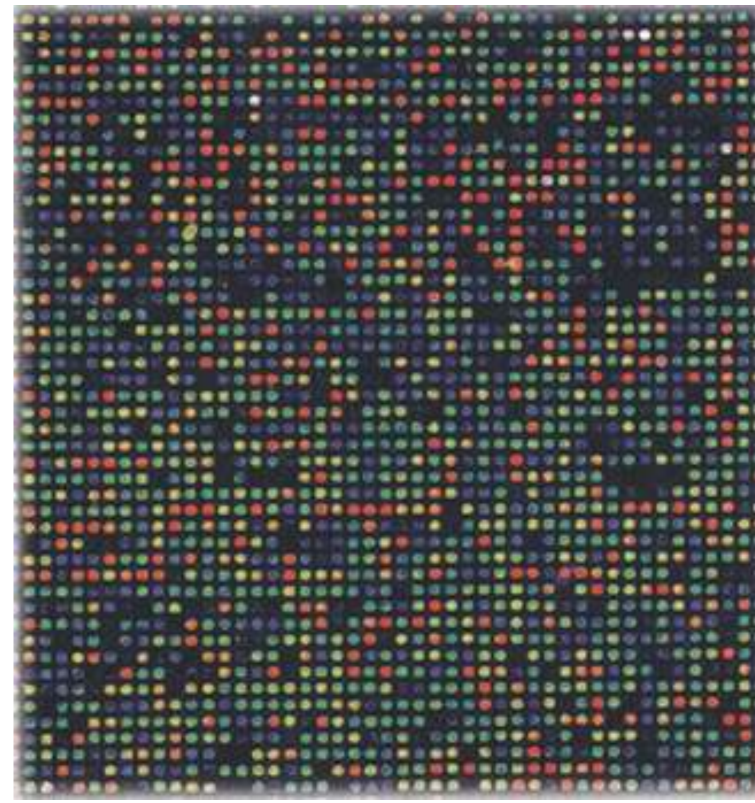
- Analyte: Labelled ss-DNA
- Recognition Molecule: cDNA, mRNA
- Transduction: Fluorescence

Affymetrix



DNA microarray



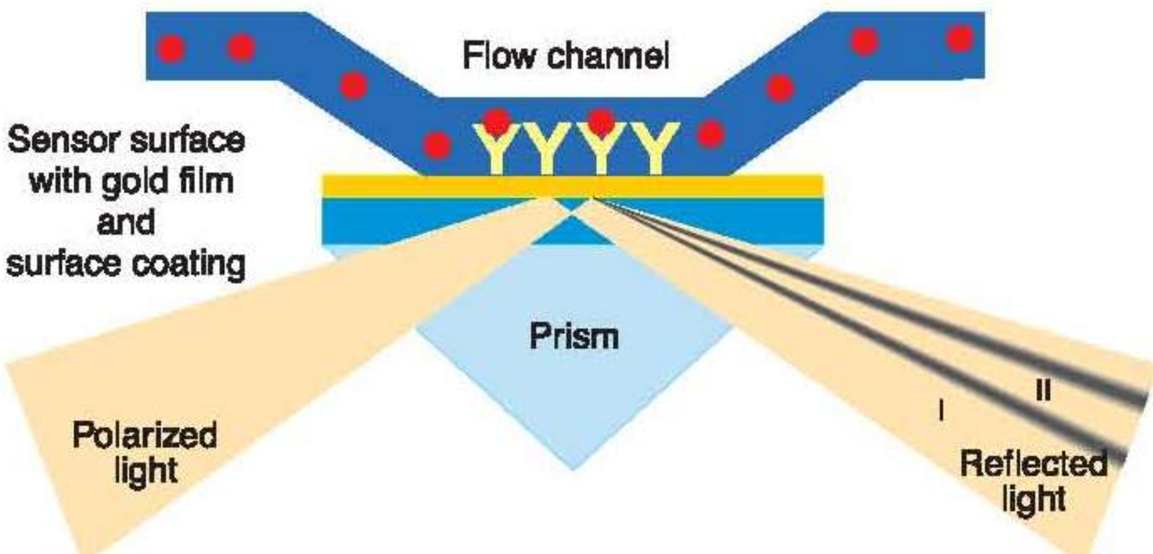


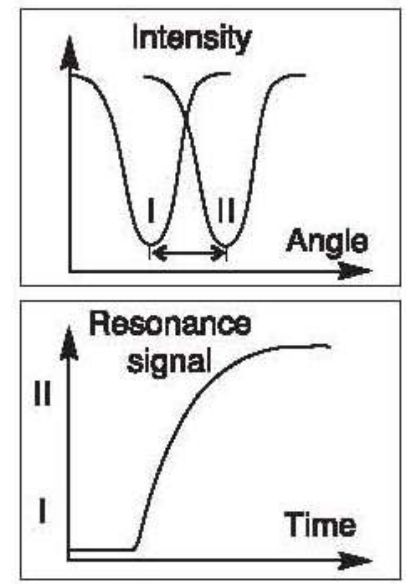
Gene-chip,
Affymetrix

Probe molecules
have to be labeled

example: surface plasmon resonance (SPR)

Biacore





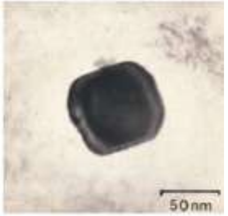
Sensorgram

plasmons: reminder

- **response of metals to optical fields**
  plasma frequency ω_p~10^{15} Hz (visible)
  collective oscillation of e^- in metal

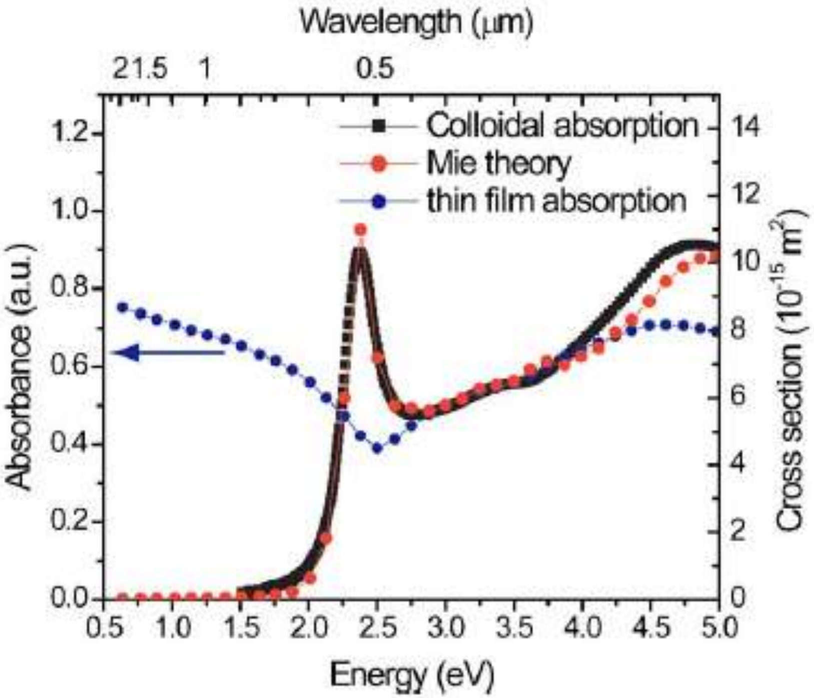
$$\omega_p = \sqrt{\frac{n_e e^2}{m^* \varepsilon_0}}$$

reflection ***transmission***



Lycurgus cup, 4th century A.D., late Roman *Britisch Museum*

SEM image of a typical nanocrystal embedded in the glass (British museum)



- calc. spectra (Maxwell) for **thin film** and **30nm Au nanoparticle** *(classical electromagnetism)*
- measured spectrum of **30nm Au**

Maier, Atwater, J. Appl. Phys review (2005)

plasmons

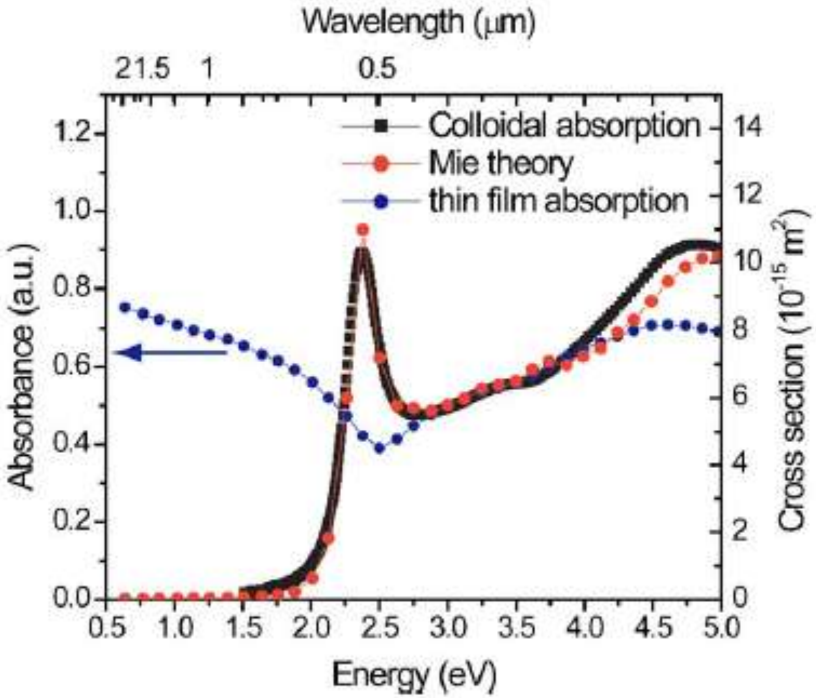
$$\omega_p = \sqrt{\frac{n_e e^2}{m^* \varepsilon_0}}$$

- **response of metals to optical fields**
  plasma frequency ω_p~10^{15} Hz (visible)
  collective oscillation of e^- in metal

- **plane-wave excitation of metal particle**
  e confined in sphere diameter d«λ

  - in-phase motion of conduction e
    ⇨ **polarization charges** at surface
  - pol. charge ⇨ restoring force
    resonance at dipole plasmon freq
    π/2 phase lag with driving field

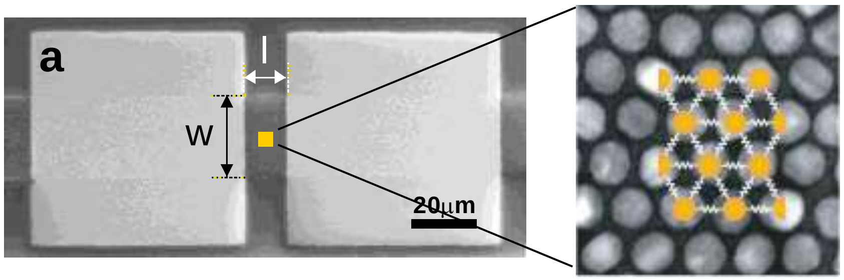


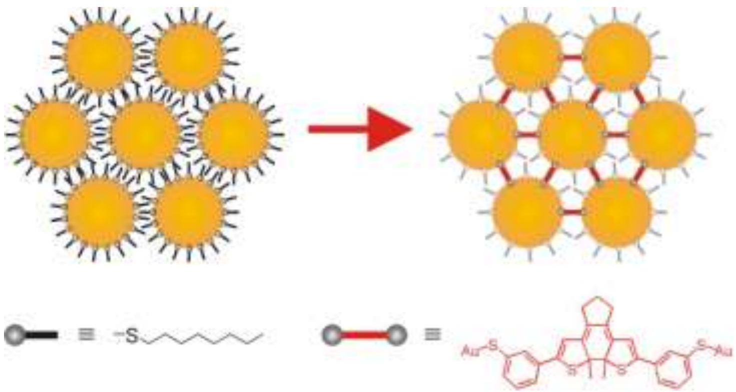
- **resulting dipolar field** (outside the particle)
  ⇨ enhanced absorption and scattering for em waves & enhanced near field at surface

- **NB: larger particles: retardation effects, higher order modes, dephasing**

Maier, Atwater, J. Appl. Phys review (2005)

Remember: NP arrays, light-controlled conductance switching



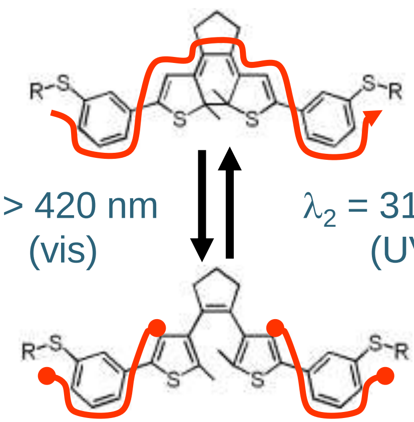


sheet resistance:
$R_{\square} = R \cdot w/l$

junction resistance
$R_J = (2/\sqrt{3}) \cdot R_{\square}$

$R_J = 1/G_J$

light-controlled molecular switch

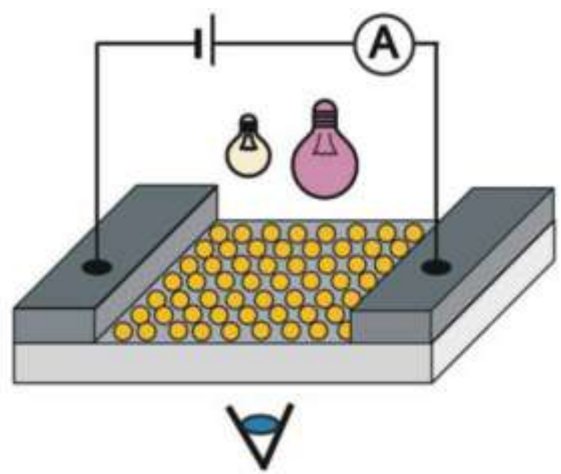


λ_1 > 420 nm
(vis)

λ_2 = 313 nm
(UV)

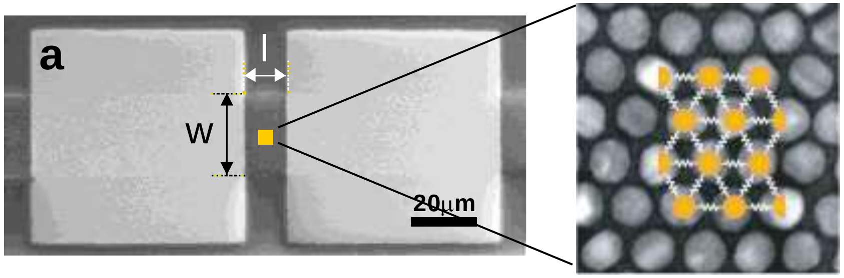
"ON" state
extended conjugation

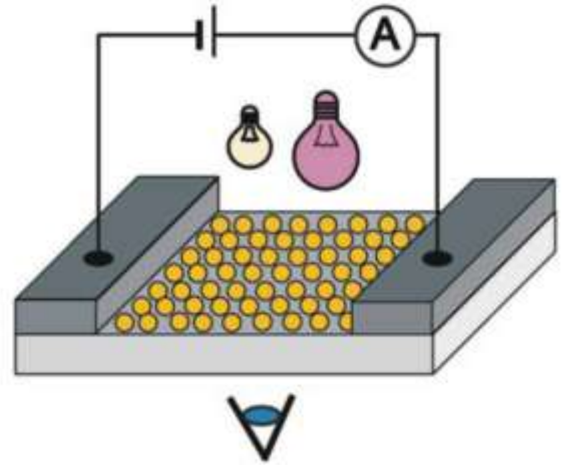
"OFF" state
interrupted conjugation



van der Molen et al., , Nano Lett. (2009); MC, Chimia (2010), Chem. Soc. Rev. (2015)

light-controlled conductance switching





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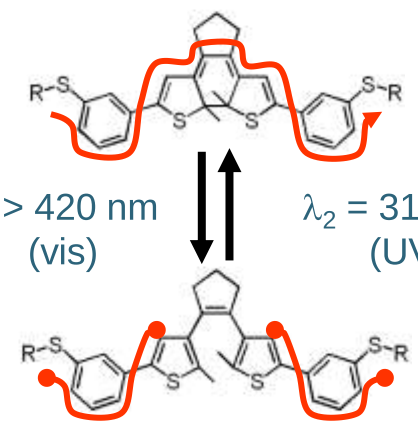

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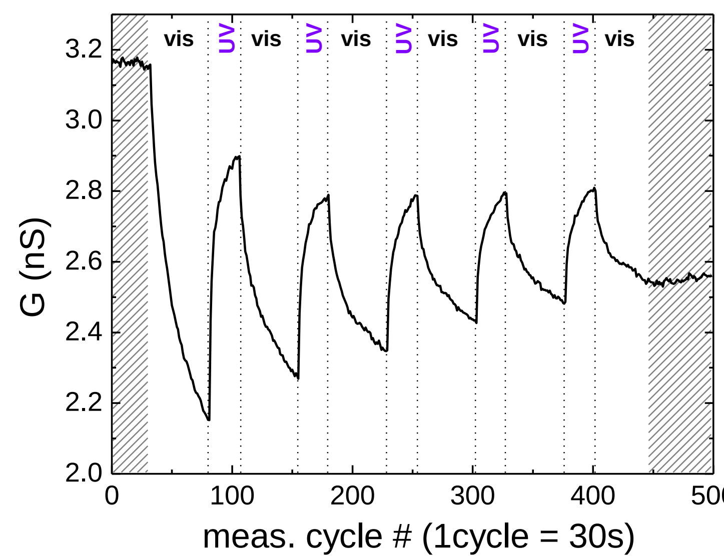


van der Molen et al., , Nano Lett. (2009); MC, Chimia (2010), Chem. Soc. Rev. (2015)

plasmon resonances in NP arrays

optical spectroscopy (absorption)

plasmon generated by E-field component of an irradiating EM wave

C16-capped Au nanoparticles (10nm ∅)

in solution (blue) and as an array (black)

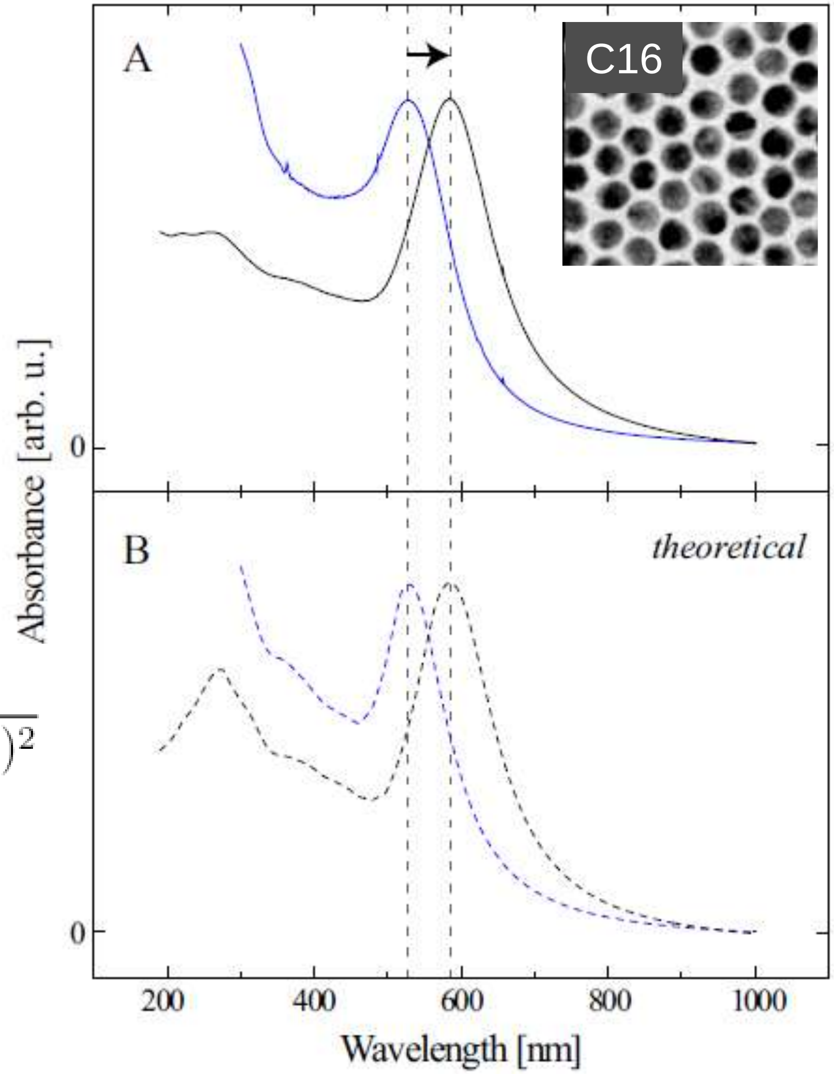
red shift of SPR due to array

absorption cross-section: Mie
(small particles, dipolar approx.)

$$\sigma(\omega) = 12\pi \frac{\omega}{c} \varepsilon_m^{3/2} R^3 \frac{\varepsilon_2(\omega)}{[\varepsilon_1(\omega) + 2\varepsilon_m]^2 + \varepsilon_2(\omega)^2}$$

medium permittivity ϵ_m

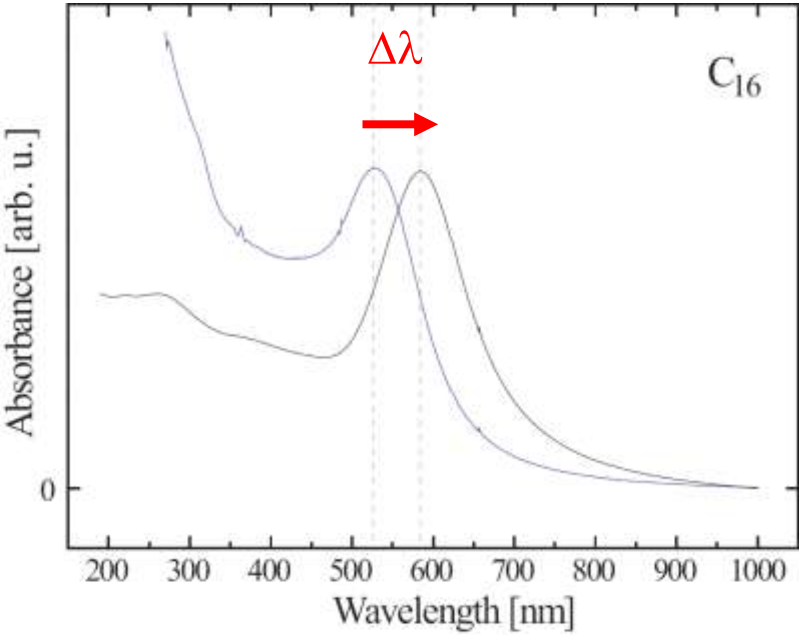
nanoparticle $\epsilon(\omega) = \epsilon_1(\omega) + \mathrm{i}\epsilon_2(\omega)$



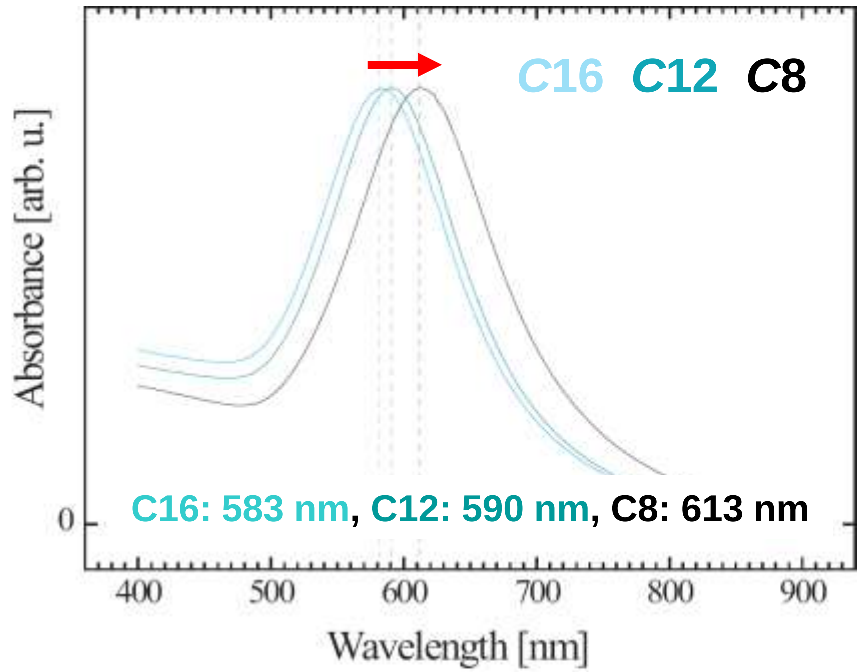
L. Bernard et al., JPC (2007)

plasmon resonances in NP arrays

solution vs array

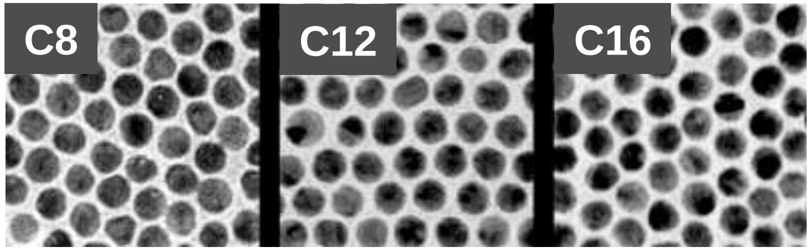


different arrays



*C*16-capped nanoparticles

in **solution (blue)** and as an **array (black),**
red shift of surface plasmon resonance:
526 nm to **583 nm**.



L. Bernard et al., JPC (2007)

characterizing plasmon resonances

absorption cross-section: Mie
(small particles, dipolar approx.)

$$\sigma(\omega) = 12\pi\frac{\omega}{c}\varepsilon_m^{3/2}R^3\frac{\varepsilon_2(\omega)}{[\varepsilon_1(\omega)+2\varepsilon_m]^2+\varepsilon_2(\omega)^2}$$

nanoparticle permittivity: Drude-Lorentz-Sommerfeld

$$\varepsilon(\omega) = 1 - \frac{\omega_p^2}{\omega(\omega + i\Gamma)} \qquad \omega_p = \sqrt{\frac{n_0 e}{\varepsilon_0 m_e}}$$

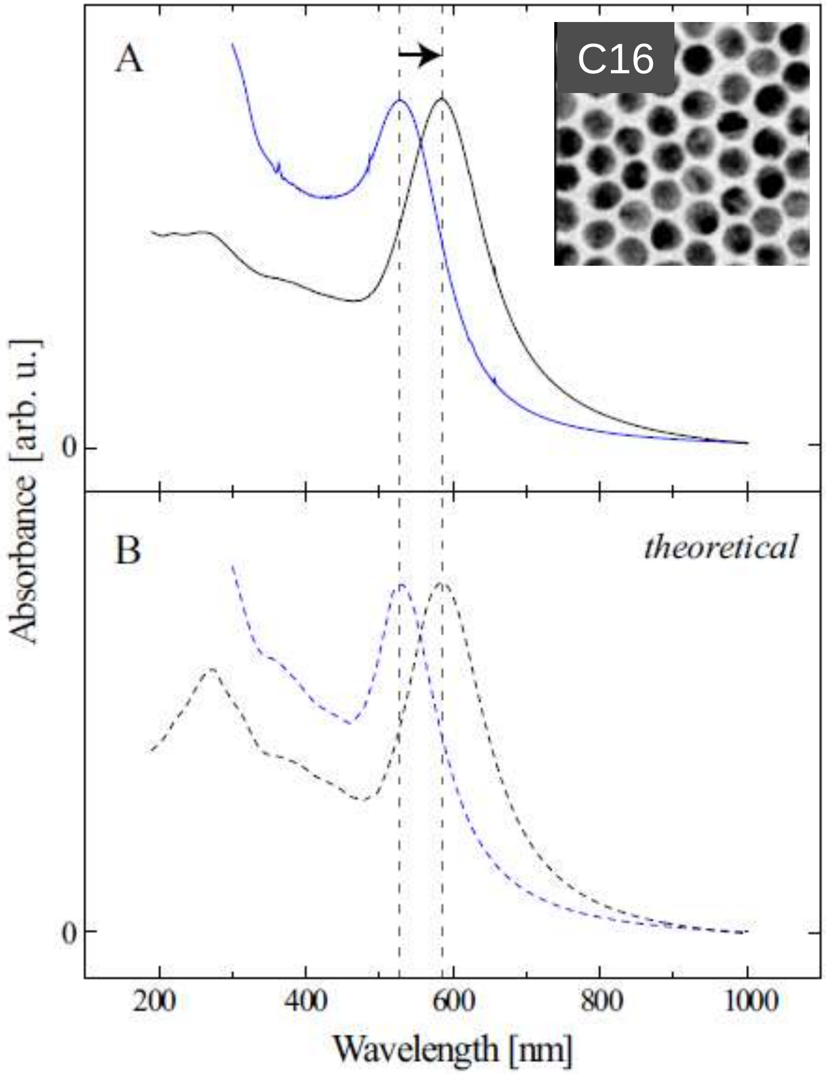
$$\epsilon_1(\omega,R) = 1 - \frac{\omega_\mathrm{p}{}^2}{\omega^2 + \Gamma^2(R)} + \epsilon_{1,\mathrm{core}}$$

$$\epsilon_2(\omega,R) = \frac{\omega_\mathrm{p}{}^2\Gamma(R)}{\omega(\omega^2 + \Gamma^2(R))} + \epsilon_{2,\mathrm{core}}$$

$$\Gamma(R) = \frac{v_\mathrm{F}}{l_\infty} + A\,\frac{v_\mathrm{F}}{R}$$

damping constant
(radius dep.)

medium permittivity ϵ_m
nanoparticle $\epsilon(\omega) = \epsilon_1(\omega) + i\epsilon_2(\omega)$



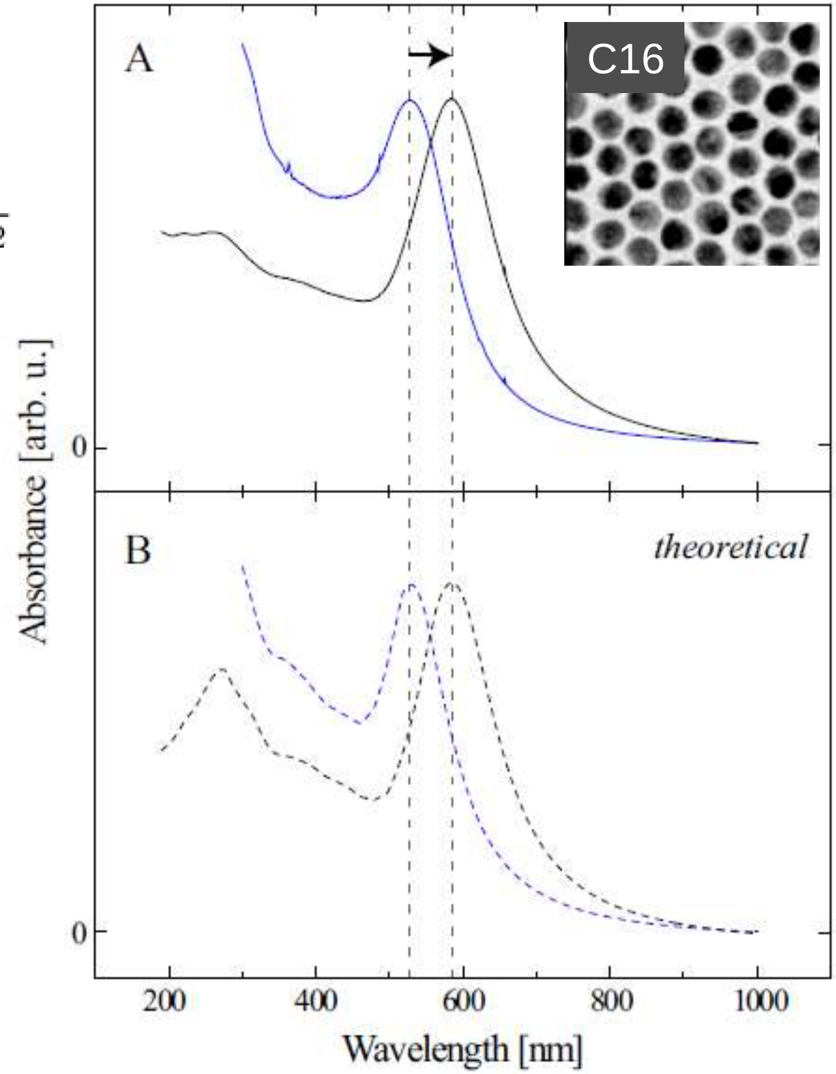
L. Bernard et al., JPC (2007)

characterizing plasmon resonances

absorption cross-section: Mie
(small particles, dipolar approx.)

$$\sigma(\omega) = 12\pi \frac{\omega}{c} \varepsilon_m^{3/2} R^3 \frac{\varepsilon_2(\omega)}{[\varepsilon_1(\omega) + 2\varepsilon_m]^2 + \varepsilon_2(\omega)^2}$$

$$\propto \frac{1}{(\omega - \omega_M)^2 + \left(\Gamma/2\right)^2} \qquad \omega_M = \frac{\omega_p}{(1+2\varepsilon_m)^{1/2}}$$



NB

in **solution**: dilute system, Mie ok

as **array** interaction between neighboring nanoparticles, red-shift

⇨ **effective medium permittivity**
Maxwell-Garnett

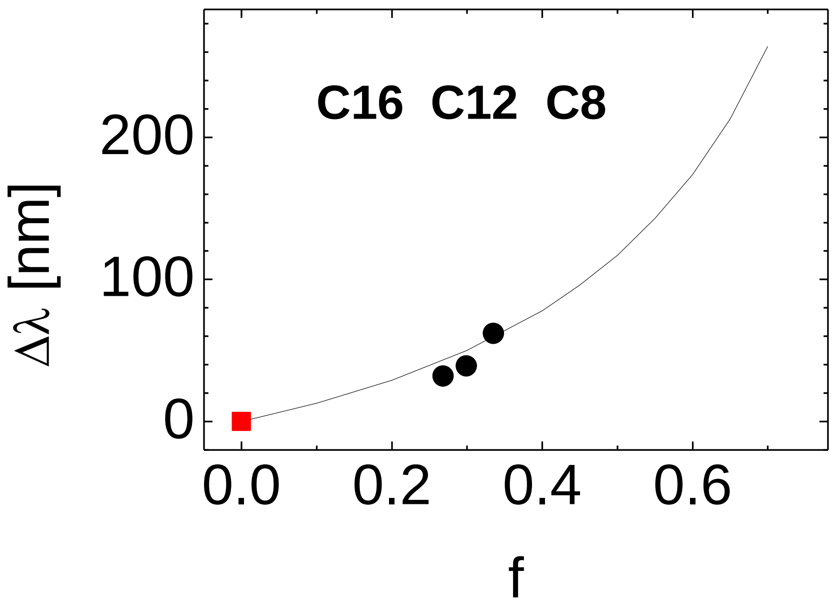
L. Bernard et al., JPC (2007)

optical absorption

in **solution**: dilute system, Mie ok

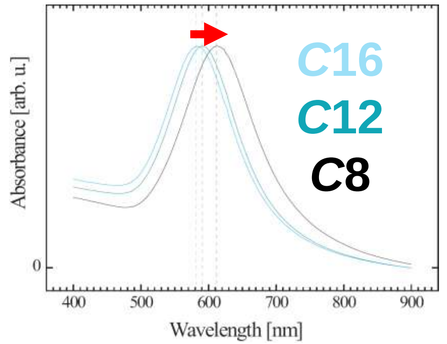
array: confined system, interaction between neighboring nanoparticles

⇨ **effective medium permittivity**
Maxwell-Garnett



$$\varepsilon_{eff}(\omega) = \varepsilon_m \frac{1+2f\Lambda}{1-f\Lambda} \qquad \Lambda = \frac{\varepsilon(\omega)-\varepsilon_m}{\varepsilon(\omega)+2\varepsilon_m}$$

filling factor $f = V_{clusters}/V_{total}$



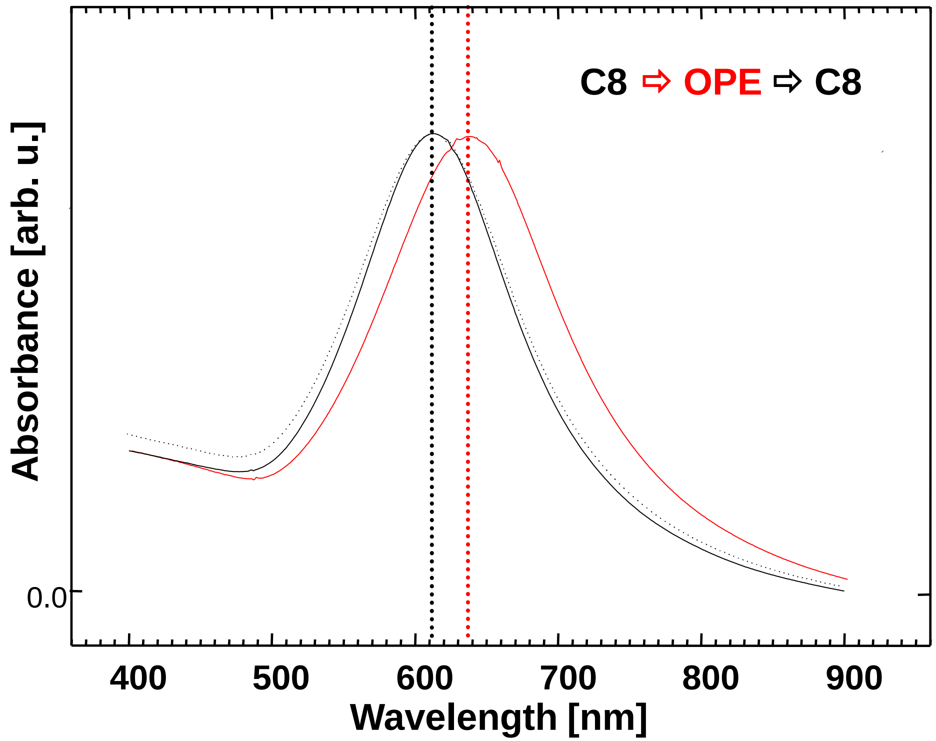
Resonance condition $\varepsilon_1(\omega_{sp})(1-f) + \varepsilon_m(2+f) = 0$

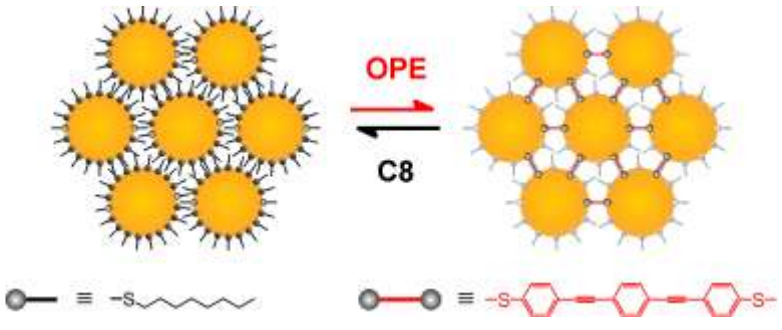
Mie: f=0 $\varepsilon_1 + 2\varepsilon_m = 0$

L. Bernard et al., J. Phys. Chem. C, 2007

plasmon resonances shift during molecular exchange

plasmon resonance for array during exchange





Δλ ≈ 20nm ⬄ Δε ≈ 0.5

ε_{C8}=1.9-2.2[(1)], ε_{OPE}=3.1-3.9[(2)]

⇨ **exchange efficiency 20% to 40%**

NB: partial exchange ensures stability of array

plasmon resonance: very sensitive to surface modification

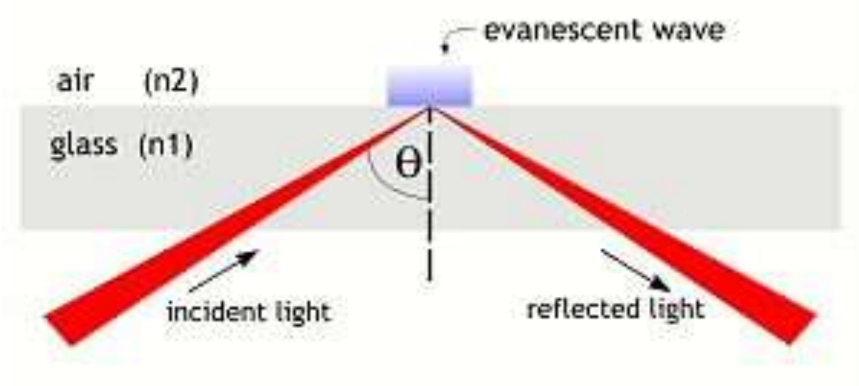
(1) G. Whitesides et al., , APL, 1998.
(2) J. Stapleton et al., Langmuir 2003.

L. Bernard et al., J. Phys. Chem. C, 2007

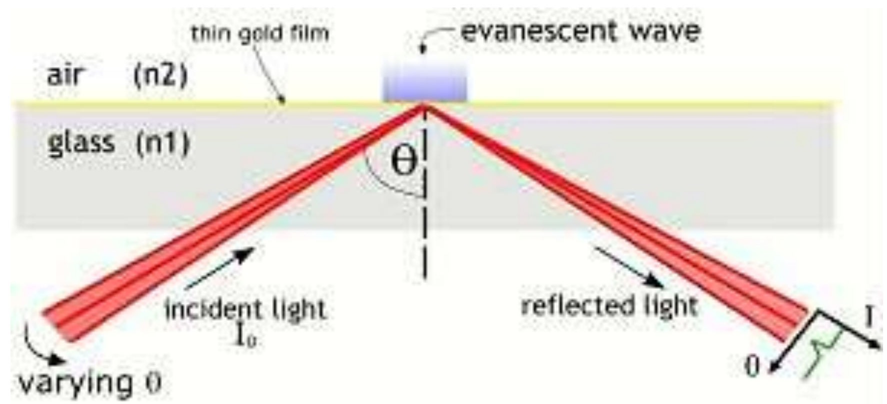
sensing using surface plasmon resonance

plasmon in thin films

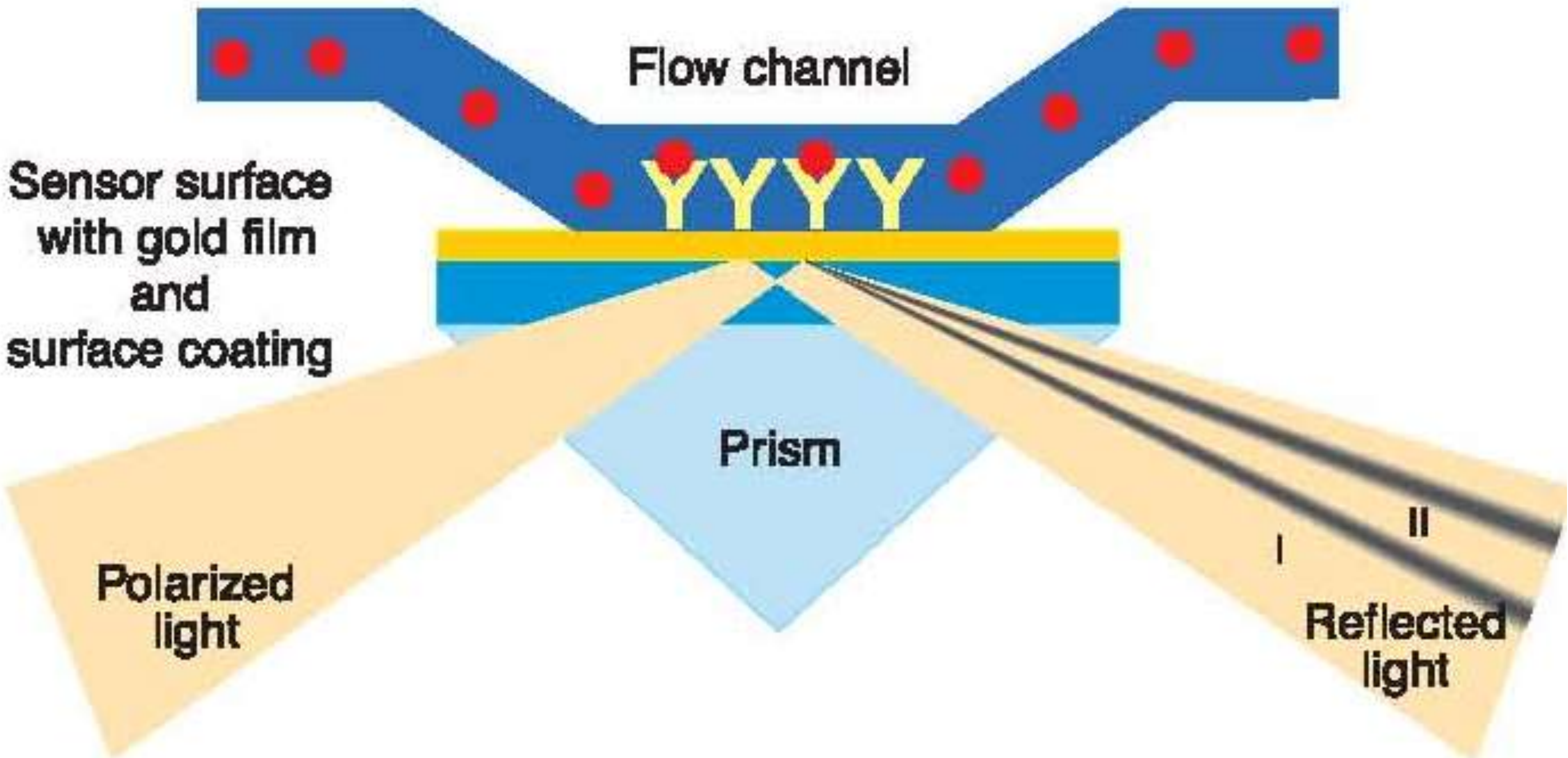
- TIR above critical angle θc (Snell's law: ni·sin(θi)=nt·sin(θt) sin(θc)=nt/ni, ni>nt)



- when plasmon induced in metallic thin film (proper incidence angle, thus resonance), the reflected intensity shows a drop



surface plasmon resonance (SPR)

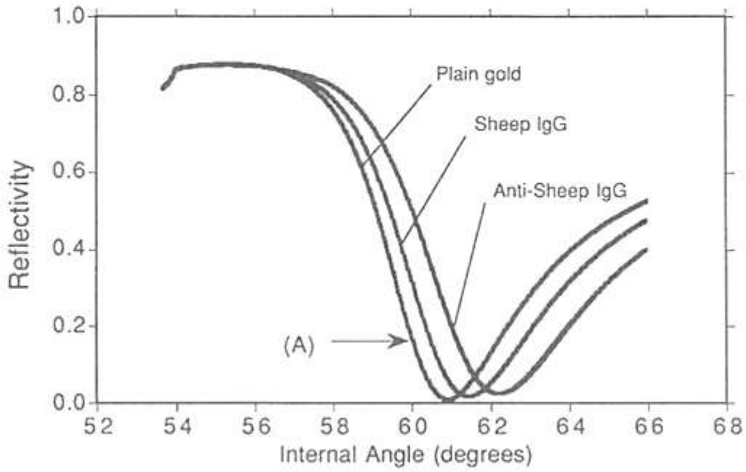


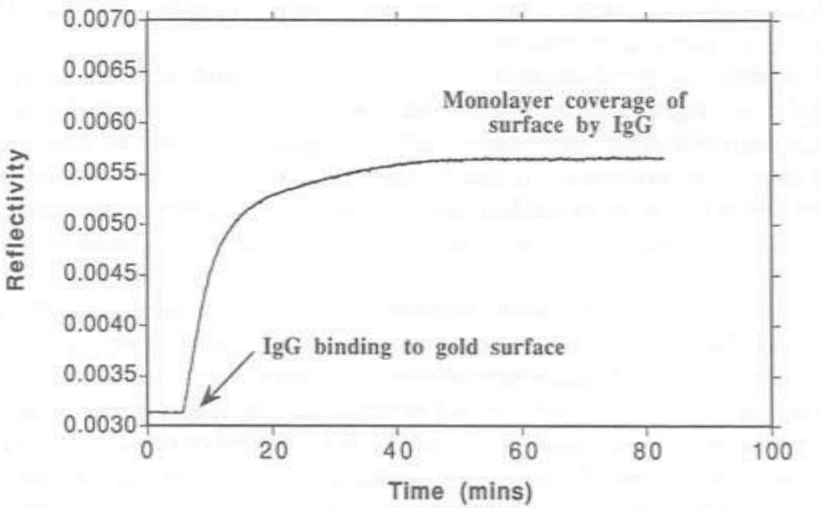
• SPR angle shift	0.12 °
• Change in protein surface concentration	1 ng/mm2
• Change in bulk refractive index	0.001

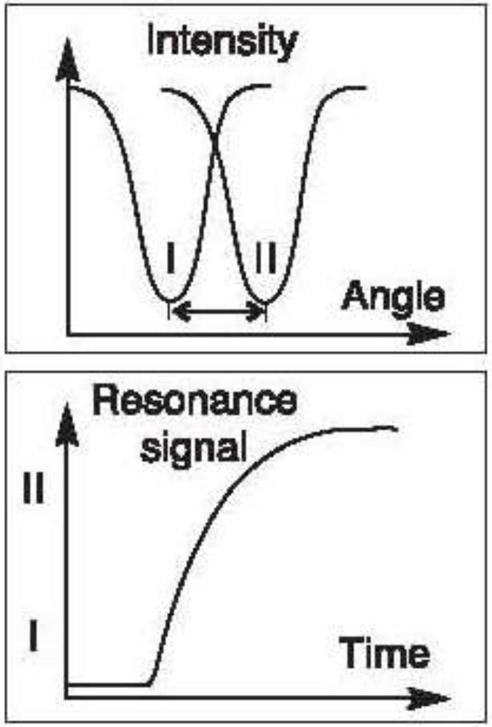
Biacore

surface plasmon resonance (SPR)

reflectivity vs angle for three different surface states



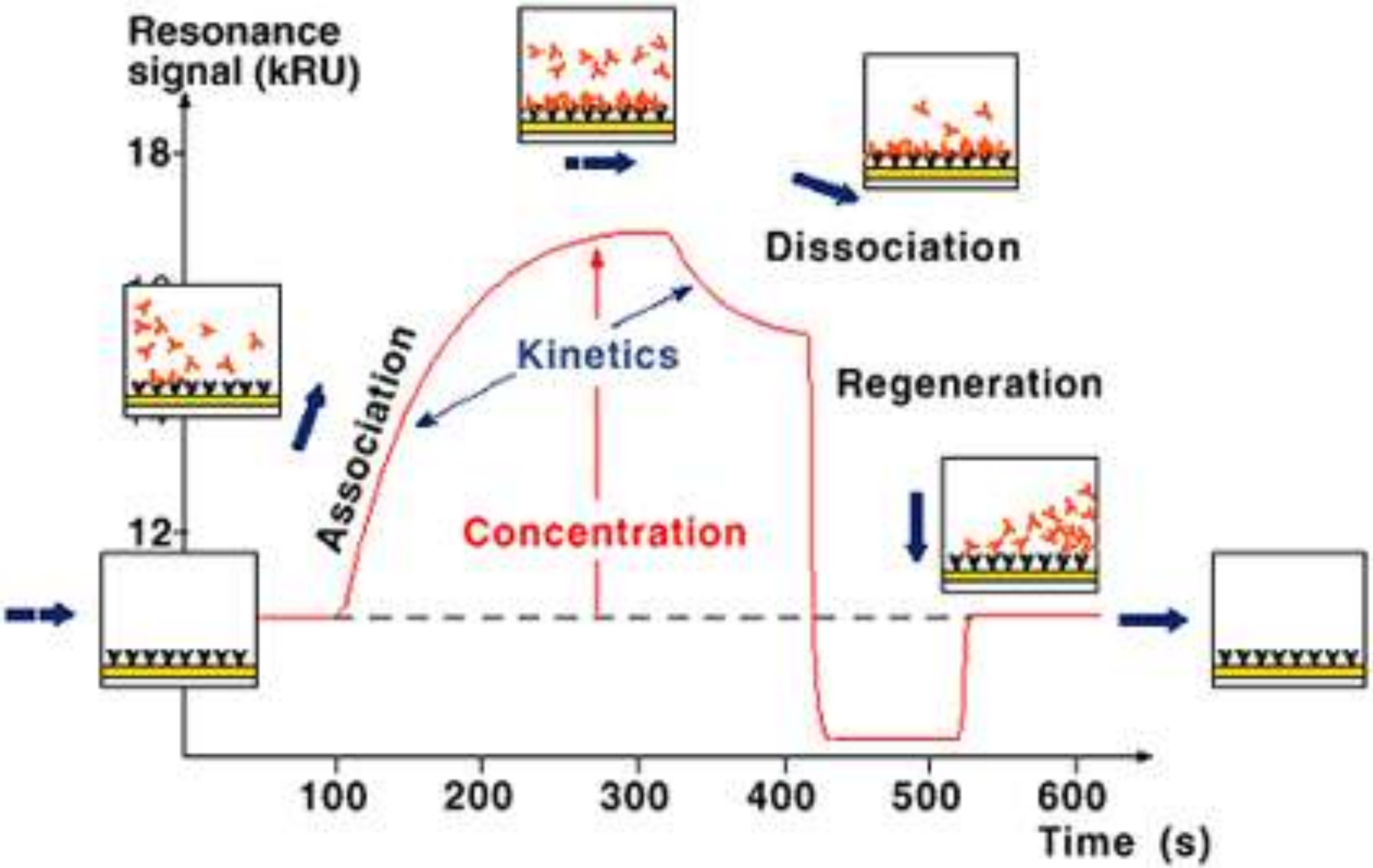




Sensorgram

Biacore

surface plasmon resonance (SPR)



drawbacks: upscalability, integration

Biacore

- **general aspects on sensing**
  sensitivity, specificity
  overview of transducers

- **field effect transistors (FETs) as charge sensors**
  MOSFET, graphene and GFET

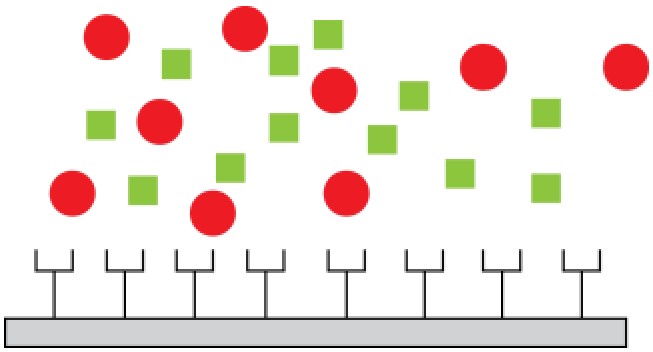
Examples

- Ion sensitive field-effect transistors (ISFETs) for pH, ionic and biochemicals detection

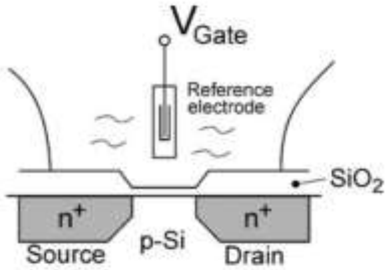
- Nanopores for sequencing

FETs for charge sensing

GOAL: specific detection of biochemicals
pH, ionic species, mRNA, DNA, proteins, ...



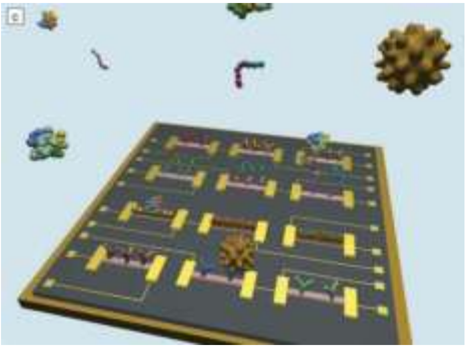
Requirements
- label-free, multi target sensor,
- quantitative
- upscalable, dense integration: Si-based
- portable, small volume, low cost, low-drift
- implantable, biocompatible



⇨ ***point of care and home diagnostics, implants, drug screening***

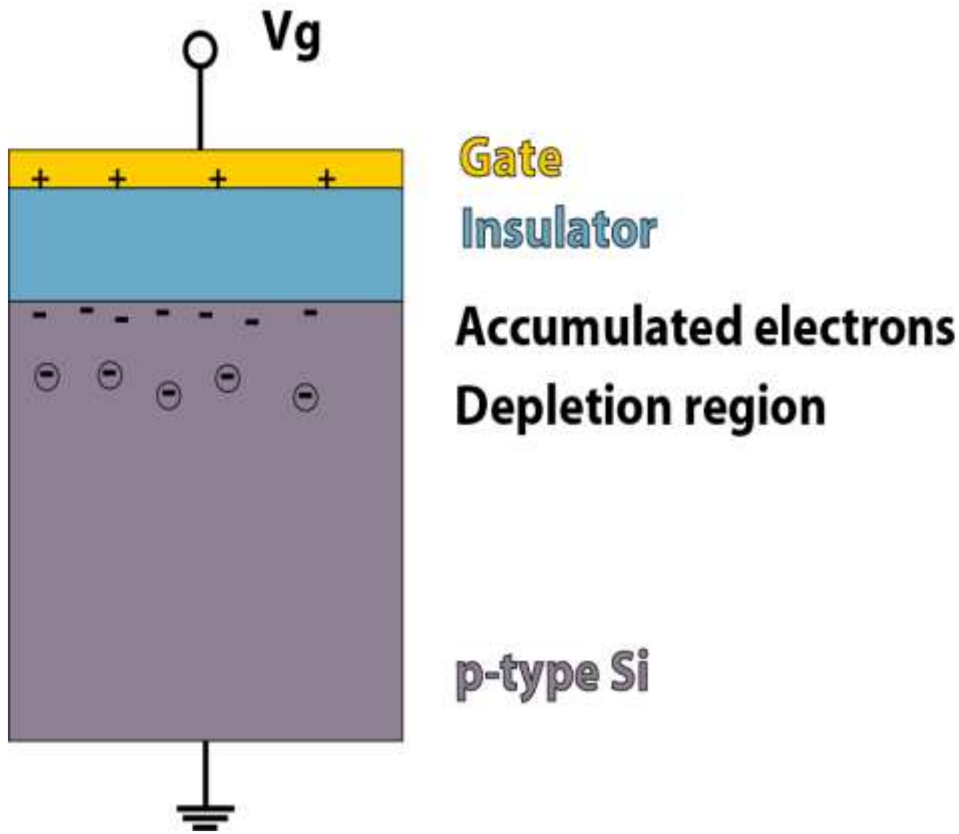
⇨ **ISFETs: ion-sensitive field-effect transistors ?**
detection of charged species, concept from the 70's

Transducer of chemical reactions in electrical signals

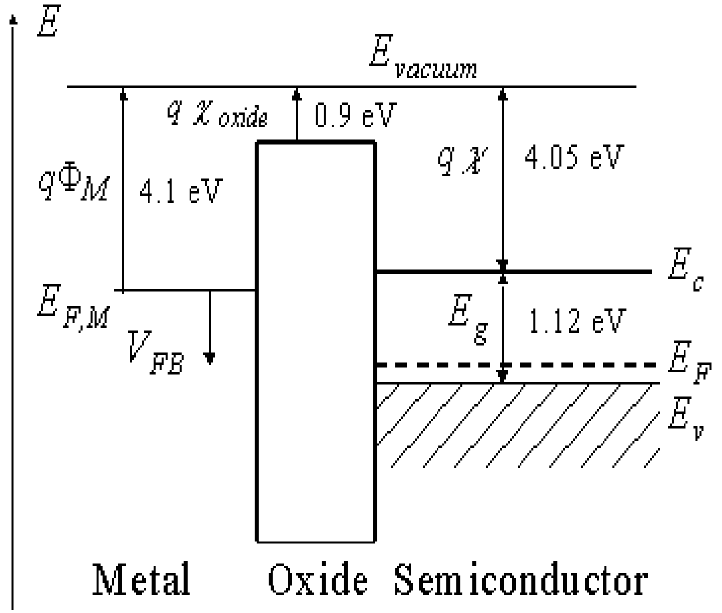


F. Patolsky, C.M. Lieber et al. (2007)

brief reminder: MOS capacitor and MOSFET



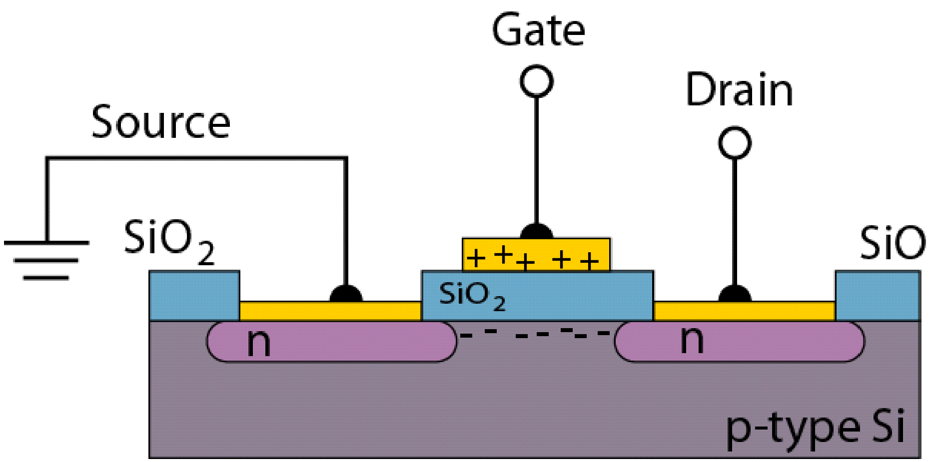
energy band diagram



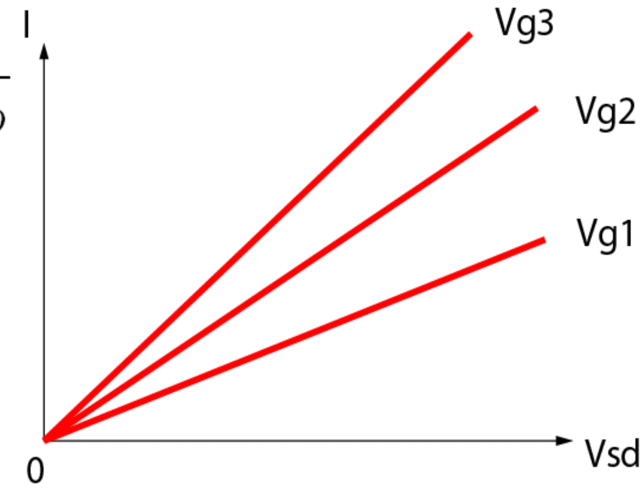
- Workfunction metal and semiconductor
- Interface charge: trapped oxide charge, mobile ionic charge, interface trapped charge

V_{th} depends on C_{ox}, the semiconductor (n_i) and doping (N_A)

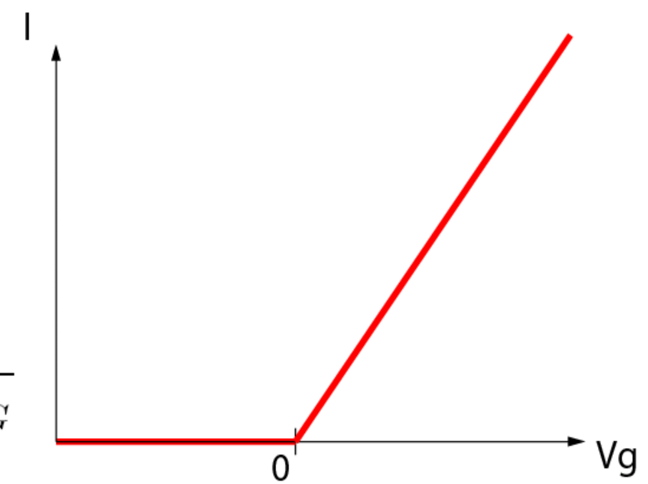
MOSFET



conductance $G_{SD} = \frac{dI}{dV_{SD}}$

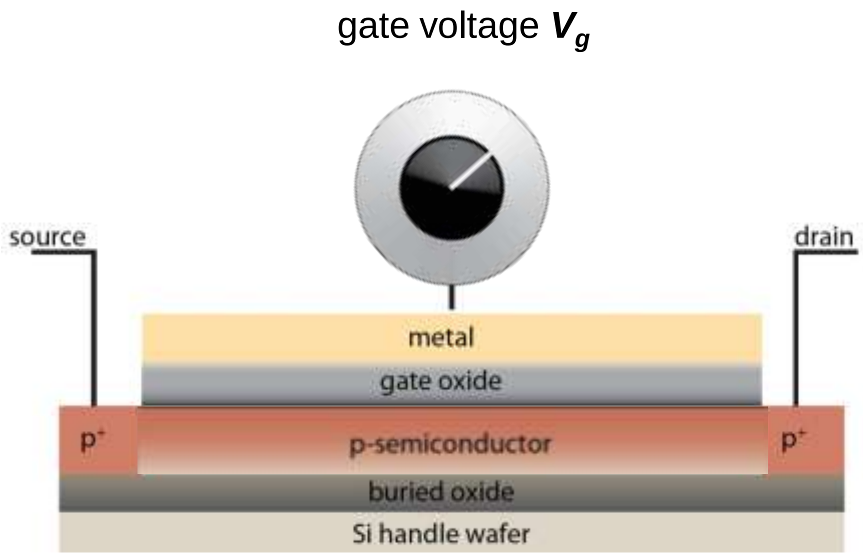


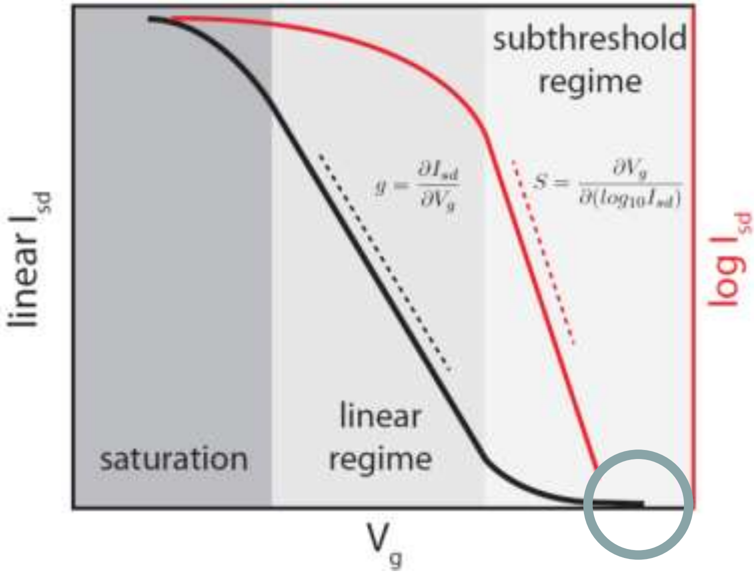
transconductance $G_{transc} = \frac{dI}{dV_G}$



MOSFET

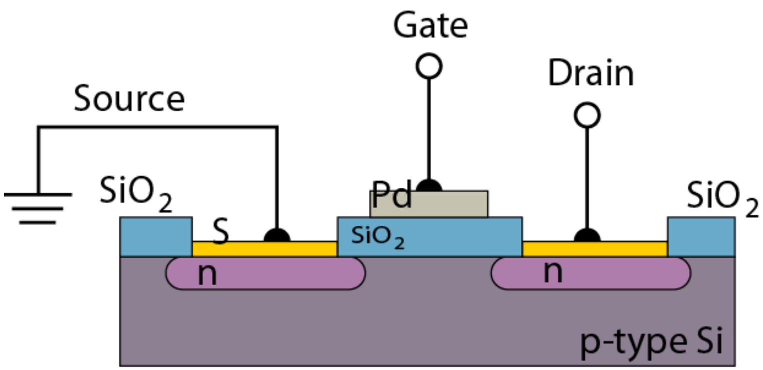
transfer characteristics (transconductance)

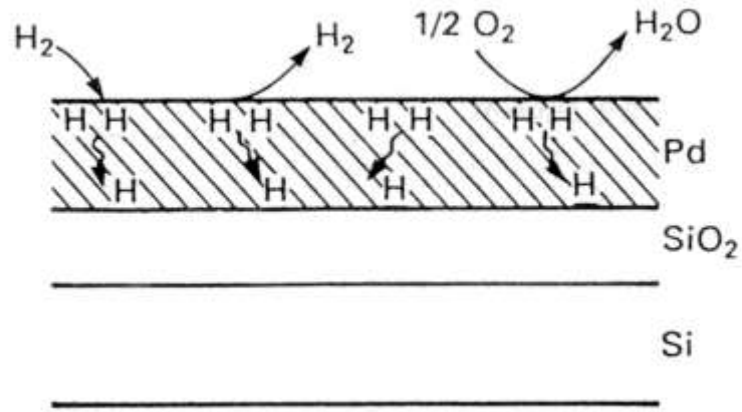




$$I_{sd} = \mu C_{ox}^{\square} \frac{W}{L} (V_g - V_{fb}) V_{sd}$$

Gas Sensitive MOSFET





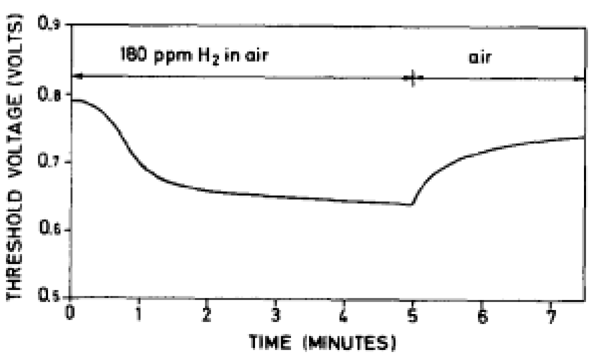


FIG. 4. Transistor threshold voltage as function of time when hydrogen is fed to the transistor and removed again. The temperature is 150°C.

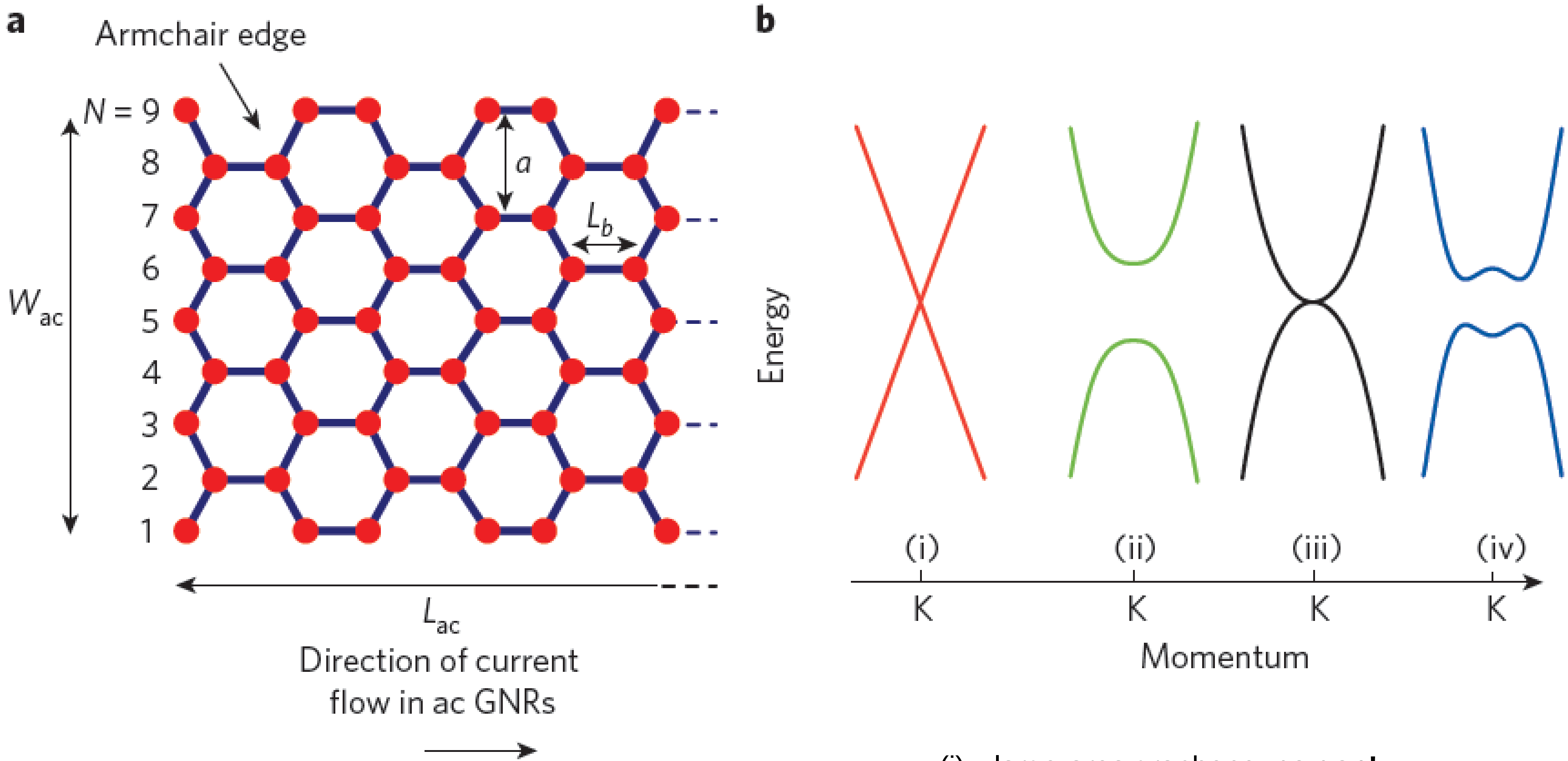
$$V_{th} = f(\Phi_{metal})$$

effect of H

hydrogen adsorbs, dissociates and diffuses to metal-oxide interface; forming a dipole layer modifying the metal - semiconductor interface (workfunction difference)

K. I. Lundström et al., J. Appl. Phy. 46, p 3876 (1975)

would graphene FETs be useful ?

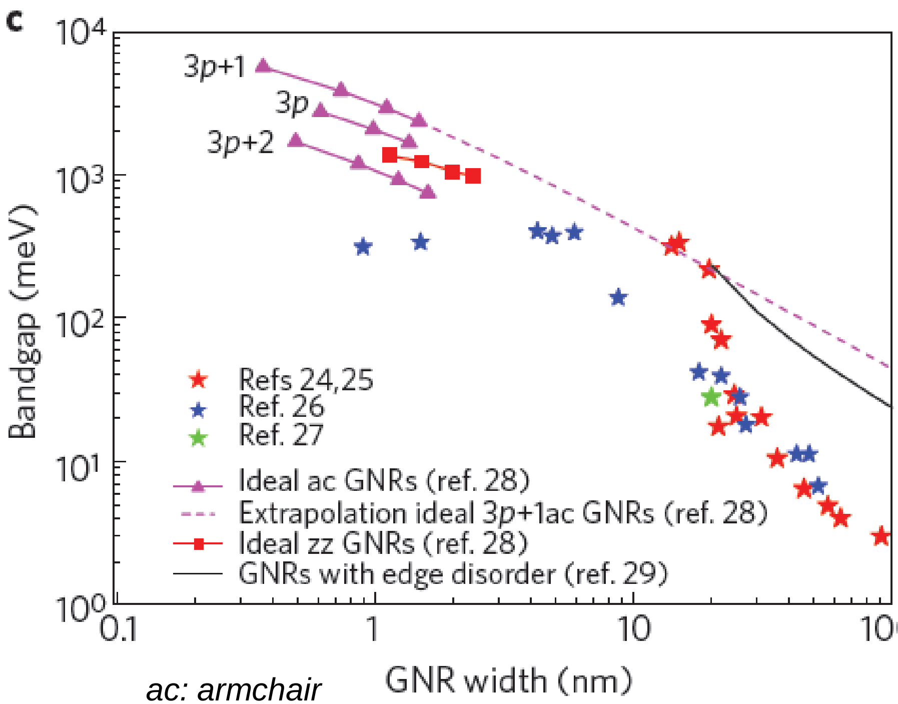


(i) large-area graphene: **no gap!**
(ii) graphene nanoribbons,
(iii) unbiased bilayer graphene,
(iv) bilayer graphene with an applied perpendicular field.

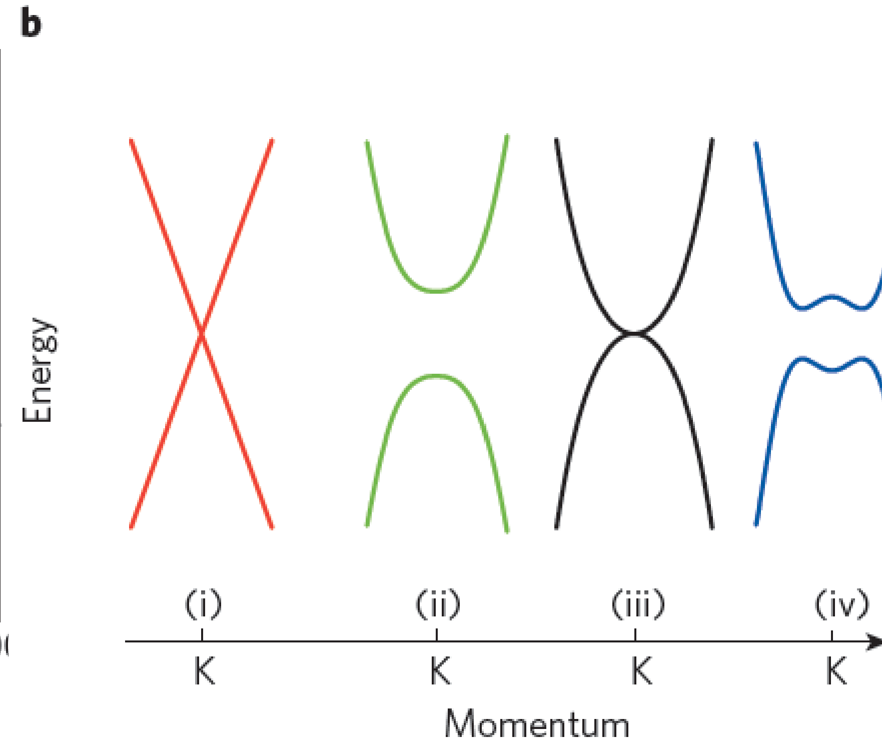
Schwierz, Nat. Nano (2010)

graphene FET

graphene nano-ribbons



ac: armchair
zz: zig-zag

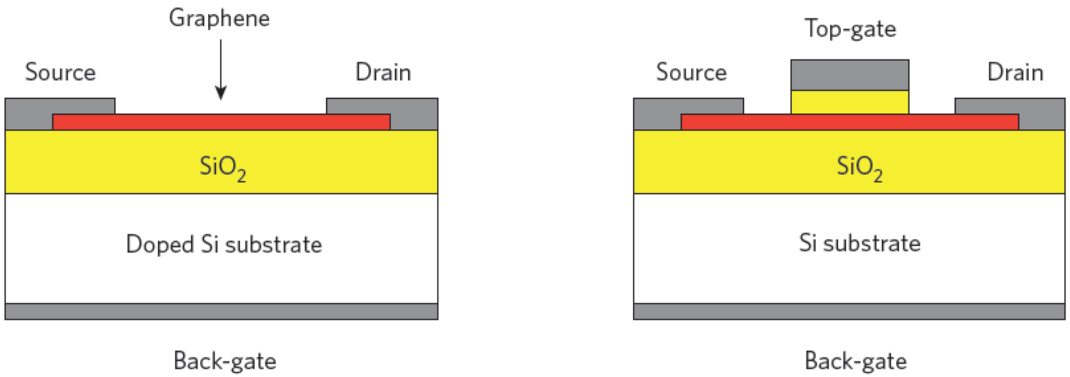


(i) large-area graphene,
(ii) graphene nanoribbons,
(iii) unbiased bilayer graphene,
(iv) bilayer graphene with an applied perpendicular field.

Schwierz, Nat. Nano (2010)

why graphene FETs

a



b

graphene
since 2004

Field-effect in graphene
Oct. 2004 (ref. 1)

2.5 years

First graphene FET
April 2007 (ref. 52)

<2 years

First gigahertz
graphene FET
Dec. 2008 (ref. 69)

CNTs
since 1991

First experimental
CNT paper
Nov. 1991 (ref. 98)

6.5 years

First CNT FET
May 1998 (ref. 99)

6 years

First gigahertz
CNT FETs
April 2004 (ref. 100)

Record cut-off frequencies:

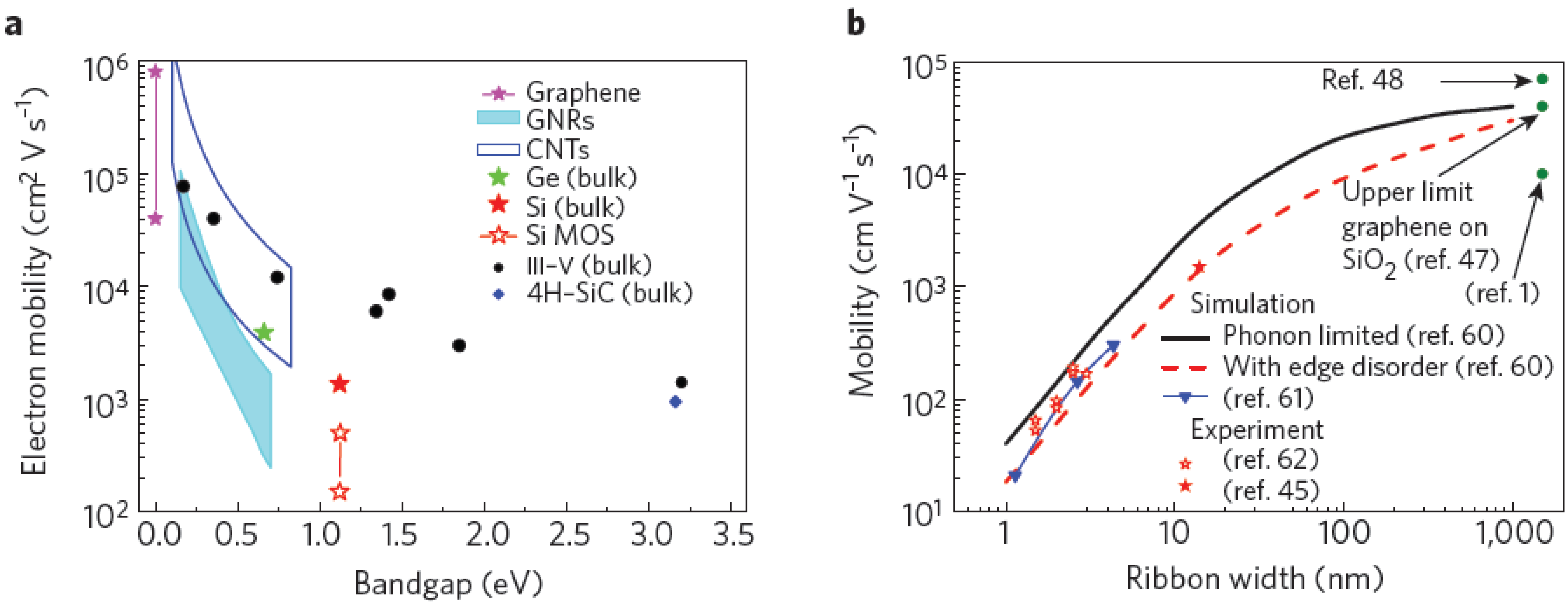
Graphene FET 100 GHz (ref. 73)

CNT FET 80 GHz (ref. 78)

Schwierz, Nat. Nano (2010)

graphene FET

charge carrier mobility in various materials & graphene



Schwierz, Nat. Nano (2010)

graphene (graphene-related materials) for sensing

Table 1 GRMs as a platform for enabling new techologies and applications, with radical [**not incremental**] advances

features	Enabled applications / technologies
Atomic thinness	Flexible devices; thin and flexible electronic components; modular assembly / distribution of portable thin devices
Foldable material	Engineering new materials by stacking different atomic planes or by varying the stacking order of homogeneous atomic planes
All-surface material	Engineering novel 2d crystals with tuneable physical/chemical properties by control of the surface chemistry. Platform for new chemical /biological sensors
Solution - processable	Novel composite materials with outstanding physical properties (*e.g.* high thermal conductivity, κ; high Young modulus and tensile strength); Novel functional materials
High carrier mobility (μ)	Ultra-high frequency electronic devices
Optical (saturable) absorption; photo-thermoelectric effect	Novel optoelectronic and thermoelectric devices; photodetectors
Field-effect sensitivity	Highly sensitive transducers

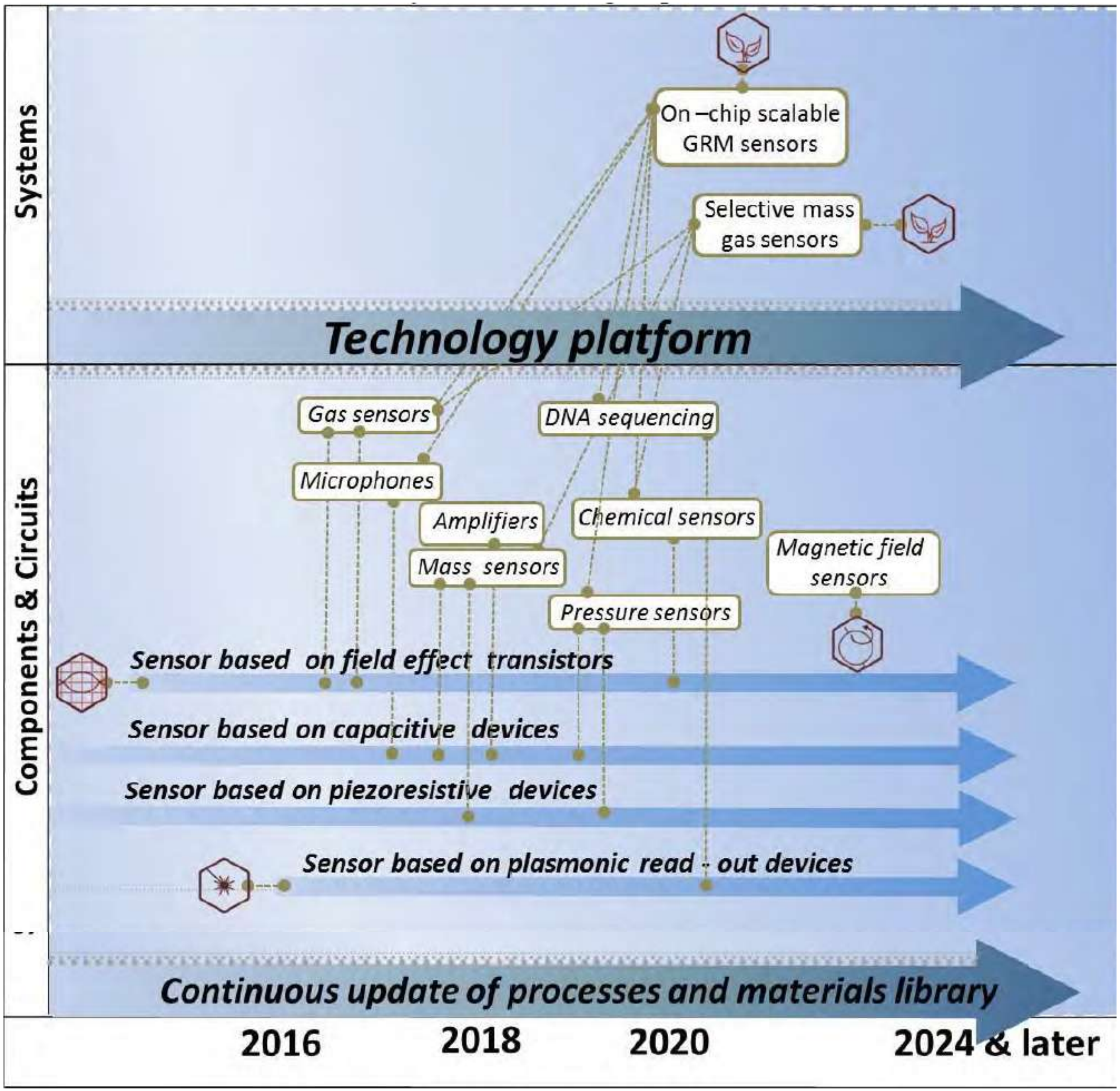
Graphene Roadmap, Ferrari et al., Nanoscale (2015)

graphene (graphene-related materials)

Optical (saturable) absorption; photo-thermoelectric effect	Novel optoelectronic and thermoelectric devices; photodetectors
Field-effect sensitivity	Highly sensitive transducers
High intrinsic capacitance; high specific surface area (SSA)	Outstanding supercapacitors
Photovoltaic effect, broad-range optical transparency; photocatalytic effects	Energy conversion; energy harvesting; self-powered devices
Theoretically predicted "chiral superconductivity"	High Tc superconductors
Dirac fermions; pseudospin	Valleytronics

Graphene Roadmap, Ferrari et al., Nanoscale (2015)

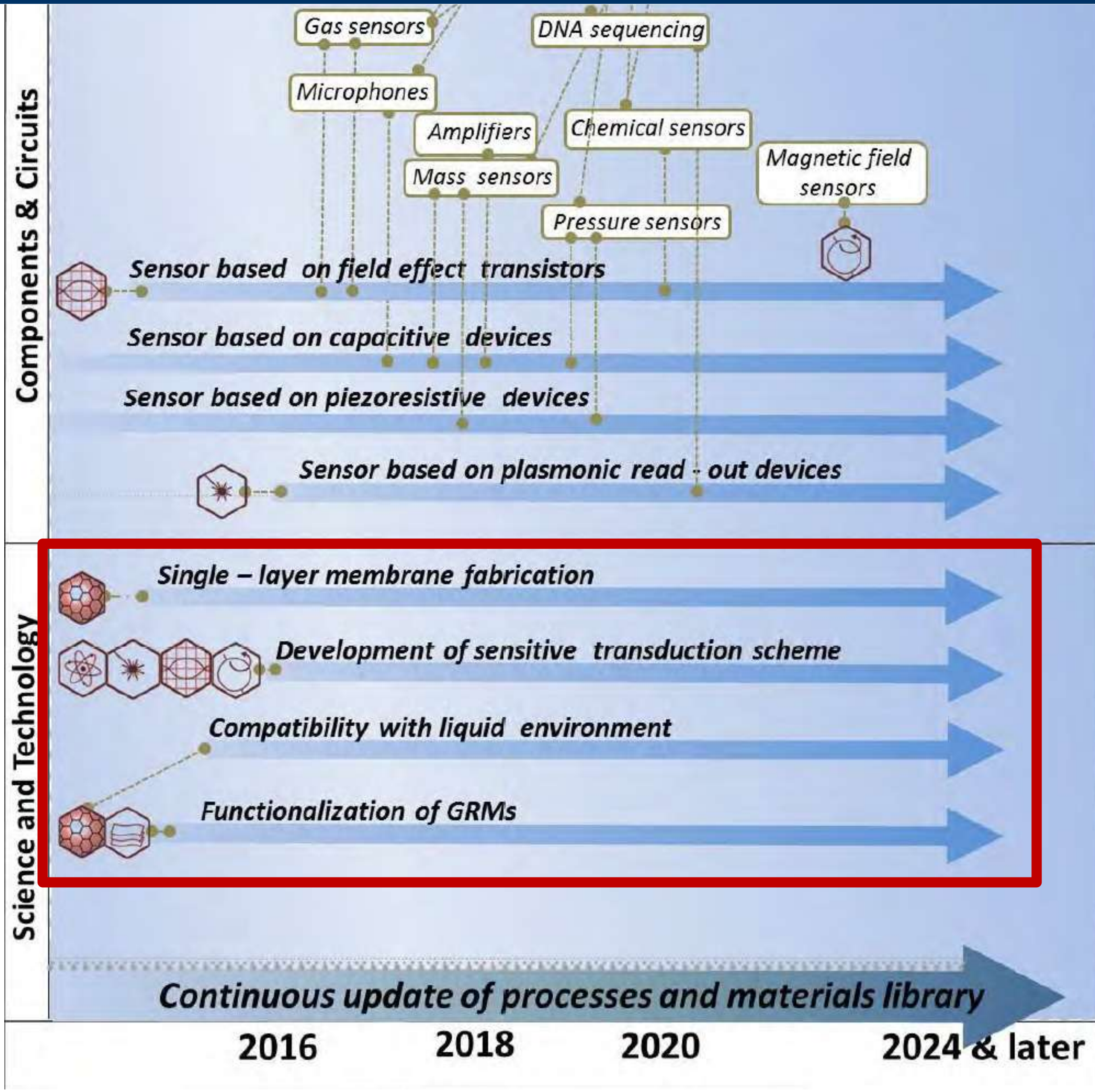
graphene (graphene-related materials)



devices

Graphene Roadmap, Ferrari et al., Nanoscale (2015)

graphene (graphene-related materials)



devices

science & tech.

Graphene Roadmap, Ferrari et al., Nanoscale (2015)

graphene (graphene-related materials)

vision….

- flexible, stretch
  (spider silk)
- biodegradable
- high energy de
- low-power, em
- analyzing air p
  traces and pro

***NOKIA Morph**: the future mobile device will act as a gateway. It will **connect users to local environment,** as well as the global **internet**. It is an attentive device that **shapes according to the context**. It can change its form from rigid to **flexible** and **stretchable**.*

http://research.nokia.com/morph - link broken in 2015

Ferrari et al., Nanoscale (2015)

- **general aspects on sensing**
  sensitivity, specificity
  overview of transducers

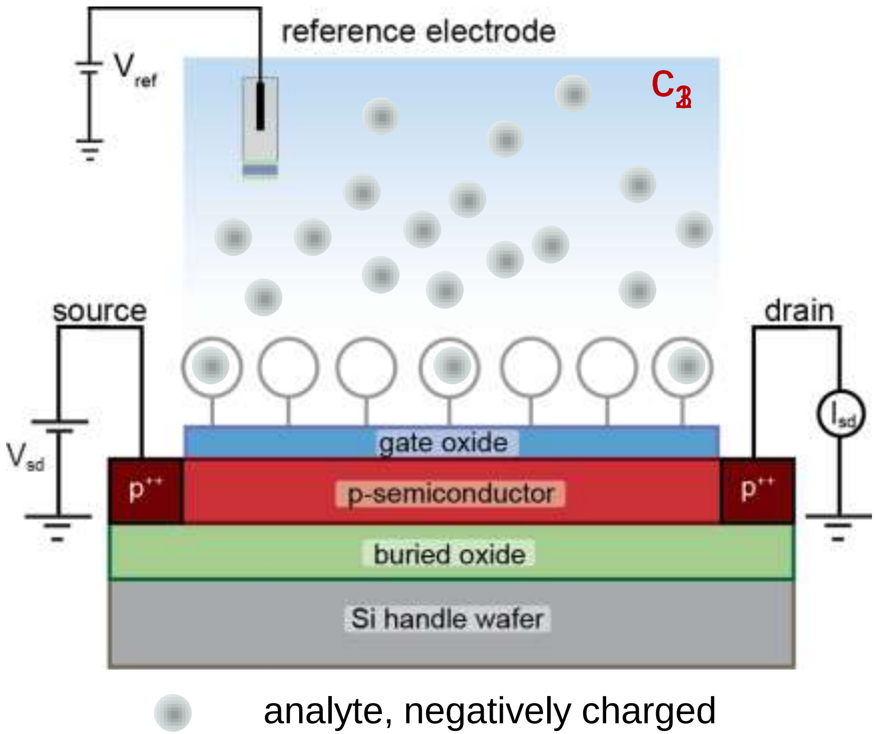
- **field effect transistors (FETs) as charge sensors**
  MOSFET, graphene and GFET

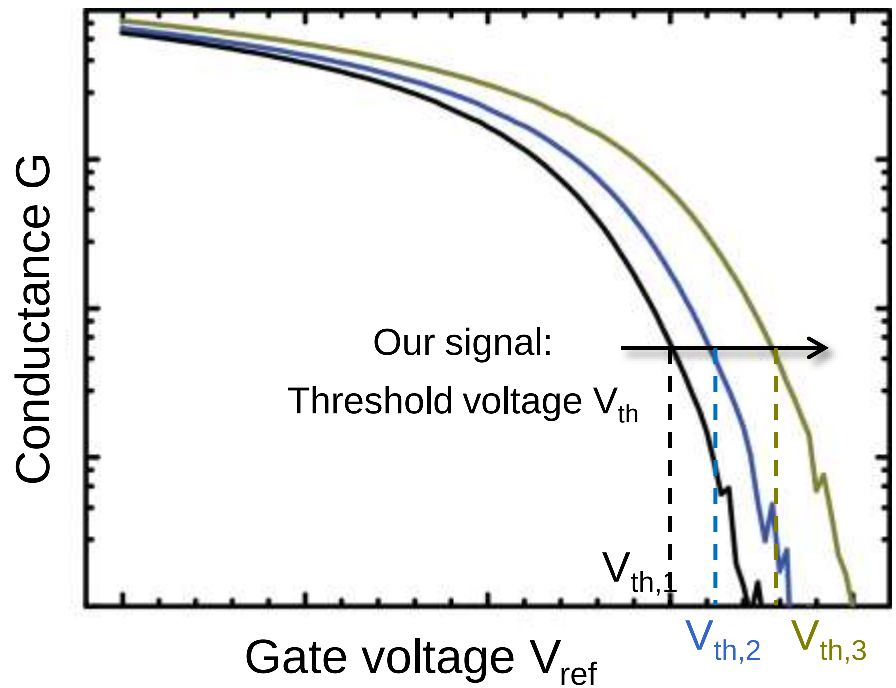
Examples

- Ion sensitive field-effect transistors (ISFETs) for pH, ionic and biochemicals detection

- Nanopores for sequencing

ISFETs as potentiometric biochemical sensors





Theoretical limit: Nernst response

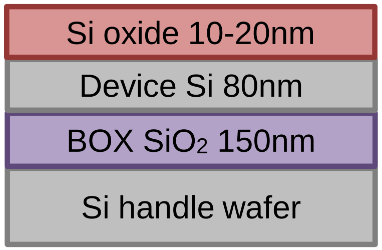
$$\Delta V_{th} = V_{th,2} - V_{th,1} = 2.3\frac{kT}{e}\log_{10}(\frac{c_2}{c_1}) \approx 59.6\,\mathrm{mV}\cdot\log_{10}(\frac{c_2}{c_1})$$

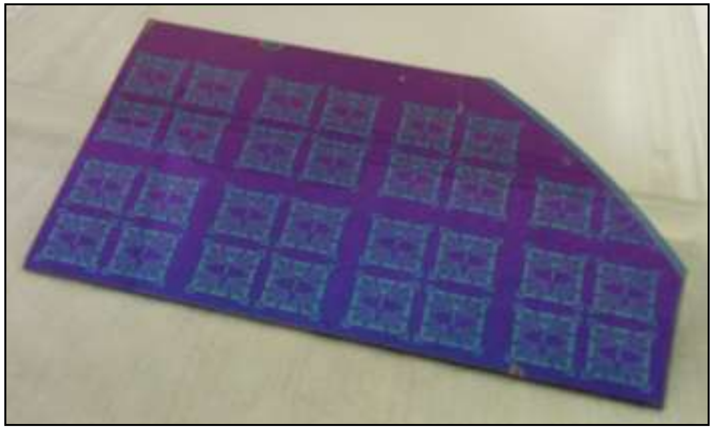
- converts a chemical reaction into an electrical signal
- signal : change in current / shift in threshold voltage

see e.g. Bergveld, IEEE Trans. Biomed. Eng (1970); Bergveld, Sensors & Actuators (2003), IEEE Sensor Conference (2003)

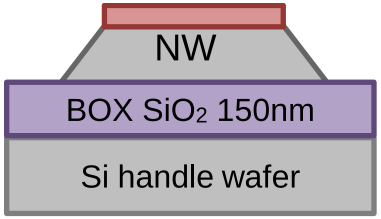
nanowire fabrication: SOI process

p-type (100) SOI

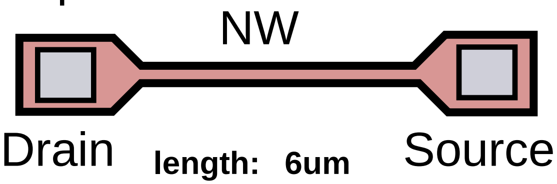




ALD oxide 10-20nm: **Al_2O_3** or **HfO_2**



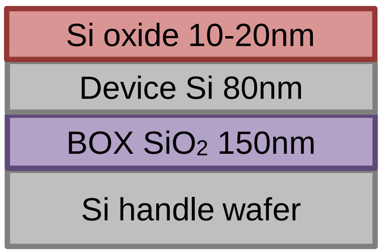
Top view:

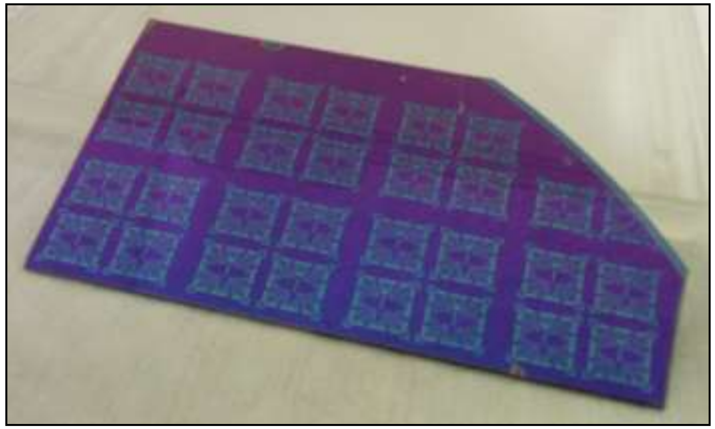


length: 6um
width: 100 nm -1um

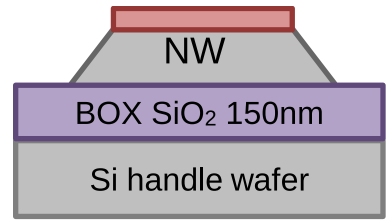
Collaboration with PSI: K. Bedner, J. Gobrecht *et al.*

p-type (100) SOI

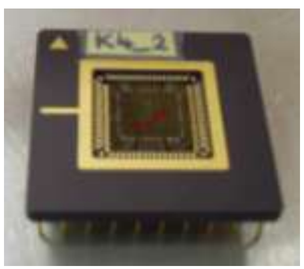


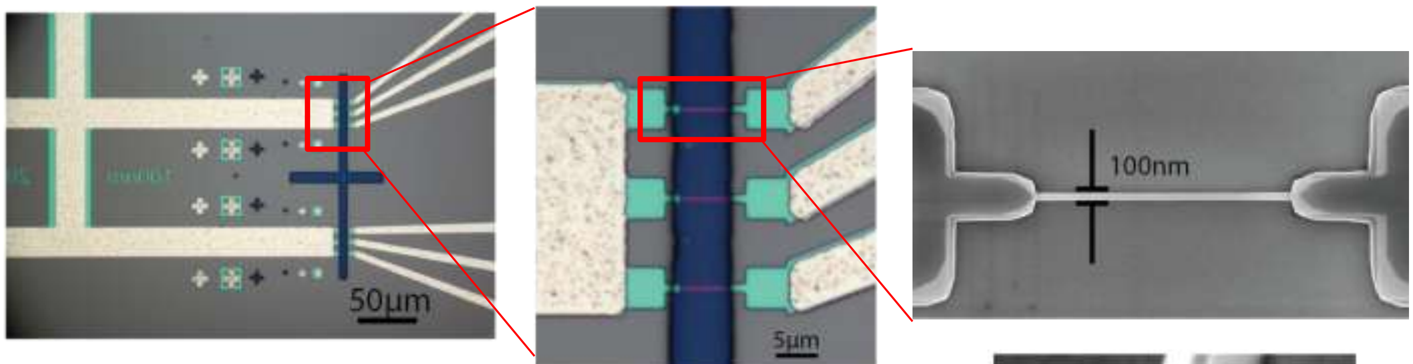


ALD oxide 10-20nm: **Al_2O_3** or **HfO_2**



chip carrier

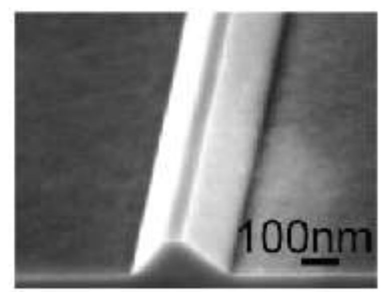




ALD layer with BF_2^+ ion implantation

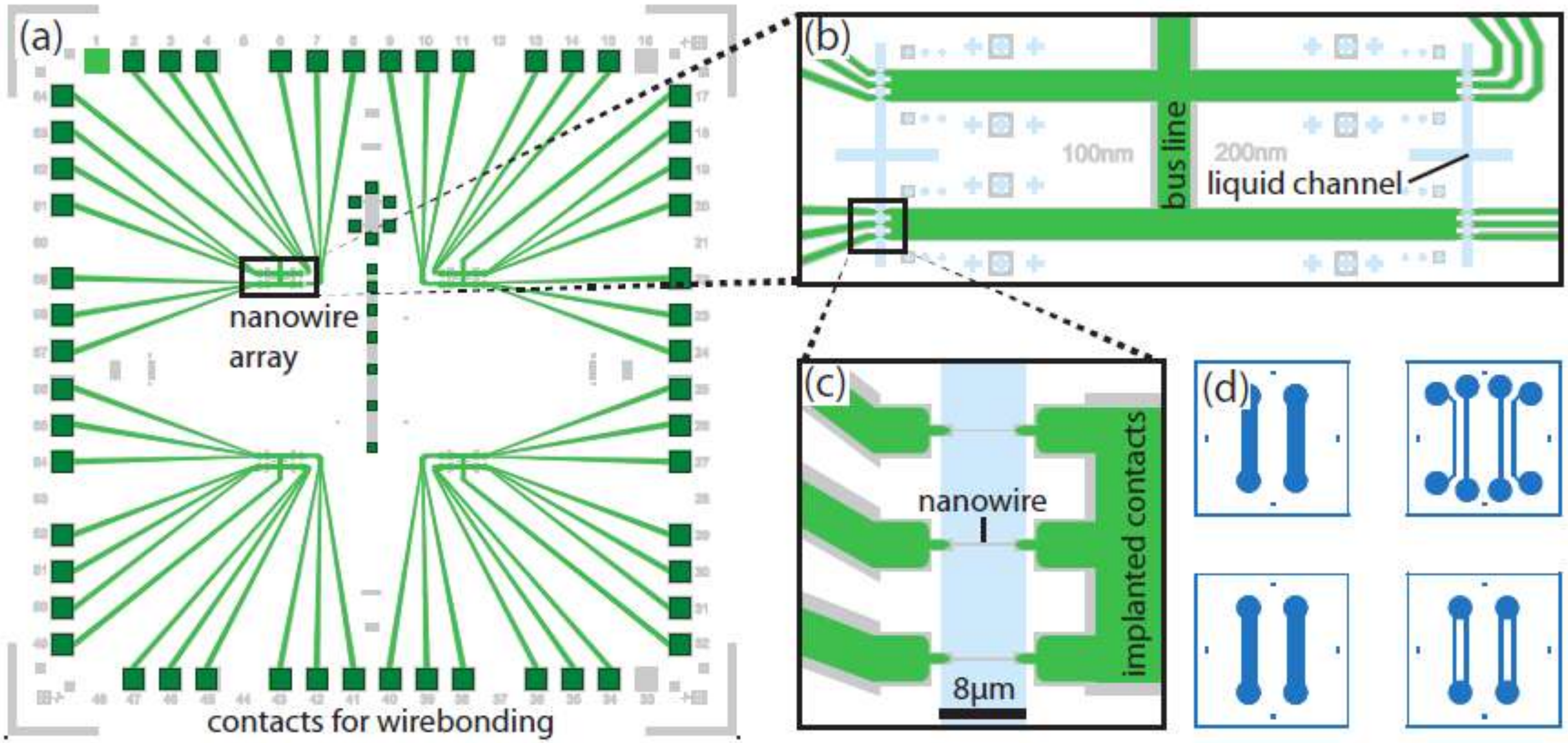
Liquid channel — Metal lines (Al)

Si nanowire with ALD layer — SU-8



PSI: K. Bedner, J. Gobrecht *et al.*

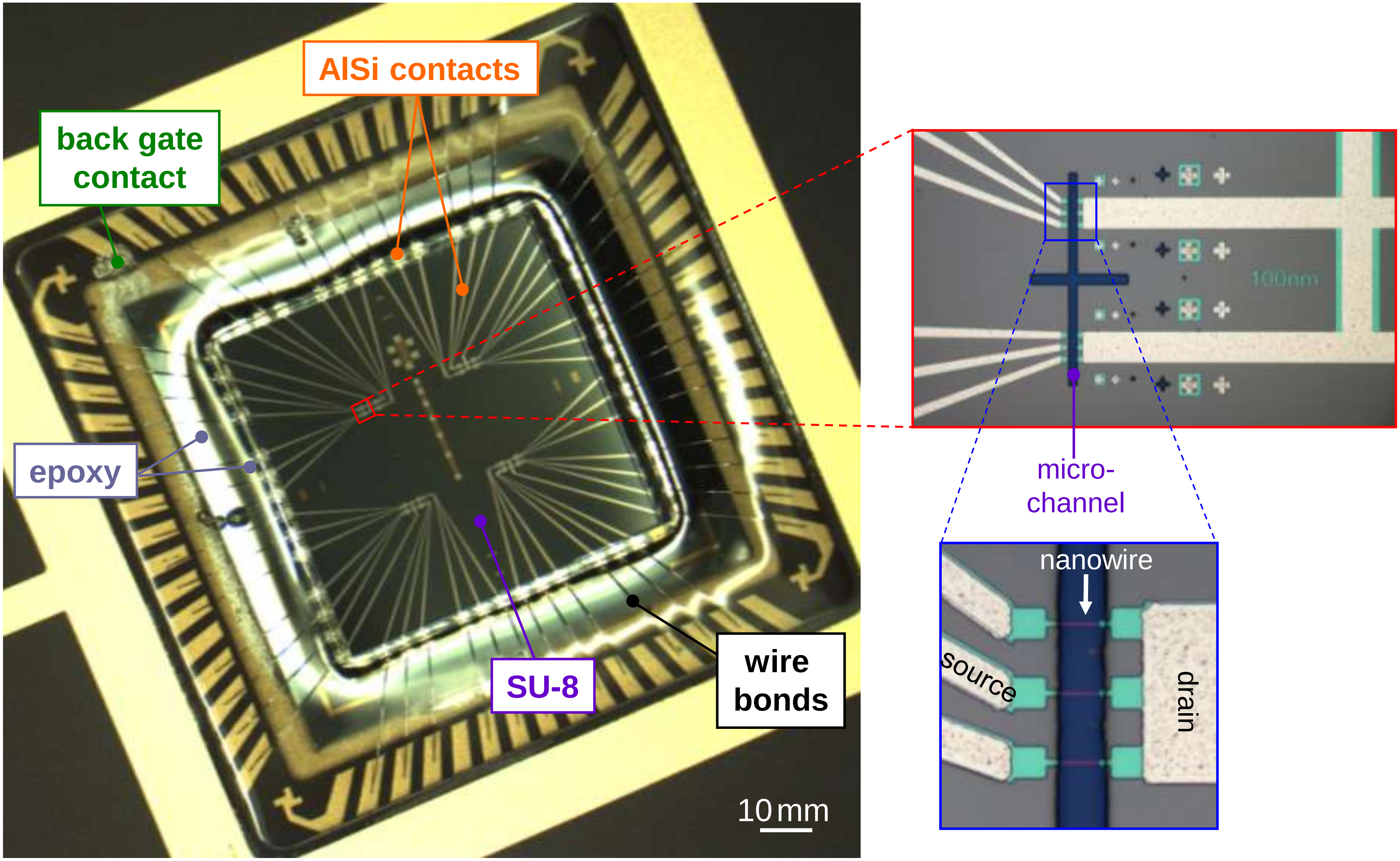
sensor device layout



- **48 individually addressable nanowires in 4 separated arrays**
- ***length*: 6um**, ***width*** (top)**: 100nm-1um,** ***thickness*** (device layer)**: 80nm**
- **fluidic channels with different designs** (functionalization, measurement)

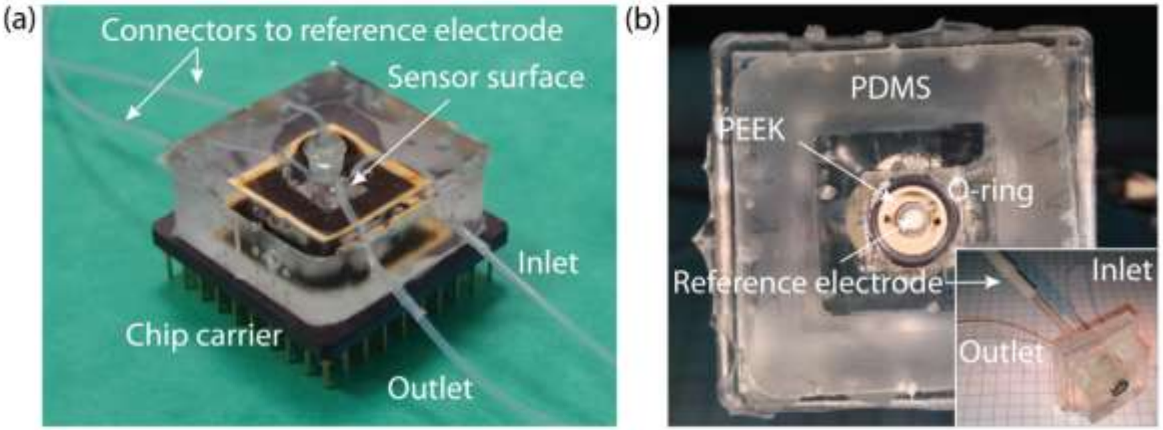
M. Wipf, R. Stoop *et al.*

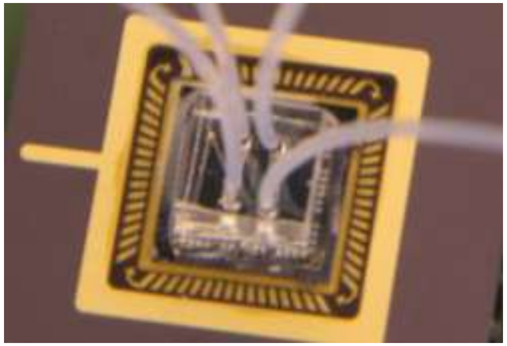
sensor device layout

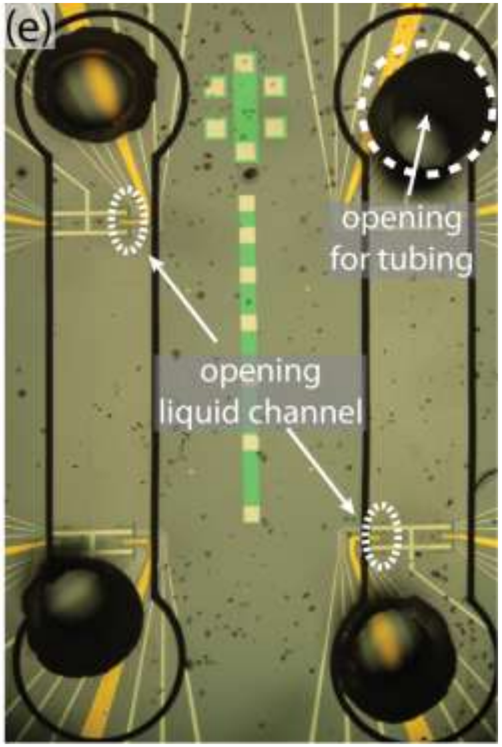


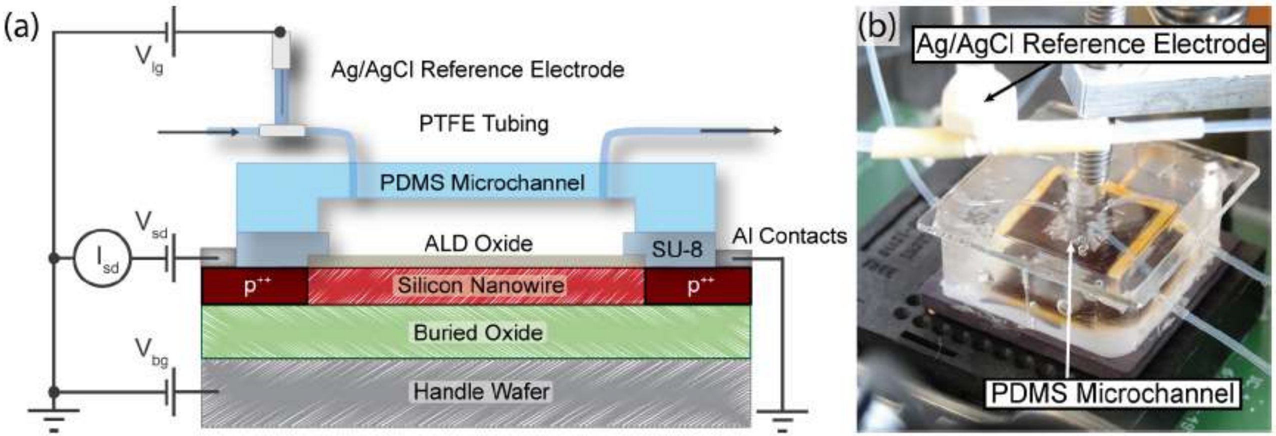
PSI: K. Bedner, J. Gobrecht *et al.*

fluidics and measurement setup









M. Wipf, R. Stoop, K. Bedner, *et al.*

characterization of SiNW FET

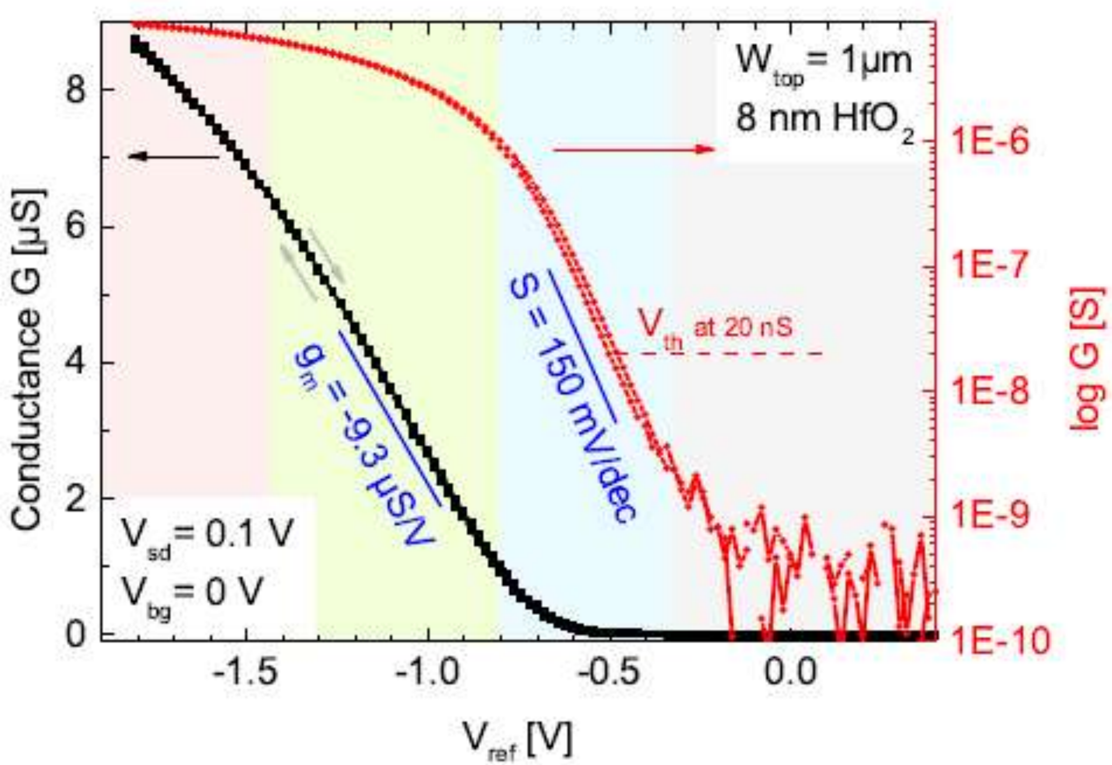
Transfer curve G vs V_{ref}

1μm wide SiNW
8nm HfO_2 gate oxide

pH 3 buffer solution
$V_{sd} = 0.1V$, $V_{bg} = 0V$

NB: back and forth traces: negligible hysteresis

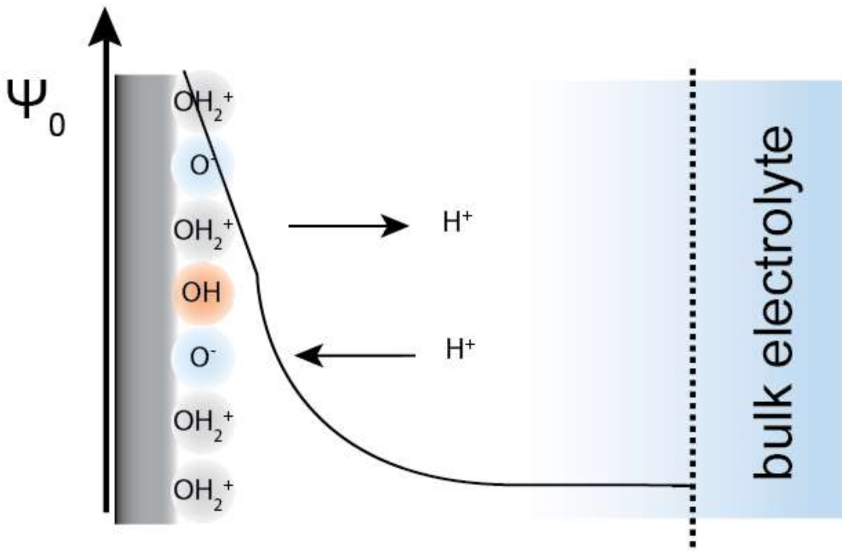
operation regimes



M. Wipf, R. Stoop *et al.*

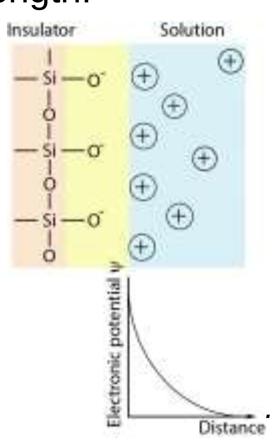
response to pH changes

Site-binding model for a metal (Me) oxide surface



surface charge density σ_0

Debye length:
$\lambda_D \propto c^{-1/2}$



$$\mathrm{MeOH} \rightleftharpoons \mathrm{MeO^-} + \mathrm{H_s^+},\ K_a = \frac{\nu_{\mathrm{MeO^-}} a_{\mathrm{H_s^+}}}{\nu_{\mathrm{MeOH}}} \quad (1)$$

K_a: eq. const. for deprotonation

$$\mathrm{MeOH_2^+} \rightleftharpoons \mathrm{MeOH} + \mathrm{H_s^+},\ K_b = \frac{\nu_{\mathrm{MeOH}} a_{\mathrm{H_s^+}}}{\nu_{\mathrm{MeOH_2^+}}} \quad (2)$$

K_b: eq. const. for protonation

total number of **surface groups N_s** (density)

$$N_s = \nu_{\mathrm{MeOH}} + \nu_{\mathrm{MeO^-}} + \nu_{\mathrm{MeOH_2^+}} \quad (3)$$

surface charge density

$$\sigma_0 = (\nu_{\mathrm{MeOH_2^+}} - \nu_{\mathrm{MeO^-}})e \quad (4)$$

from eqs 1-4

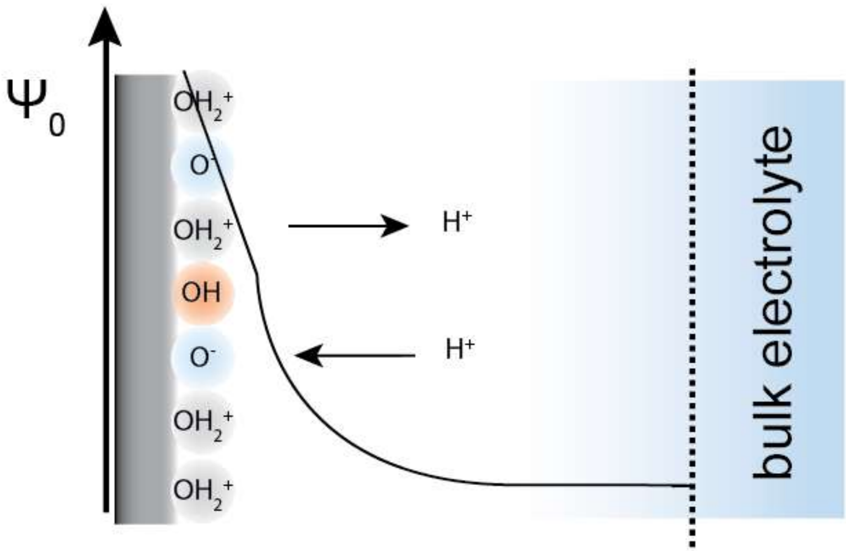
$$\sigma_0 = eN_s\left(\frac{a_{\mathrm{H_s}}^2 - K_aK_b}{a_{\mathrm{H_s}}^2 + a_{\mathrm{H_s}}K_b + K_aK_b}\right) \quad (5)$$

$a_{\mathrm{H_s^+}}$ activity of surface protons
ν density of surface groups

see e.g. P. Bergveld , Sensors and Actuators B 88 1–20 (2003)
. Knopfmacher et al., Nano Lett. (2010); A. Tarasov et al., Langmuir (2012)

response to pH changes

Site-binding model



Debye length:
$\lambda_D \propto c^{-1/2}$

surface charge density σ_0

Surface charge is screened by double layer ions

$$\sigma_0 = C_{dl}\Psi_0 = eN_s\left(\frac{a_{H_s}^2 - K_aK_b}{a_{H_s}^2 + a_{H_s}K_b + K_aK_b}\right) \quad (6)$$

Convert surface proton to bulk proton activity via surface potential ψ_0

$$a_{H_s^+} = a_{H_b^+}\exp\left(-\frac{e\Psi_0}{kT}\right) \quad (7)$$

From (6),(7): relation between ψ_0 and pH_b=-log(a_{Hb+})

$$\Delta V_{th} = -2.3\frac{k_BT}{e}\alpha\Delta pH \qquad \alpha = \frac{1}{1+C_{dl}/C_s}$$

$$\boxed{\Delta V_{th} = -59.5mV\alpha\Delta pH}$$

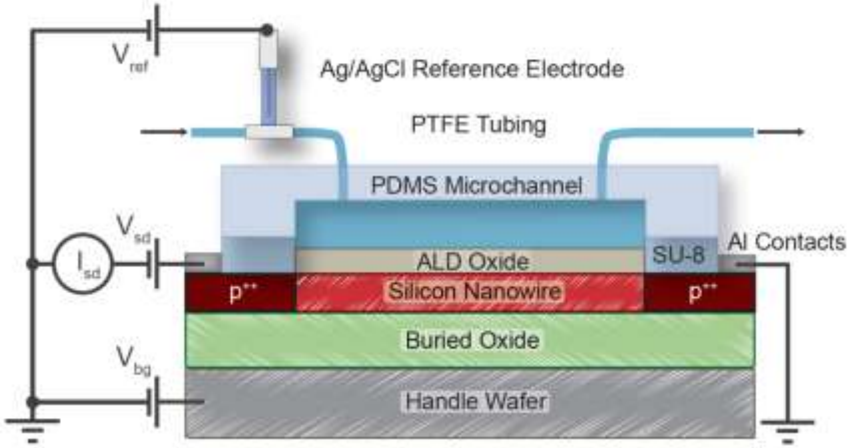
Nernst limit, case C_s » C_{dl} (α=1) at T=300K
C_s: surface buffer capacitance (nb of sites)
C_{dl}: double layer capacitance

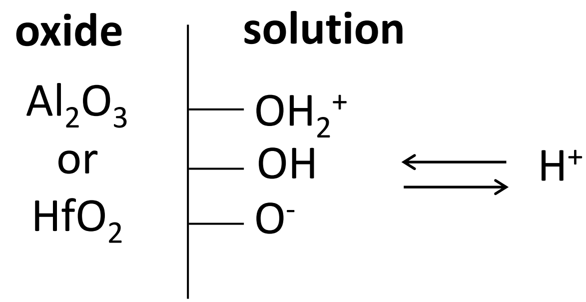
$$C_s = \frac{e^2N_s}{2.3k_bT}$$

see e.g. P. Bergveld , Sensors and Actuators B 88 1–20 (2003)

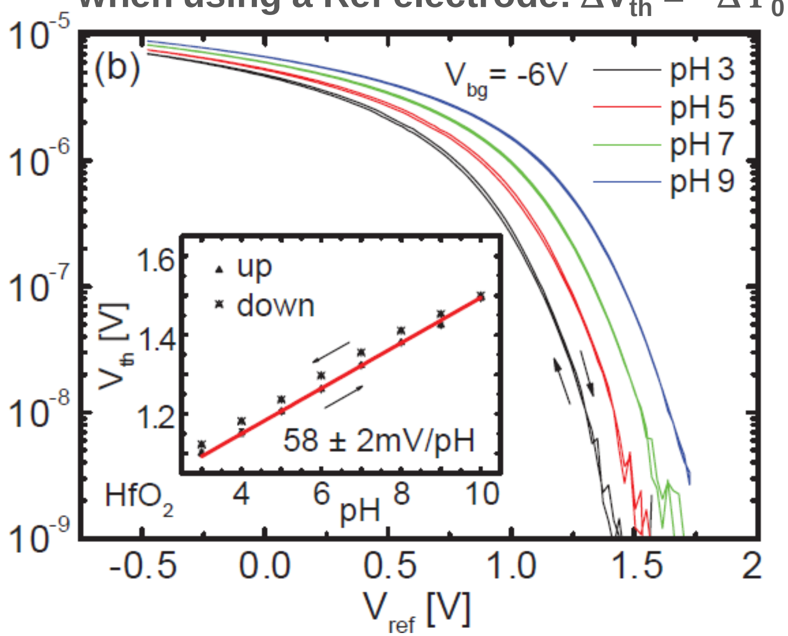
O. Knopfmacher et al., Nano Lett. (2010); A. Tarasov et al., Langmuir (2012)

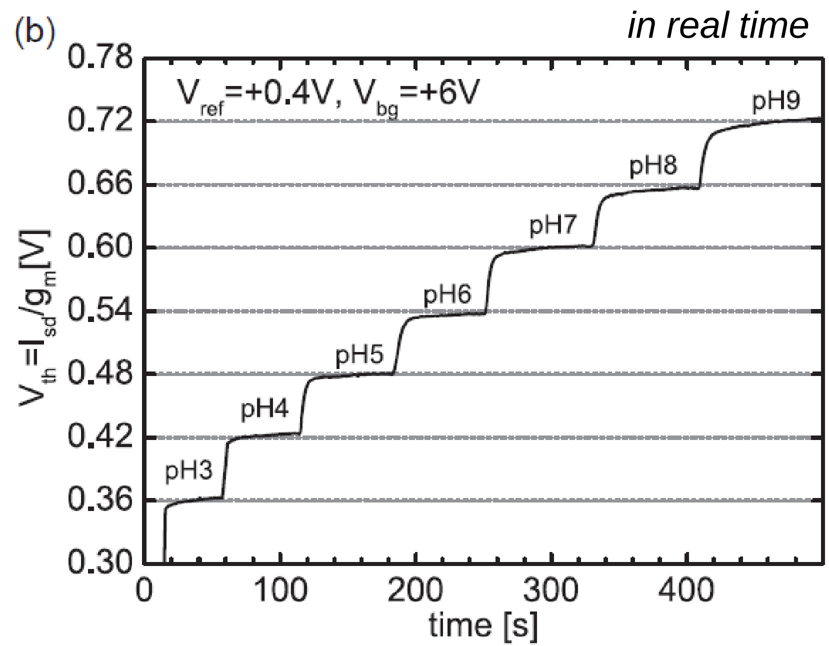
NW response: pH sensing





when using a Ref electrode: $\Delta V_{th} = - \Delta\Psi_0$





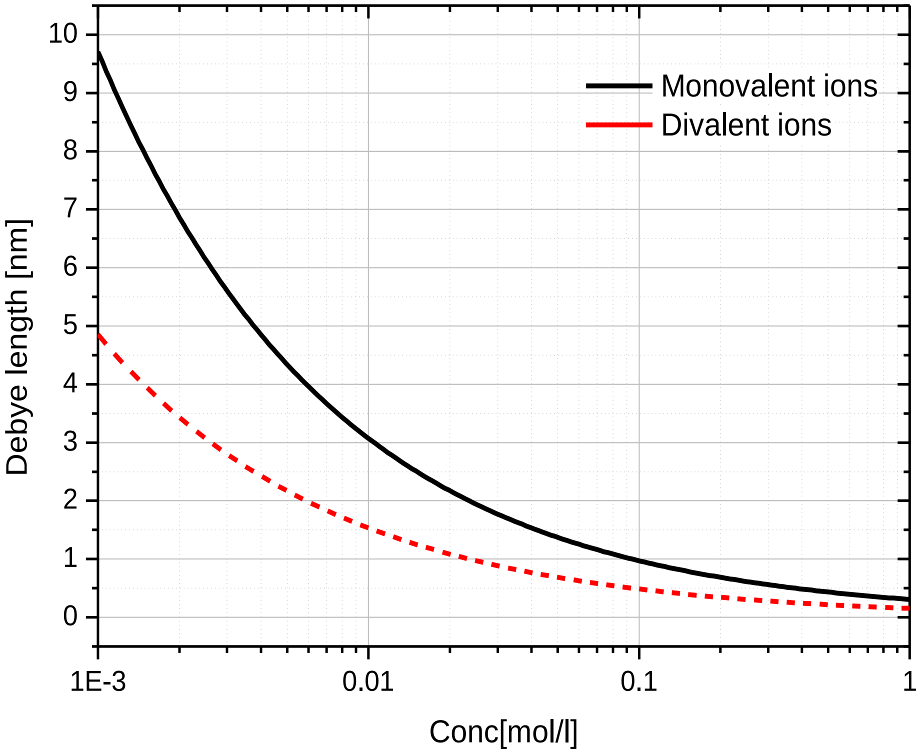
O. Knopfmacher et al., Nano Lett. (2010); A. Tarasov et al.; M. Wipf et al., ACS Nano (2013)

importance of charge screening (Debye length)

$$\lambda_D = \sqrt{\frac{\varepsilon_0 \varepsilon_r k_B T}{2 N_A e^2 I}} \qquad I = \frac{1}{2}\sum_{i=1}^{n} c_i z_i^2$$

I – ionic strength (I=c for 1:1 electrolyte)

Debye length λ_D at room temperature



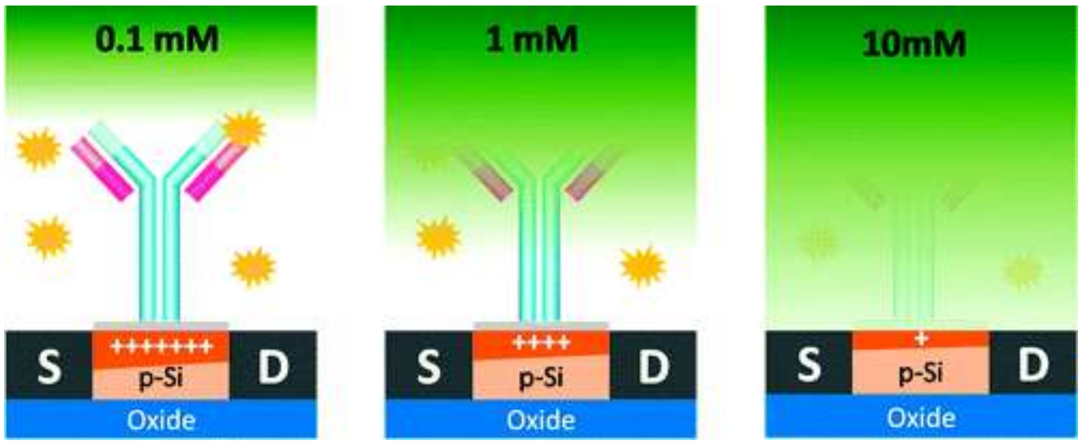
Example: PBS - Phospate buffered saline

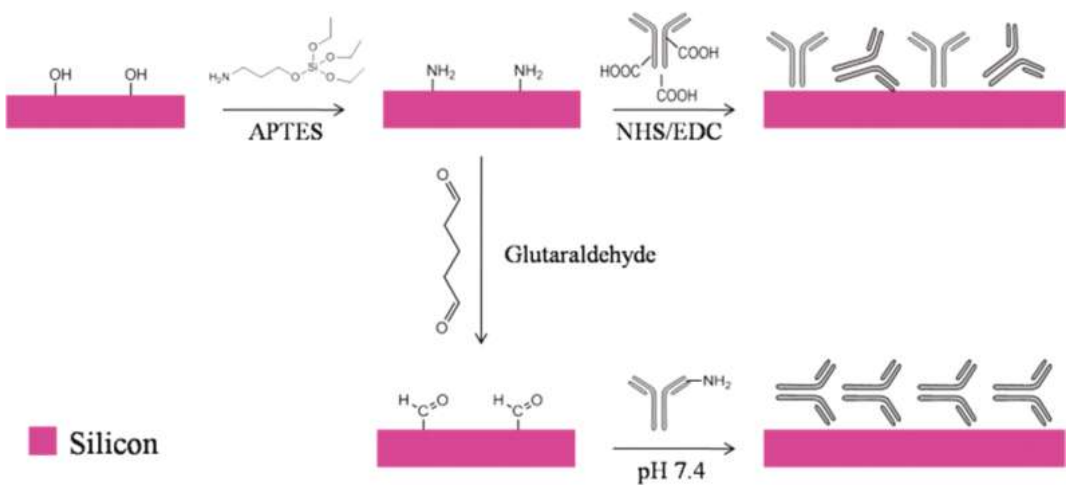
- 137mM NaCl
- 2.7mM KCl
- 12mM phosphate

→ 1 x PBS ~150mM, pH7.4

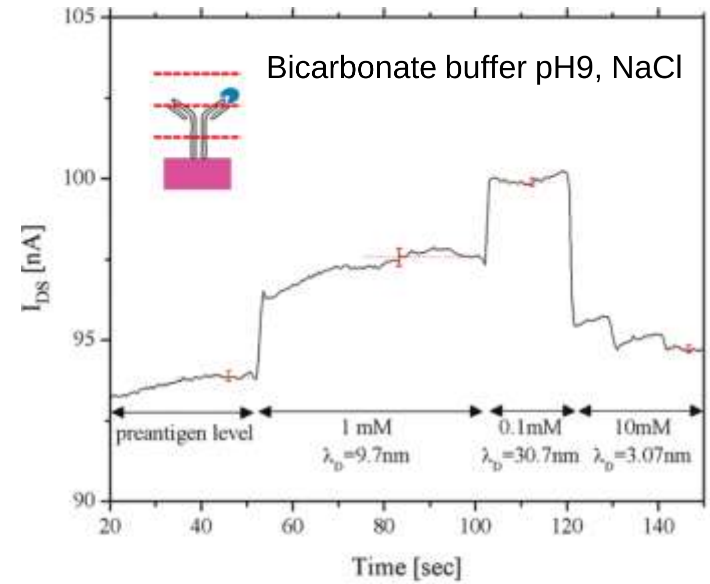
PBS dilution	Concentration [mM]	λ_D
1	150	0.7 nm
0.1	15	2.3 nm
0.01	1.5	7.3 nm

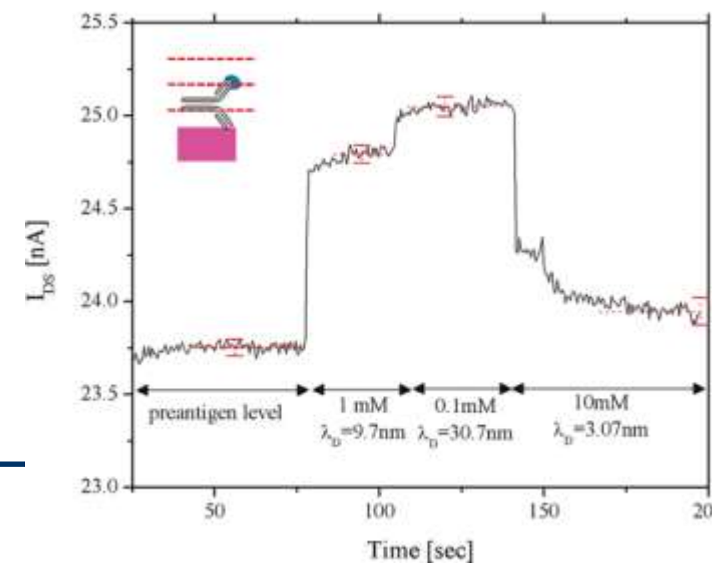
importance of charge screening (Debye length)





Anti – CA15.3 / Breast cancer biomarker



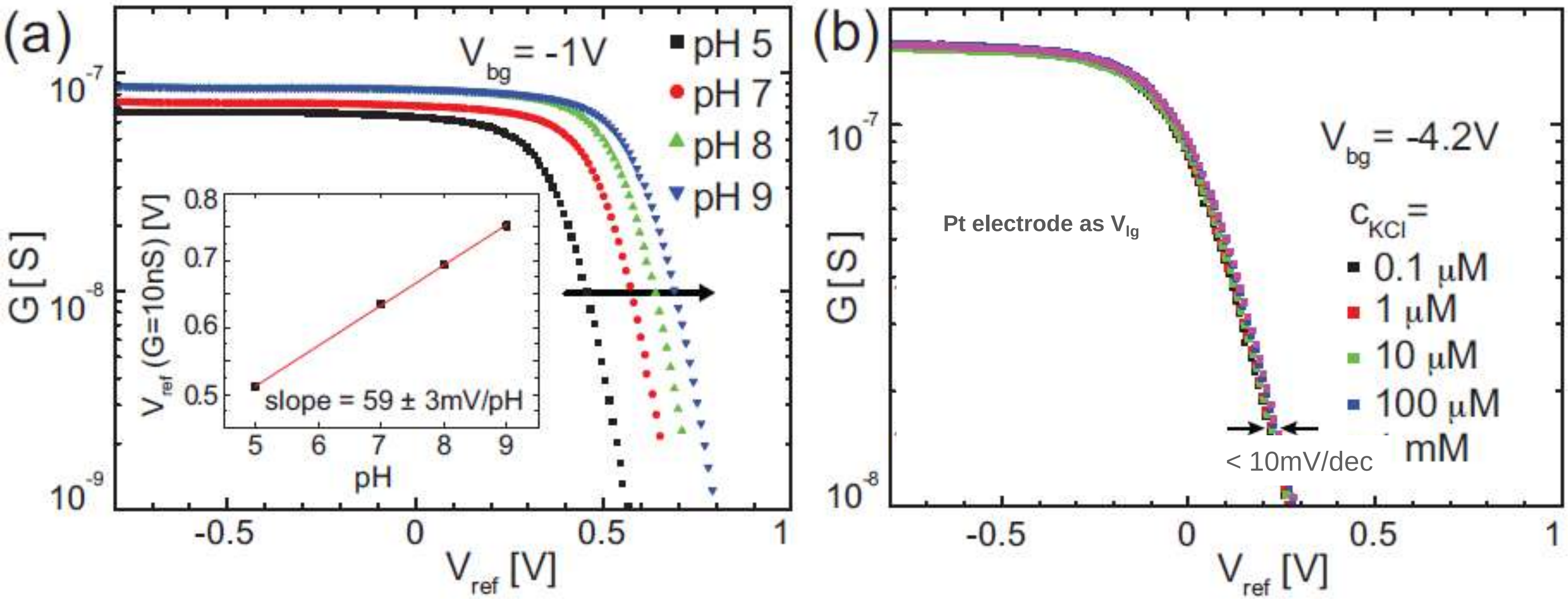


A. Vacic et al. J. Am. Chem. Soc. 2011, 133, 13886-13889

effect of an increasing background ionic concentration

varying pH

constant pH
varying ion (KCl) concentration



$$C_{dl} \propto \sqrt{c} \quad ?$$

$$\alpha = \frac{1}{1 + C_{dl}/C_s} \approx 1$$

$$\Delta V_{th} = -2.3\frac{k_B T}{e}\alpha \Delta pH$$

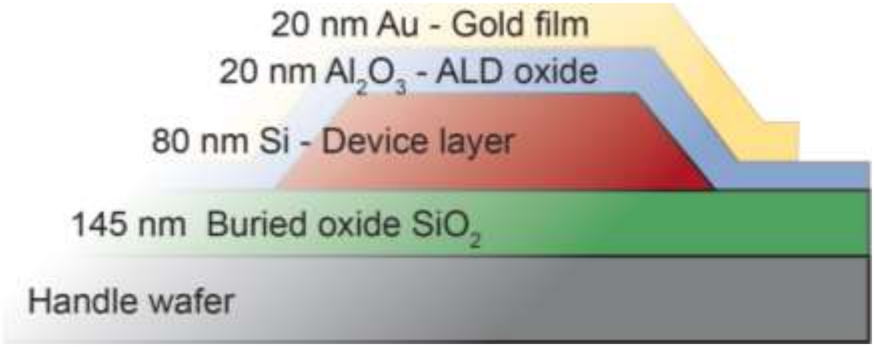
$$\Leftrightarrow C_s \gg C_{dl}$$

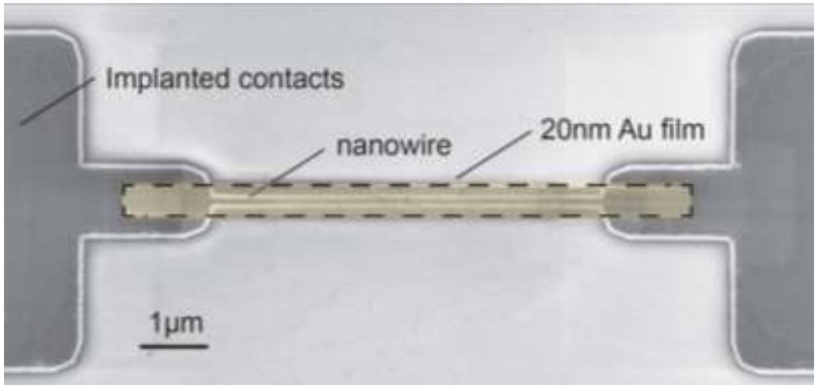
NB: not the case for SiO2

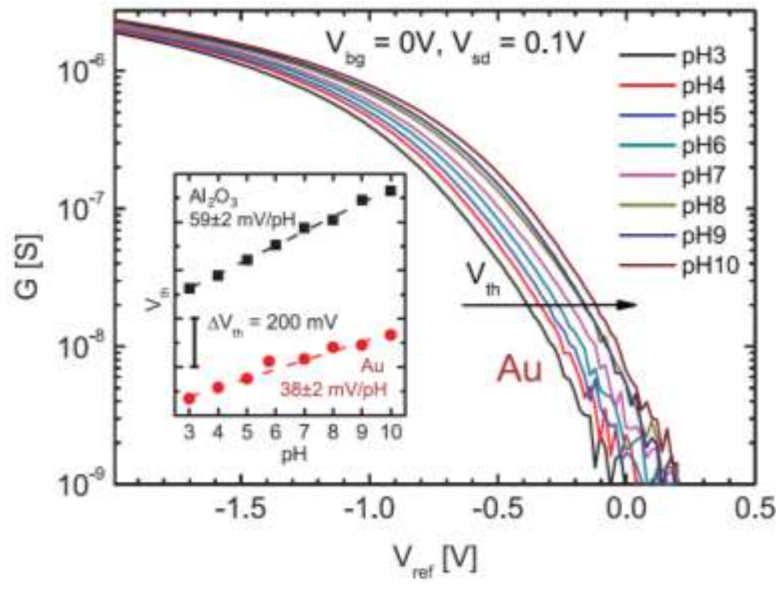
Also true for other ions, e.g.: $MgCl_2$, Na_2SO_4

O. Knopfmacher et al., ChemPhysChem (2012)

metal-coated surface: alternative functionalization possibility







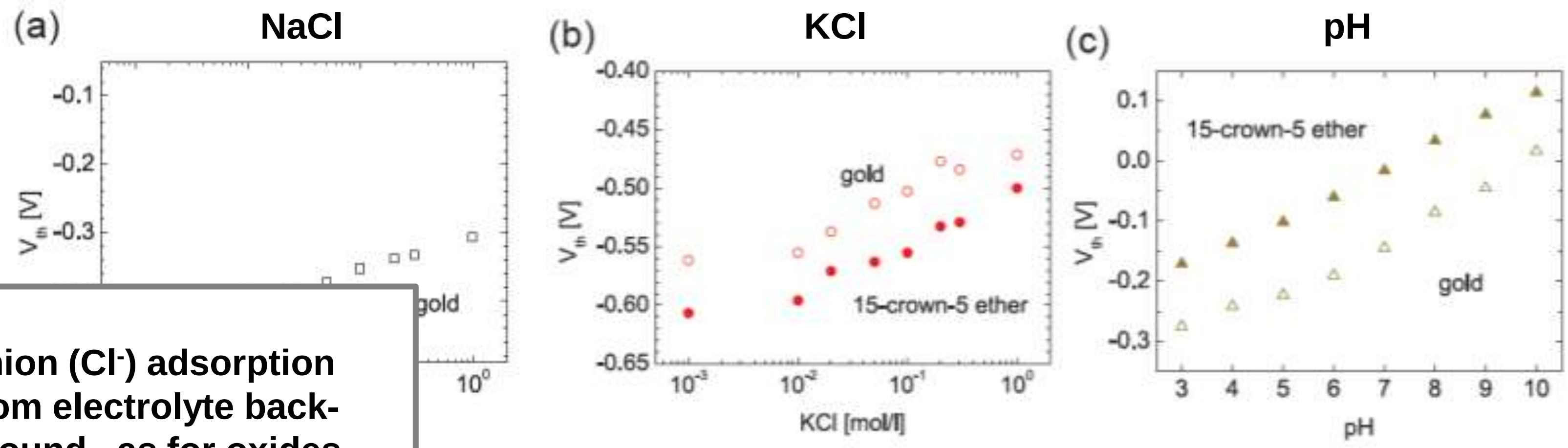
Au film: different surface chemistry

- weaker pH response of Au
  compared to oxide Al_2O_3, HfO_2

⇨ N_s ~ 2 orders of magnitude smaller compared to Al_2O_3
~1% of surface atoms oxidized

Wipf et al. ACS Nano 2013

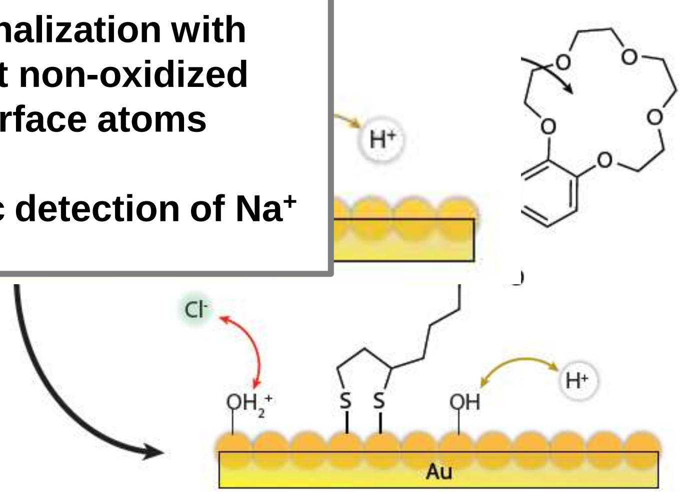
specific ion detection



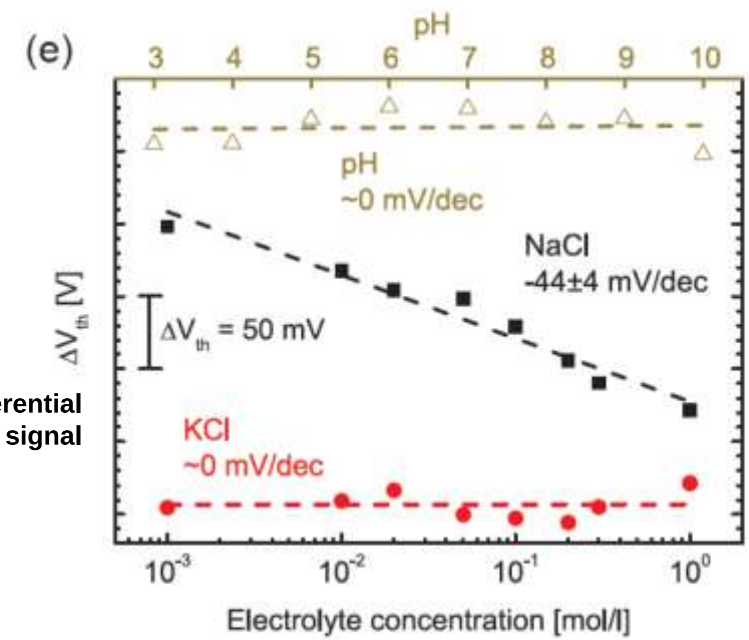
anion (Cl^-) adsorption from electrolyte back-ground, as for oxides

functionalization with thiols at non-oxidized gold surface atoms

specific detection of Na^+



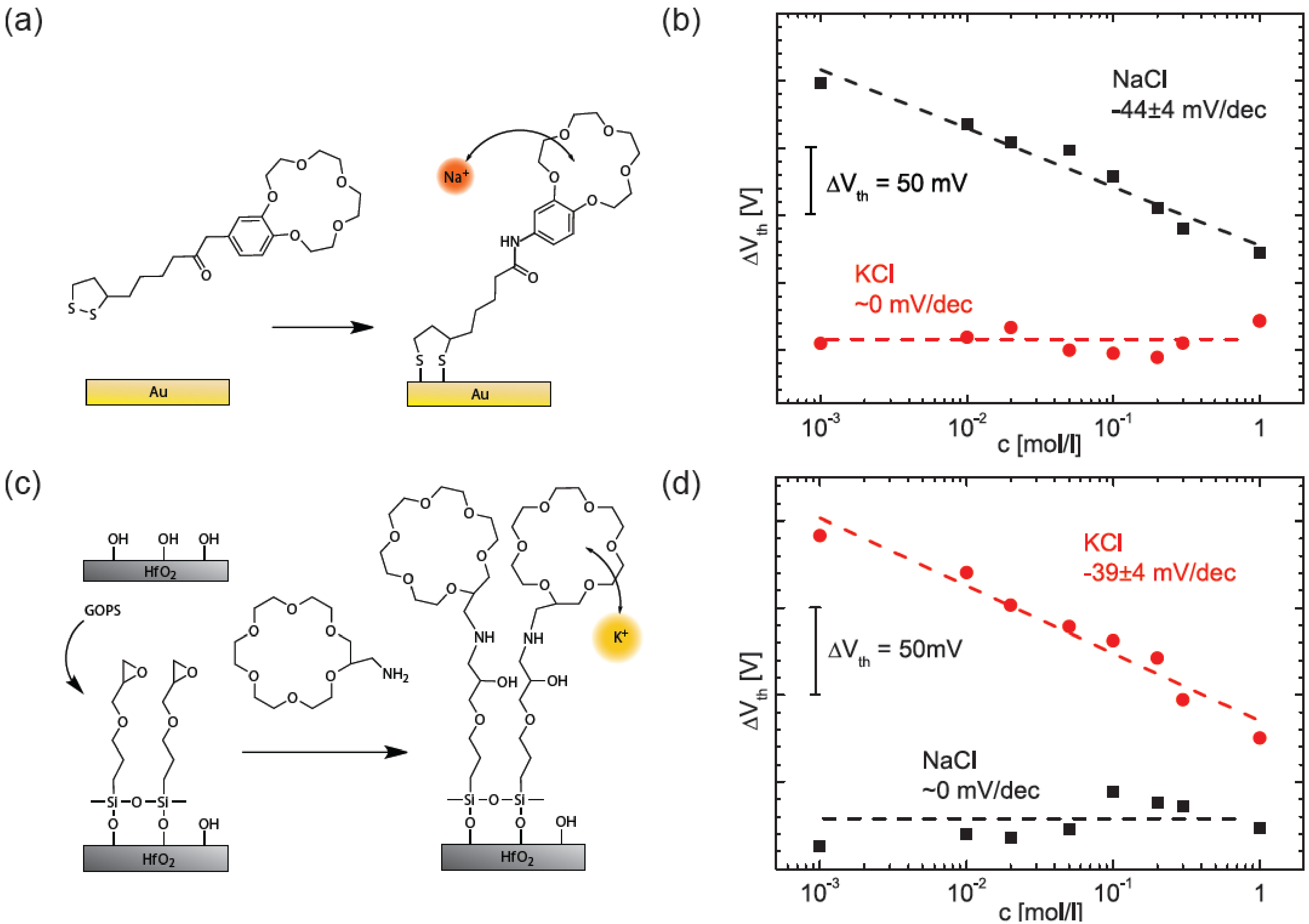
differential signal



molecule: I. Wright, C. Martin, S. Müller, E. Constable

Wipf et al. ACS Nano 2013

multiple ions detection: Au and AlO surfaces

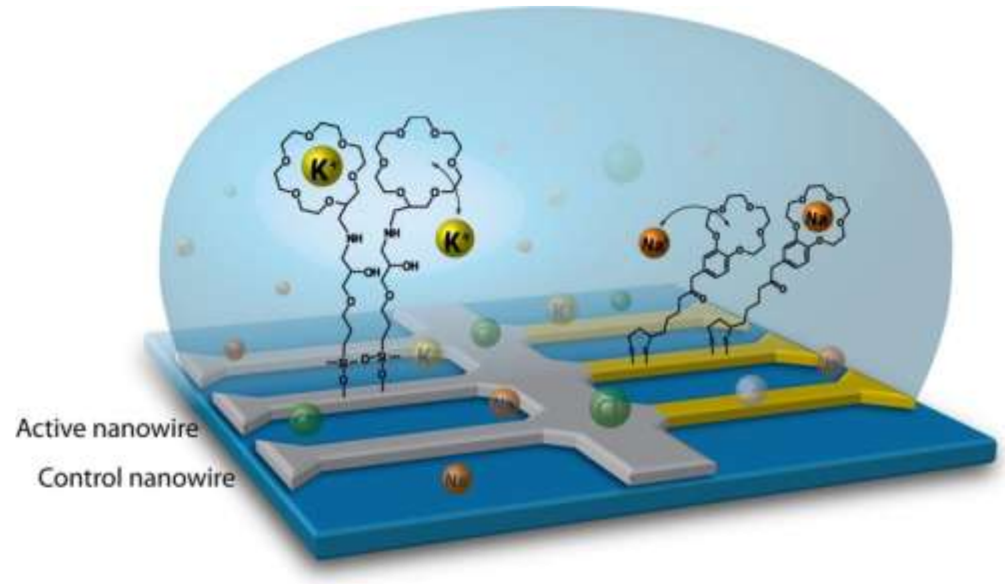


M. Wipf, R. Stoop *et al.*

multifunctional platform

ions detection

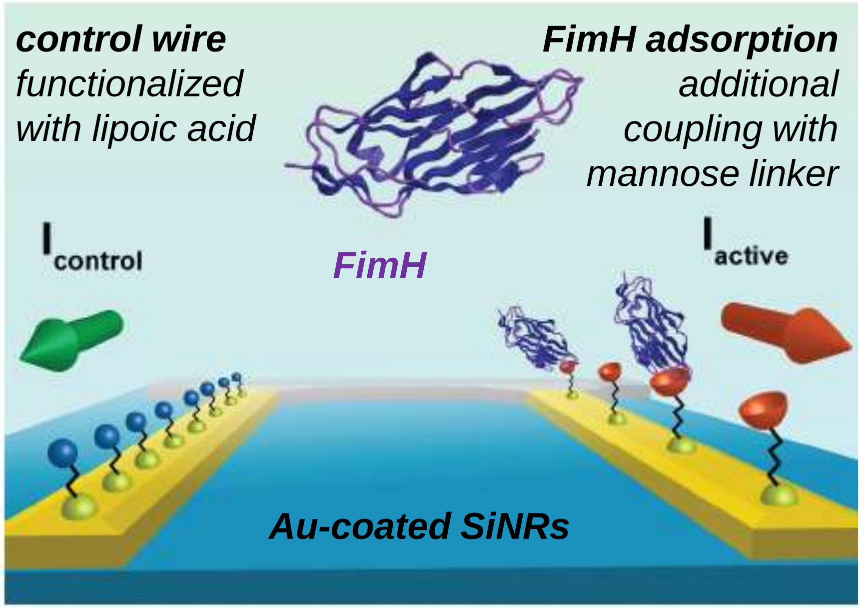
- pH, Na^+, K^+, Ca^{2+}, F^- sensing with good selectivity using appropriate receptor molecules
- *in-situ* functionalization on different surfaces with microchannels
- so far, up to 4 different functionalizations in a differential configuration on one chip



beyond ions: biomolecules kinetics

FimH detection *(bacterial lectin)*

with B. Ernst, G. Navarra, Dpt. Pharmacology, Uni Basel



lectins: carbohydrate-binding proteins involved in physiological and pathophysiological processes

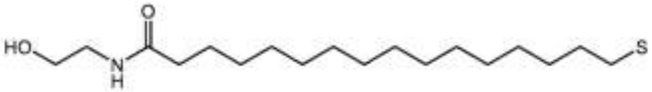
e.g.: cell-cell recognition, inflammation, infectious diseases (UTI), immune response, cancer
see Sharon, J. Biol. Chem. 2007; Oppenheimer et al., Acta Histochem. 2010

UTI therapy: high-affinity FimH antagonists
⇨ affinity screening tests: **SPR**
Ernst et al., J. Med. Chem. 2010, 2012; Chemmedchem 2012

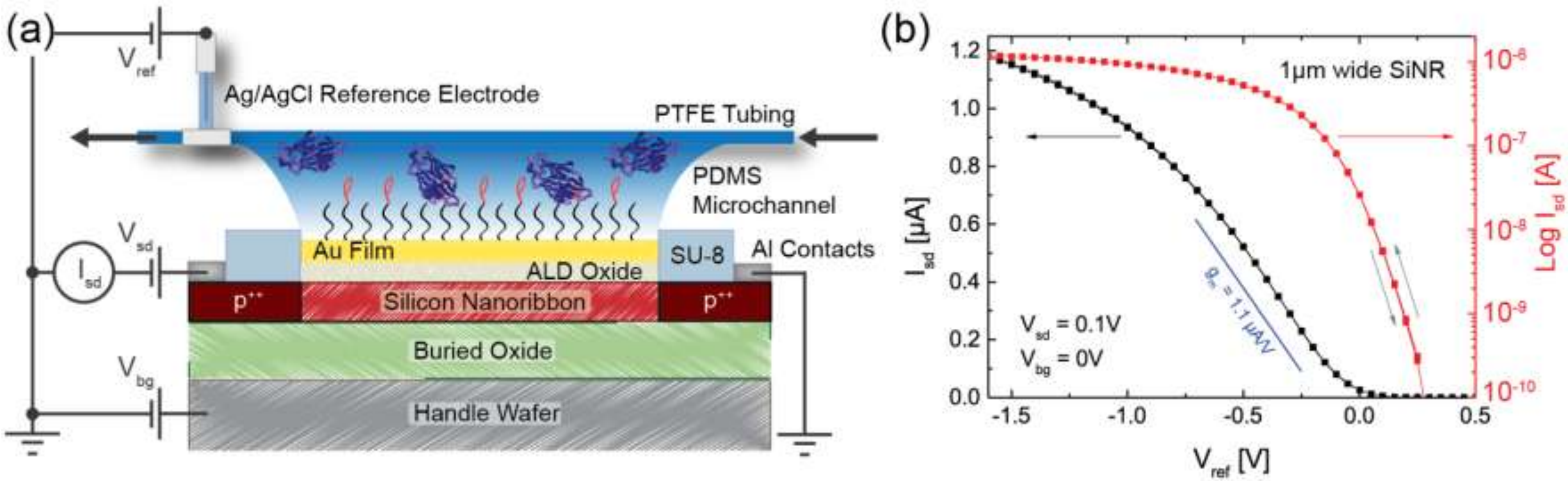
⇨ can SiNW do the job ?

functionalization
- mercaptohexadecanoic acid (MHDA)
- amine coupling for ligand

Control



beyond ions

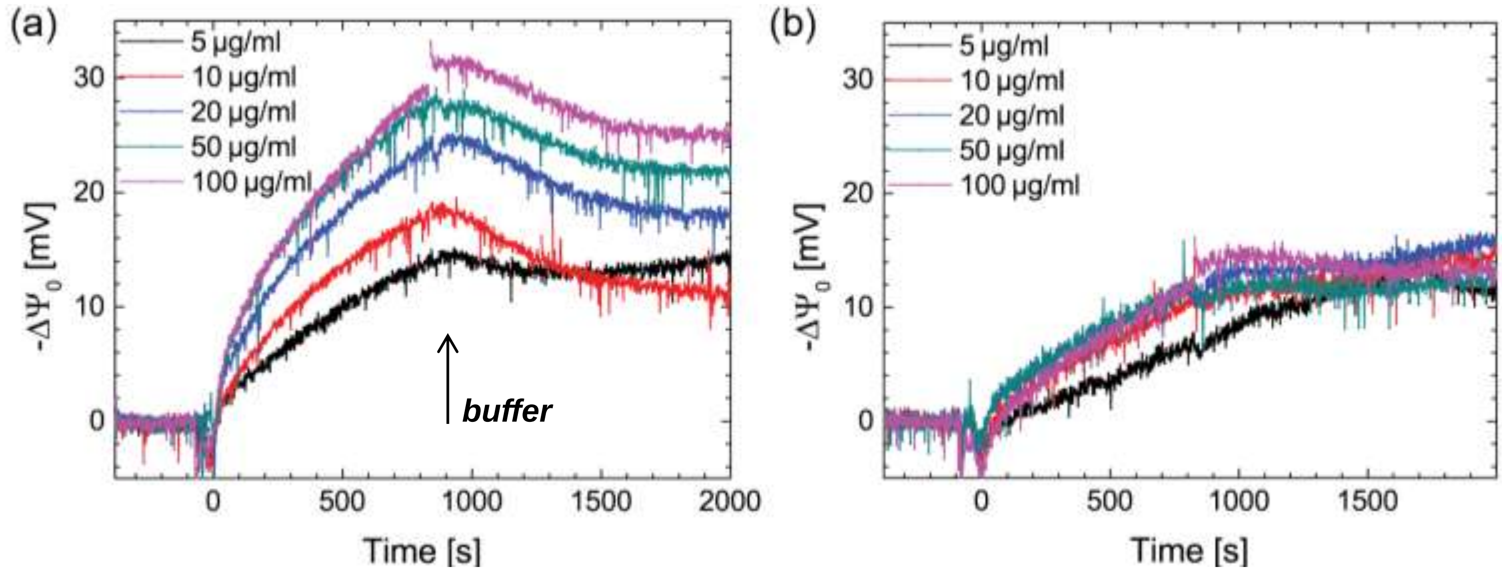


- reduced ionic strength buffer: 10mM HEPES, pH 8 (Debye length $\lambda_D \geq 3$ nm)
  ensure that the proteins are within the electrical double to affect the surface potential
- at pH 8: FimH neg. charged ⇨ I_{sd} increase upon binding
- SiNW operated in **linear region (constant transconductance g_m)**

FimH binding kinetics vs concentration

active wire *with mannose linker* ***control wire*** *(lipoic acid)*

SiNRs



SiNRs

- **non-specific adsorption** (control wire)
  lipophilic character of MHDA layer
- **signal only a function of surf. pot. change**
  site binding model see Reed et al., Nat. Nano 2012.

surface bound ligands/m2

charge per analyte

$$\Delta\Psi_0 = -\Delta V_{th} = -\frac{\Delta I_{sd}}{g_m} = \frac{q_A}{C_0}[B]_0 \times \frac{[A]}{K_D + [A]}$$

analyte bulk concentration

$$(g_m = \partial I_{sd}/\partial V_{ref})$$

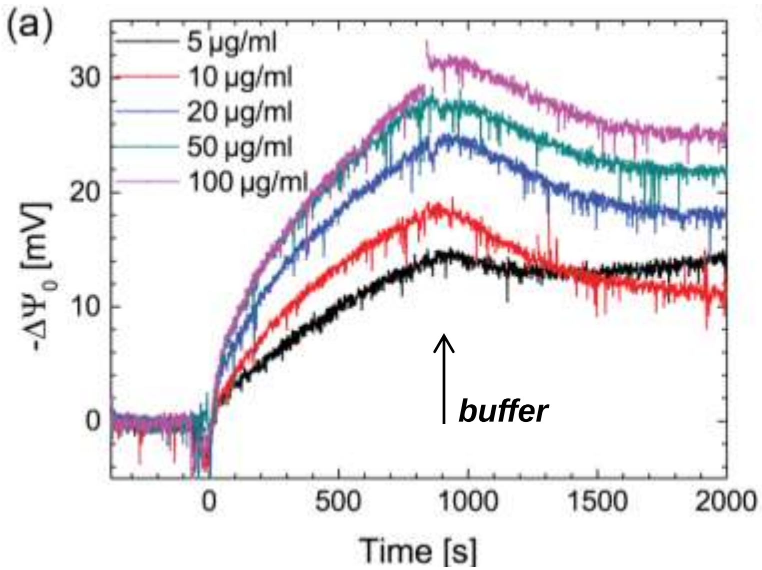
equilibrium dissociation constant

M. Wipf, R. Stoop, et al., ACS Sensors 1(6), 781 (2016)

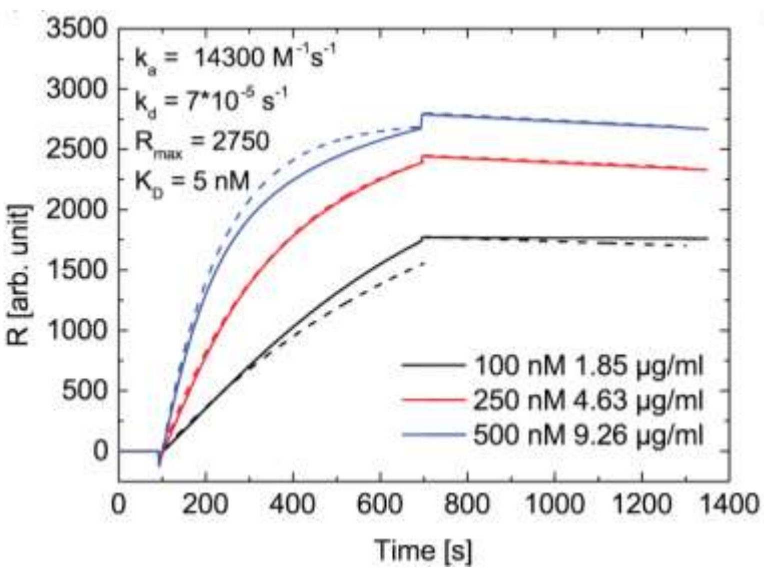
FimH binding kinetics vs concentration

active wire *with mannose linker* ***control wire*** *(lipoic acid)*

SiNRs



SPR



SiNRs

- **non-specific adsorption** (control wire)
  lipophilic character of MHDA layer
- **signal only a function of surf. pot. change**
  see Reed et al., Nat. Nano 2012.

SPR (Biacore T200, Navarra, Ernst et al., Basel)

- **saturation at lower FimH concentrations**
- **dissociation less pronounced**
  dashed lines: Langmuir kinetics
  K_D ~ 5nM is obtained.

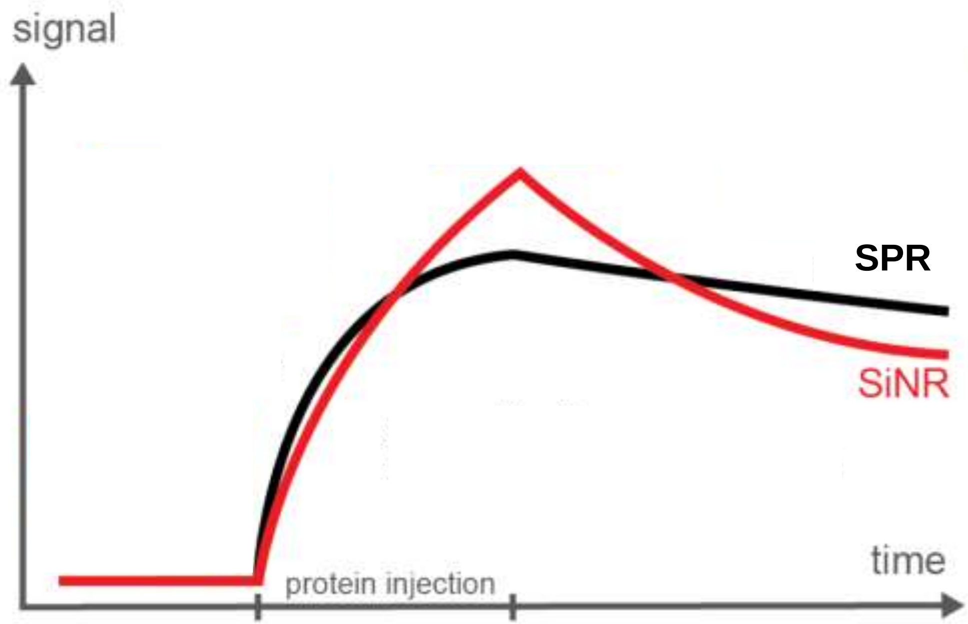
M. Wipf, R. Stoop, et al., ACS Sensors 1(6), 781 (2016)

FimH binding kinetics vs concentration

comparison SiNRs & SPR

- different **association and disso-ciation rates** (ka, kd)

NB: variations between SPR systems!
Cannon et al., Anal. Biochem. 2004; Katsamba et al., Anal. Biochem. 2006



possible origins of differences

- **flow rate at sensor surface & different surface areas**
  *- FimH-mediated bacterial **adhesion affected by shear forces***
  see e.g. Vogel et al., J. Bacteriol. 2007,. J. Biol. Chem. 2008
  ***- re-adsorption** of proteins in flow*

Fluidic channel	BioFET	Biacore
Flow rate	26 μL/min	20 μL/min
Height	100 μm	40 μm
Width	500 μm	500 μm
Length	4 mm	2.4 mm
Volume	$\approx 0.2\,\mu$L	$\approx 0.05\,\mu$L

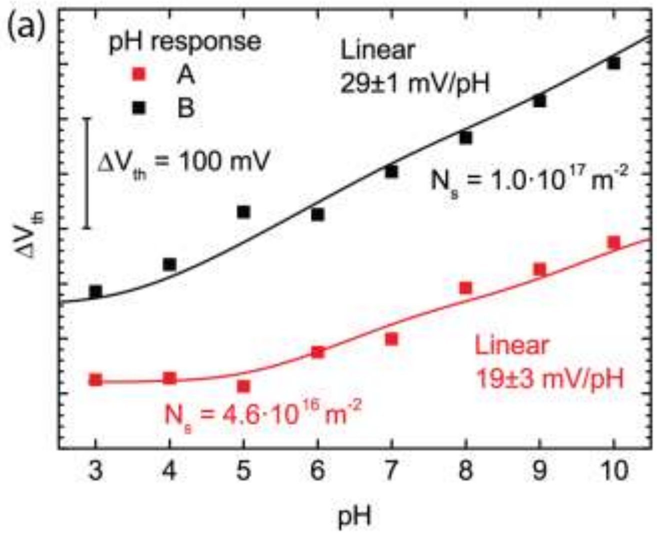
- **different effective protein concentration** *(fluidics)*

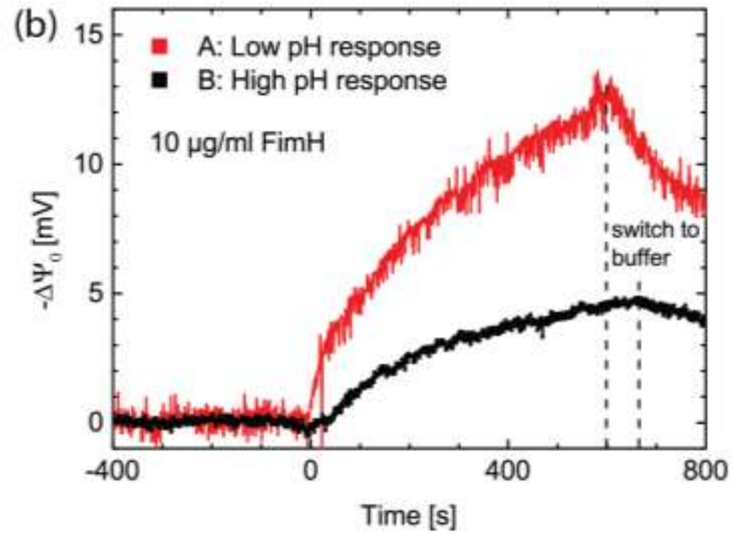
- **different sensing mechanisms: optical** (λ_{evan} ~ 300nm) **or charge** (λ_D ~ 3nm)
  ⇨ protein surface rearrangements affect SiNRs stronger than SPR, **longer time const.**

Rabe et al., Adv. Colloid Interface Sci. 2011, Roach et al., JACS 2005

M. Wipf, R. Stoop, et al., ACS Sensors (2016)

proteins detection: competing reactions



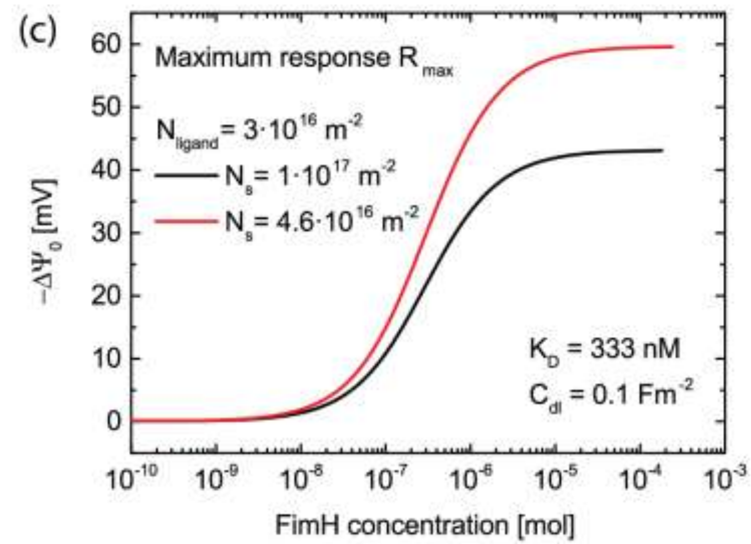


(a) pH response: gradual increase*
lines: site binding model at different hydroxyl group density *Ns (pKa = 9, pKb = 7)*

⇨ ***dependence of linear response on Ns*** *varies from 19mV/pH to 29mV/pH at pH 8*

(b) real time response to FimH, same device
increased noise at low pH: air bubbles

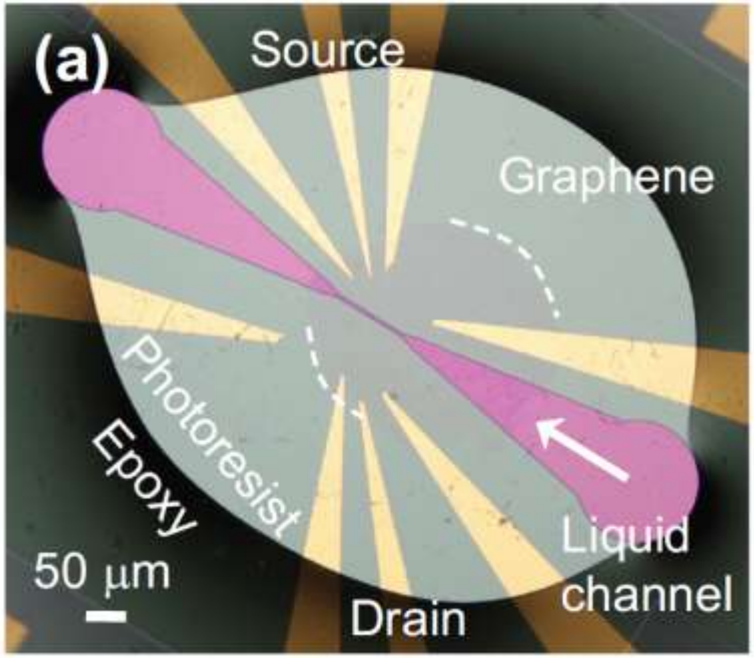
(c) site binding model for two different hydroxyl group densities *Ns*
⇨ importance of competing reactions
R. Stoop et al., Sens. & Act. B (2015)

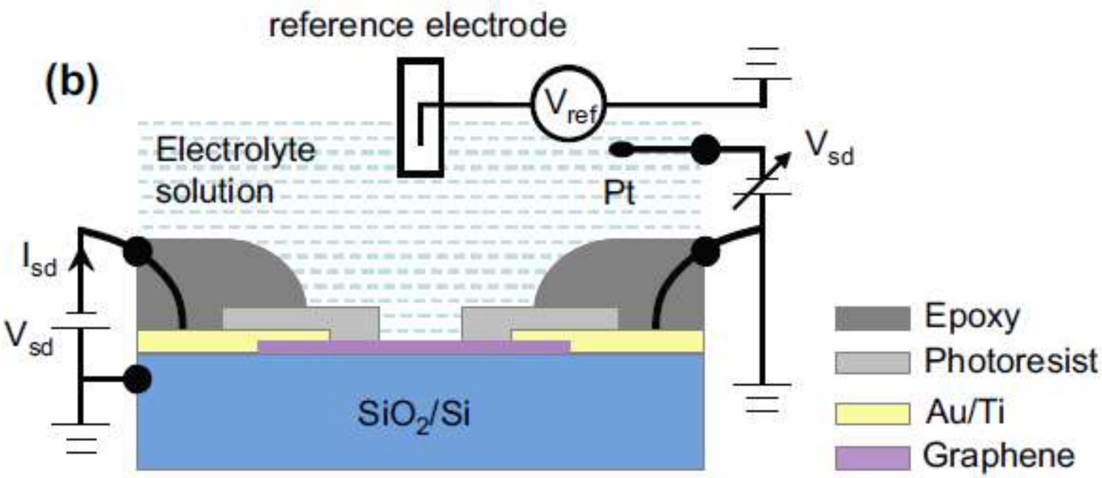


*several cleaning & functionalizing steps on the same wire: degradation of the surface state

M. Wipf, R. Stoop, et al., ACS Sensors (2016) can we do it with graphene?

Graphene ISFET





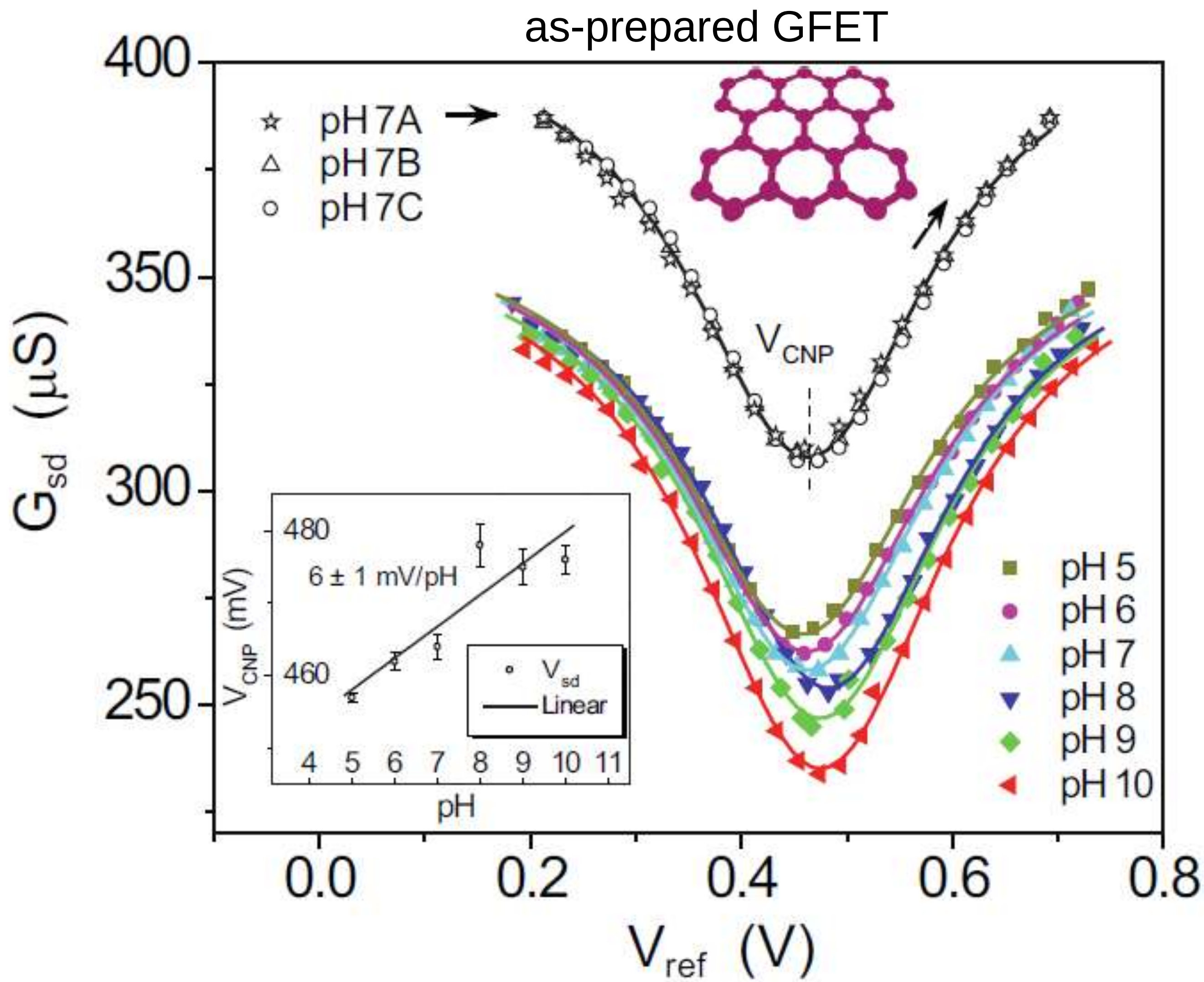
reported literature values for pH sensitivity

~12 mV/pH to ~100 mV/pH
(vs liquid gate)

Ang et al., JACS (2008)
Ristein et al., J. Phys. D: Appl. Phys. (2010)
Cheng et al., Nano Lett. (2010)
Ohno et al., Nano Lett. (2009)
Heller et al., JACS (2010)

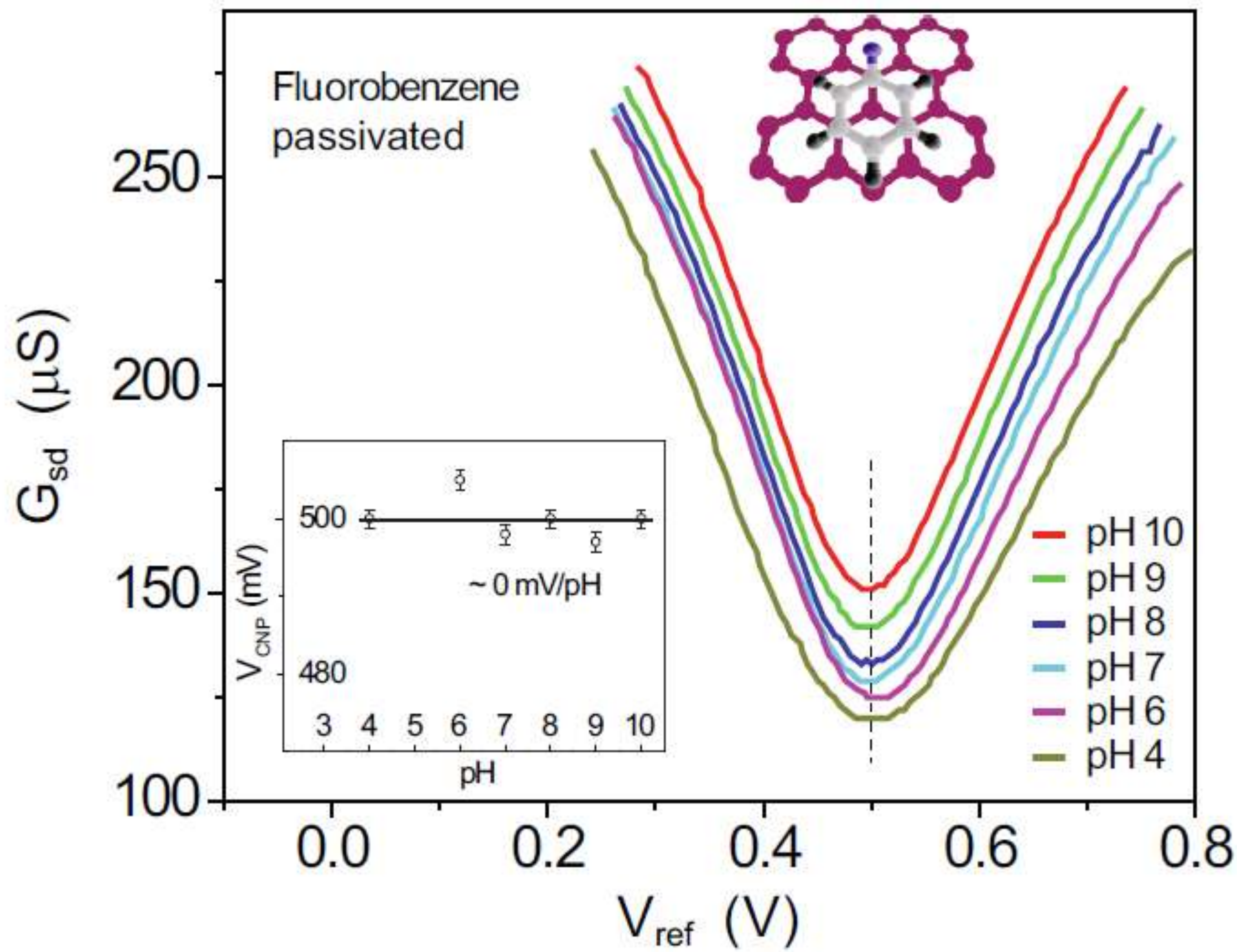
W. Fu, C. Nef et al., Nano Lett. 2011

Graphene ISFET



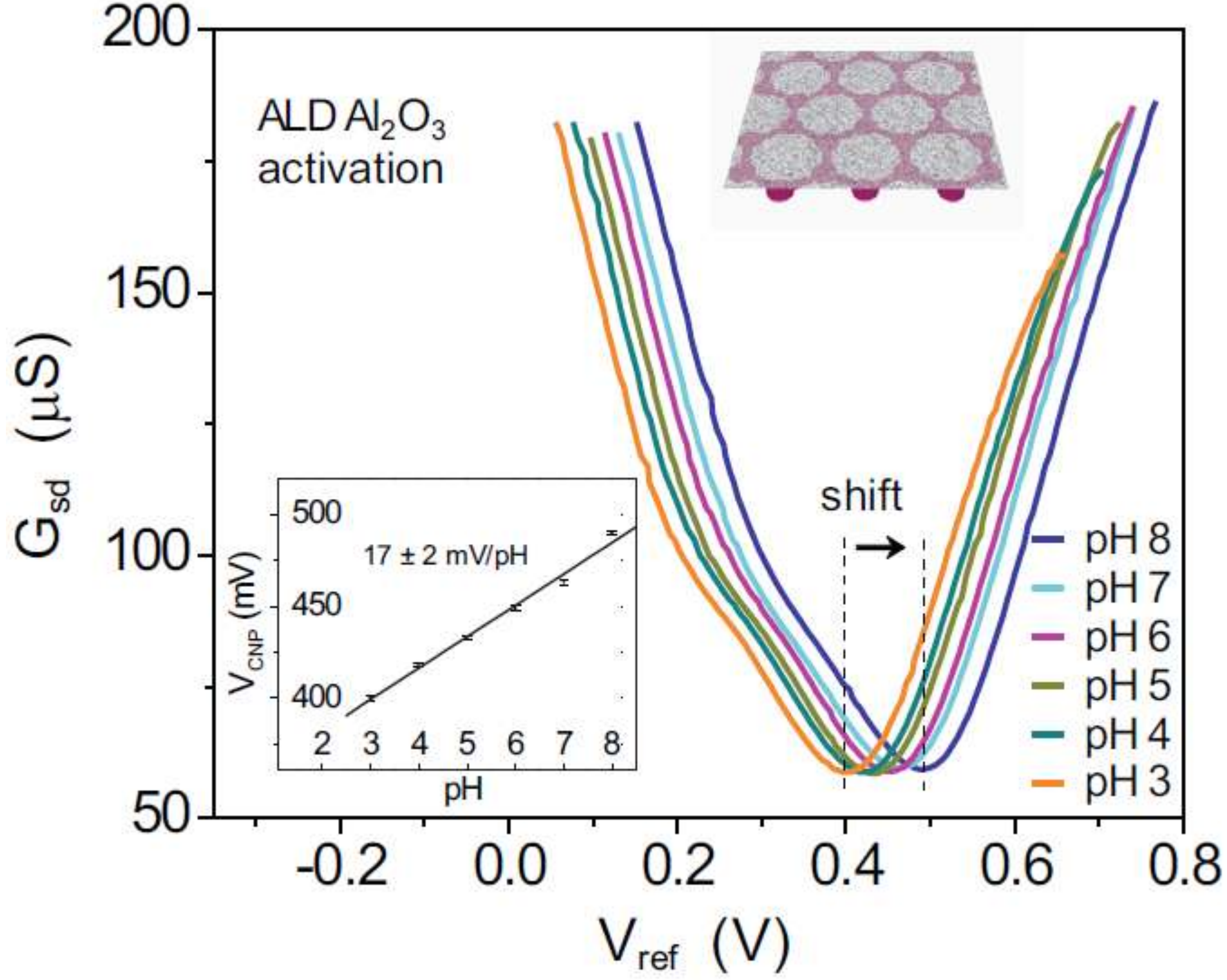
W. Fu, C. Nef et al., Nano Lett. 2011

Graphene ISFET: passivation



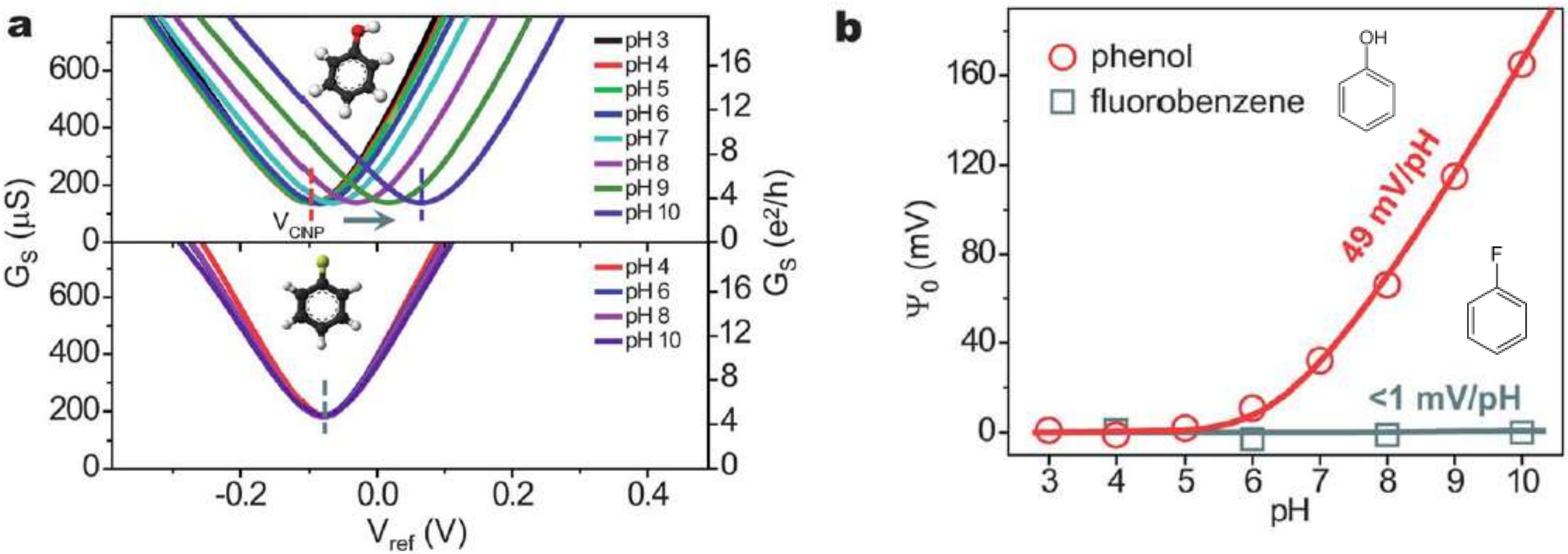
W. Fu, C. Nef et al., Nano Lett. 2011

Graphene FET: oxide layer



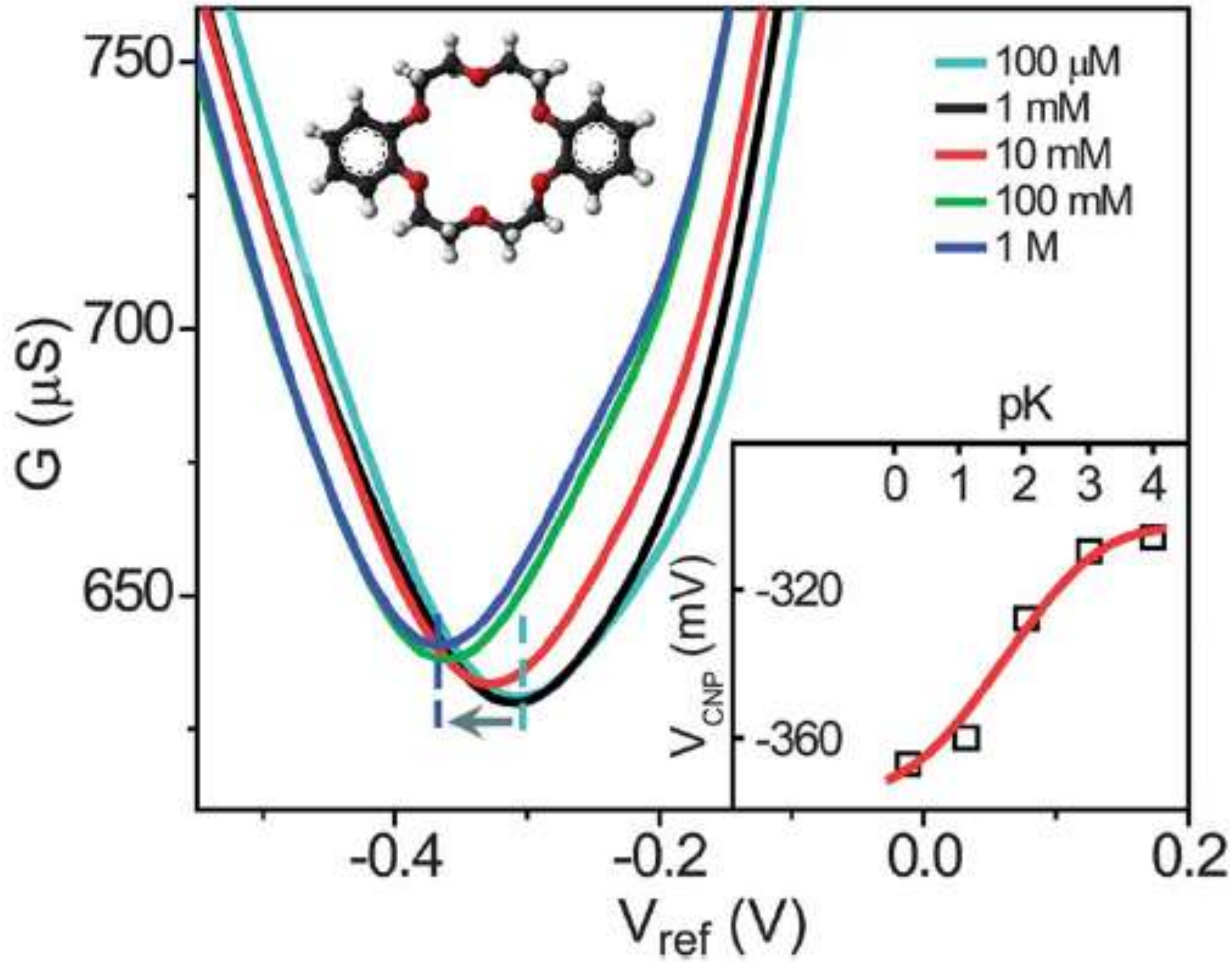
W. Fu, C. Nef et al., Nano Lett. 2011

Graphene ISFET: "active" molecule functionalization



W. Fu, C. Nef et al., Nanoscale. 2013

Graphene ISFET: response to K^+ ions



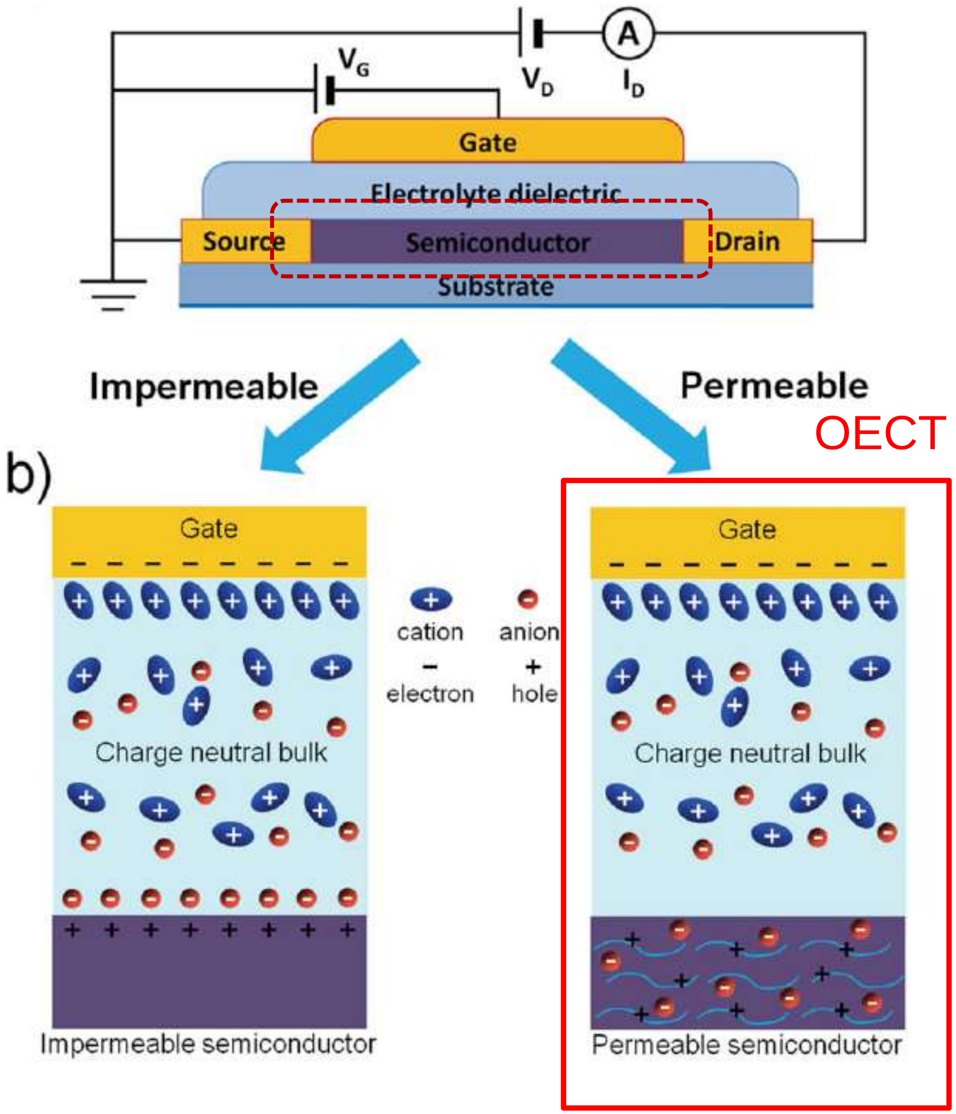
NB: similar research for CNTs

see e.g. M. Hersam et al., Chem. Soc. Rev. 42, 2824 (2013)

W. Fu, C. Nef et al., Nanoscale. 2013

can we do it with … conducting polymers ?

organic electrochemical transistors (OECTs)

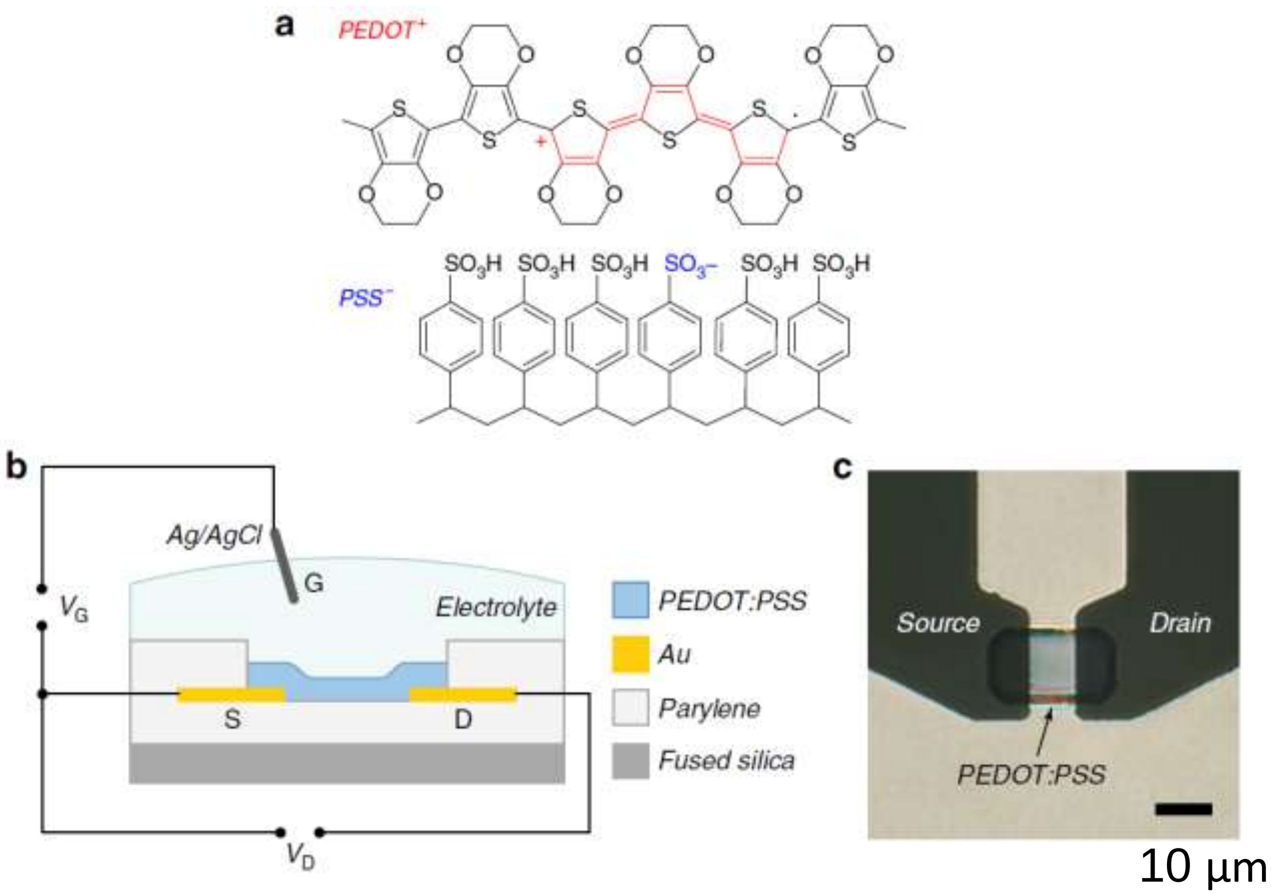


Common assumptions:

- p-type semiconductor (n_p=10^{21}-$10^{23}$$cm^{-3}$)
- constant mobility (μ_h=0.045-1 cm^2/Vs)
- Injected ions distribute homogenously

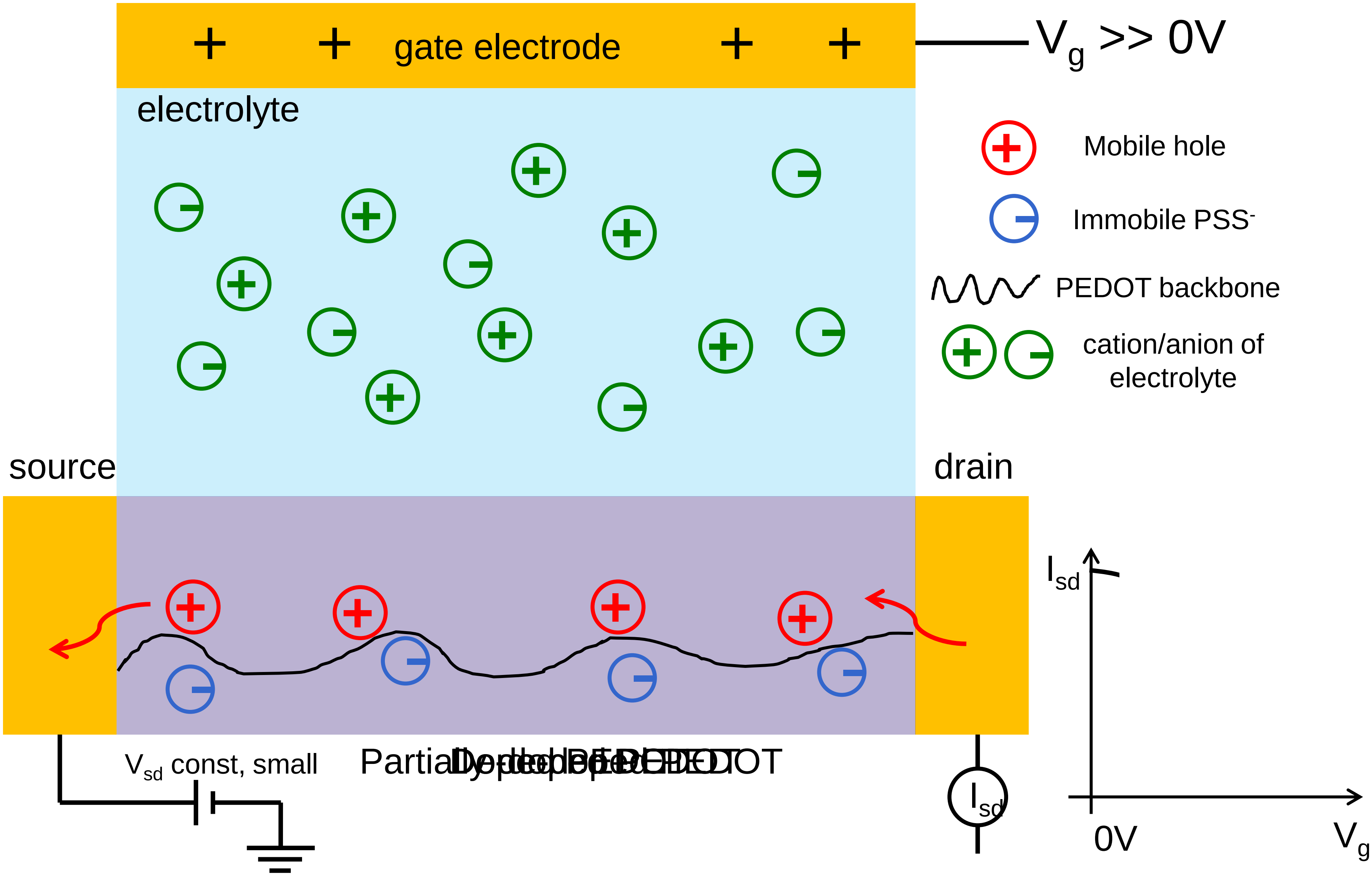
S. H. Kim et al. Advanced Materials 2012
Bernards et al. Advanced Materials 2007

organic electrochemical transistors (OECTs): PEDOT:PSS



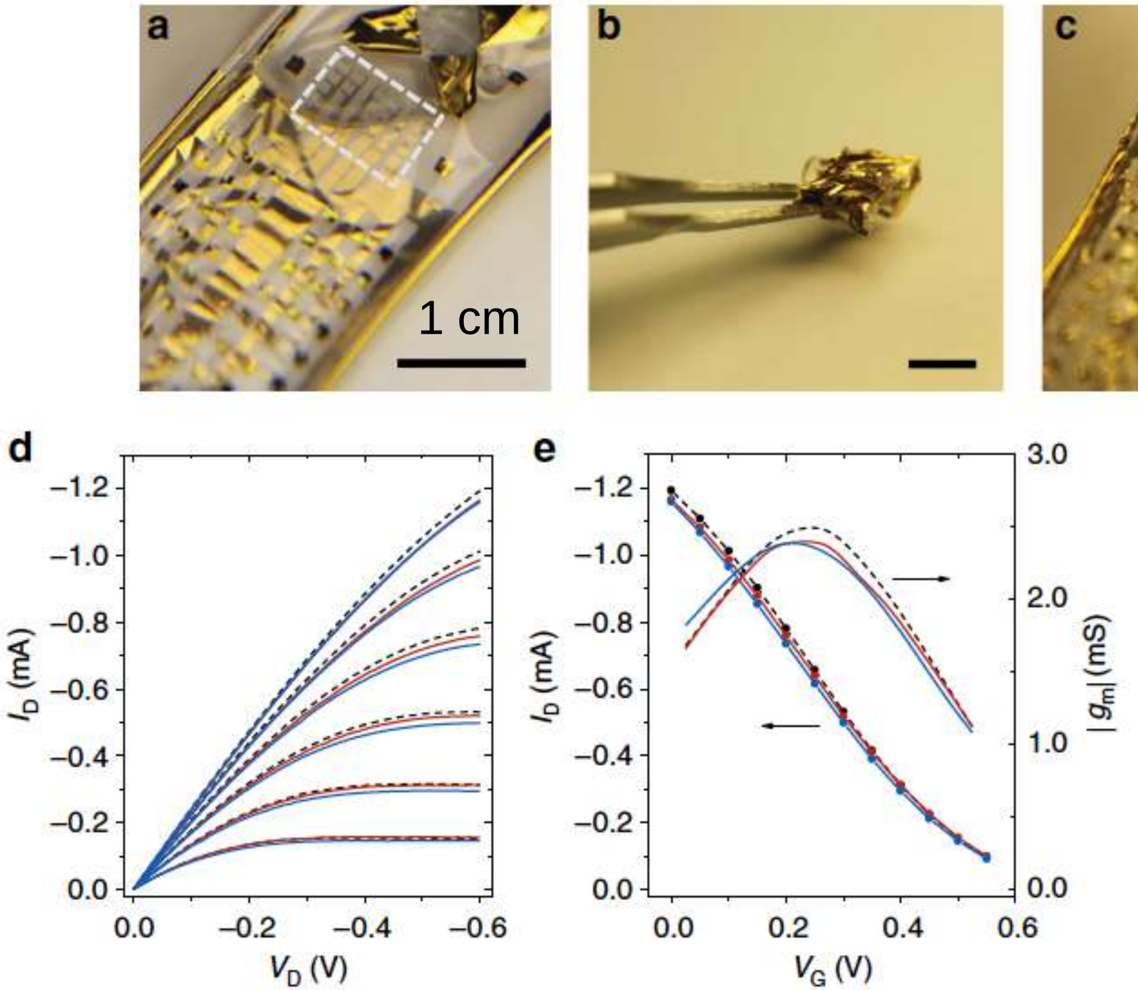
D. Khodagholy et al. Nature Commun. 2014

working principle PEDOT:PSS OECT



G. Malliaras et al.

OECTs - mechanical stability



black: as prepared

red: after peeling

blue: after crumpling

⇨ **R. Stoop, M. Sessolo et al.: characterization & noise measurements**
Phys Rev. Applied (2017)

D. Khodagholy et al. Nature Commun. 2013

- **general aspects on sensing**
  sensitivity, specificity
  overview of transducers

- **field effect transistors (FETs) as charge sensors**
  MOSFET, graphene and GFET

Examples

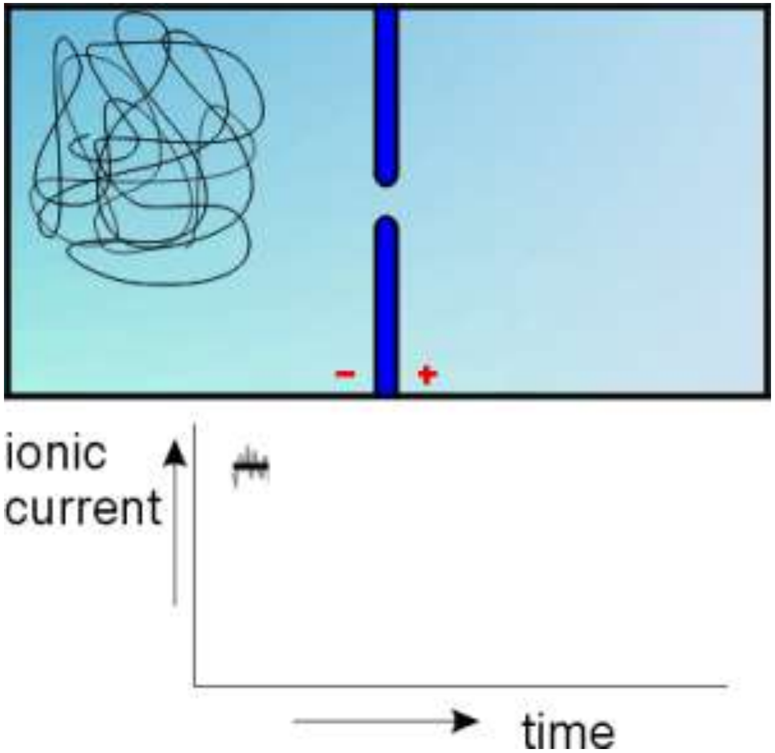
- Ion sensitive field-effect transistors (ISFETs) for pH, ionic and biochemicals detection

- Nanopores for sequencing

DNA sequencing using nanopores

- **basic principle: DNA translocation and current blockade**
  cf Coulter counter for single cells

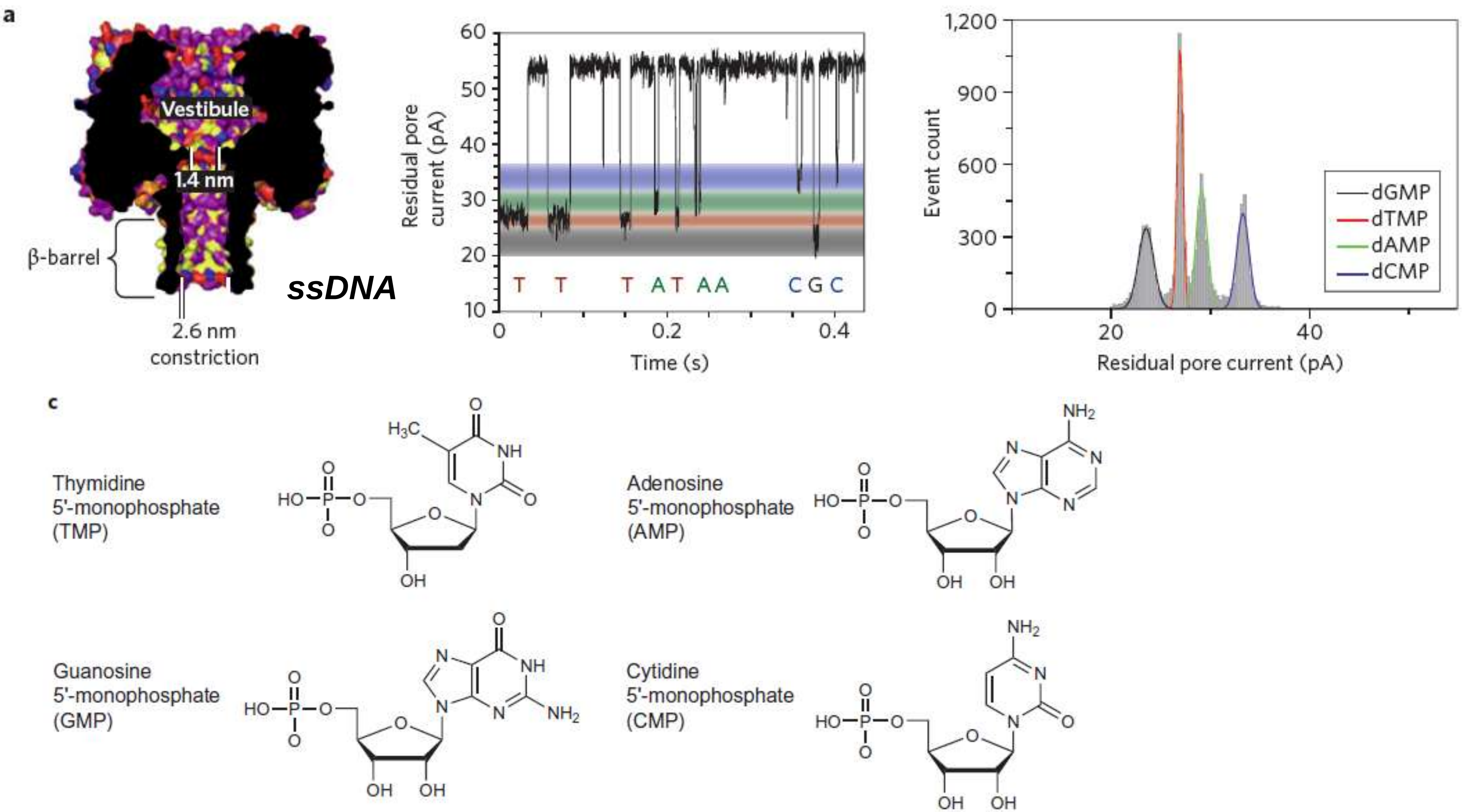
small diameter, high repetition rate
identification of bases?



Dekker et al.

DNA sequencing using nanopores

biological nanopores structural cross-section of α-haemolysin

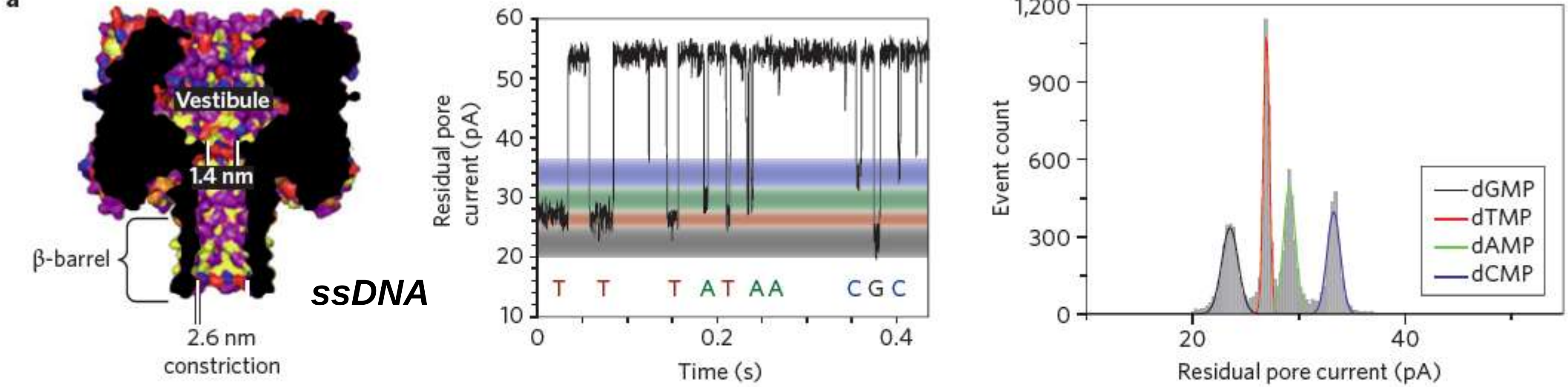


Bashir et al., Nat. nano (2011)

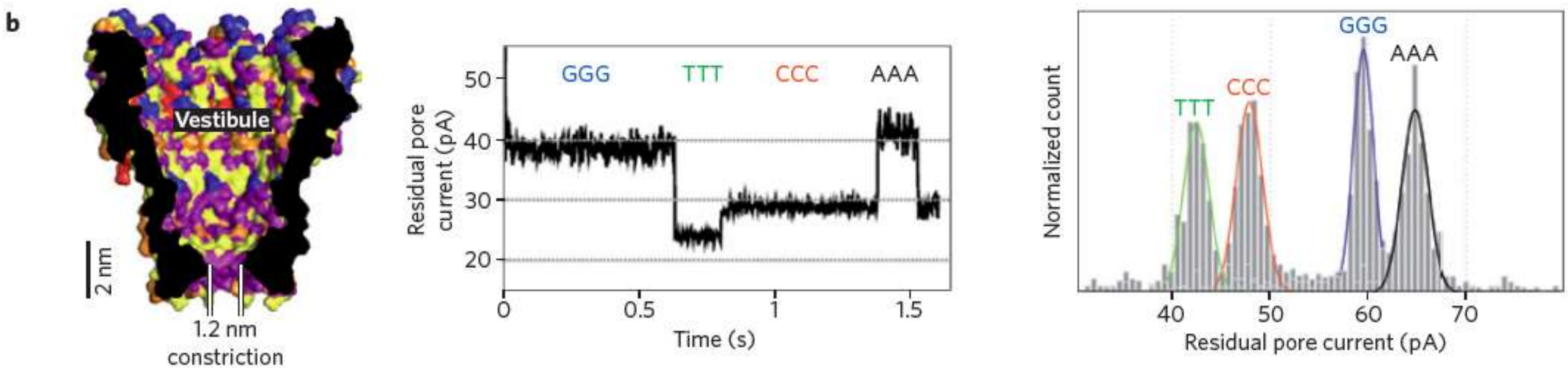
DNA sequencing using nanopores

structural cross-section of α-haemolysin

modified channel



structural cross-section of MspA

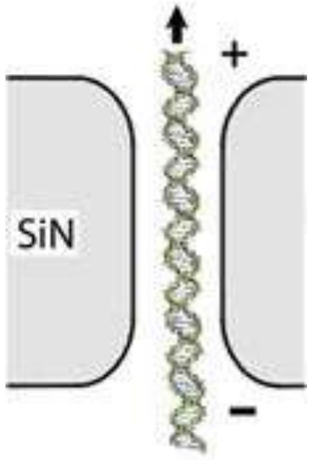


dsDNA segment with ssDNA triplets

dsDNA temporariliy blocks translocation until dsDNA dissociates due to high local electric field

Bashir et al., Nat. nano (2011)

solid state nanopores

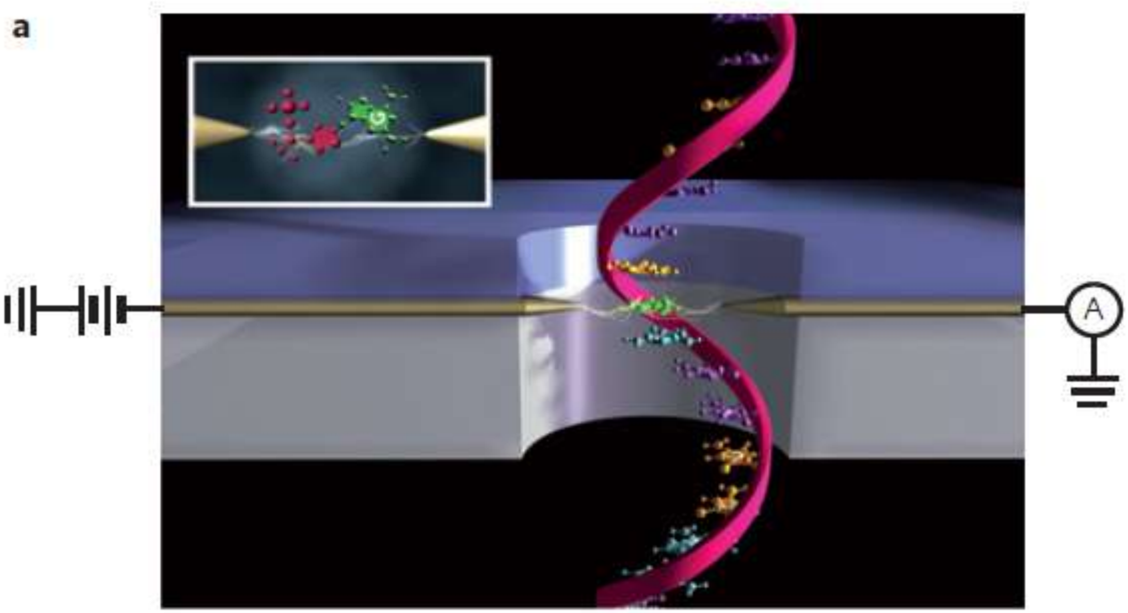


drawback: thickness of channel (SiN membrane)
chanel will contain many bases (base to base: <0.5nm)

⇨ no high-resolution DNA sequencing

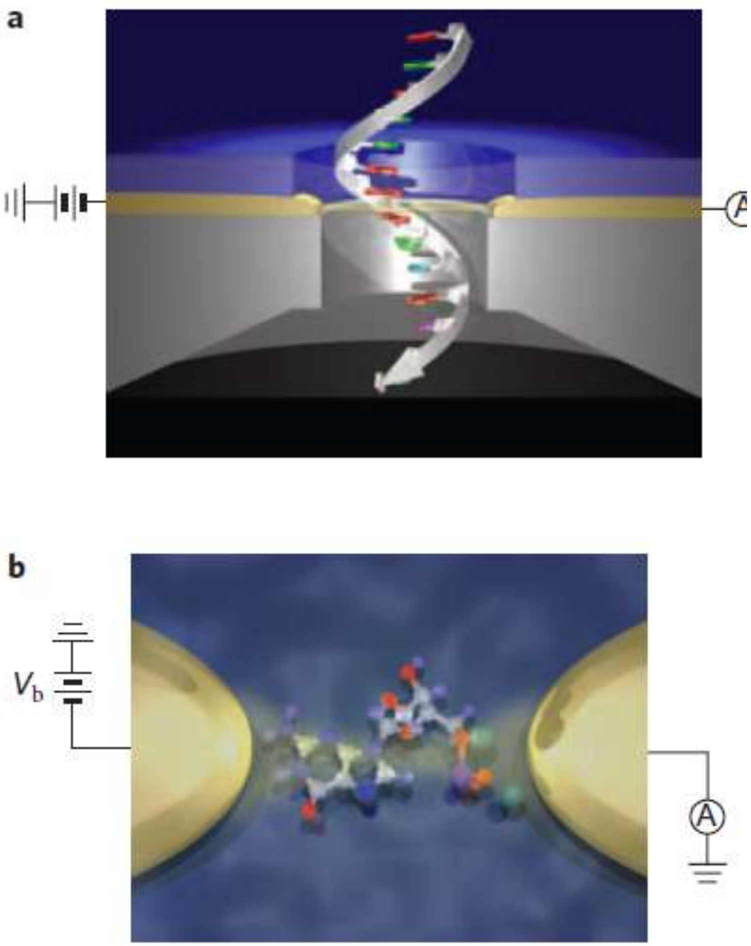
Dekker et al.,

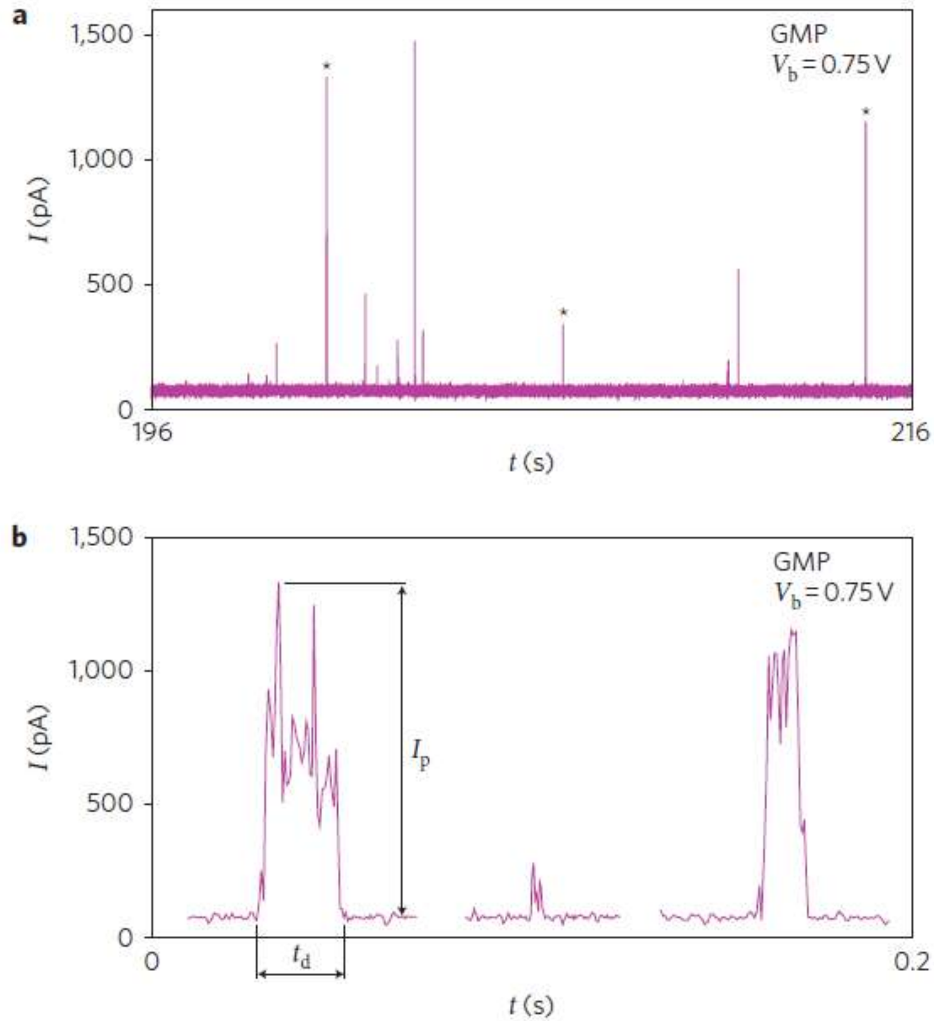
posible solution: integrate tunnel device



Bashir et al., Nat. Nano, (2011)
Kawai et al., Nat. Nano (2010)

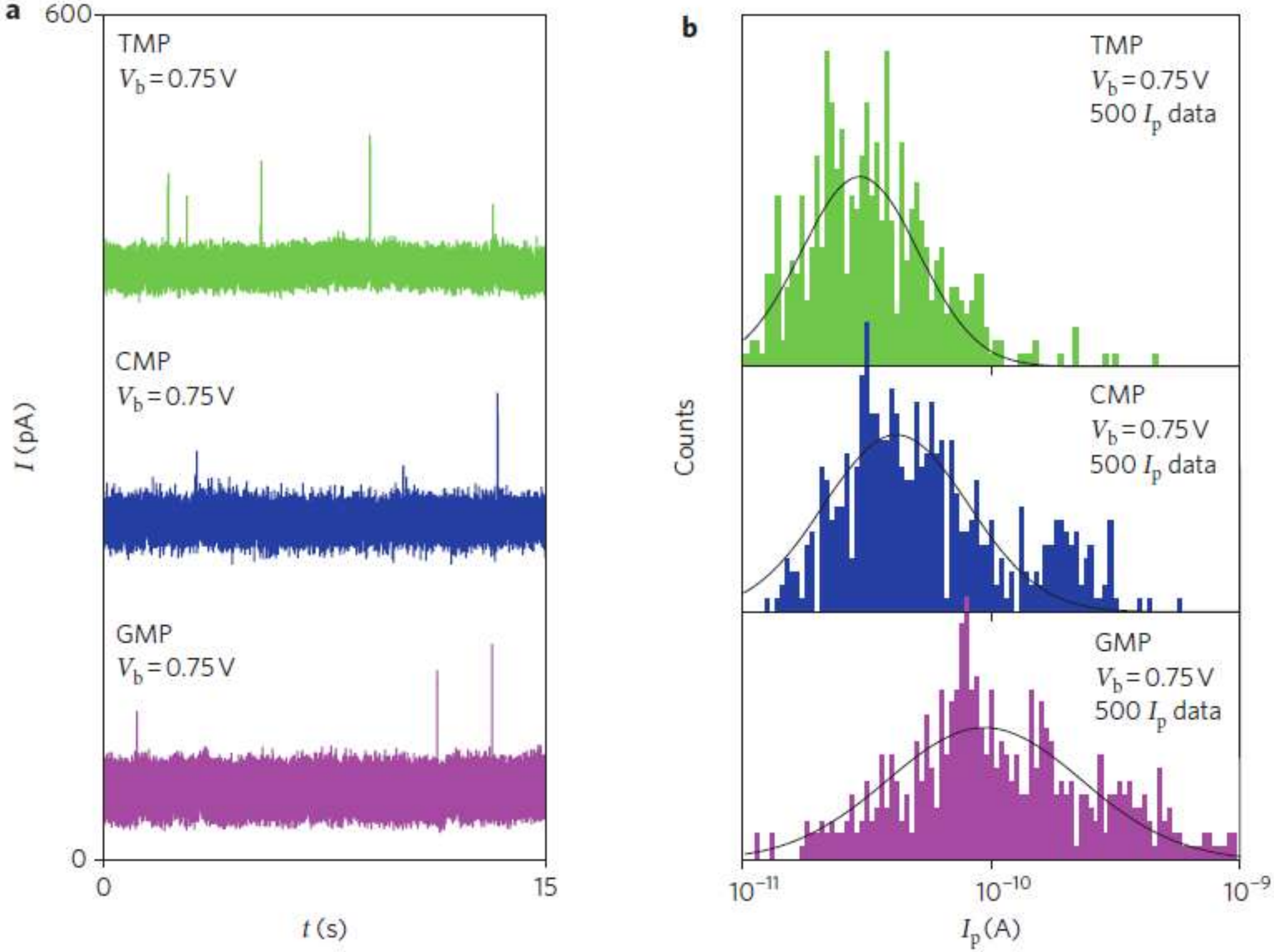
solid state nanopores





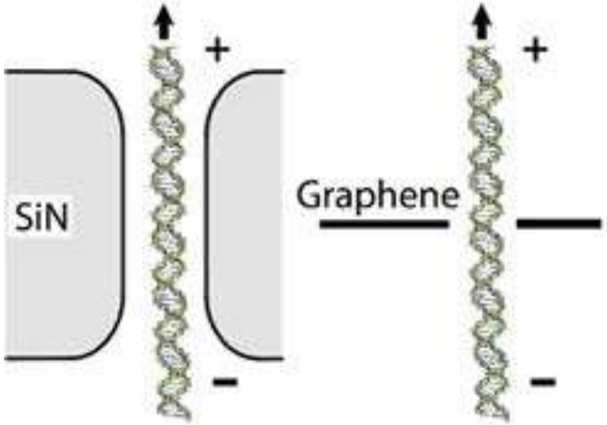
Kawai et al., Nat. Nano (2010)

solid state nanopores



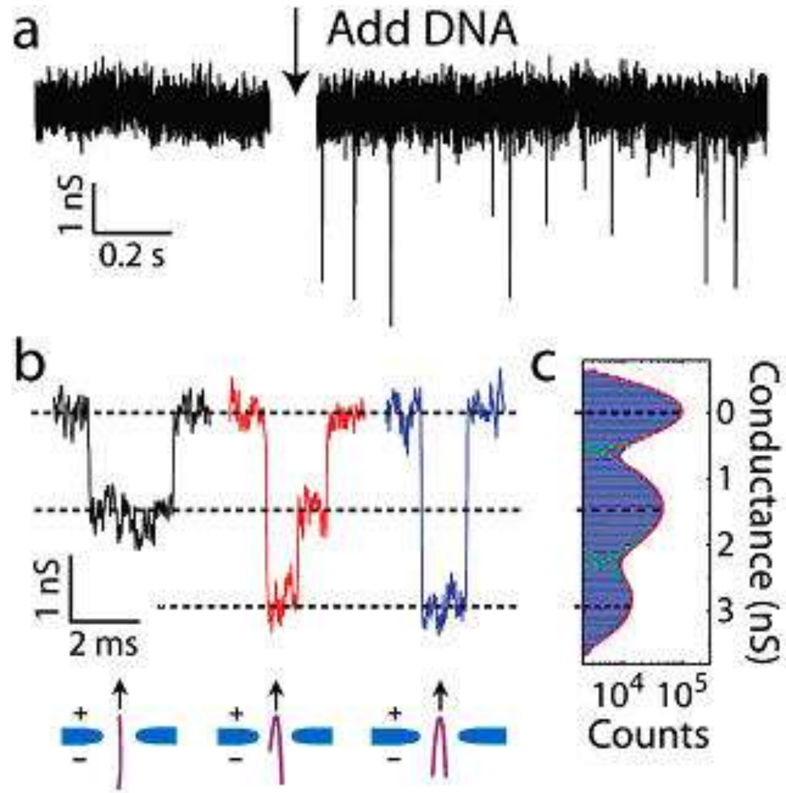
Kawai et al., Nat. Nano (2010)

graphene nanopores

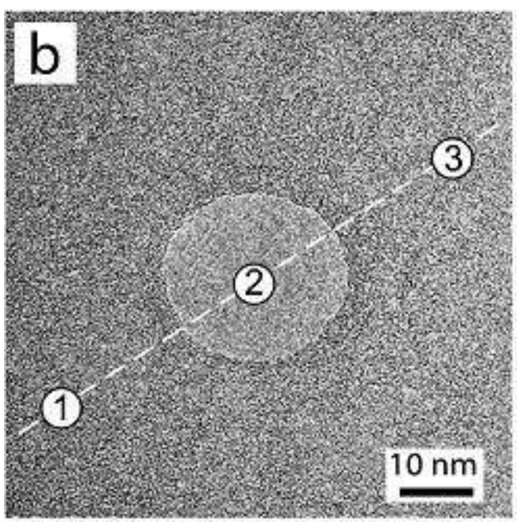


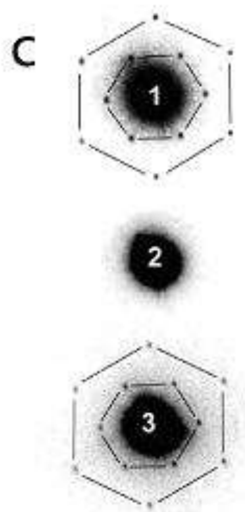
+ thinner than 1 base
+ can be used as electrode to detect base

- hydrophobic



proof of concept: 22nm hole, monolayer graphene lambda DN translocation





Dekker , Schneider et al., NL 2010, Nat. Comm. (2013)

NB: sequencing using .... ISFETs

ARTICLE

Rothberg et al., Nature (2011)

doi:10.1038/nature10242

An integrated semiconductor device enabling non-optical genome sequencing

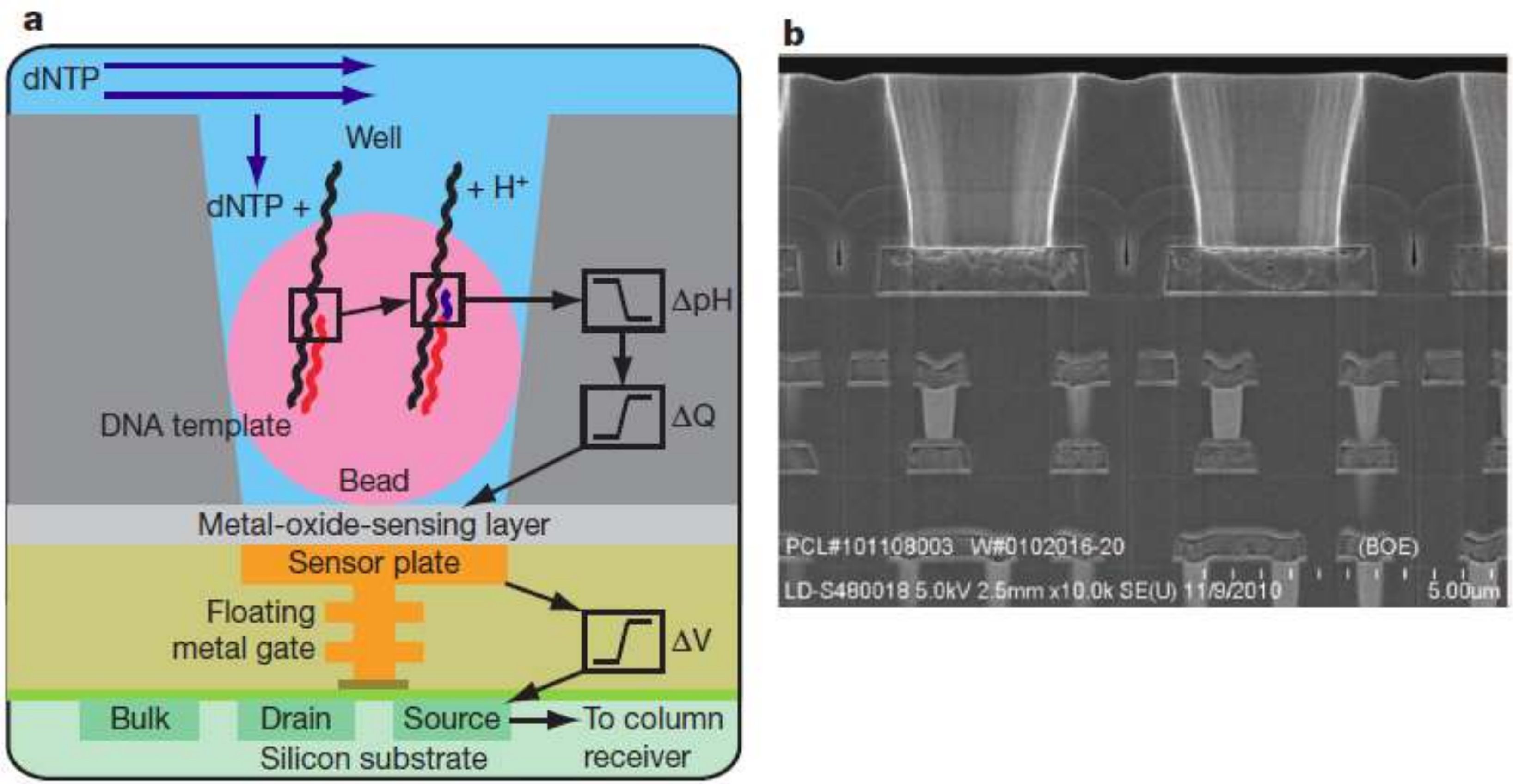
Jonathan M. Rothberg[1], Wolfgang Hinz[1], Todd M. Rearick[1], Jonathan Schultz[1], William Mileski[1], Mel Davey[1], John H. Leamon[1], Kim Johnson[1], Mark J. Milgrew[1], Matthew Edwards[1], Jeremy Hoon[1], Jan F. Simons[1], David Marran[1], Jason W. Myers[1], John F. Davidson[1], Annika Branting[1], John R. Nobile[1], Bernard P. Puc[1], David Light[1], Travis A. Clark[1], Martin Huber[1], Jeffrey T. Branciforte[1], Isaac B. Stoner[1], Simon E. Cawley[1], Michael Lyons[1], Yutao Fu[1], Nils Homer[1], Marina Sedova[1], Xin Miao[1], Brian Reed[1], Jeffrey Sabina[1], Erika Feierstein[1], Michelle Schorn[1], Mohammad Alanjary[1], Eileen Dimalanta[1], Devin Dressman[1], Rachel Kasinskas[1], Tanya Sokolsky[1], Jacqueline A. Fidanza[1], Eugeni Namsaraev[1], Kevin J. McKernan[1], Alan Williams[1], G. Thomas Roth[1] & James Bustillo[1]

The seminal importance of DNA sequencing to the life sciences, biotechnology and medicine has driven the search for more scalable and l… scribe a DNA sequencing technology in which scalable, low-cost semicon… es are used to make **an integrated circuit able to directly perform… ng of genomes**. Sequence data are obtained by directly sensing the io… d DNA polymerase synthesis using all-natural nucleotides on this massi… sing device or ion chip. The ion chip contains **ion-sensitive, field-effe… in perfect register with 1.2 million wells**, which provide confinement … s detection of independent sequencing reactions. Use of the most widely u… integrated circuits, the complementary metal-oxide semiconductor (**CMOS… , large-scale production and scaling of the device to higher densities and larger array sizes**. We show the performance of the system by sequencing three bacterial genomes, its robustness and scalability by producing ion chips with up to 10 times as many sensors and sequencing a human genome.

1000 US$ / genome sequencing

IonTorrent/ ThermoFischer

NB: sequencing using .... ISFETs



Rothberg et al., Nature (2011)