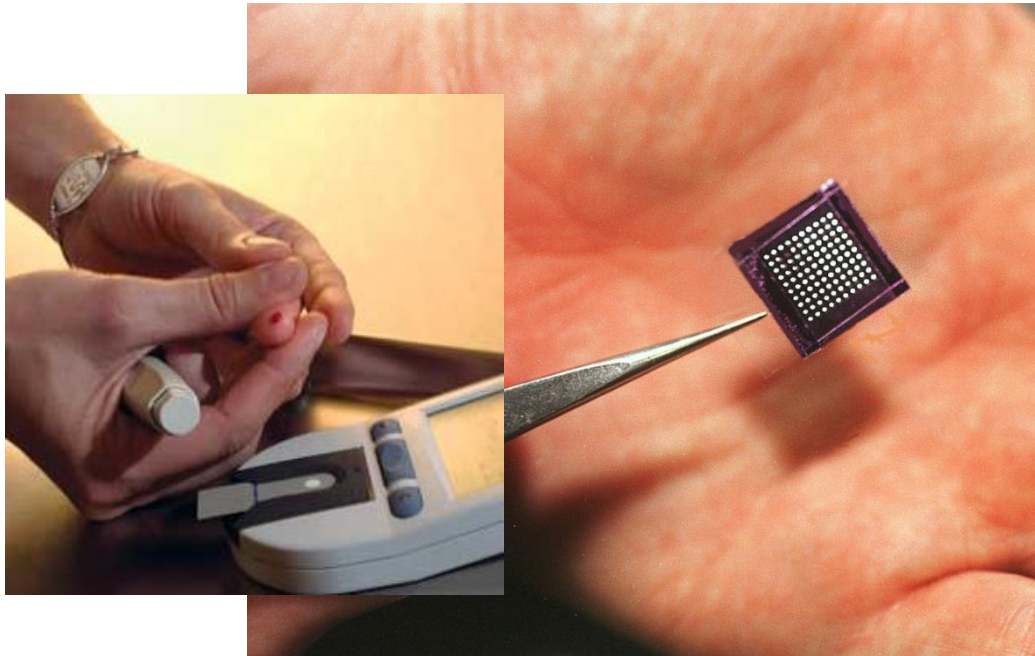


Chemical sensors and biosensors



Chemical- and biosensors

Industrial, Environmental, and Clinical Applications

- **Chemical sensors**
measure and characterize chemical compounds.
- These sensors include conduct metric sensors, catalytic sensors, and gas sensors.
- **Biosensors**
measure and characterize organic materials.
- These sensors include enzyme sensors and DNA analysis systems



We want to measure?

- Presence/Absence**
- Identity**
- Concentration**
- Qualitative or Quantitative**



How can we measure?

- Magnetic & Electric Fields
- Resistance
- Capacitance
- Inductance
- Frequency
- Optical
- etc etc..



Some examples

Measured physical parameter	Chemically sensitive material	Devices	Detected species	Sensors
Resistivity / conductivity	Semiconducting metal oxides, conducting polymers	Thin films or pellets of metal oxides Thin polymer films	Combustible gases Ad/absorbing species	Metal oxide sensors (Taguchi, FIS, Lambda) Conducting polymers
Mass changes (due to frequency changes)	Organic thin films, thin metal films	Oscillating piezoelectric crystals	Ad/absorbing species enzymes, cells	Quartz Crystal Microbalance, (QMB), Surface Acoustic Wave (SAW)
Electrical polarization	Catalytic metals, polymers, metal oxides	Field effect devices: transistors, capacitors, Schottky diodes	H ₂ , NH ₃ , H ₂ S, amines, alcohols, hydrocarbons, etc.	MOSFET sensors, MISiC sensors
Heat generation	Catalytic metals and metal oxides Immobilized enzymes or cells	Catalysts, diodes, thermocouples and thermopiles, thermistors	Combustible gases, substrates for enzymes, poisons	Calorimetric sensors Thermistors
Optical properties absorption, reflection, fluorescence	Organic and inorganic films, dyes, fluorescent species	Optical fibers, reflecting surfaces, absorption cells	Ad/absorbing species	Optical sensors, optical fibers
Surface Plasmon Resonance	Organic films and thin metal films	Thin metal films on quartz substrates	Ad/absorbing species	SPR-sensors (BIA core)
Potential changes	Ion selective films	Field effect devices	Ions, pH, enzymes, cells	ISFET sensors
Dielectric properties	Organic and inorganic films	Ellipsometry	Ad/absorbing species	Ellipsometry





What can we gain by micro/nanotechnology?



- Microdomain => laminar flow conditions => difficult to mix
- Shorter diffusion distances => rapid diffusional mixing

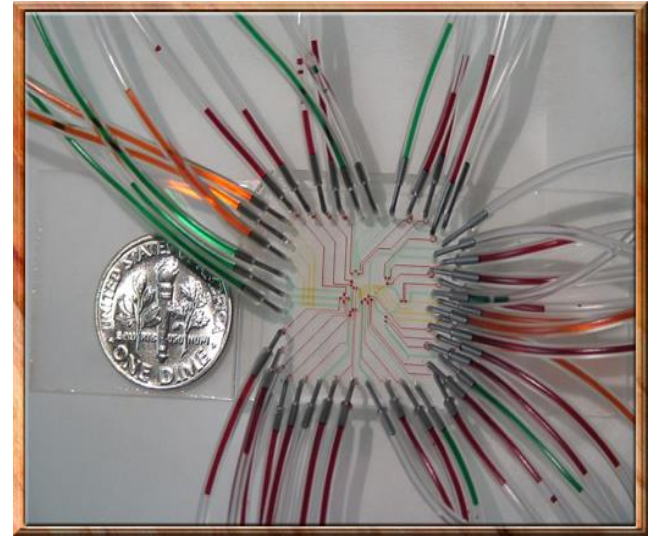
Time to diffuse across a channel increases with (channel width)²
e.g 1 mm channel takes 100 seconds to diffuse accross =>
=>10 um channel takes 10 milliseconds

- Surface area to volume ratio increases with r^{-1} => surface influence increases
- Surface tension and viscosity befores ruling fluidic parameters over inertia
- Evaporation becomes a very influential parameter
- Miniaturised sample volumes => multiple/alternative analysis



What are the possible challenges?

- Noise
- Drift
- Low sensitivity
- System stability
- Reuse possible?
- Sampling problems
- Measurements system
- Complexity and cost
- User prejudice against technology?
- ...

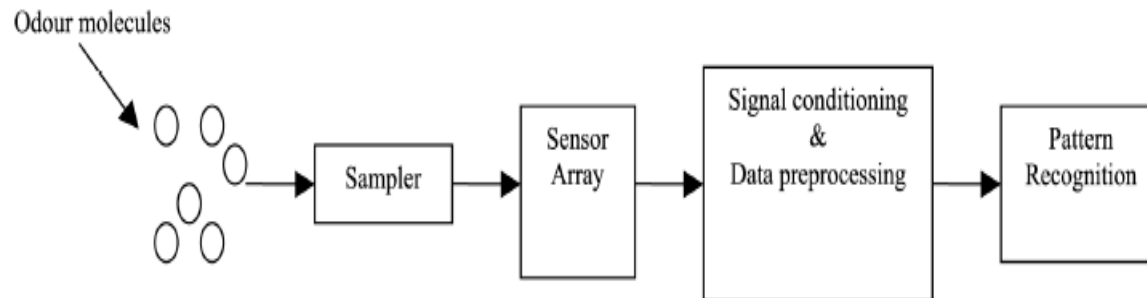
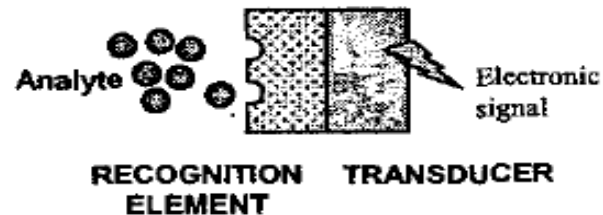


Problems with scaling down

- **Smaller volumes = less analyte**
1 nL injection at 1pM = 600 molecules
- Requires high sensitivity detection
- Integration issues (connections and other equipment)
- Fouling/clogging
- False-positives with single mol.?

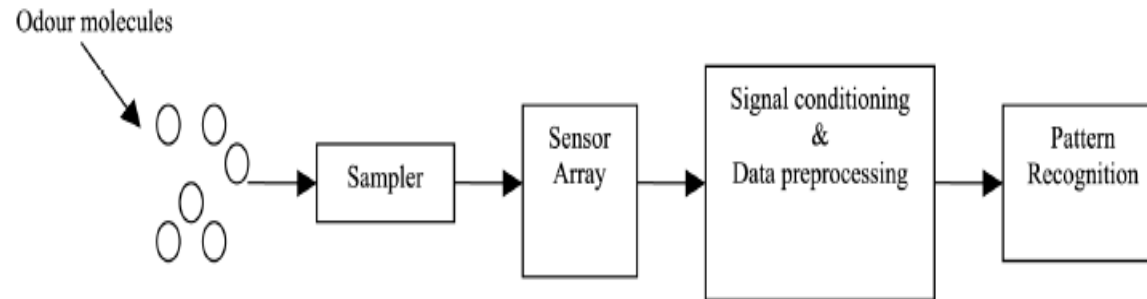
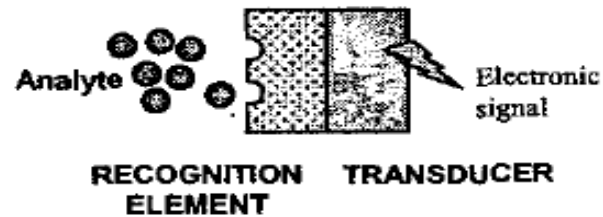


Chemical Sensors



Biosensors

a biological element senses



Biosensor = a biological element senses

The component used to bind the target molecule.

Must be highly specific, stable under storage conditions, and immobilized.

Microorganism

Tissue

Cell

Organelle

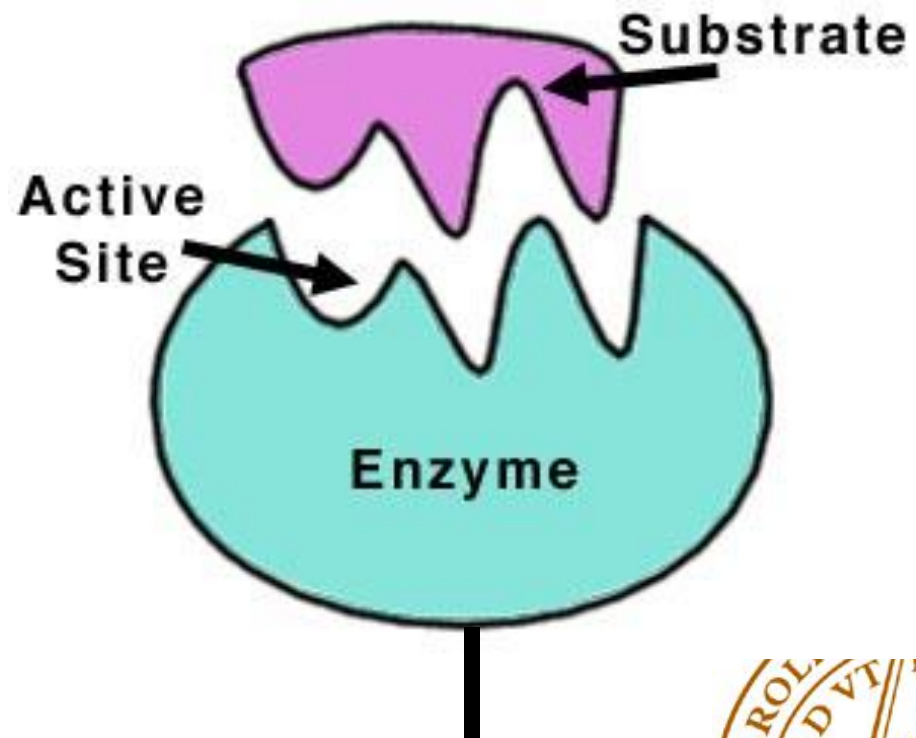
Nucleic Acid

Enzyme

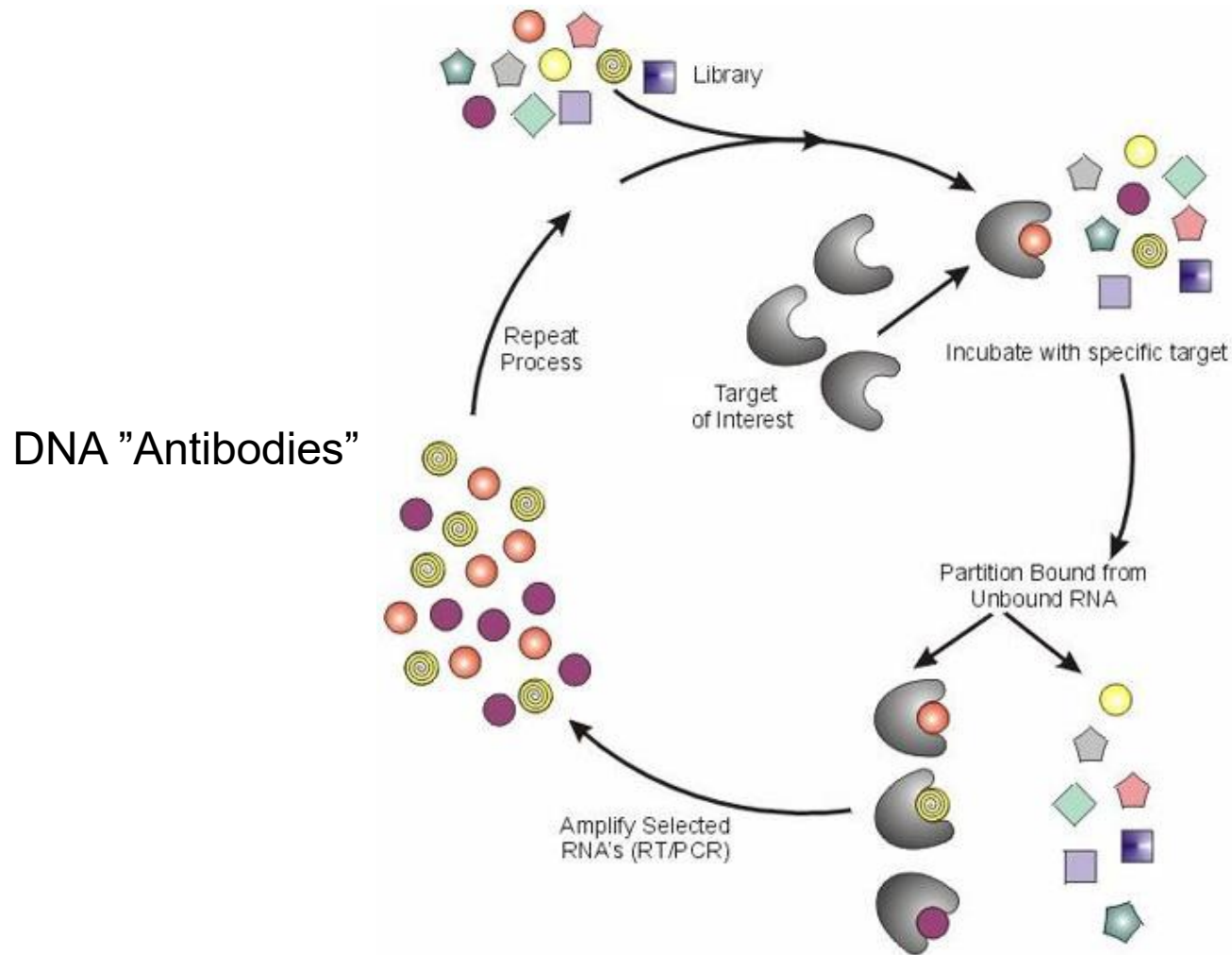
Enzyme Component

Receptor

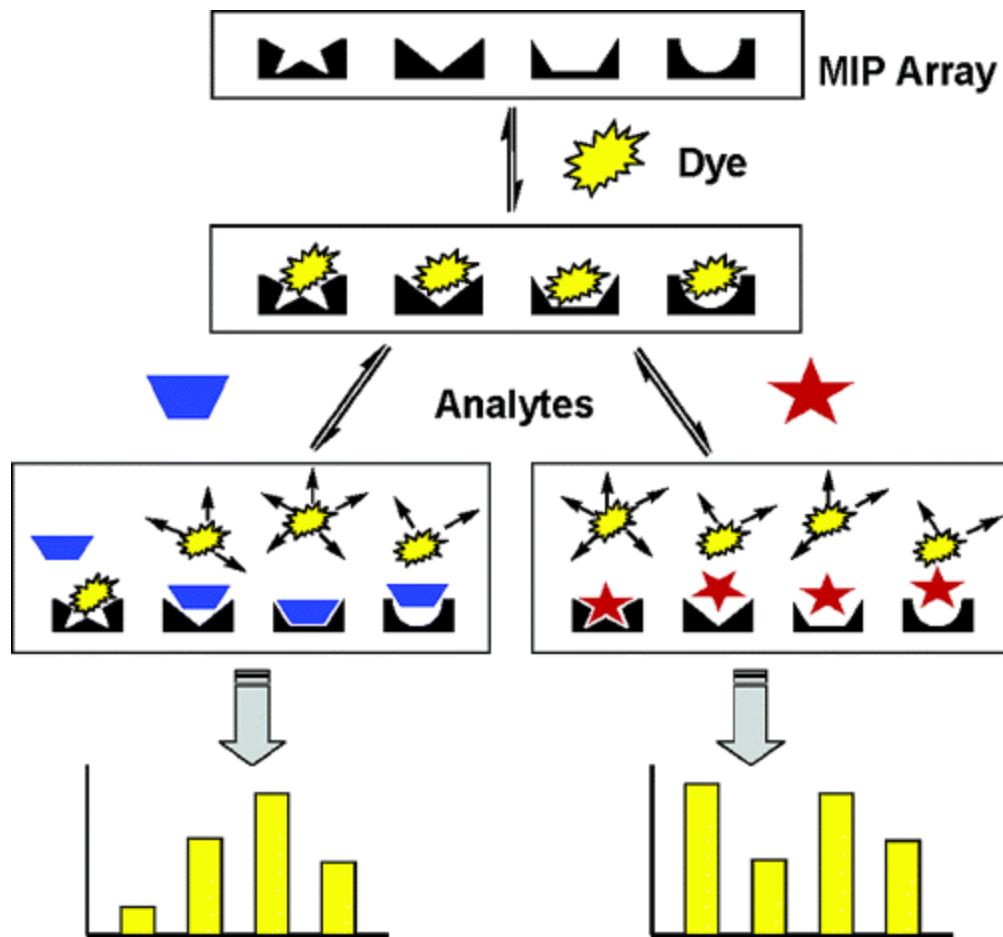
Antibody



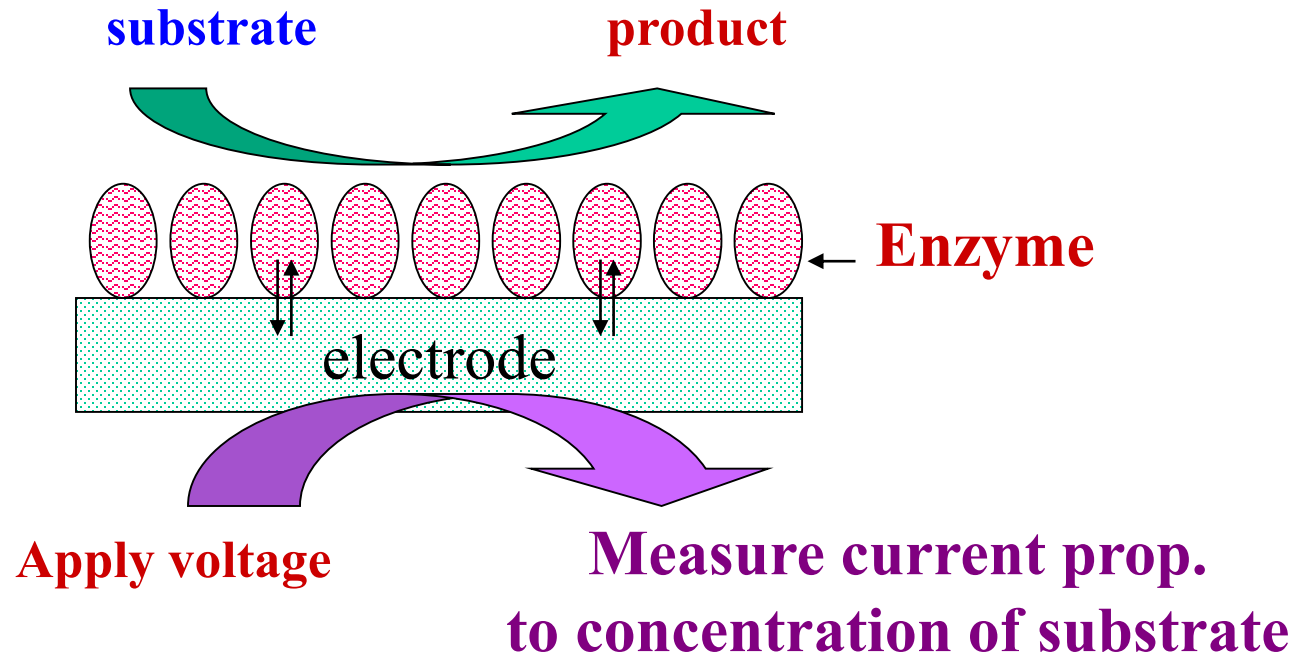
Systematic Evolution of Ligands by Exponential Enrichment (SELEX)



Molecularly Imprinted Polymer (MIP) Sensor Array

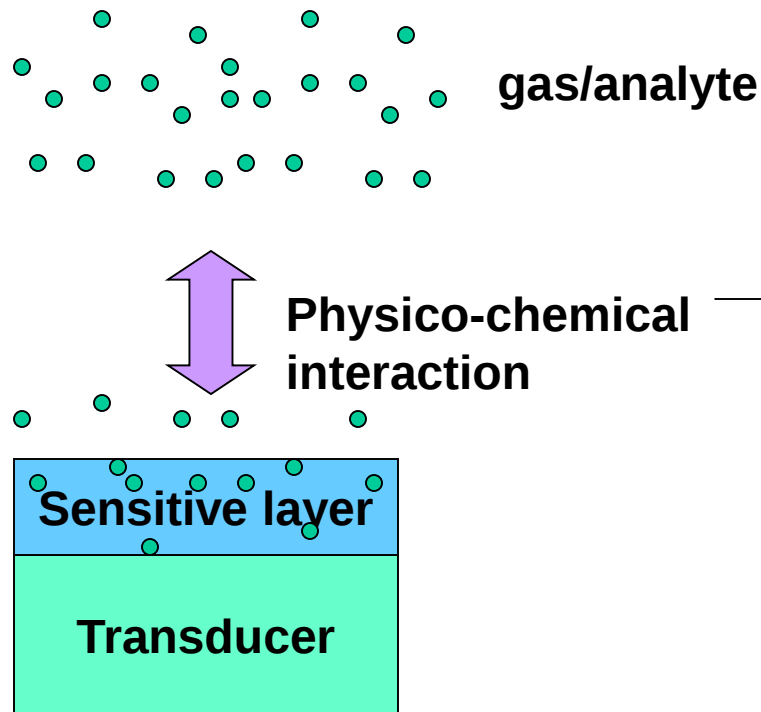


Principle of Electrochemical Biosensors



Chemical Sensor Modalities

- Sensing modes**



Sensing Mode:

Example Device Type:

Resistive

Chemresistor

Capacitive

Chemocapacitor

Calorimetric

Thermistor
Pellistor

Mass

Surface Acoustic Wave
Cantilevers



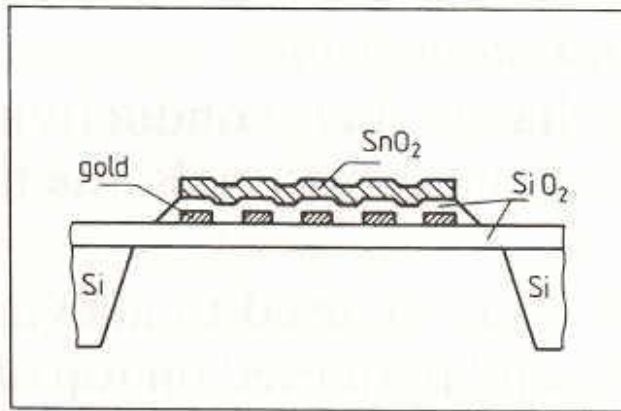
CO sensor on the wall

- Measures the CO in order to regulate the ventilation
- Pris 3400 sek

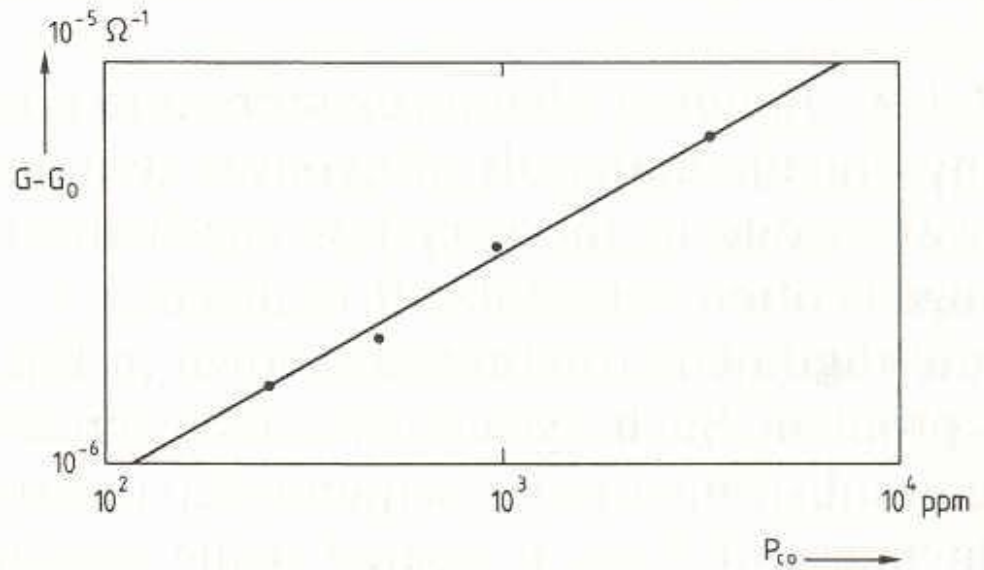


Metal-oxide sensors

- CO sensor



(a)



(b)

- Consists of a heater and a thin layer of SnO_2



Metal-oxide sensors - operation

- Conductivity of the oxide can be written as:

$$\sigma = \sigma_0 + kP^m$$

σ_0 is the conductivity of the tin oxide at 300°C, without CO present

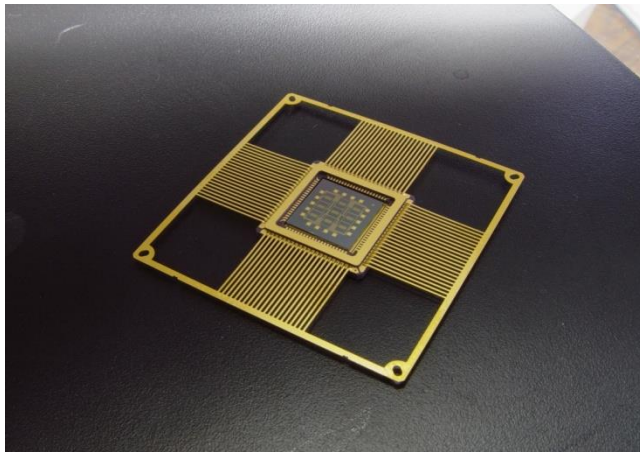
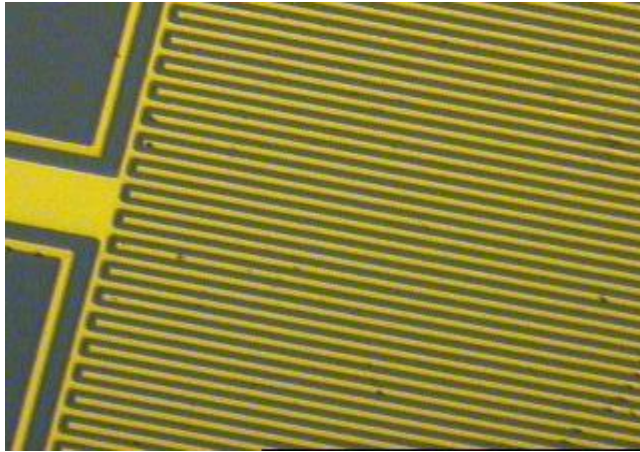
P is the concentration of the CO gas in ppm (parts per million),

k is a sensitivity coefficient (determined experimentally for various oxides)

m is an experimental value - about 0.5 for tin oxide.



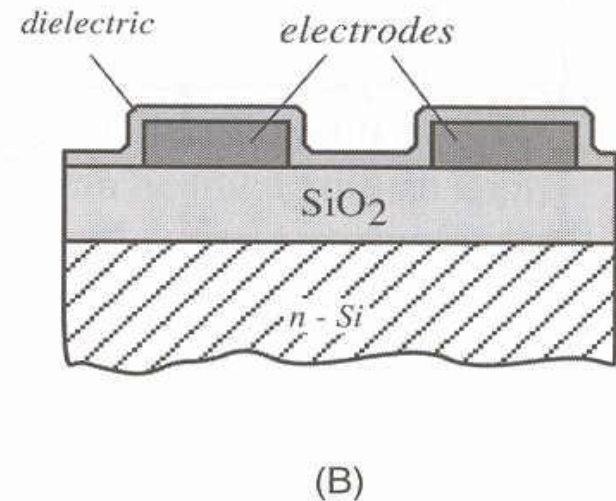
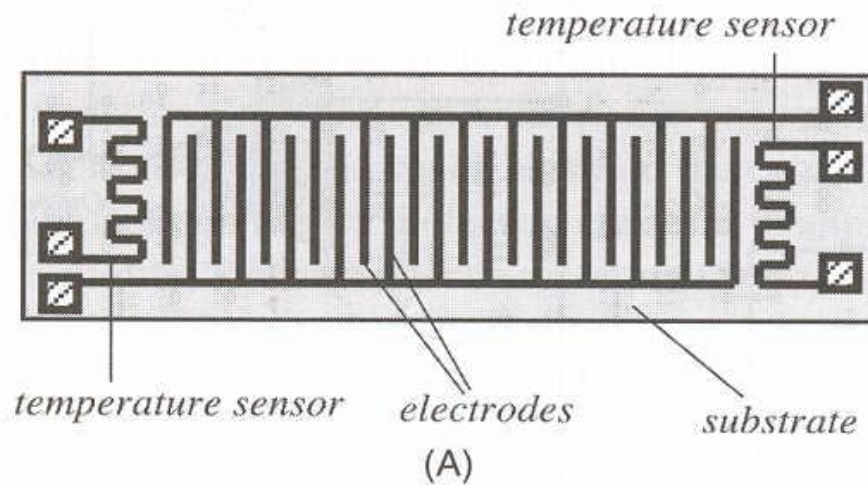
Using Interdigitated Capacitors as Chemical Sensors



- Interdigital geometry maximizes capacitance.
- Highly Sensitive to environmental changes.
- Arrays can be used to increase selectivity.
- Compatibility with MEMS fabrication Processes.

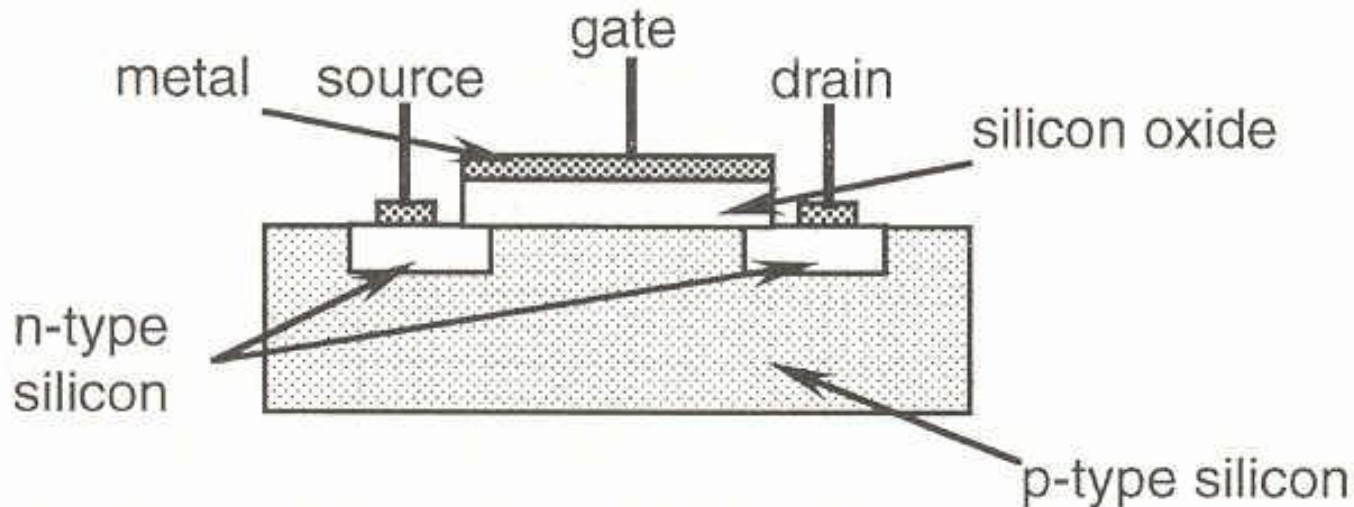


Capacitive moisture sensor



MOS chemical sensors

- Example, by simply replacing the metal gate with palladium, the MOSFET becomes a hydrogen sensor



FETs for Forensic applications

**Drugs, bombs,
biowarfare agents.....**



Chemical Sensors

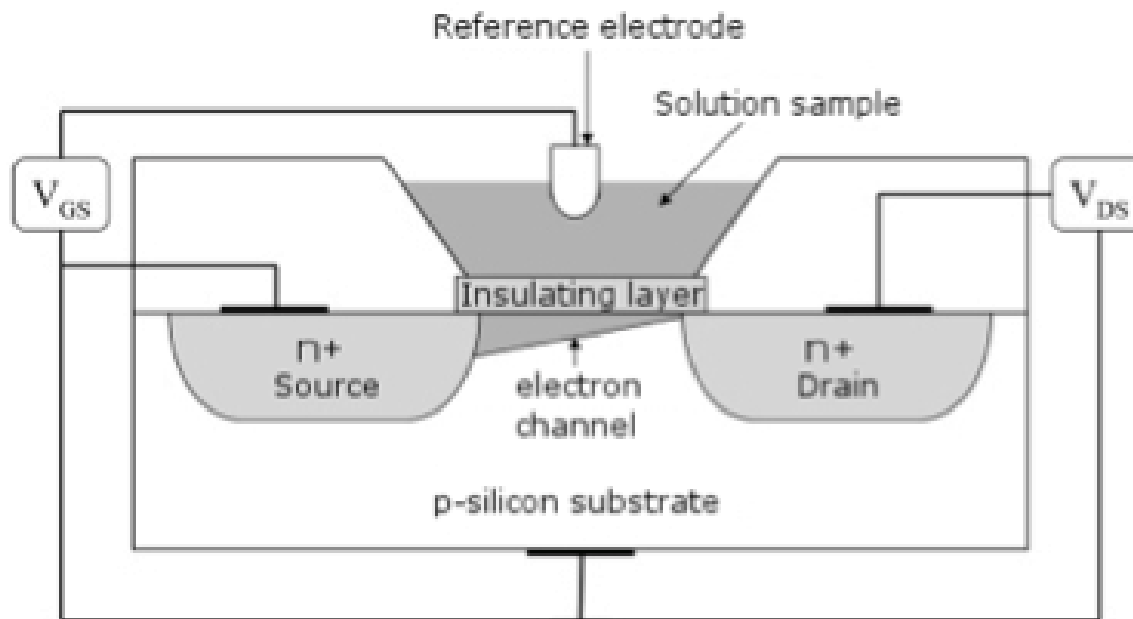
- Hydrogen Cyanide (HCN)
- Ammonia (NH₃)
- Chlorine (Cl₂)
- Acetaldehyde (C₂H₄O)
- Sulfur Dioxide (SO₂)
- Hydrochloric Acid (HCl)



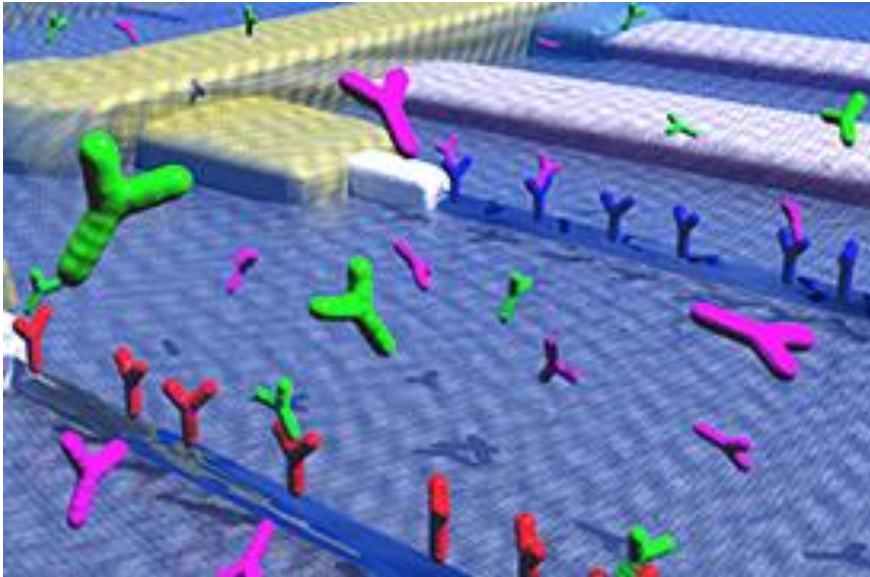
MOS chemical sensors

ISFET

- The ISFET requires an external reference electrode where the gate voltage is applied.



Nanowire FET



- Label free
- CMOS-compatible
- Low fM sensitivity

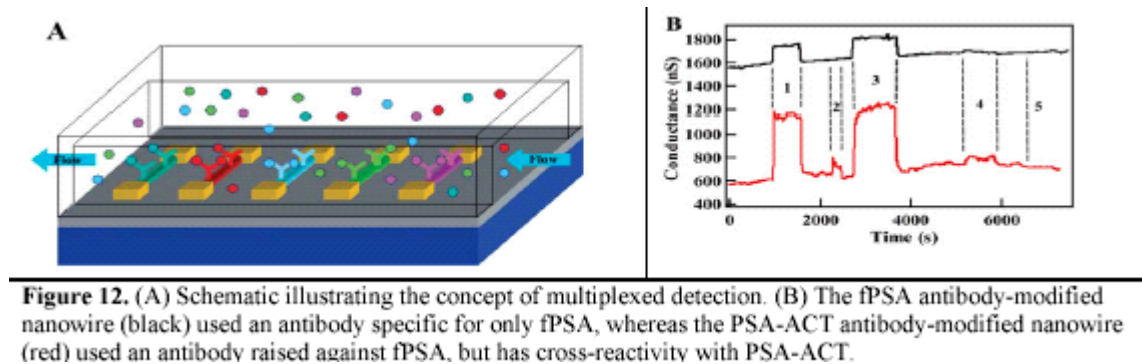


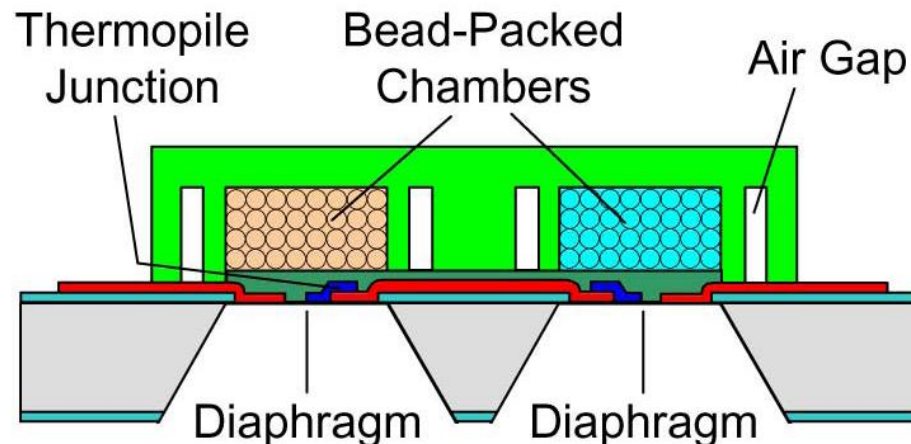
Figure 12. (A) Schematic illustrating the concept of multiplexed detection. (B) The fPSA antibody-modified nanowire (black) used an antibody specific for only fPSA, whereas the PSA-ACT antibody-modified nanowire (red) used an antibody raised against fPSA, but has cross-reactivity with PSA-ACT.

Patolsky, F. et al. 2004. Electrical detection of single viruses. *Proceedings of the National Academy of Sciences* 101:14017-14022.
Eric Stern, et. al., *Nature* 445, 519-522 (1 February 2007)



Thermistor based chemical sensors

- Principle: sense the small change in temperature due to the chemical reaction.
- A reference temperature sensor is usually employed to sense the temperature of the solution
- The difference in temperature is then related to the concentration of the measured substance.
- The most common approach is to use an enzyme based reaction (enzymes are highly selective - so the reaction is known).



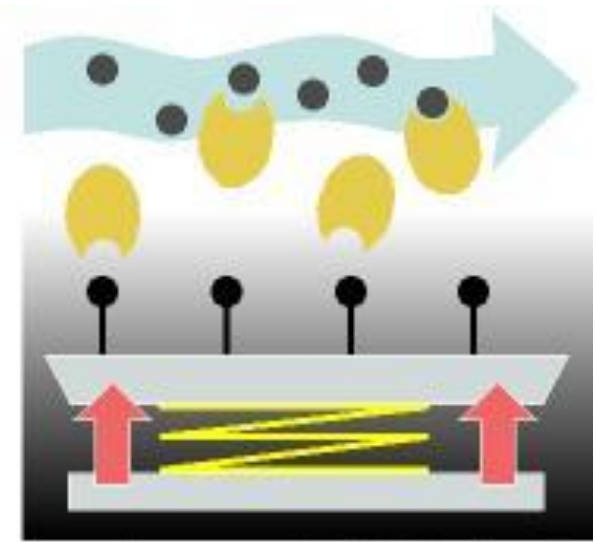
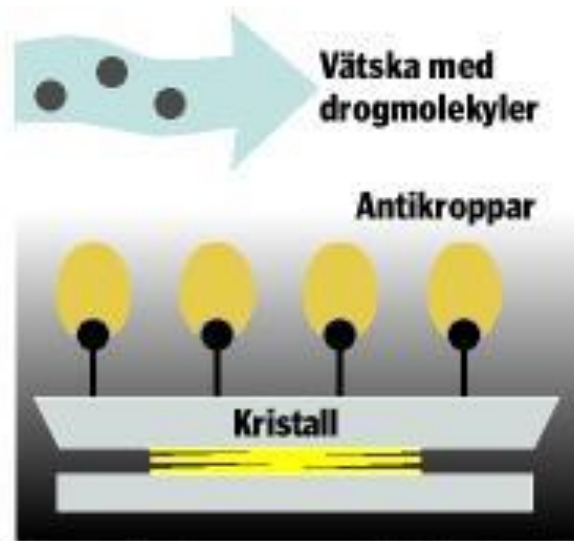
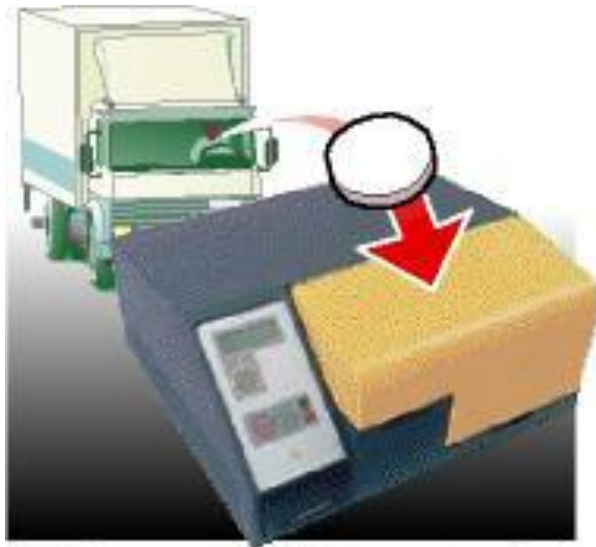
Mass sensors

- Uses piezoelectric crystals such as quartz
- Setting them into oscillation at their resonant frequency
- This resonant frequency is dependent on the way the crystal is cut and on dimensions but once these have been fixed, any change in mass of the crystal will change its resonant frequency.
- The sensitivity is generally very high - of the order of 10^{-9} g/Hz and a limit sensitivity of about 10^{-12} g.
- Since the resonant frequency of crystals can be very high, the change in frequency due to change in mass is significant and can be accurately measured digitally.



Biosensor for drug detection

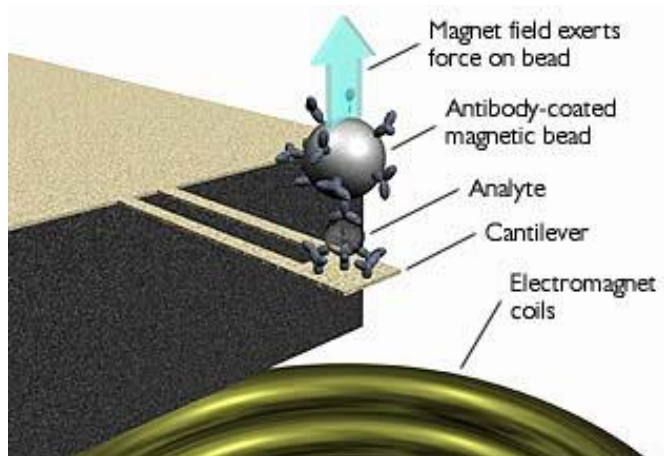
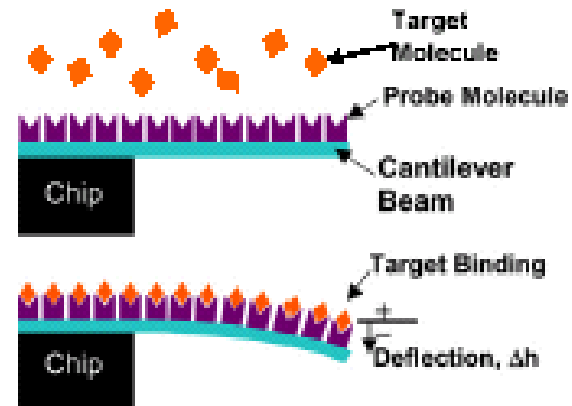
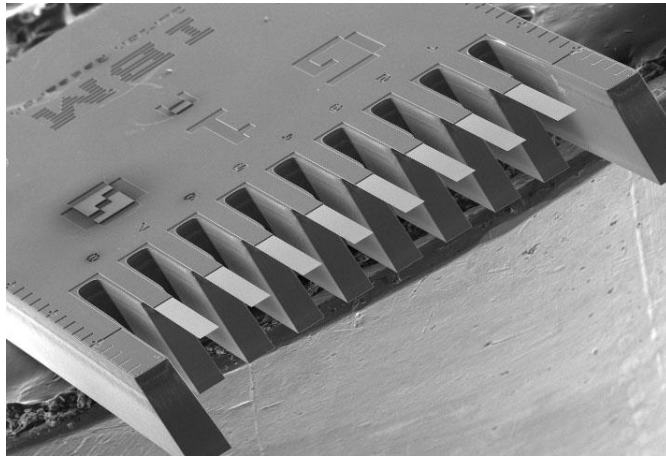
Narcotics discovery without a dog



www.nyteknik.se



Mass sensor - cantilevers



Optical sensors

- **Opto-chemical sensing are the properties of some substances to fluoresce or phosphoresce under optical radiation.**
- **These chemiluminescence properties can be sensed and used for indication of specific materials or properties.**
- **Luminescence can be a highly sensitive method because the luminescence is at a different frequency (wavelength) than the frequency (wavelength) of the exciting radiation.**
- **This occurs more often with UV radiation but can occur in the IR or visible range as well and is often used for detection.**

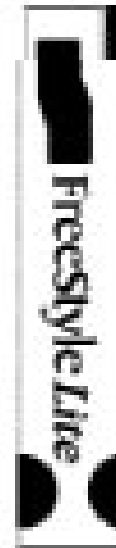


Blood sugar

- 0.3 ul blood
- 5 sec
- Pris 400 sek



Blodprovstagare



Teststicka



Mätare



www.abbott.se

Array-based fluorescence detection of biomolecules

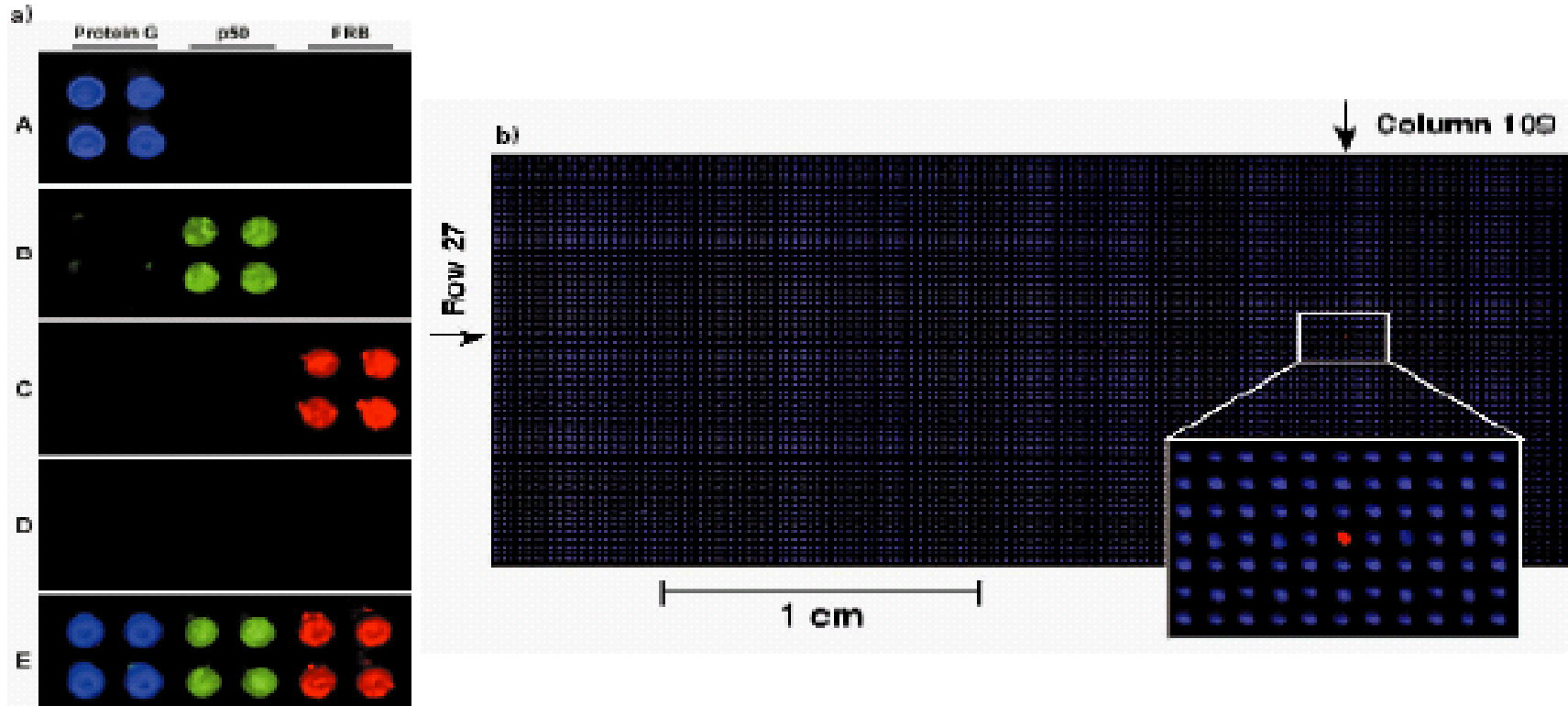


FIGURE 6.34 • Detection of protein-protein interactions on protein microarrays.

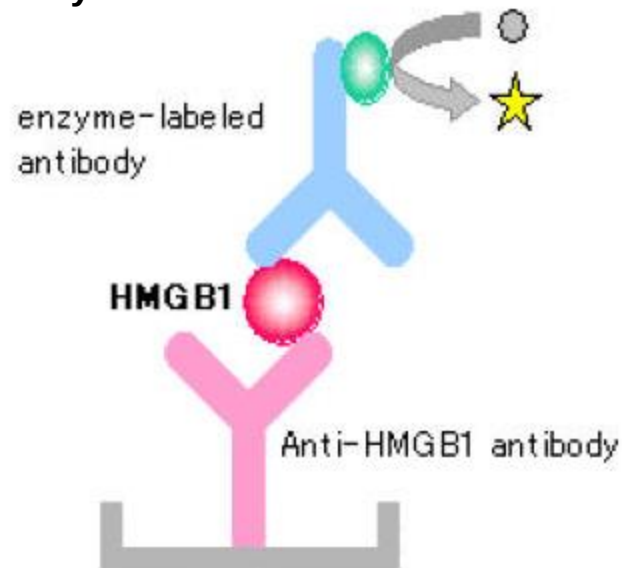
Surface area, chemistry and deposition technique important



Amplifying the signal for optical biosensors

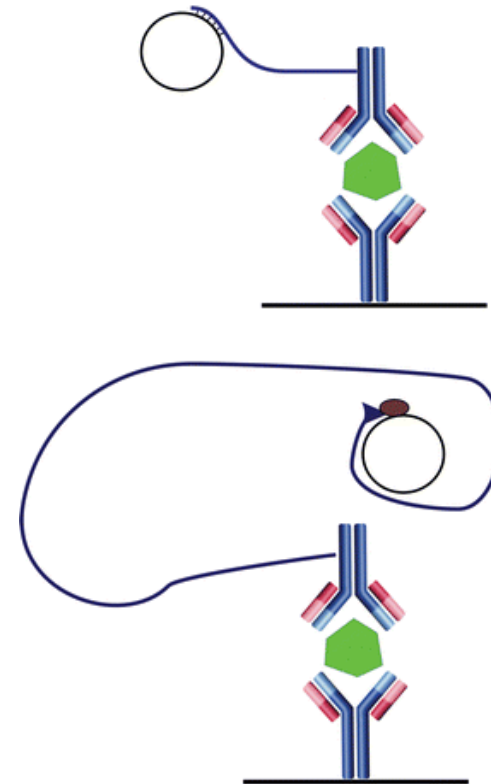
Elisa

Enzyme-Linked Immunosorbent Assay



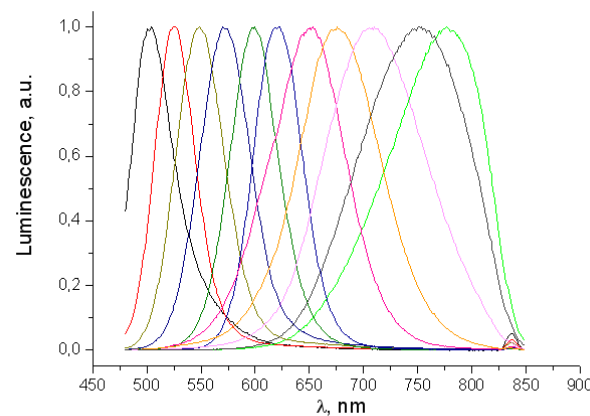
RCA

Rolling circle amplification

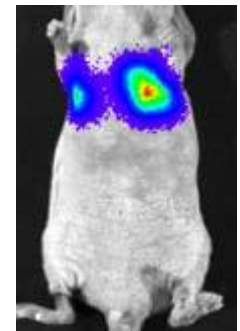
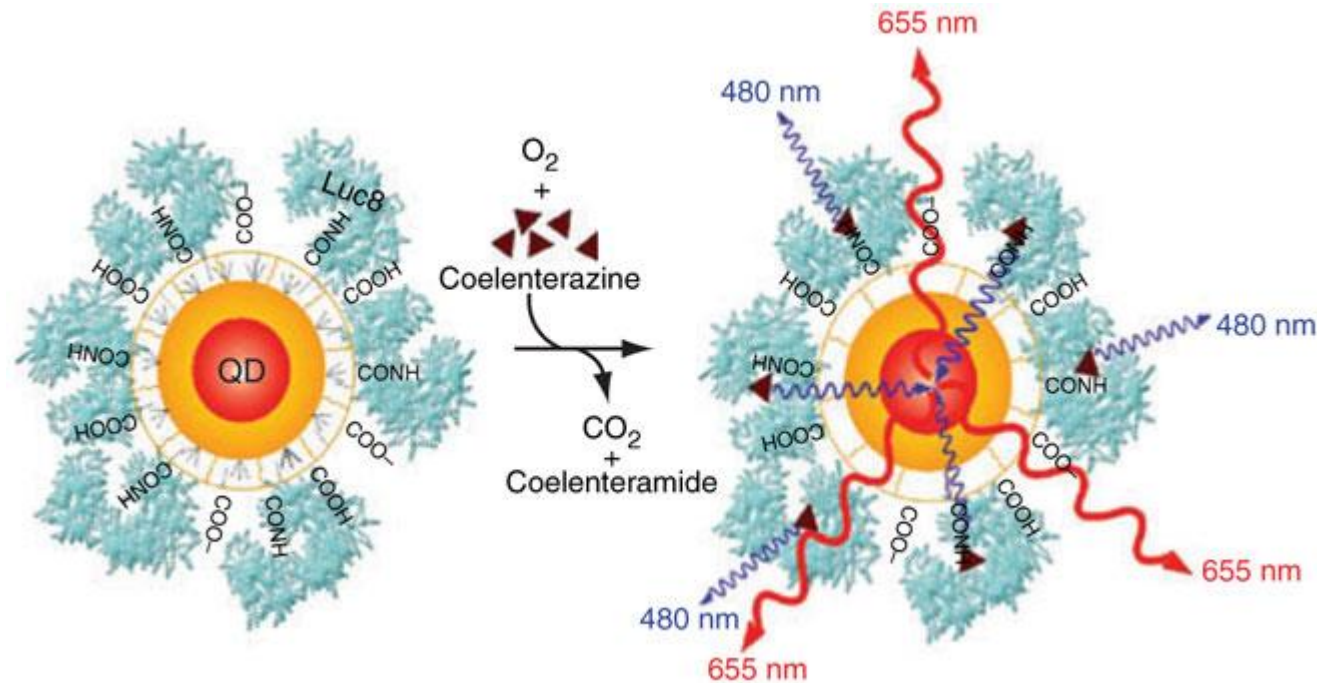


Quantum dot's

- Use as a labels on e.g. an antibody
- 2 to 10 nanometers, corresponding to 10 to 50 atoms
- Size defines color of emitted light



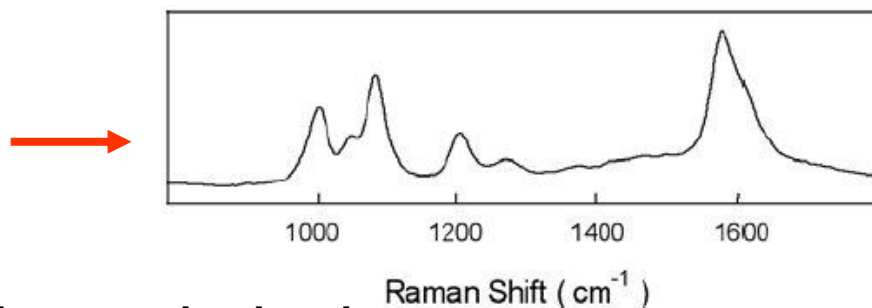
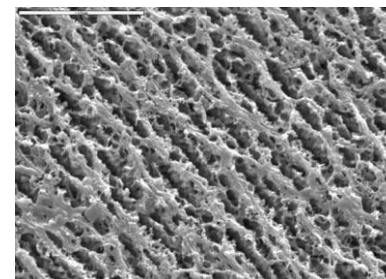
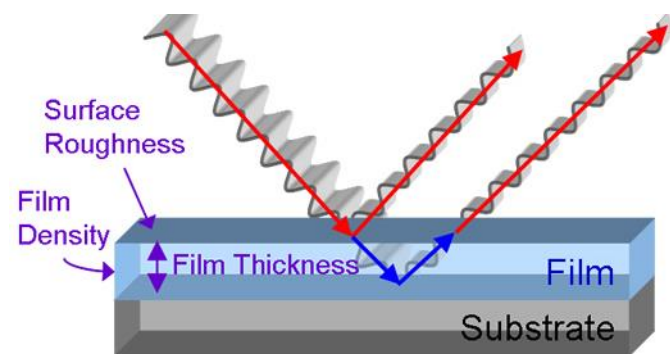
Bioluminescent quantum dots



So, M. K.; Xu, C.; Loening, A. M.; Gambhir, S. S.; Rao, J. Self-Illuminating Quantum Dot Conjugates for in vivo Imaging. *Nat. Biotechnol.* 2006, 24, 339-343.



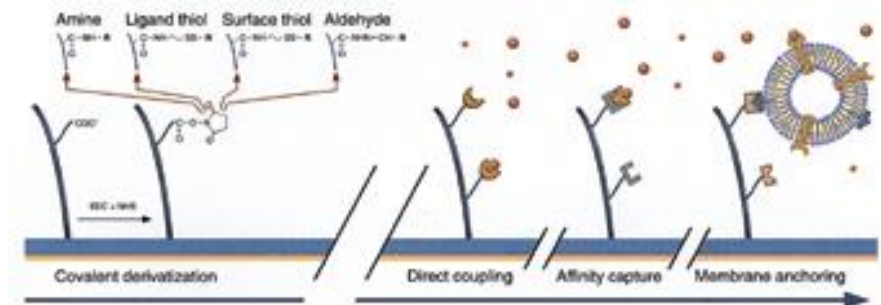
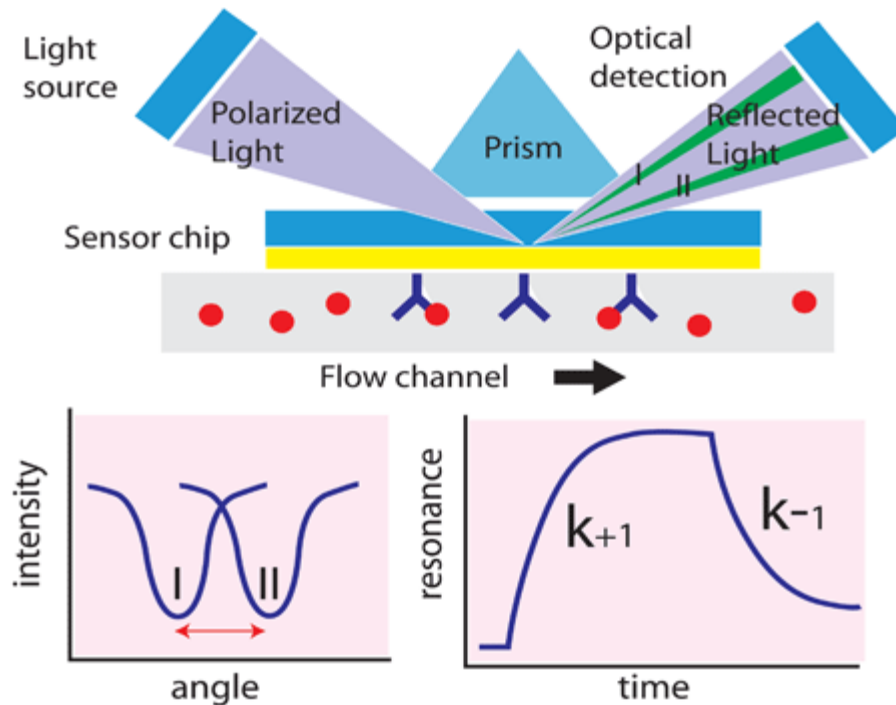
Surface Enhanced Raman Spectroscopy - SERS



- Nanostructured surface gives 10^6 - 10^9 increase in signal
- High sensitivity, on par with heterogeneous, amplified systems
- SERS signal is photostable and, unlike fluorescence, cannot be “quenched”
- Signal is unaffected by ionic strength or temperature variations
- Does not work for all analytes



SPR (Surface plasmon resonance)

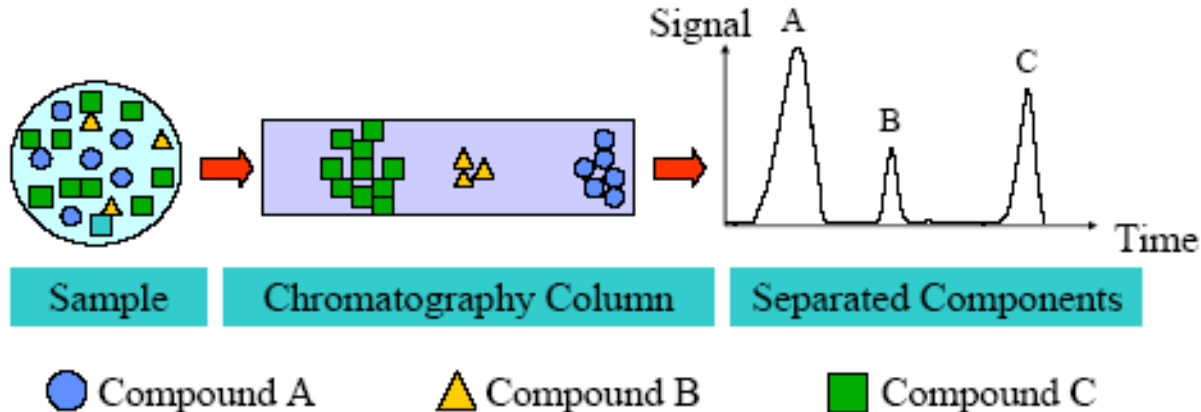


www.biacore.com

Surface plasmons, are surface electromagnetic waves that propagate parallel along a metal/dielectric interface



Chromatography



- Multicomponent samples are separated in specially treated separation columns before measurement with a detector
- Samples are separated by different migration speed inside column due to differing adsorption characteristics
 - Liquid/Ion Chromatography (HPLC, IC)
 - Solid column, liquid samples
 - Gas Chromatography (GC)
 - Solid column, gas samples

Migration speed : $\bar{v} = u(1 + KV_s / V_M)$

(u : flowrate of eluent, K : equilibrium coef. between adsorbed amples and mobile samples,

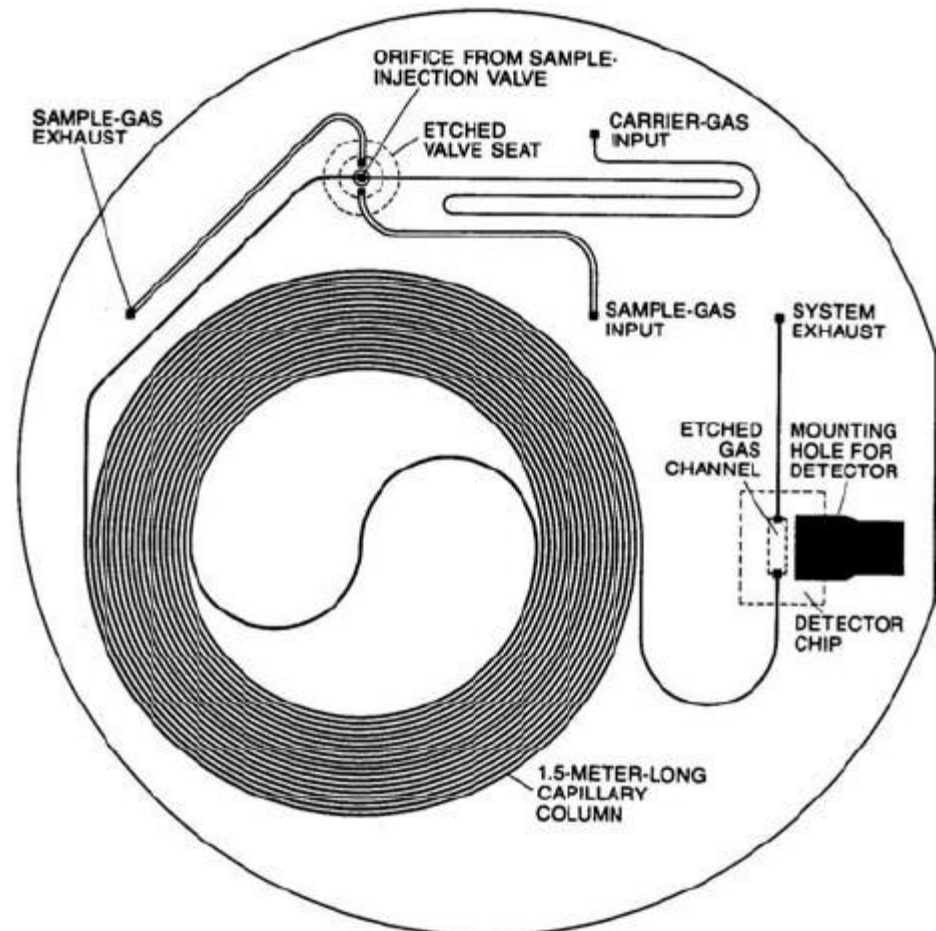
V_M : volume of mobile samples, V_s : Volume of stationary sample)



Chromatography

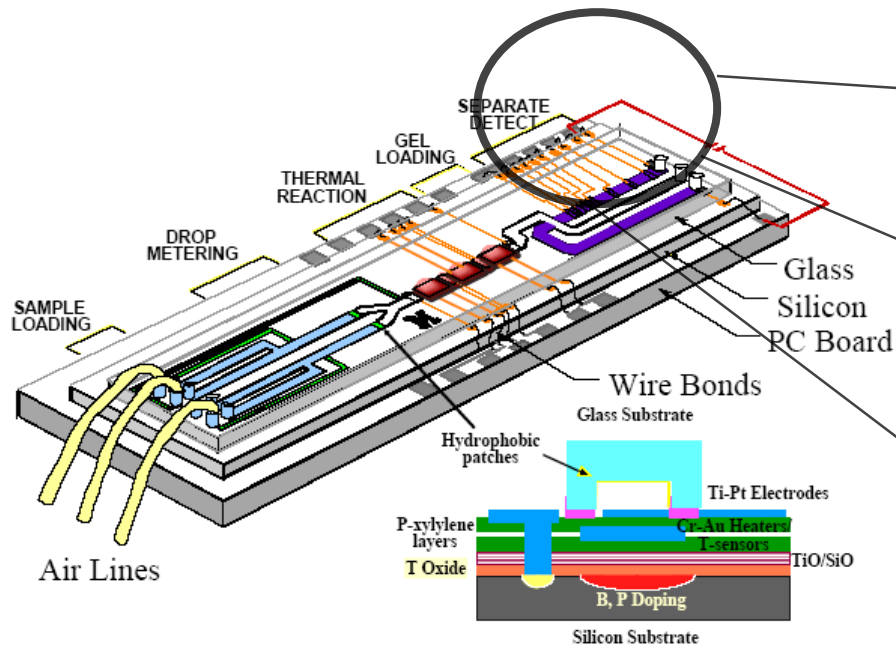
Stanford Gas chromatograph

- 2" silicon wafer
- Isotropic etch
- Pyrex lid
- 1.5 meter column

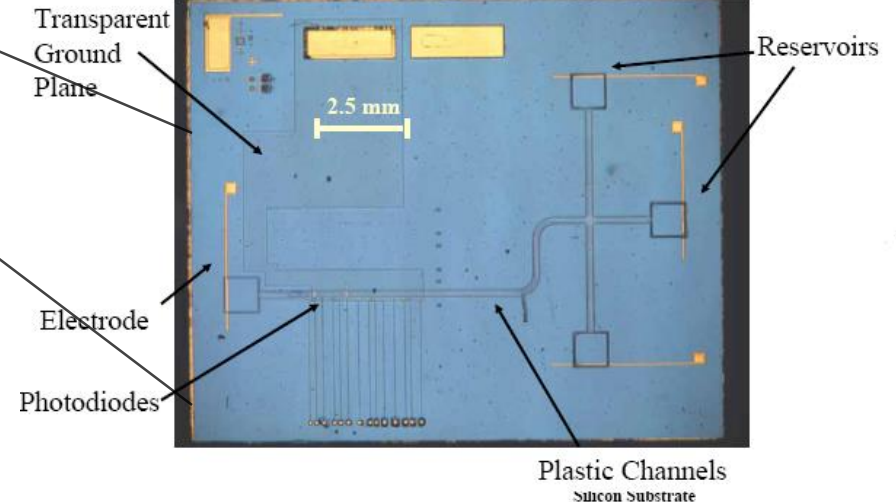


Terry SC (1975)

Micromachined Capillary Electrophoresis



**Microfluidic Chips
for Integrated
DNA Assays
(University of Michigan)**

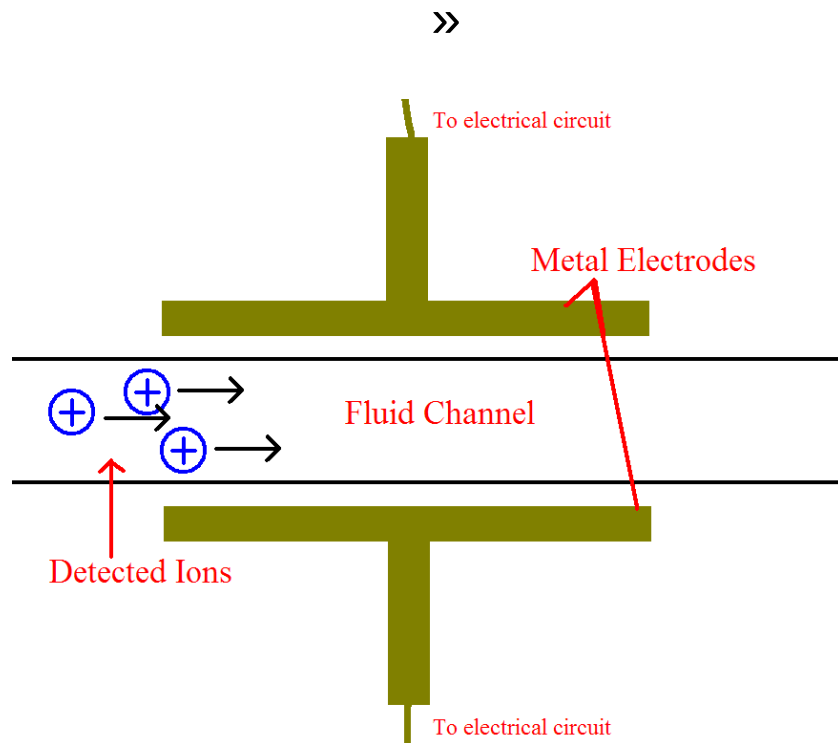


**Electrophoresis Chip
with Integrated
Fluorescence Detector
(University of Michigan)**



Parallel Plate Capacitance Detection

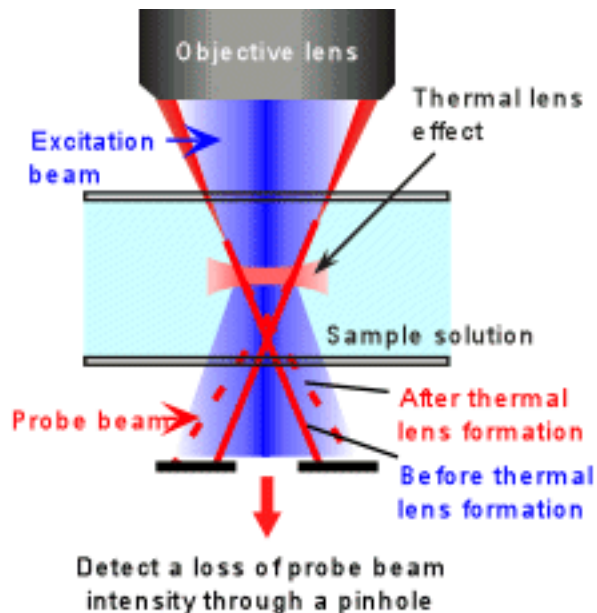
– Application: Sensing particle concentration in a fluid sample



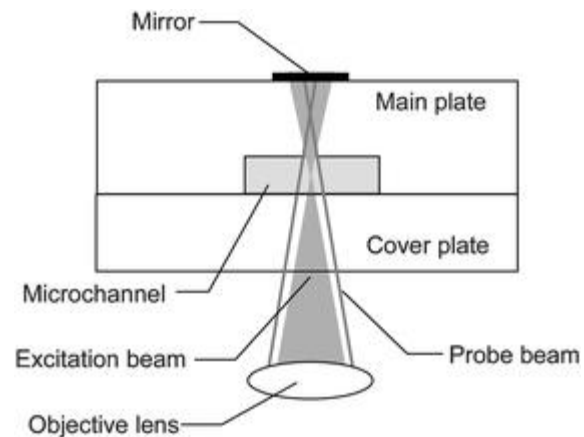
How it works: The dielectric constant of the fluid between the plates fluctuates with varying concentrations of the particles to be detected. This change in the dielectric constant results in a change in the capacitance of the plates, which is then measured in an electric circuit. Minute changes in capacitance are used to determine concentration



Thermal lens

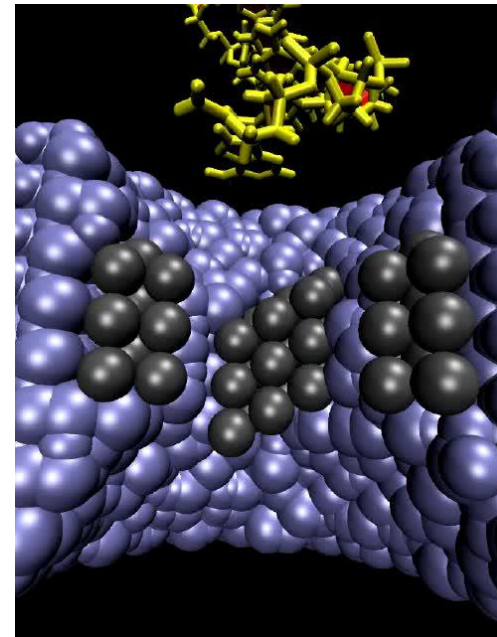
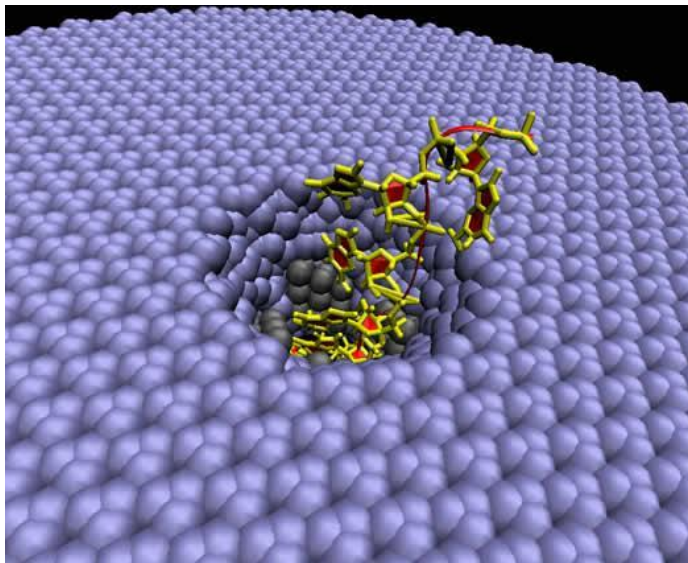


Label free, but requires a clean sample



Nanopore DNA reader

The device would work by running an electric current across a DNA strand as it is drawn through a nanopore, using electrodes built into the pore's sides. Detecting the changes in current that correspond to the four different bases, or "letters", that make up DNA would read off the sequence as it passed.



Meller, A., L. Nivon, E. Brandin, J. Golovchenko, and D. Branton. 2000. Rapid nanopore discrimination between single polynucleotide molecules. *Proc. Natl. Acad. Sci. USA* 97: 1079-1084.



Important dates

Project meeting	Thursday 21/5
Poster finished	Monday 27/5, 12.00
Poster presentation	Wednesday 29/5, 9.15 - 12
Tenta, E:1328	Thursday 3/6, 8-12



Project meeting 3

Sensor	Time
Accelerometer	21/5, 9.15
Pressure sensor	21/5, 10.15
Flow sensor	21/5, 11.15



Poster presentation 29 / 5



Piezoresistive Pressure Sensor

- A three step overview -

Sajjad Haider & Axel Ekenstierna
Elektrisk Mätteknik, LTH, Lund, Sweden



What is a Pressure Sensor

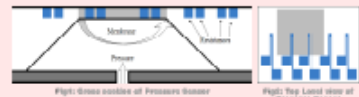
A pressure sensor measures the pressure, typically of gases or liquids. Pressure is an expression of the force required to stop a gas or fluid from expanding, and is usually stated in terms of force per unit area. A pressure sensor generates a signal related to the pressure required.

Physics

When put under mechanical stress piezoresistive materials change resistivity due to deformation of the crystal structure which causes a change in band structure. Effectively this is used to transform the mechanical energy then present to an electric signal.

Construction

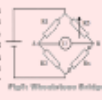
The sensor is created by doping with the pattern seen in figure 1 and 2 to create the piezoresistive elements. Part of the silicon plate is then etched so that only a thin membrane remains (the grey area). The etched pressure chamber is sealed with a glass lid through wafer bonding. Lastly the sensor is mounted on a circuit board and metal contacts are bonded to provide easier access for measurements.



Experiment Setup

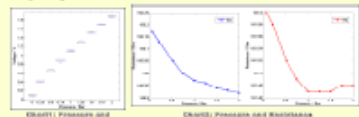


The pressure sensor is connected to an external pressure source through a setup of two elastic valves enabling precise regulation of the flow. A reference pressure sensor is also used. To shield the sensor from light a special dark box was constructed. The piezoresistive elements are connected in a Wheatstone bridge configuration to minimize interference and thermal effects. Together with an amplifier and power supply this forms the basis of the experiment setup.



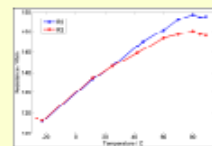
The Most Interesting Thing

The most interesting information about a pressure sensor is of course how input is related to output. As stated above, this relationship should be linear with a Wheatstone bridge configuration.

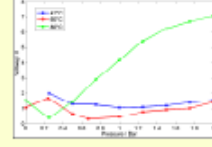


When applying pressure the voltage and resistance were measured. As expected a linear curve can be seen in the voltage measurement whereas the resistance show a non-linear relationship. Please compare the difference in resistance change due to pressure and temperature seen in the top right box.

Temperature Effect



Keeping the zero pressure over the membrane, voltage was measured while varying the temperature. Table below of the big resistance change compared to the effect of pressure.



More different lines are shown where each represents a different temperature, by applying different pressure voltage was measured.

Conclusion

It is obvious that the piezoresistive technology satisfies many crucial attributes of use in sensors. With high accuracy, integrative with silicon electronics and the possibility of using a Wheatstone bridge it has many advantages. The price to pay is, as can be seen in the results, a high thermal dependence. Though not accounted for in the results, the sensor, being made of silicon, is also affected by light and other electromagnetic radiation. Further experiments required to fully characterize the piezoresistive sensor mostly involve comparative measurements to provide better statistical data. Other factors such as sensitivity, possible pressure range and long term stability would also be of interest to anyone.



Piezoresistive Accelerometer in Silicon

J. Khan and R. Trygg
Microsystem, TEM 010, Lund University, Lund, Sweden, 2008-05-19
"Headliner": Lars Wallsten



Background and Manufacturing

Accelerometer is an important physical characteristic of a system, and can be used to describe many safety properties of the system, for example, mechanical and structural proof, mass measurements, a force proportional to the acceleration. The piezoresistive accelerometer measures the force or acceleration in the form of a resistance change in the resistive element used as the transducer for the sensor mass. Changing this a piezoresistive element requires a Wheatstone bridge circuit (Figure 1) that converts change in the resistance of the elements into a voltage for bridge and provides a signal output by a measuring device, in order to obtain a signal of acceleration or force after effect in the system (piezoelectric for example).

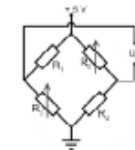


Figure 1. Wheatstone bridge with two variable and two constant resistors.

The piezoresistive accelerometer is manufactured from a silicon wafer to take advantage of the large development in the field of silicon technology and existing infrastructure and to create the smallest possible sensor with minimum cost. The piezoresistive accelerometer has a wide range of applications.

Figure 2 shows the piezoresistive accelerometer fully built, characterized. With a total of four piezoresistive elements made from doped silicon where four constitute the bridge and the remaining four serve as a current load for the measurement system. Good characterization of the sensor is an important as useful measurement of the sensor. Simply put, the sensor that we would work for a given range to know the output with a minimum error deviation from inspection and other effects in order to maintain the number of standard deviation to be small. This stage is an interesting to know about the sensor and the piezoresistive element in the sensor bridge, the acceleration and the knowledge about the sensor, e.g. frequency dependence and effect of temperature variation.

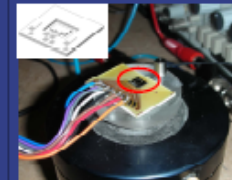


Figure 2. Our accelerometer with principal characteristics.

Characterization

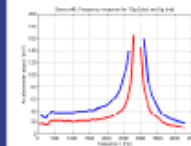


Figure 3. Frequency response of the sensor.

Frequency Response and Resonance Frequency

The important parameter is to have the response of the accelerometer with varying frequency. Figure 3 shows the frequency response of the sensor for 100 kPa and 150 kPa. This shows that the accelerometer should be operated in the frequency range of 0 to 100 Hz, which is the range of interest for most applications. The figure also shows a resonance peak at 1.5 kHz, confirming the resonance frequency measured through the analysis of the response in a high frequency range. The resonance frequency is around 1.5 kHz, which is the range of interest for most applications.

The width of the resonance peak displays the range from 0 to 100 Hz and the width of the peak is around 10 Hz, which is the range of interest for most applications.

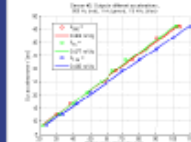


Figure 4. Output for a range of acceleration and frequency, and the resonance frequency for each curve.

Sensitivity

The most important parameter in which a sensor should be calibrated is the sensitivity. It is the ratio between the output voltage and the input voltage. The sensitivity of the sensor should be known for the range of frequency in the range of 0 to 100 Hz. The sensitivity of the sensor is around 10 mV/g, which is the range of interest for most applications.

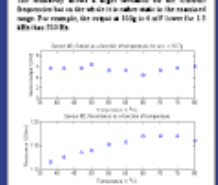


Figure 5. Temperature dependence of the sensor output voltage and for 100 kPa and 150 kPa.

Temperature Dependence

The range of the piezoresistive accelerometer would be the temperature dependence, but the Wheatstone bridge is not temperature dependent. The piezoresistive element is not temperature dependent, but the Wheatstone bridge is temperature dependent. The output voltage is around 10 mV/g, which is the range of interest for most applications.

Looking at the resistance versus with temperature, Figure 6, we can see that the resistance is not temperature dependent. The output voltage is around 10 mV/g, which is the range of interest for most applications.

Conclusion

Being aware of a number of sensors of the same type and their characteristics is the ability to select a sensor that is suitable for the application. The piezoresistive accelerometer is a good choice for many applications, but it is important to know the characteristics of the sensor and the piezoresistive element in the sensor bridge, the acceleration and the knowledge about the sensor, e.g. frequency dependence and effect of temperature variation.

Poster presentation

Wednesday 29/5 9.15 - 12

10 minutes presentation from the group

5 minutes questions from the opponents

Questions from the audience....-----



Tenta

Monday 3/6

8 - 13

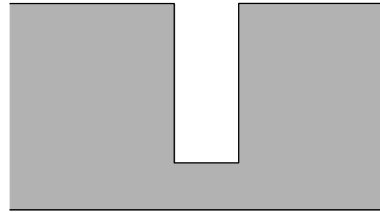
Calculator, ruler,

20 short questions 1p

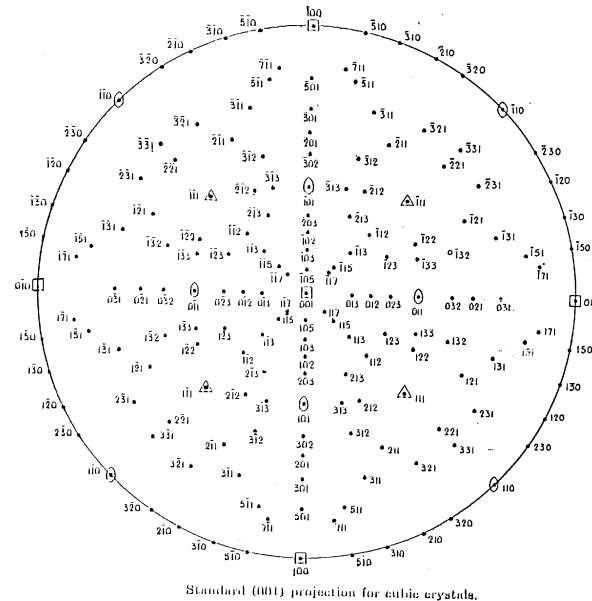
1 longer 5p



1. So what's the big deal about microsensors?
How can you answer to that? Write at least four advantages of microsensors compared to traditional sensors.
2. There are two main production techniques for silicon for electronics and micromechanics: Czochralski and Float-zone. Describe the two techniques.
3. Write two etch methods that give you the etch profile showed below.



4. The figure show a projection map of a silicon $\langle 100 \rangle$ wafer crystal structure. I you intend to etch a so called v-groove in such a wafer, how would you orient your mask. Mark a line in the projection map where your channels should be aligned.

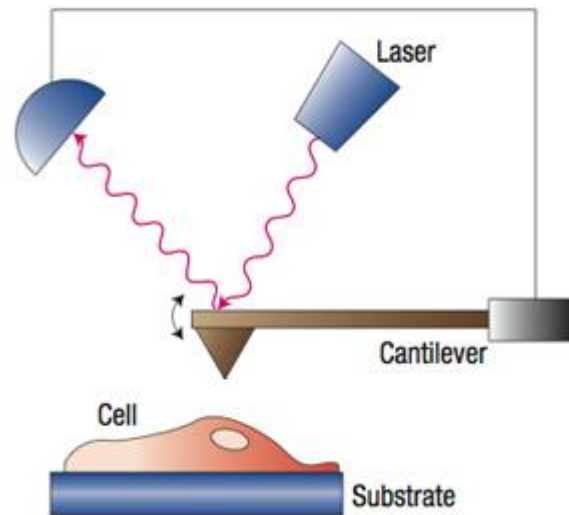




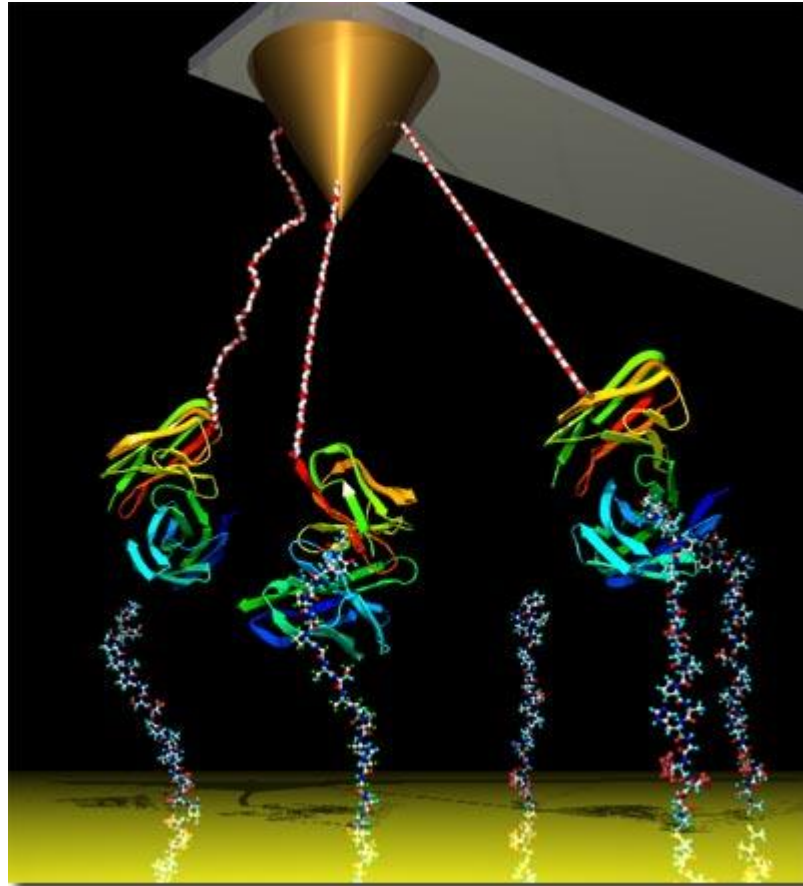


Atomic force microscope

- Detecting cancer by probing the elastic properties of cells. The elasticity of benign cells and malignant cancer cells were mechanically probed with an atomic force microscope.



AMF binding measurement



T. Sulchek et al., "Dynamic Force Spectroscopy of Parallel Individual Mucin1-Antibody Bonds," Proc. Natl. Acad. Sci. 102, 16638 (2005).



End users for the technology

- **Research- discover new biology by faster and more sensitive analysis**
- **Diagnostics – biomarkers, POCT, personal medicine**
- **Biopharmaceuticals - screening, QA mm**
- **+ Food Industry, Environmental, forensic and military applications**



Detection of Magnetic Beads

Giant MagnetoResistive (GMR) Sensor

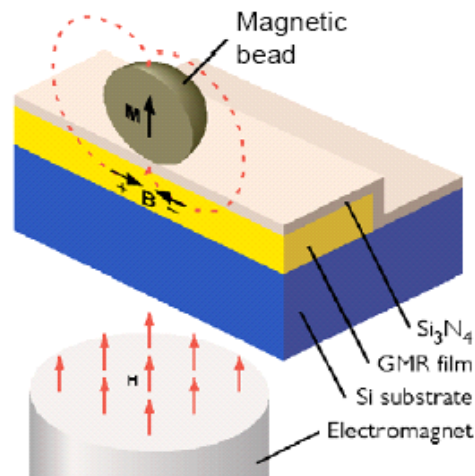
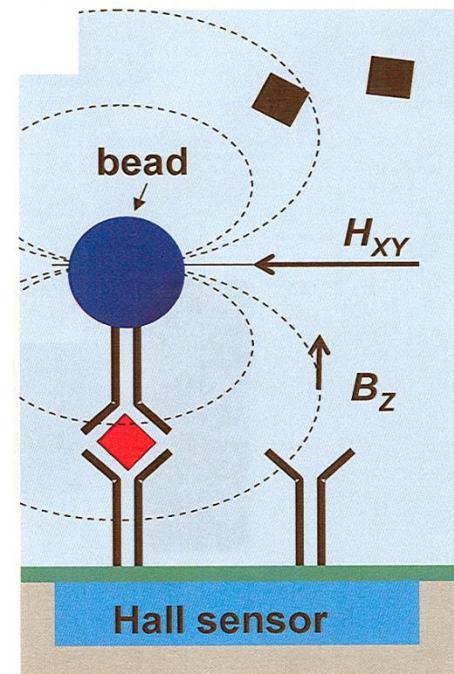


Fig. 5. Schematic of sensor magnetics. An external field induces a magnetic moment in the paramagnetic bead, and its induced field causes a decrease in the resistance of the GMR film.

(Source: NRL Technical Proposal
ATL-415-NAVALRL-FPTECH-4)

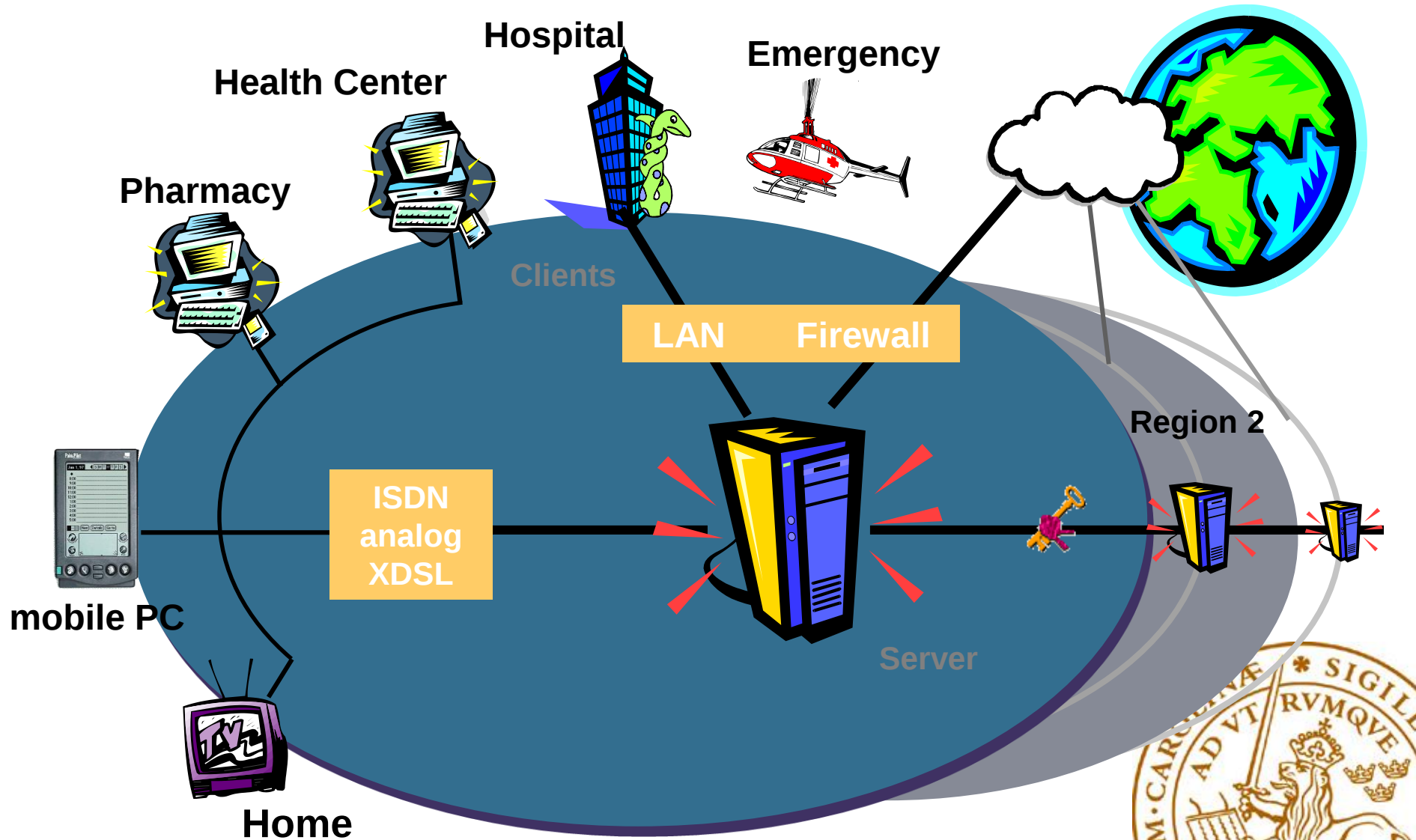
Hall Sensor



(Source: B. Boser, European IAB, 2004)

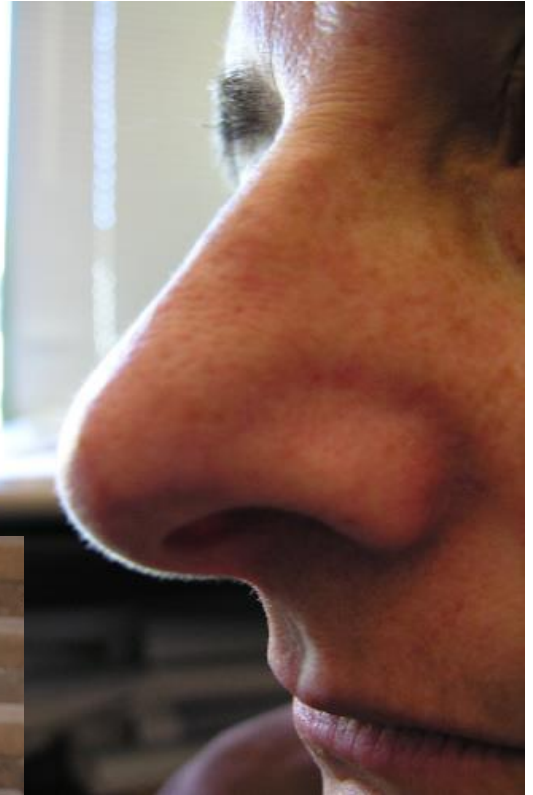


Future scenario

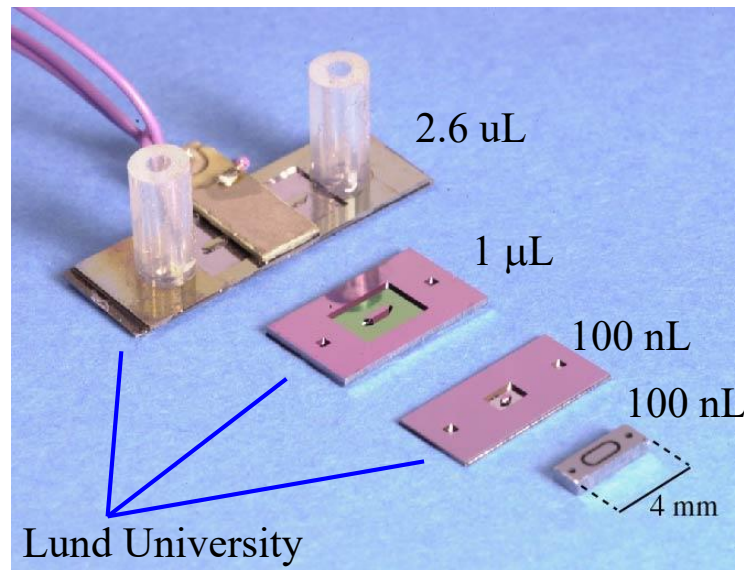
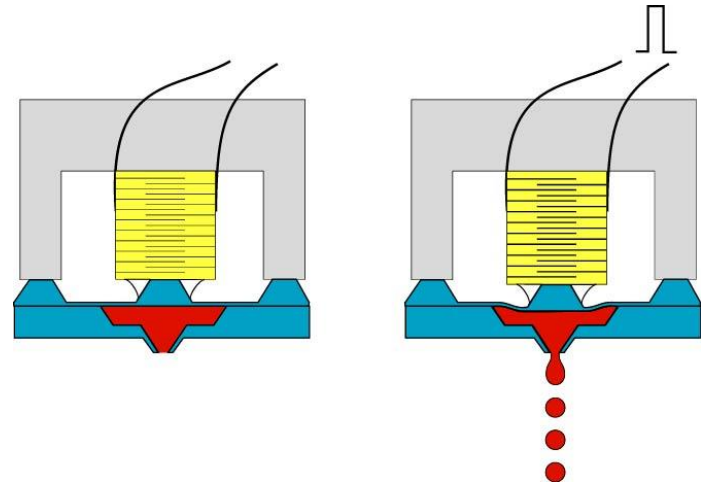
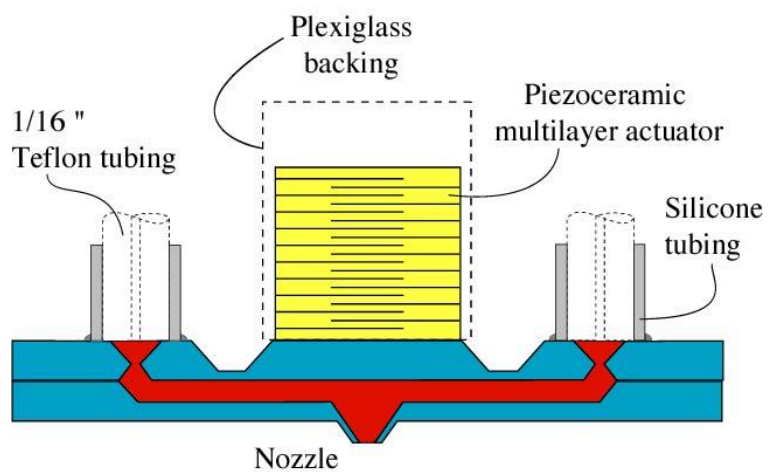


Multi-analyte Differential Sensing

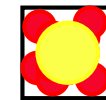
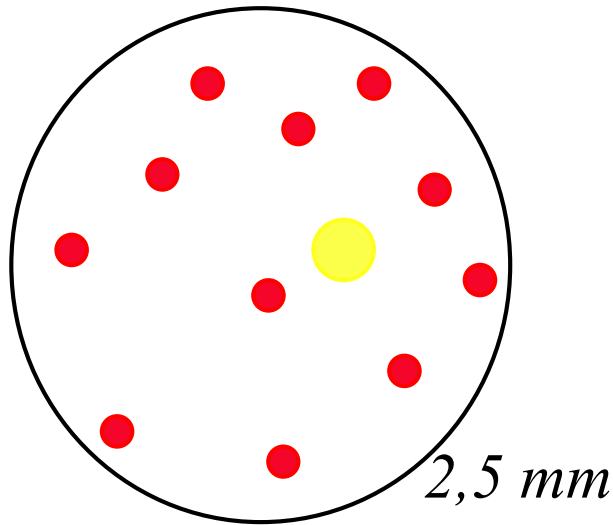
- Nature often does not use highly selective receptors
- “Differential” receptors used in arrays
- Response from each of these receptors for a particular mixture of stimuli creates a pattern



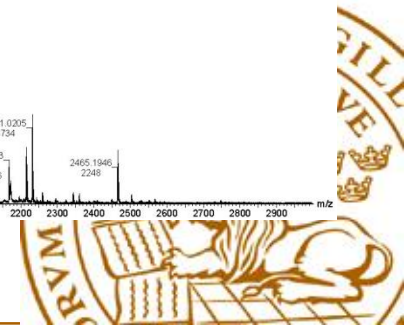
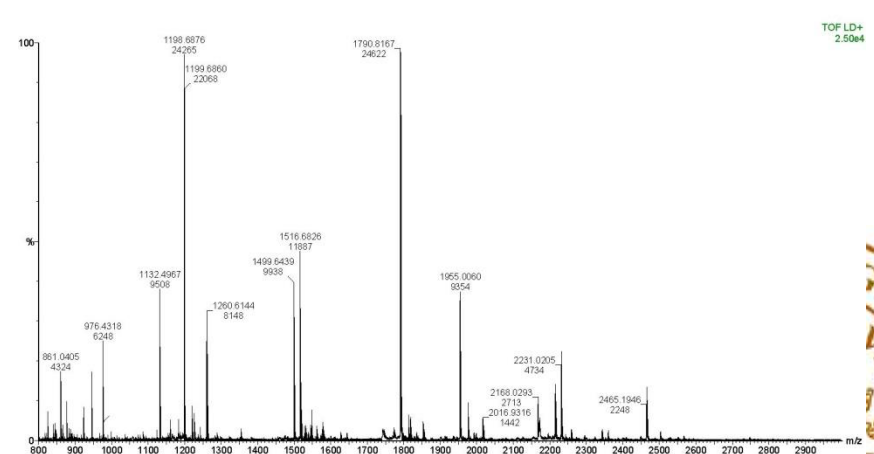
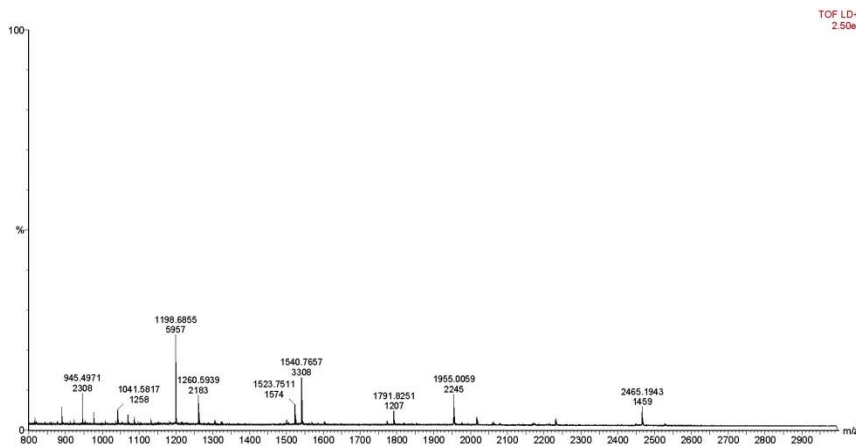
Microdispensing



Small spots = higher MALDI MS sensitivity

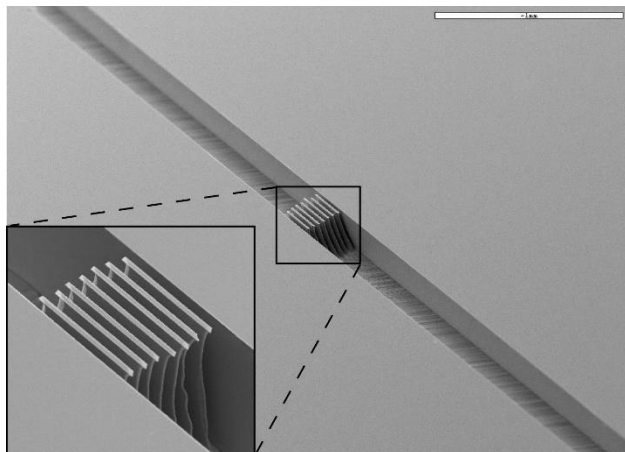


0,4 mm

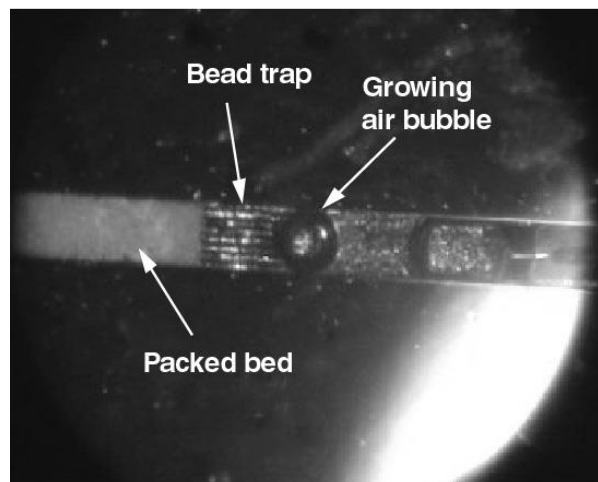


Chip integrated solid phase microextraction

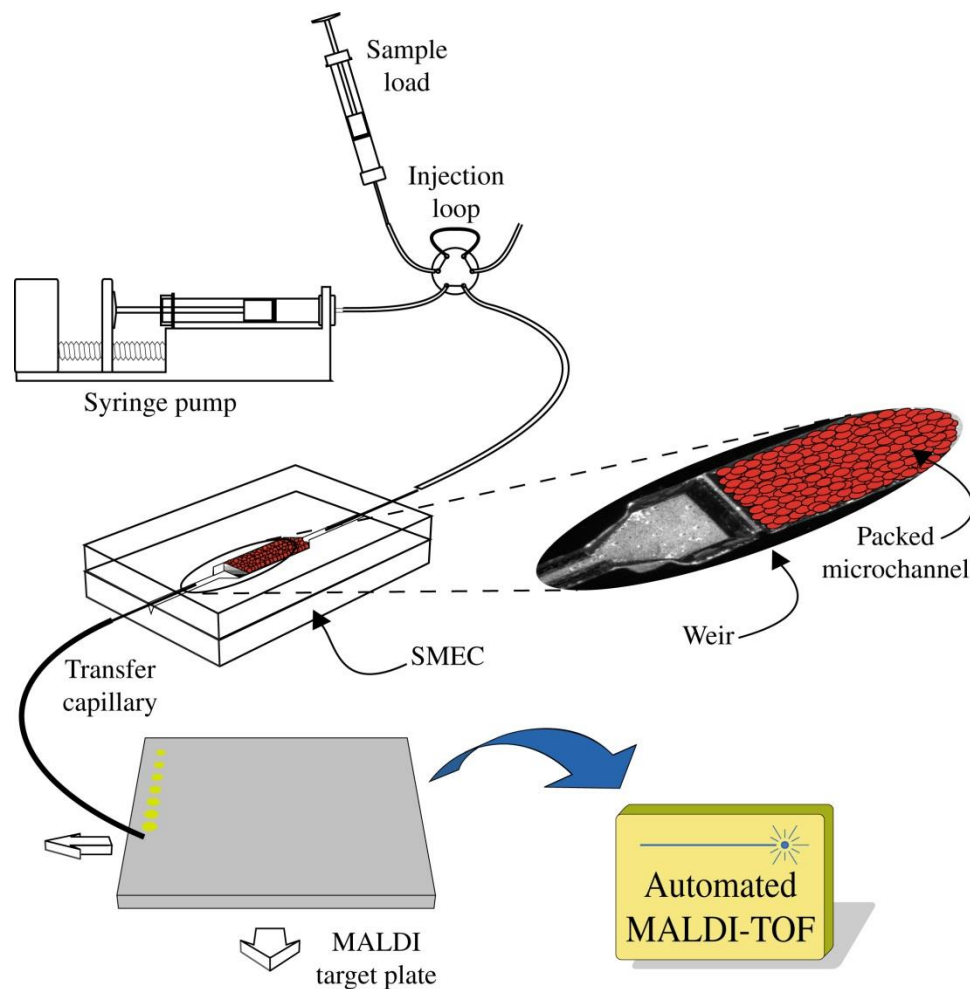
Bead trapping silicon microgrid
in a chip capillary



Problem

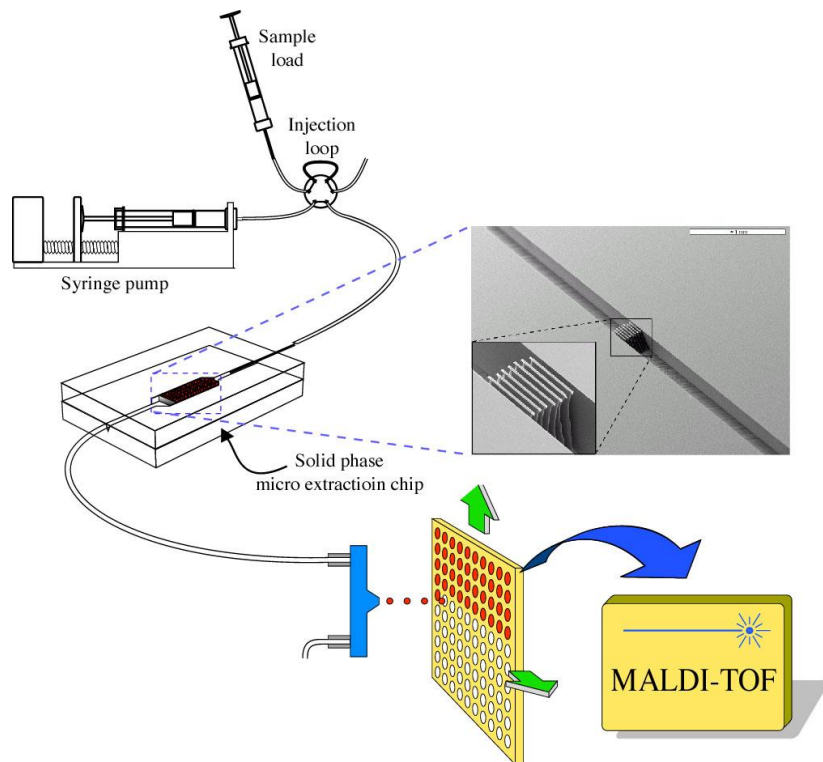


System set-up for solid phase microextraction



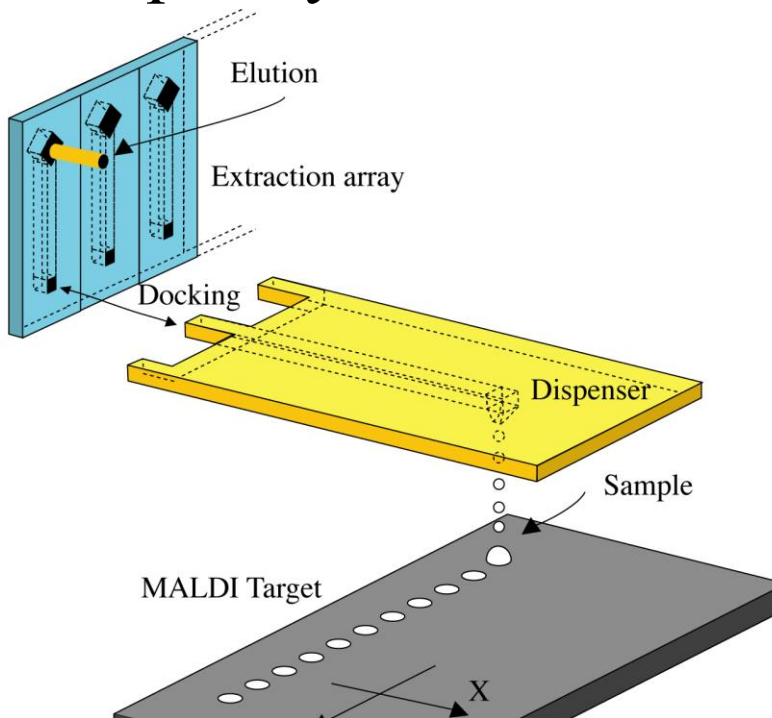
Solid-phase extraction

Pressure driven flow



Proteomics, 2002, 2, 413–421

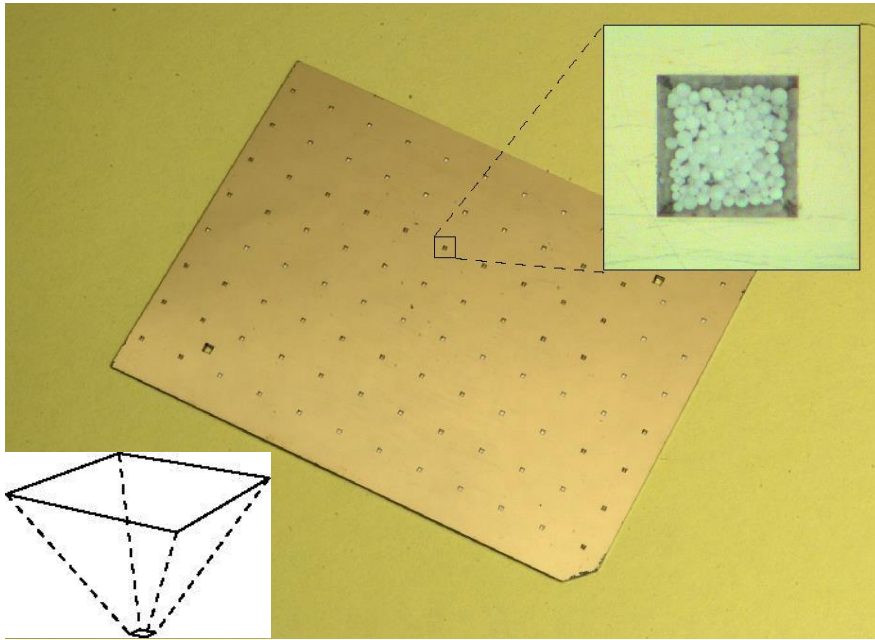
Capillary driven flow



Electrophoresis
2004, 25, 3778-3787



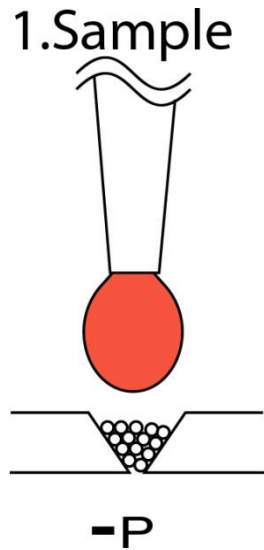
Integrated Sample Enrichment Target



Same dimensions as the standard MALDI target. e.g. 5.5 x 5 cm and 96 perforated nanovials (30 nL volume)

- Very low complexity
- Interfaces standard pipetting robotics
- Highly parallel
- Short path length
- Minimal no. of transfers as the ISET is both a sample preparation and presentation device

ISET- sample preparation and presentation



Detection of Analytes

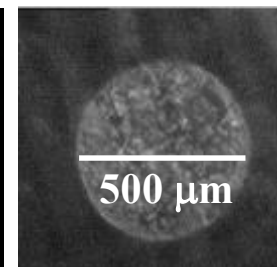
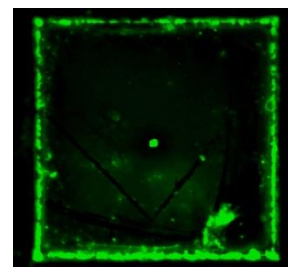
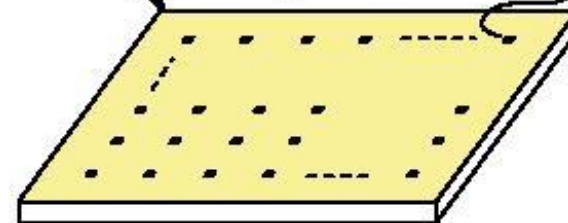
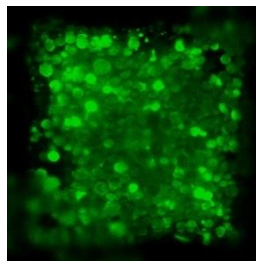
FLOURESCENCE ANALYSIS

MALDI MS AND/OR
FLOURESCENCE ANALYSIS

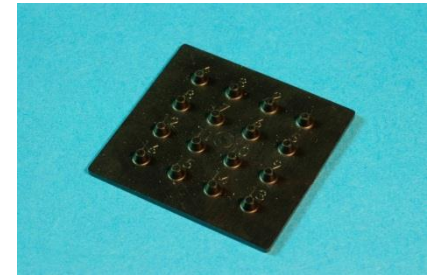
Turn up-side
down

Outlet surrounded
by analyte

Inlet, bead volume



ISET Applications



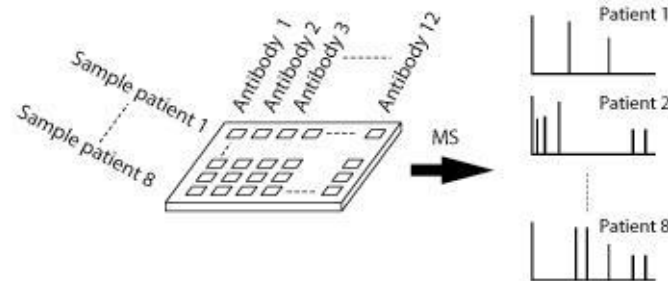
Protein separation

2-D Gel electrophoresis
2-D Liquid chromatography
CE, IEF, FFE

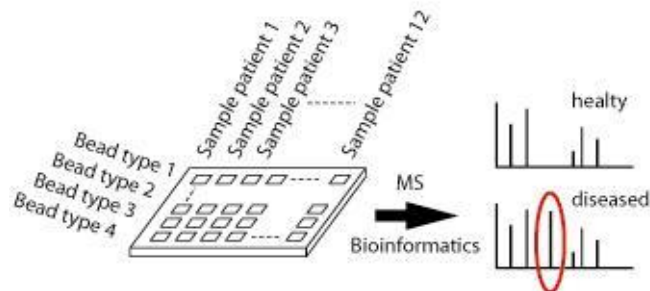


SPE
On-bead digestion - SPE
On-bead chemistry - SPE

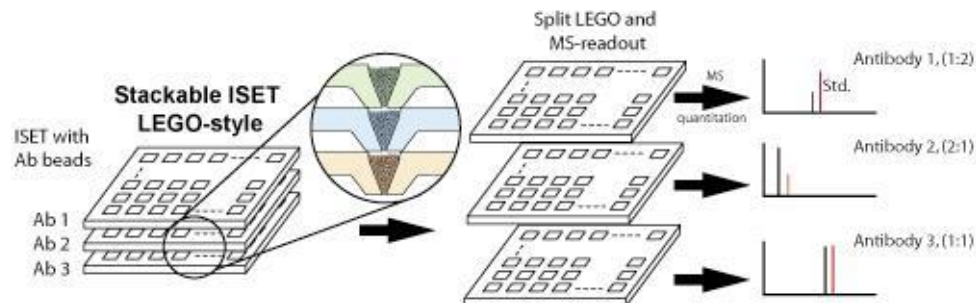
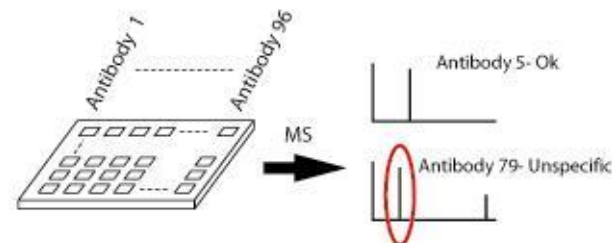
Diagnostic ISET using signature peptides



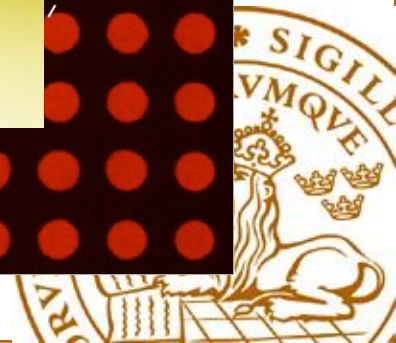
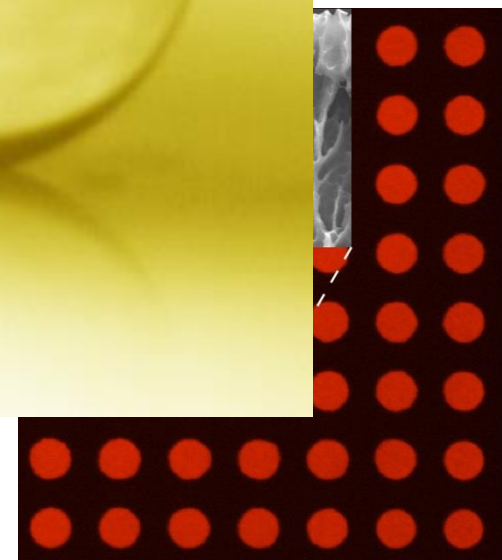
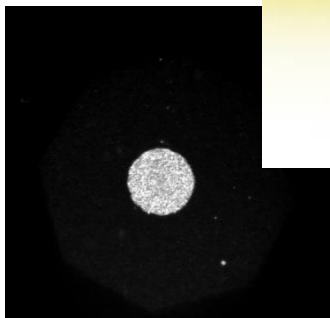
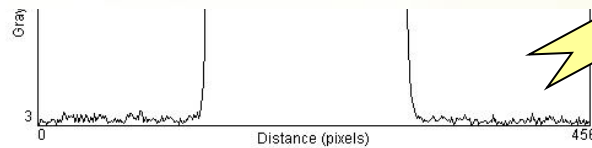
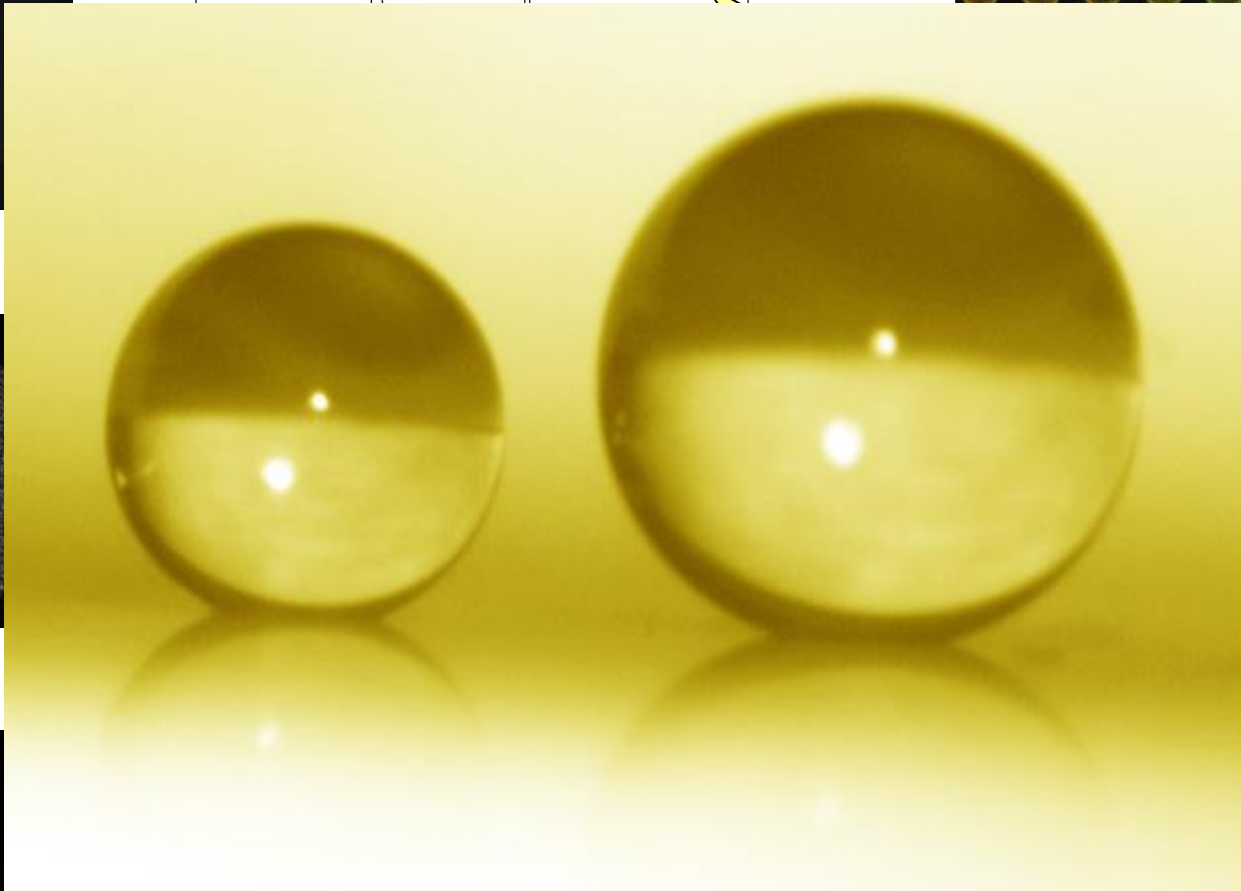
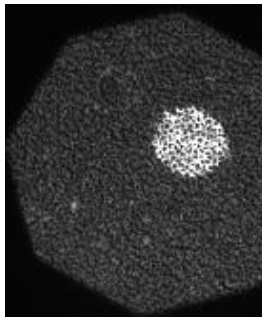
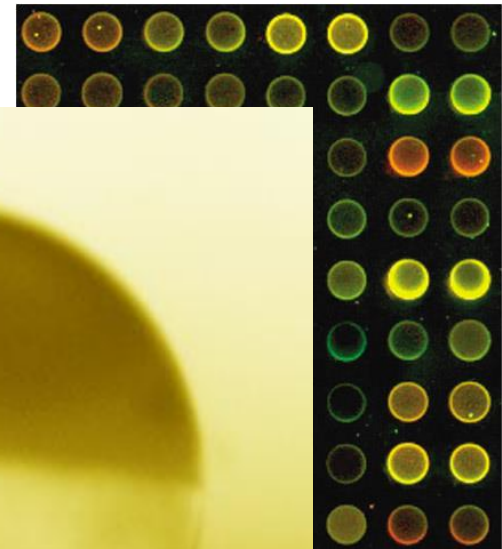
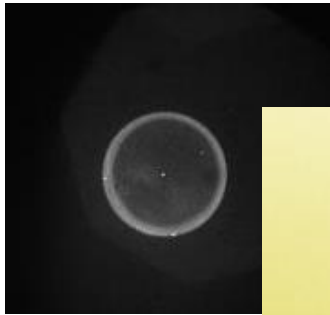
Biomarker discovery



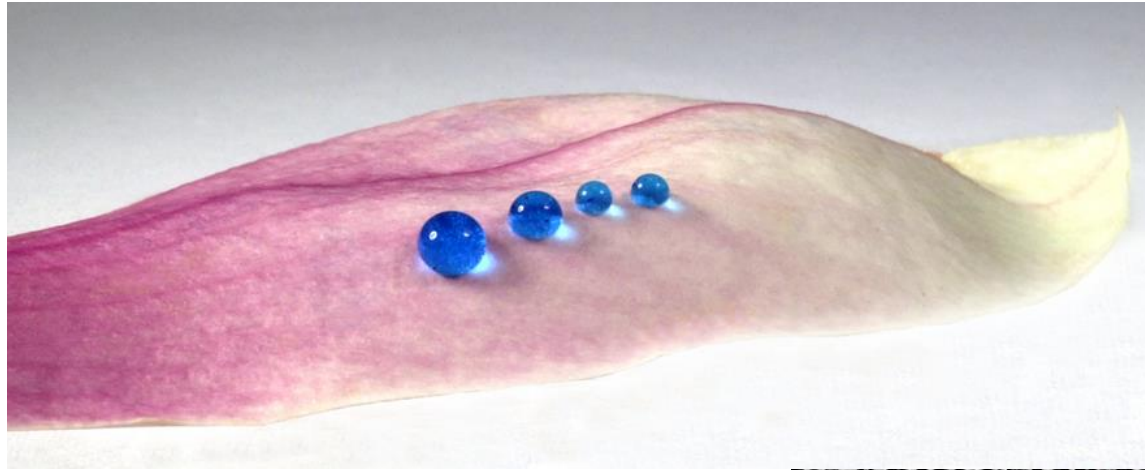
ISET validation of Antibody specificity



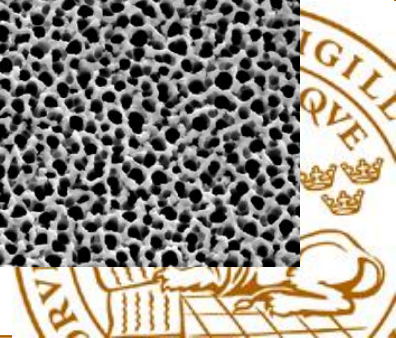
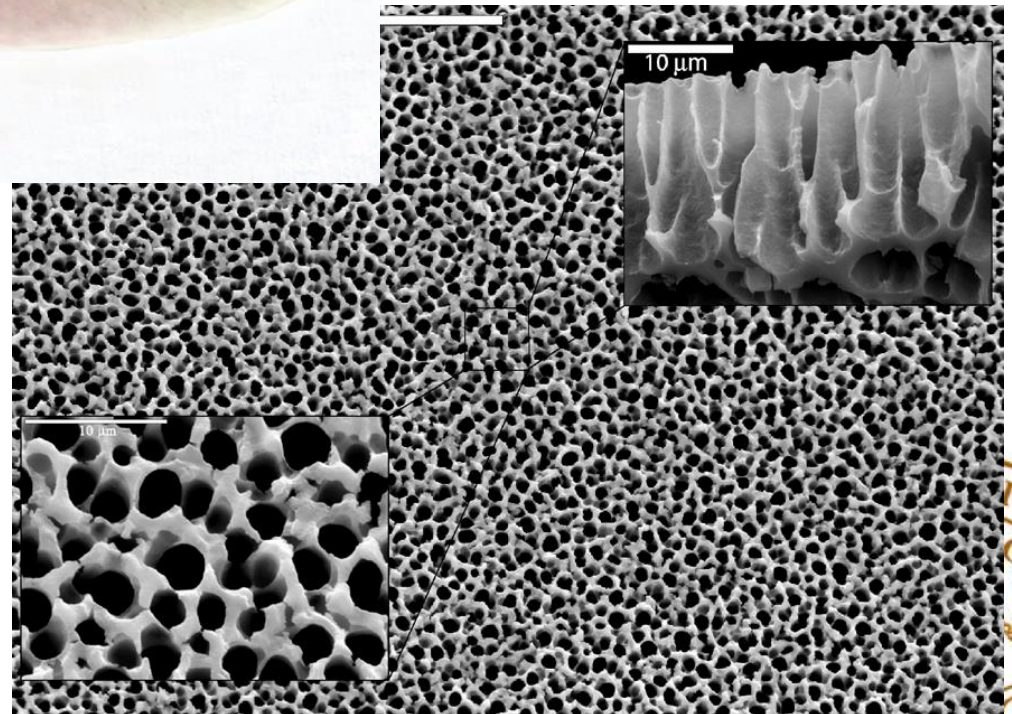
Spothomogeneity



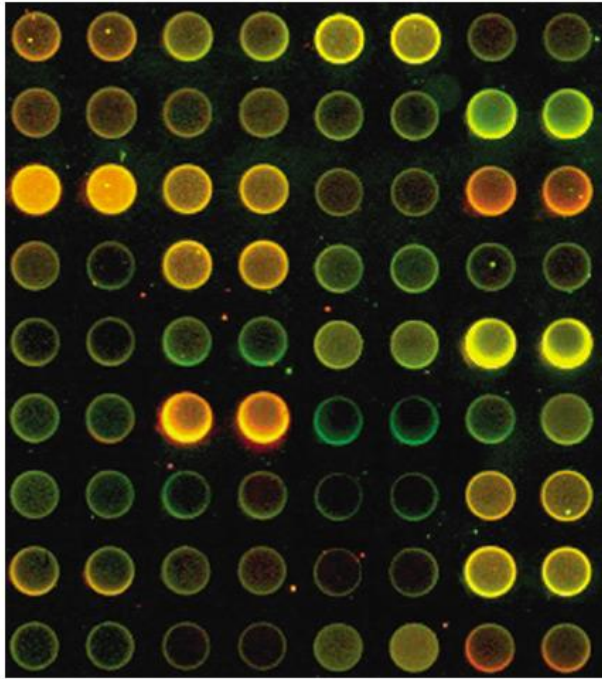
Protein chips based on porous silicon as substrate surface



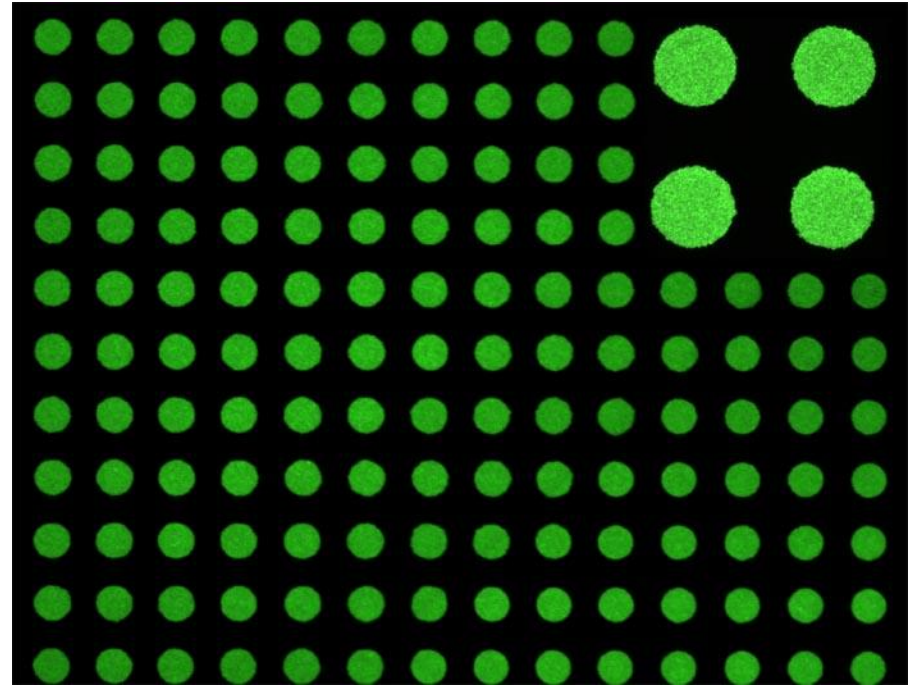
- Increased surface area
- Reduced spot size
- Homogenous spot profile



Non-homogenous spots “coffee stain” effect



Silanized glass



Macroporous silicon







Different Manufacture Process

MEMS technologies such as;

- **SOI, CMOS, etc, etc, process**
- **Vapor deposition (metaloxide)**
- **Serial Electrodeposition**
- **Printing process (conductive polymers)**
- **.....**

