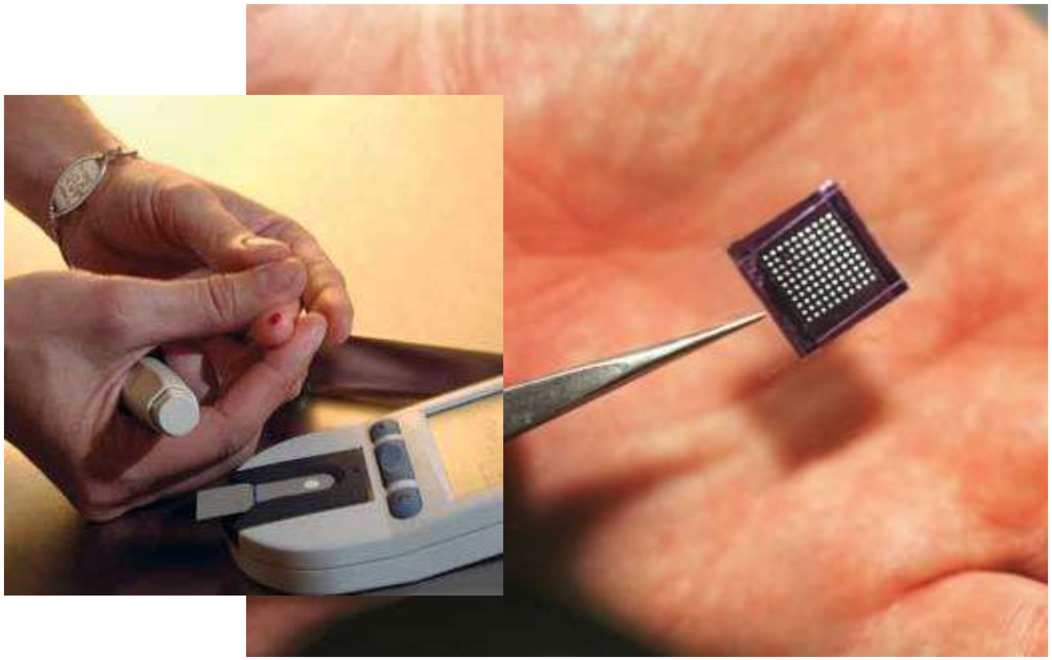
Chemical sensors and biosensors



Simon Ekström

Department of Electrical Measurements/Create Health

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 Qantitative

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_2S, 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 =>
$\Rightarrow$10 um channel takes 10 milliseconds

• Surface area to volume ratio increaes with r^{-1} => surface influence increases

• Surface tension and viscosity befomes ruling fluidic parameters over inertia

• Evaporation becomes a very influential parameter

• Miniaturised sample volumes => multiple/alternative analysis

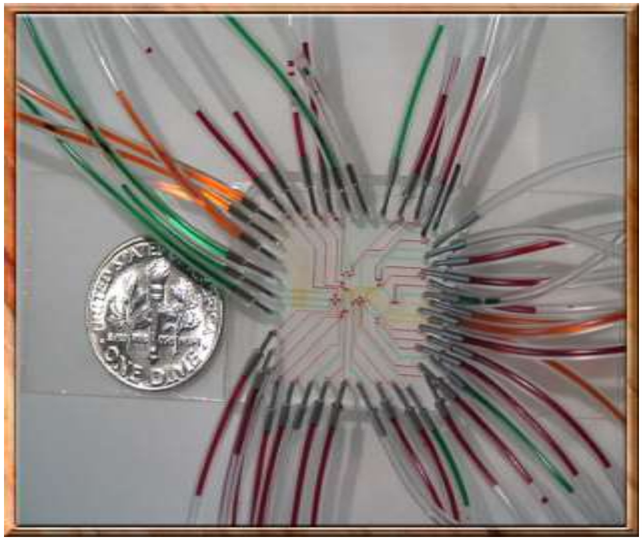
Different Manufacture Process

MEMS technologies such as;

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

What are the possible challenges?

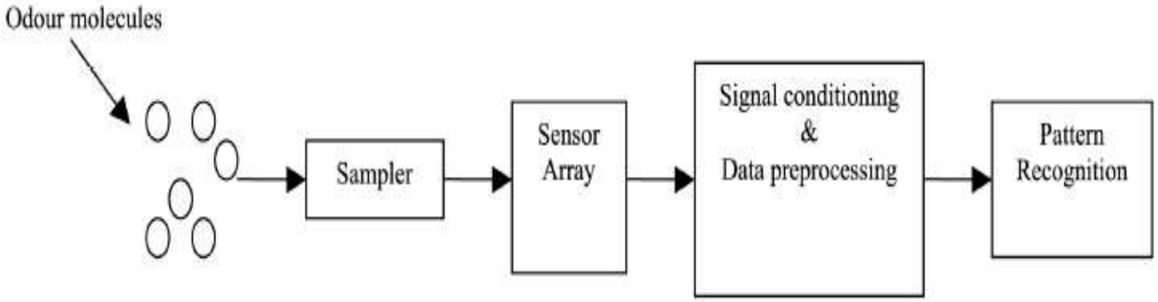
- Noise
- Drift
- Low sensitivity
- System stability
- Reuse possible?
- Sampling problems
- Measurements system
- Complexity and cost
- User prejudice against technology?
- …

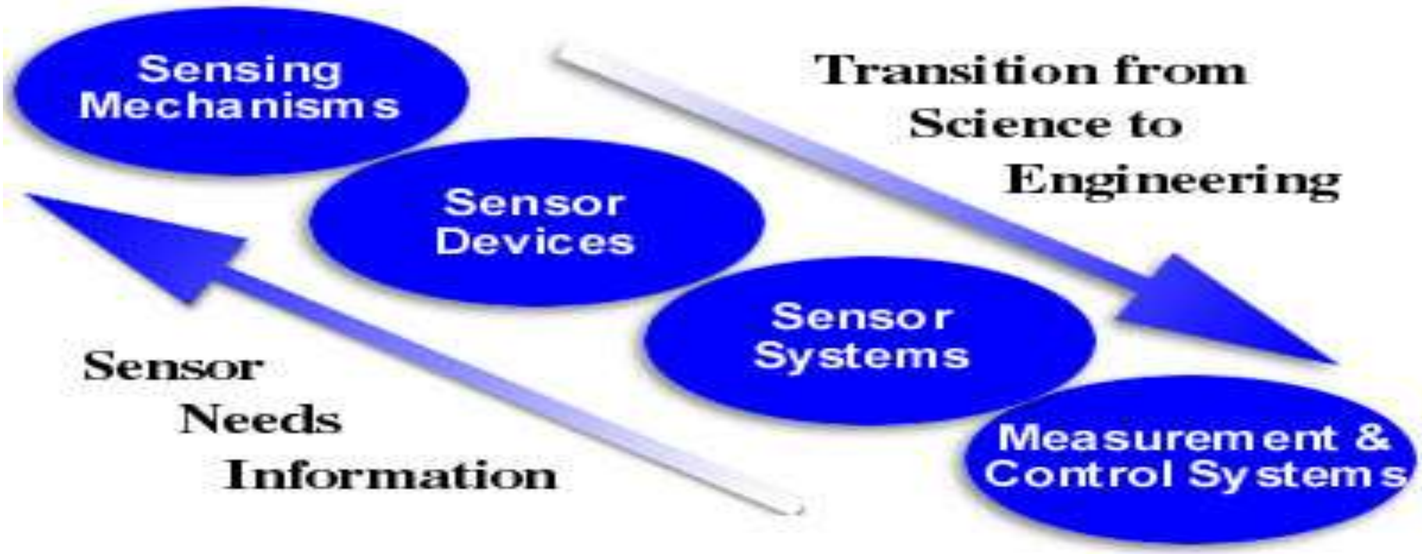


Problems with scaling down

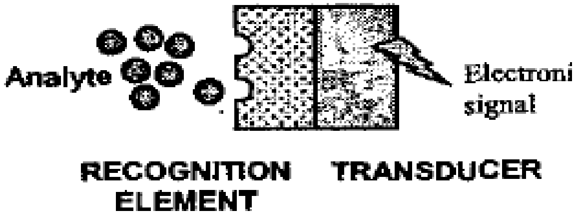
- **Smaller volumes = less analyte**
  1 nL injection av 1pM = 600 molecules
- Requires high sensitivity detection
- Integration issues (connections and other equipment)
- Fouling/clogging
- False-positives with single mol.?

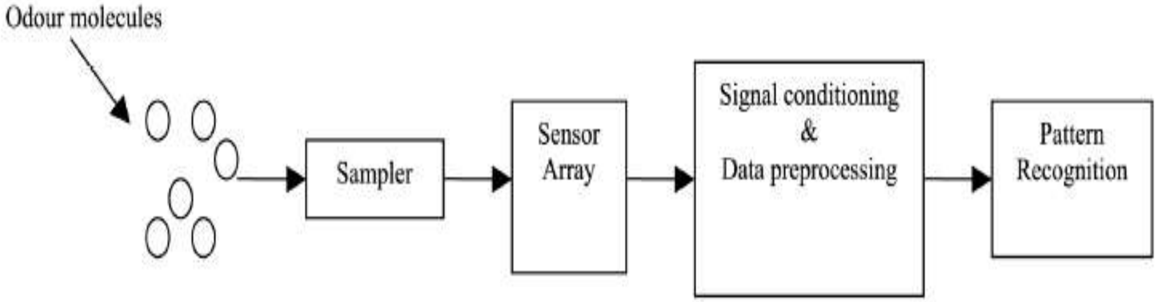
Chemical Sensors



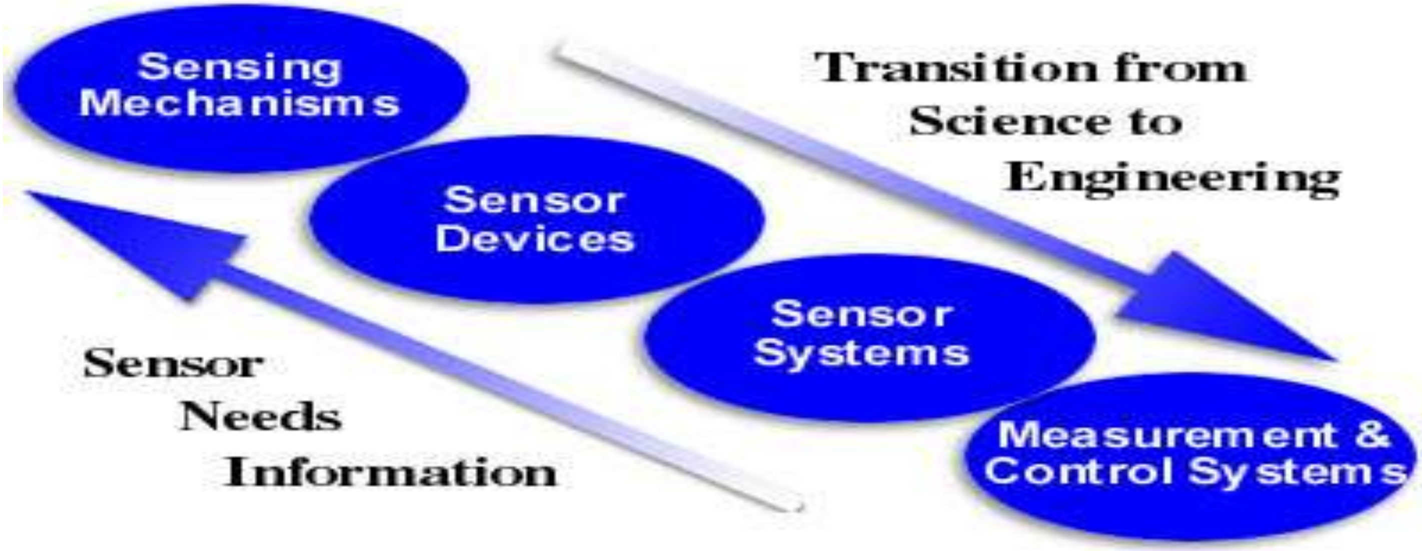


Biosensors





Biological element

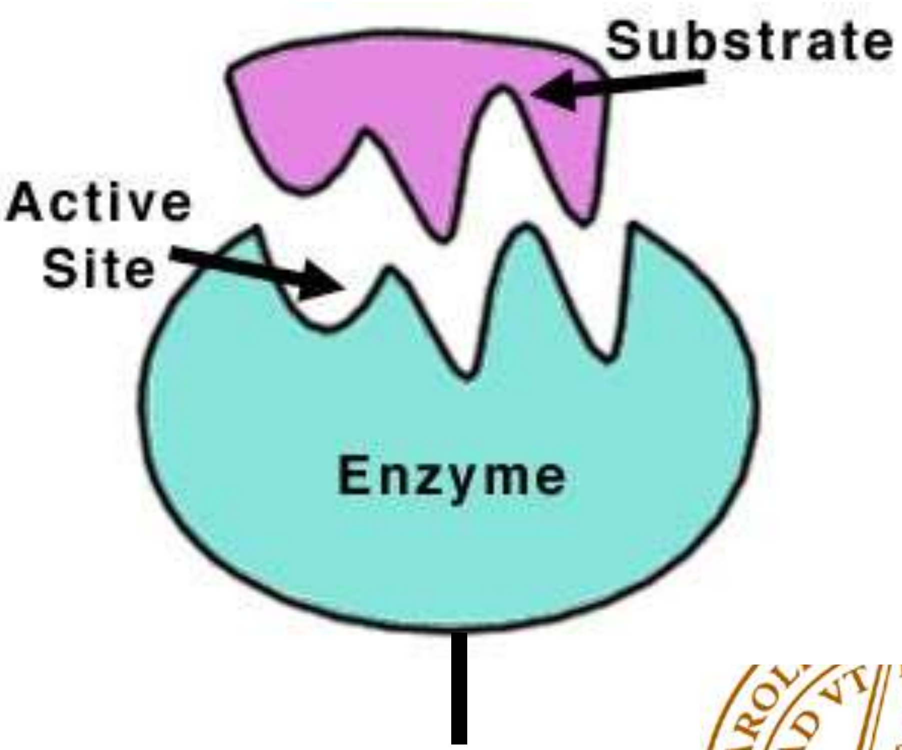


Biosensor = a biological element senses

The component used to bind the target molecule.

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

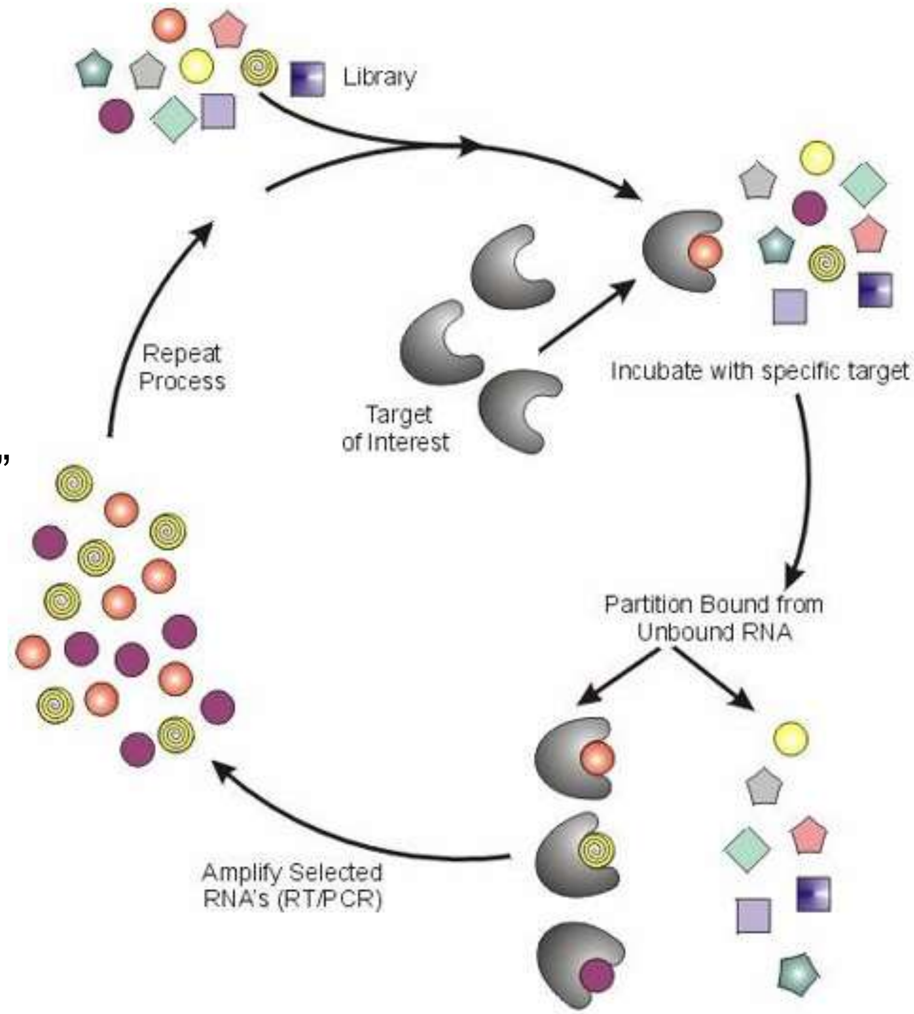
Microorganism
Tissue
Cell
Organelle
Nucleic Acid
Enzyme
Enzyme Component
Receptor
Antibody



http://www.chemistry.wustl.edu/~edudev/LabTutorials/HIV/DrugStrategies.html

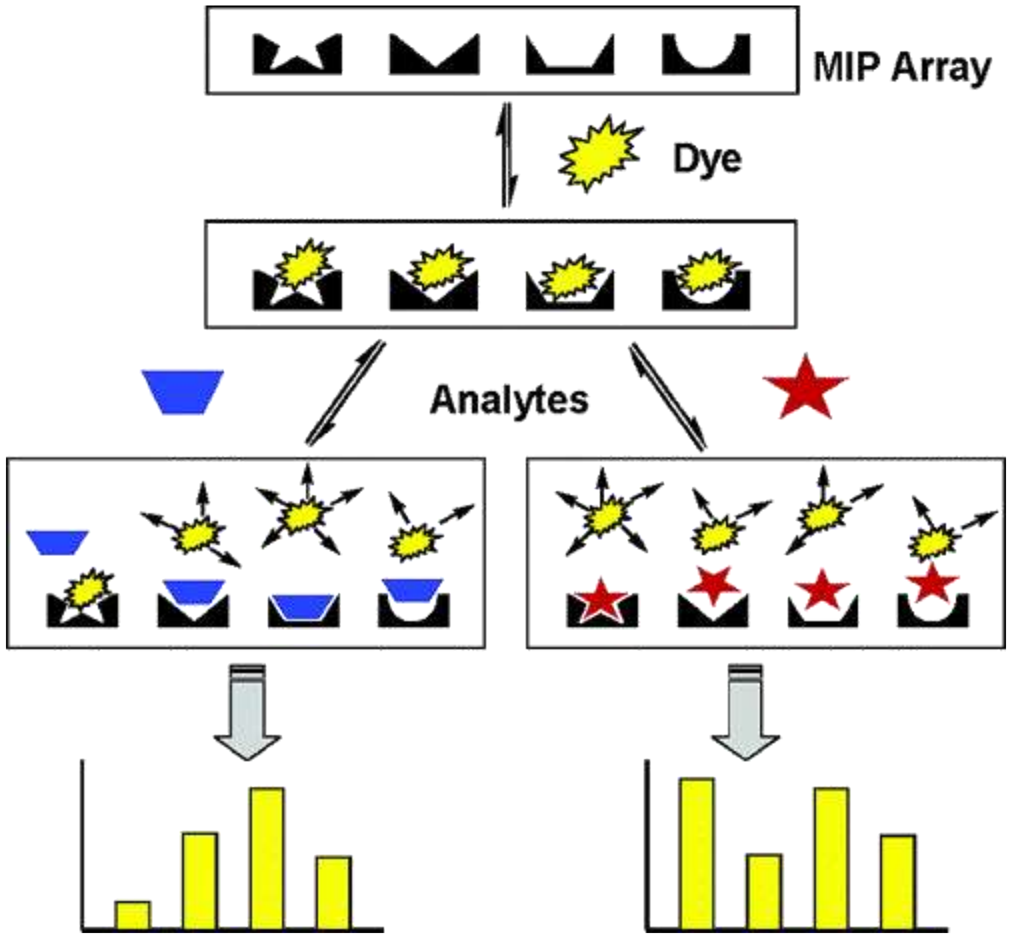
Systematic Evolution of Ligands by Exponential Enrichment (SELEX)

DNA ”Antikroppar”



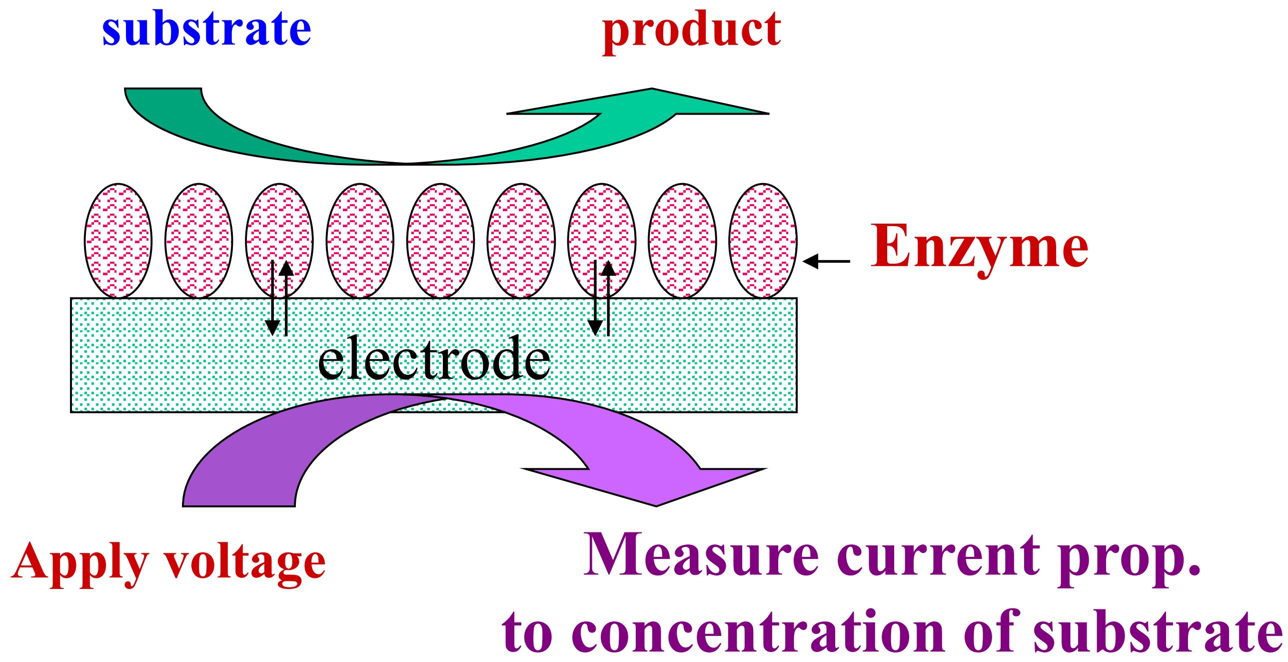
Schematic Reproduced From: http://surgery.duke.edu/wysiwyg/images/surgery_SELEX.jpg

Molecularly Imprinted Polymer (MIP) Sensor Array



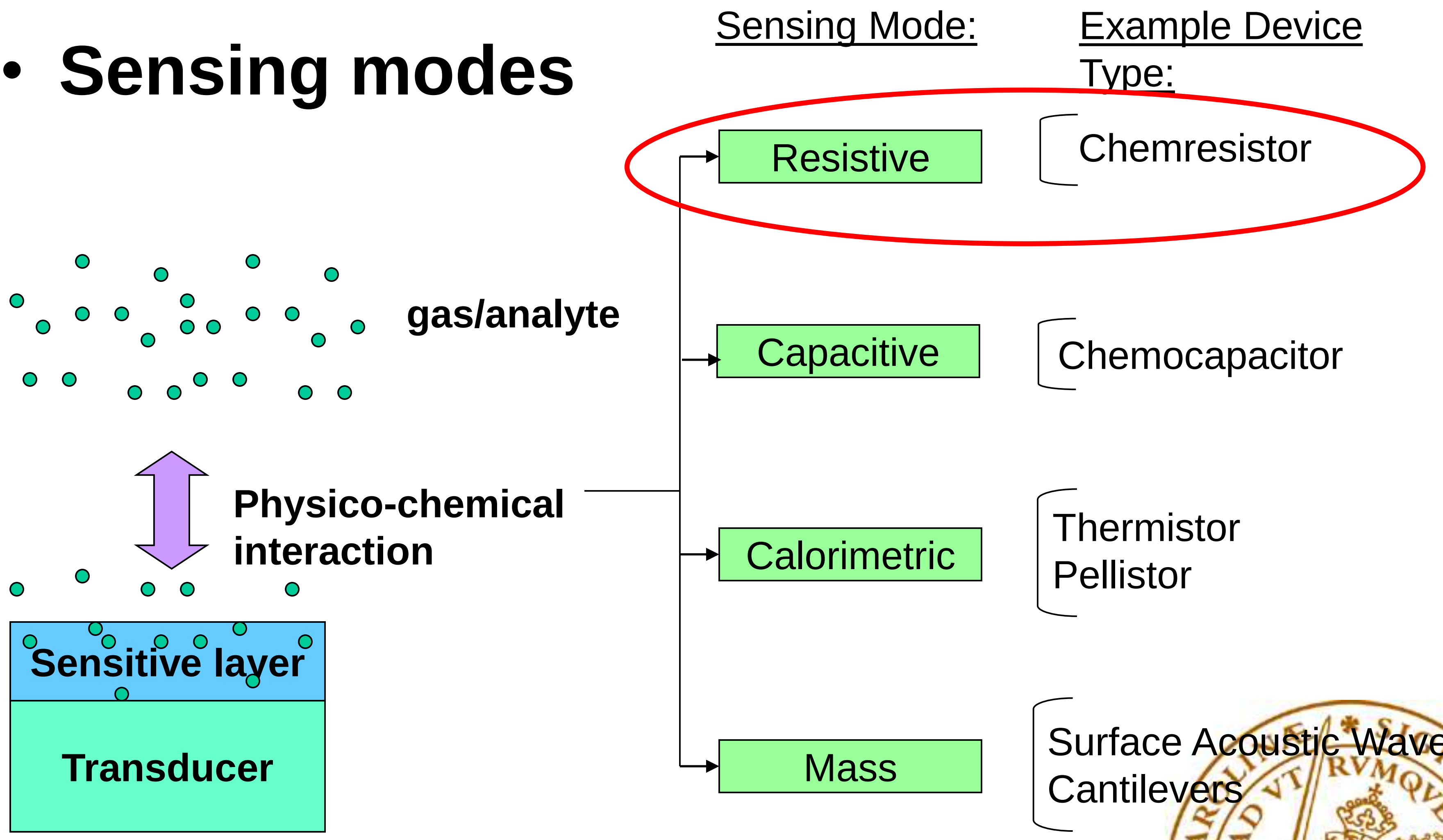
Greene, N.T.; Shimizu, K.D. *J. Am. Chem. Soc.* **2005**, 127, 5695

Principle of Electrochemical Biosensors



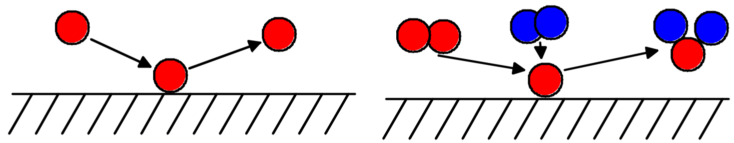
Chemical Sensor Modalities

- **Sensing modes**

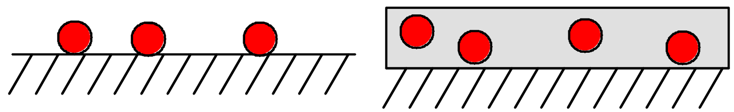


Gas sensor principles

adsorption/desorption or chemical reactions



on surfaces or in (thin) films



cause
PHYSICAL CHANGES

- mass
- conductivity
- polarisation
- temperature
- optical properties

which depend on
MOLECULAR PROPERTIES

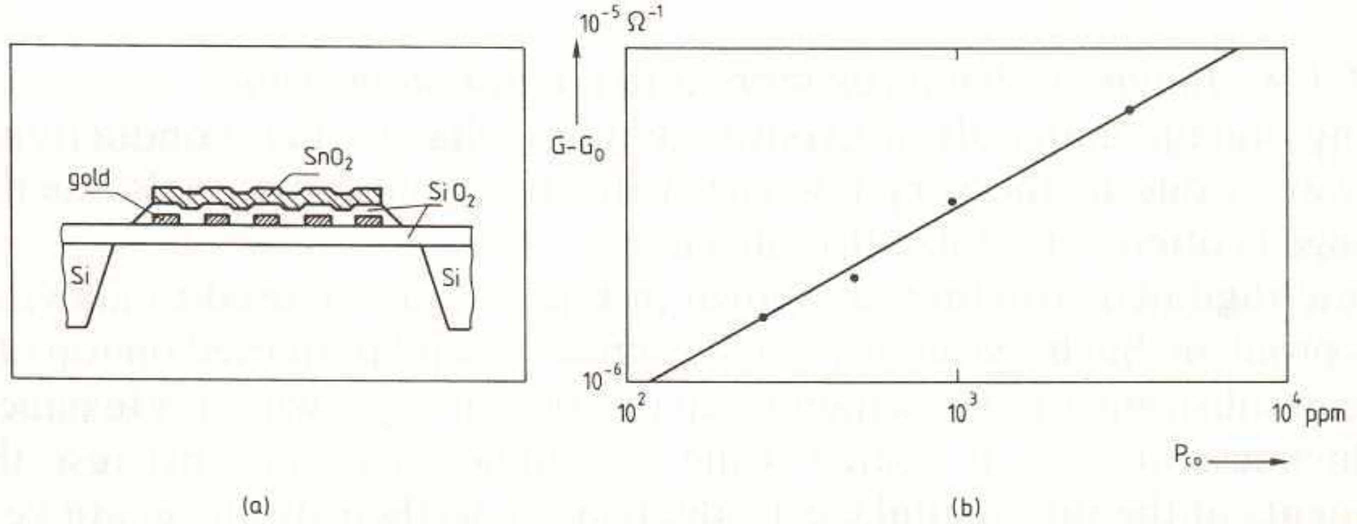
- size
- reactivity
- affinity
- polarity
- polarisability

which can be used in several types of
DEVICES

- calorimetric
- fibre optic
- acoustic
- resistive
- field effect

Metal-oxide sensors

- **CO sensor**



- **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.

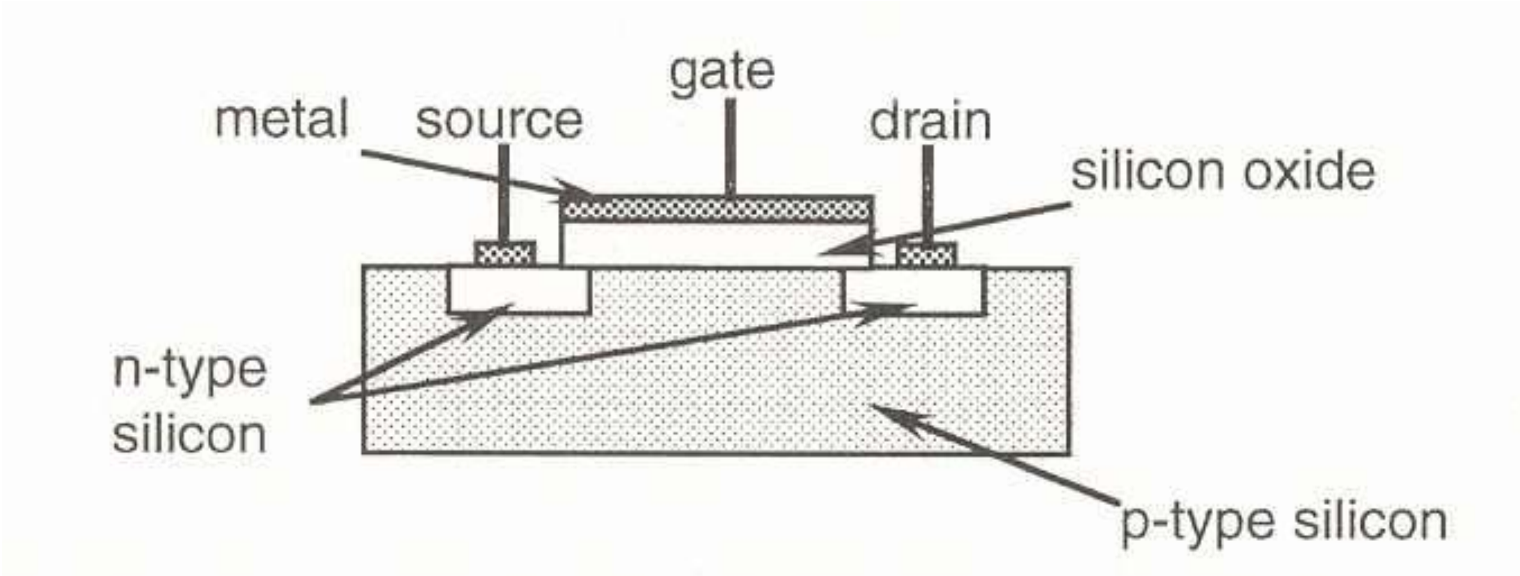
CO sensor on the wall

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

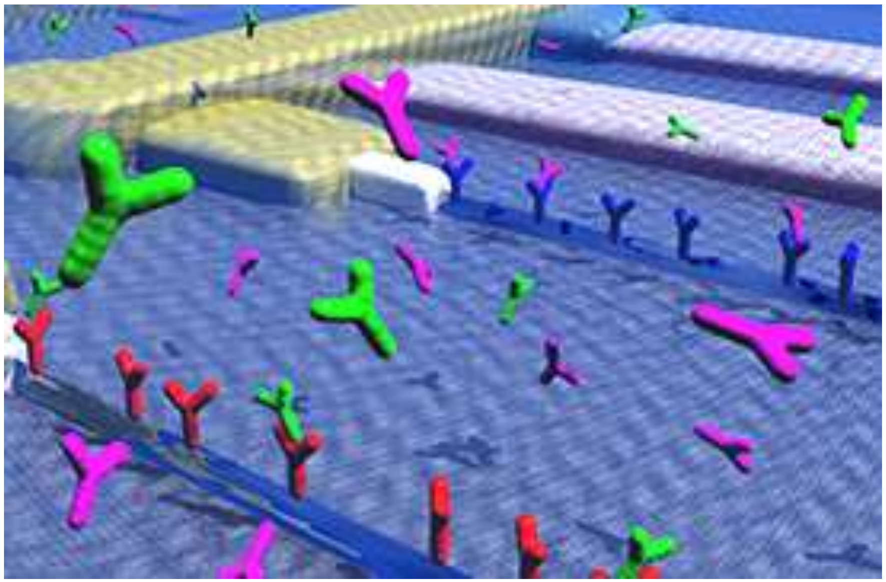
www.senseair.se

MOS chemical sensors

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



Nanowire FET



- Label free
- CMOS-compatible
- Low fM sensitivity

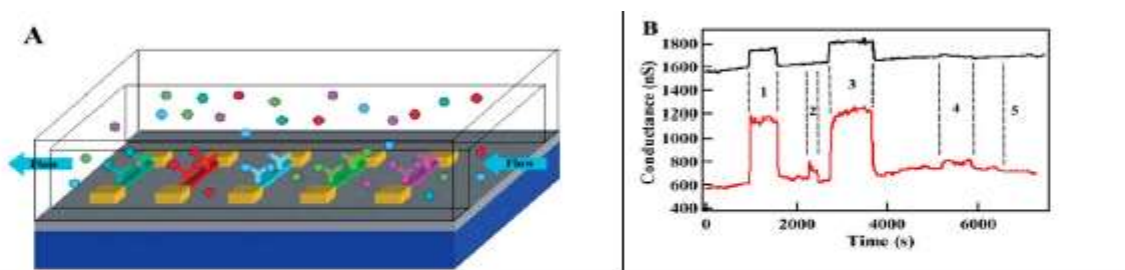


Figure 12. (A) Schematic illustrating the concept of multiplexed detection. (B) The fPSA antibody-modified nanowire (black) used an antibody specific for only fPSA, whereas the PSA-ACT antibody-modified nanowire (red) used an antibody raised against fPSA, but has cross-reactivity with PSA-ACT.

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)**

Forensic applications

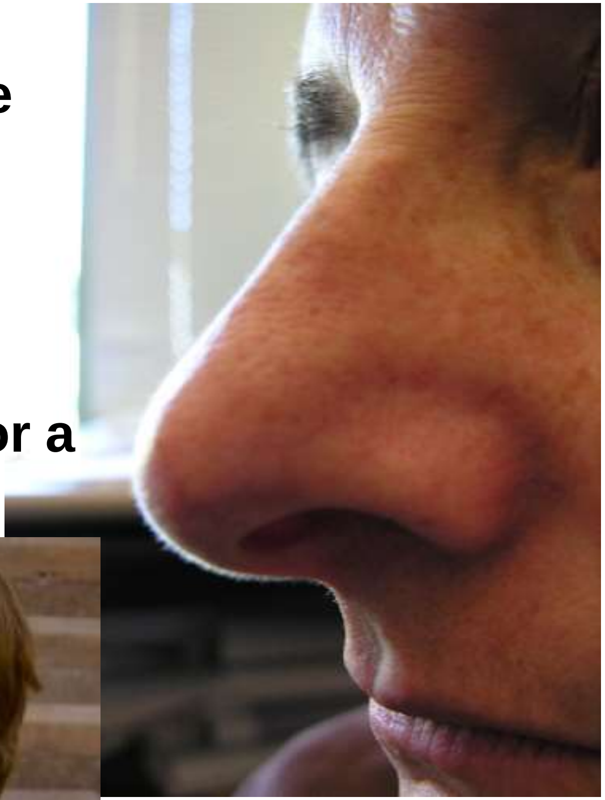
Drugs, bombs, biowarfare agents.....

Chemical Sensors

- Hydrogen Cyanide (HCN)
- Ammonia (NH_3)
- Chlorine (Cl_2)
- Acetaldehyde (C_2H_40)
- Sulfur Dioxide (SO_2)
- Hydrochloric Acid (HCl)

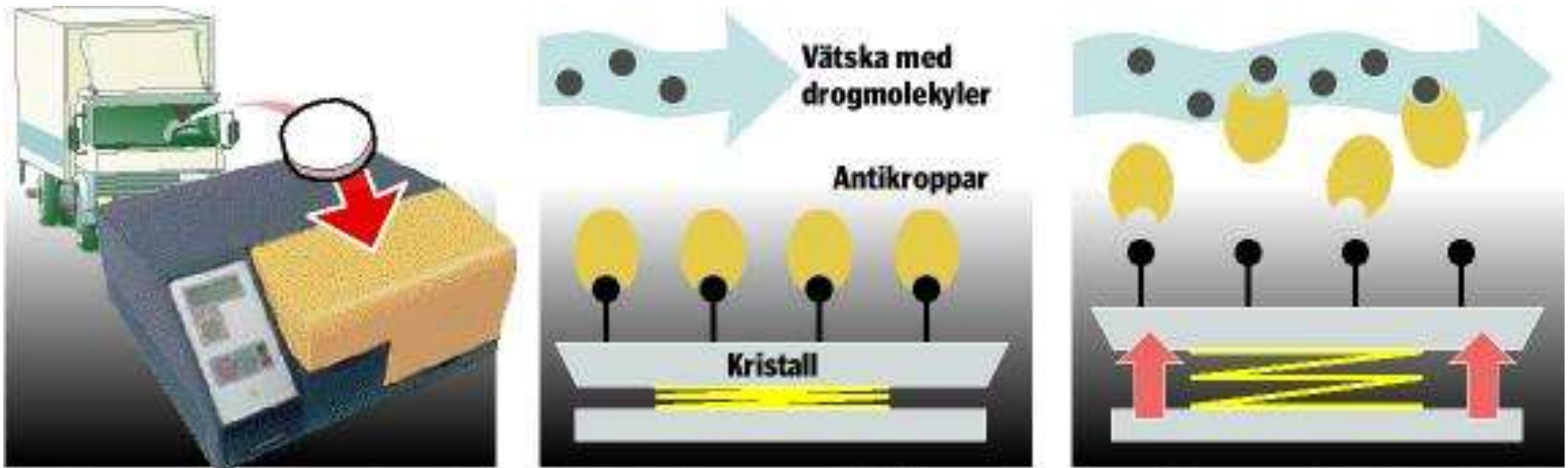
Multi-analyte Differential Sensing

- 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



Biosensor for drug detection

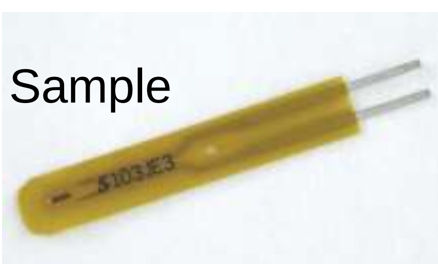
Narcotics discovery without a dog



www.nyteknik.se

Thermisotor 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).**



Optical sensors

- Opto-chemical sensing are the properties of some substances to fluoresce or phosphoresce under optical radiation.
- These chemiluminescence properties can be senses 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

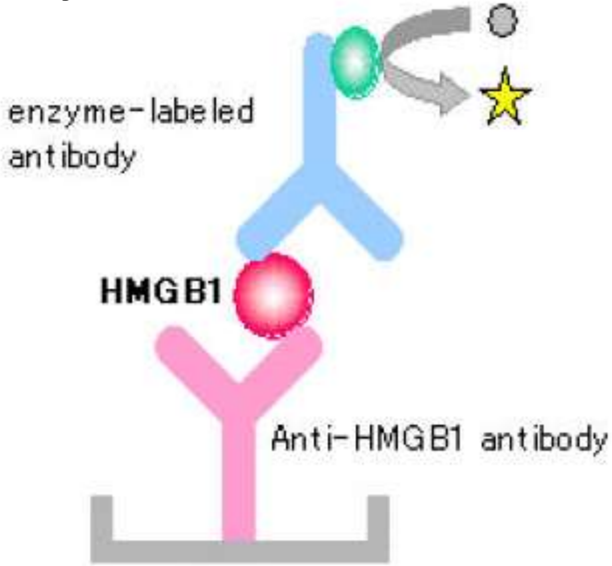
Mätare

www.abbott.se

Amplifying the signal for biosensors

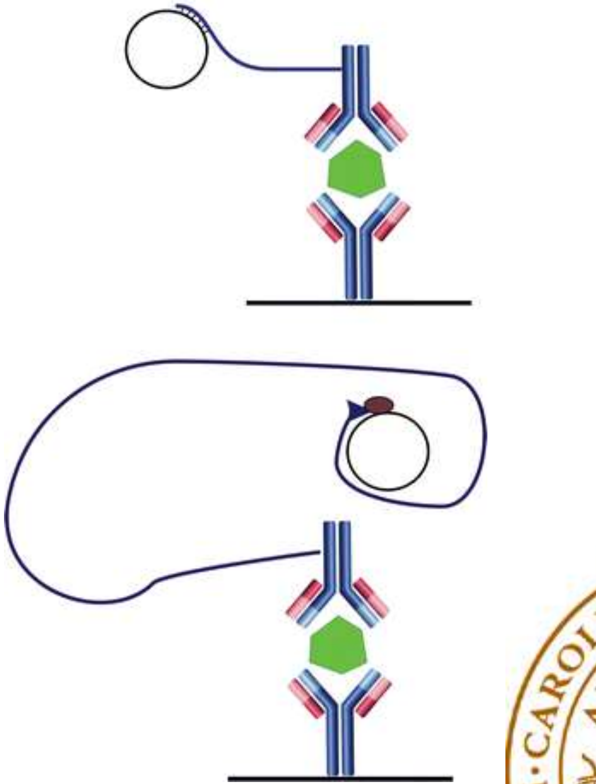
Elisa

Enzyme-Linked Immunosorbent Assay



RCA

Rolling circle amplification



Array-based fluorescence detection of biomolecules

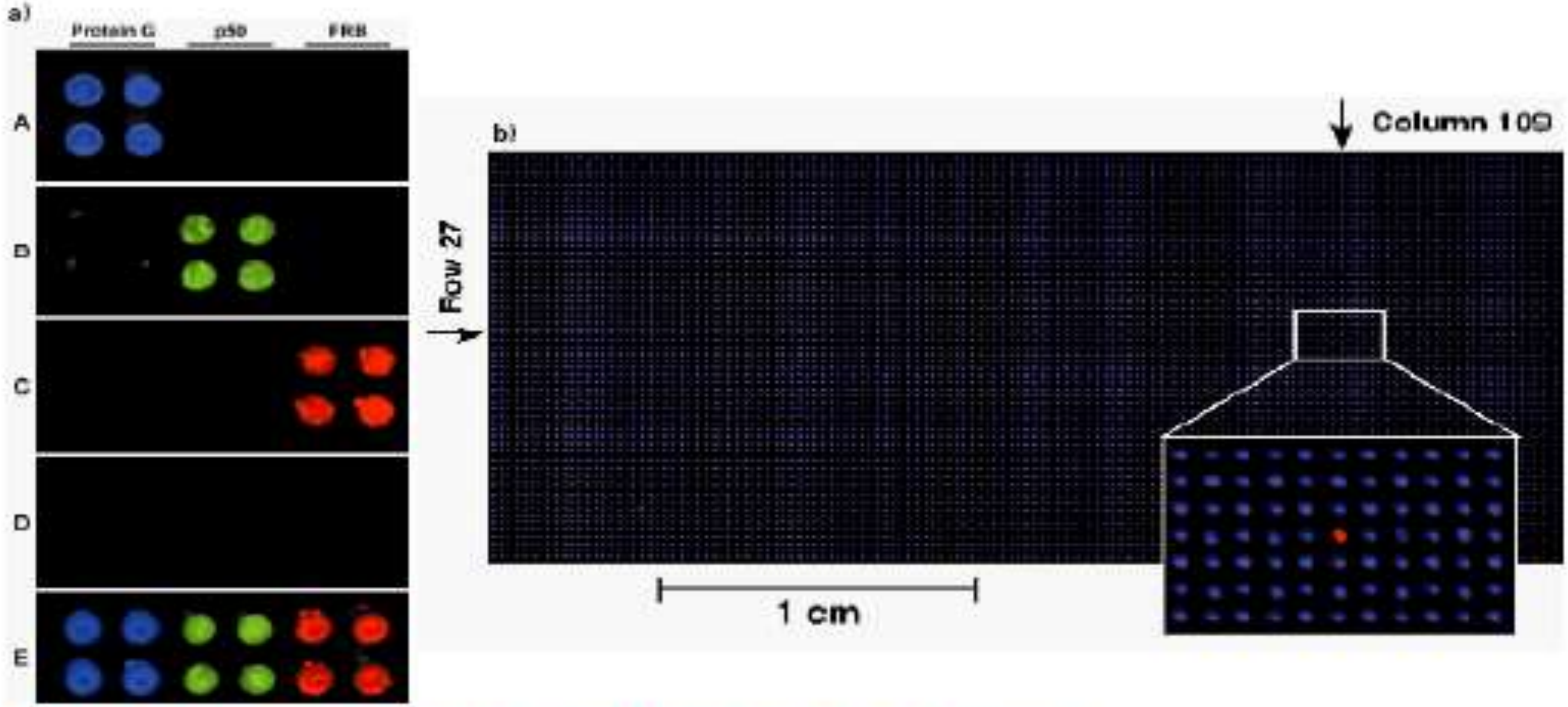
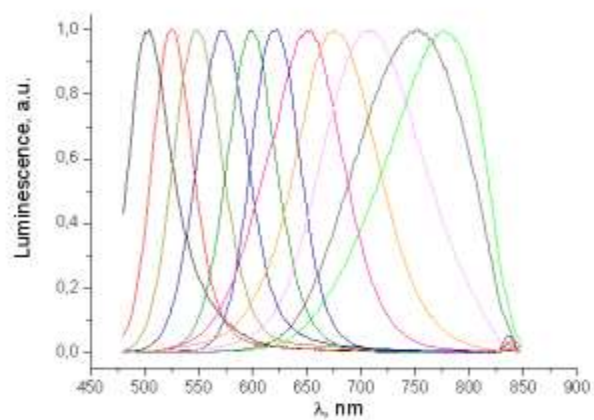


FIGURE 6.34 • Detection of protein-protein interactions on protein microarrays.

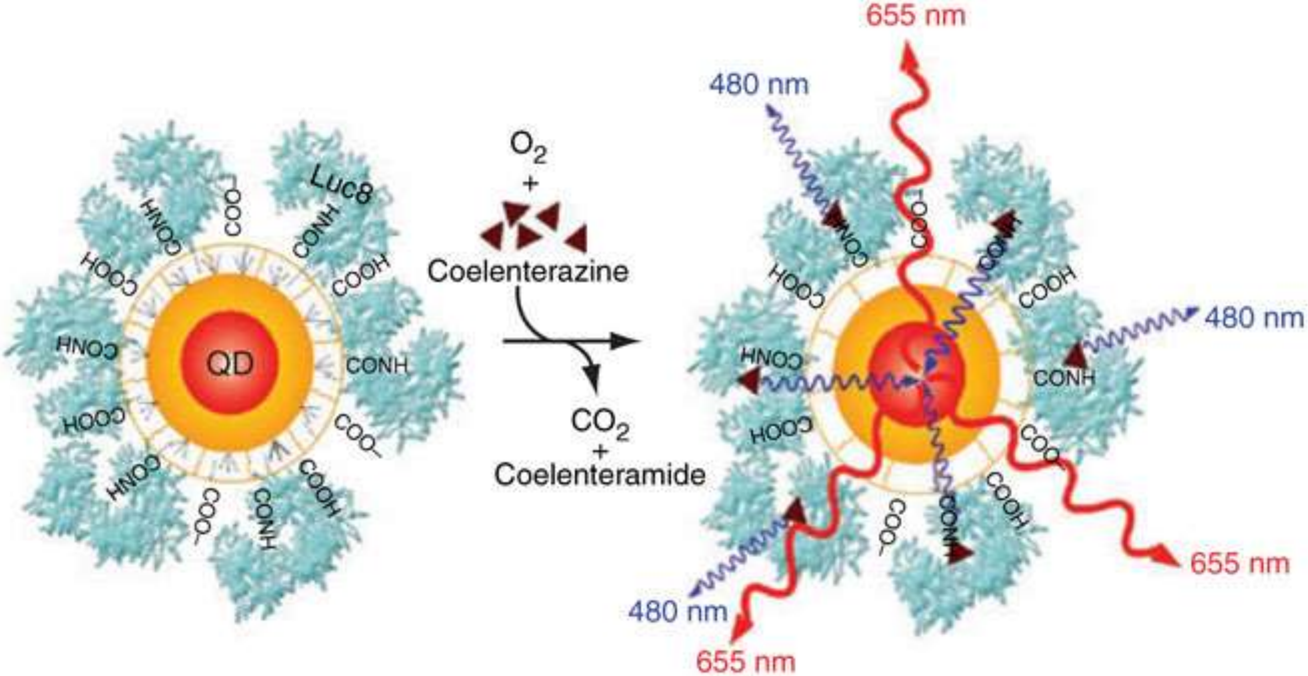
Surface area, chemistry and deposition technique important

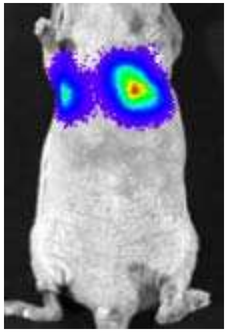
Quantum dot's

- 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



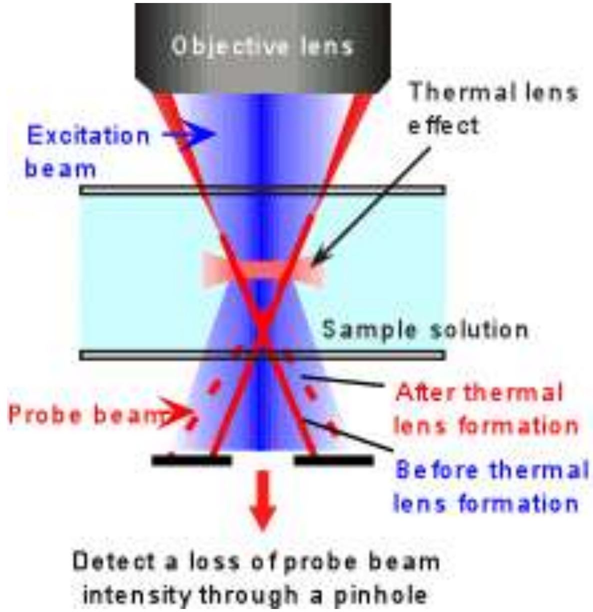
Bioluminescent quantum dots



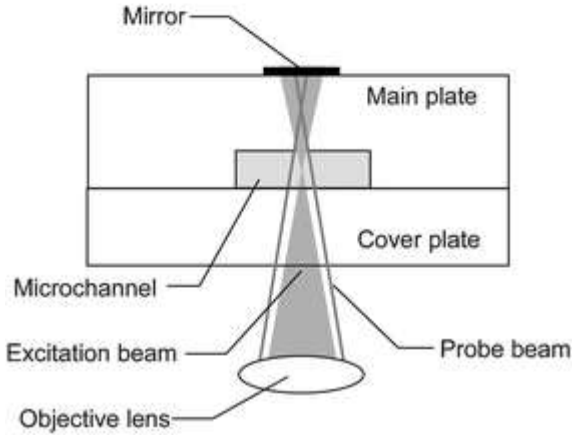


So, M. K.;Xu, C.;Loening, A. M.; Gambhir, S. S.; Rao, J.Self-Illuminating Quantum Dot Conjugates for in vivo Imaging. Nat. Biotechnol.2006, 24, 339-343.

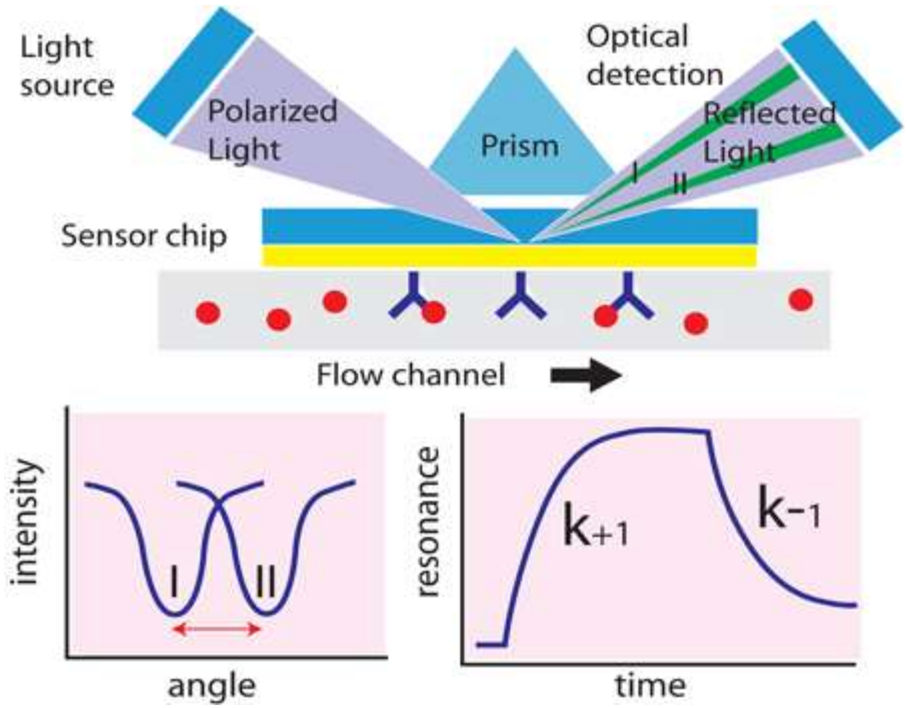
Thermal lens

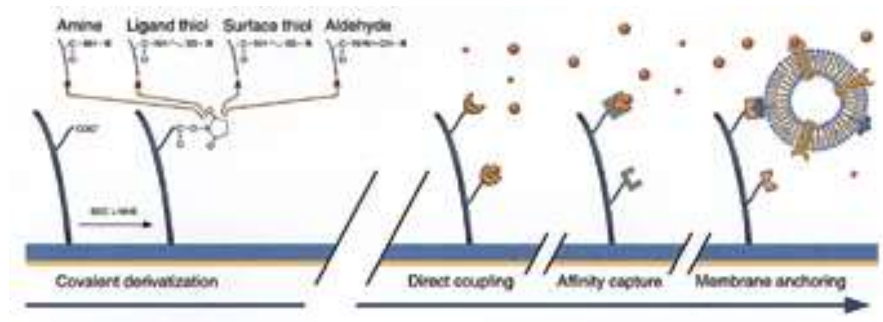


Lablel free, but requires a clean sample



SPR (Surface plasmon resonance)

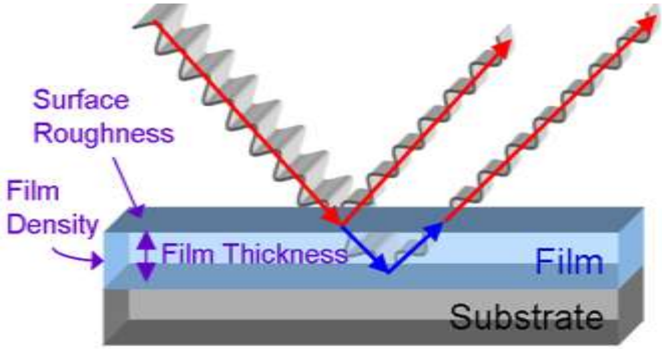


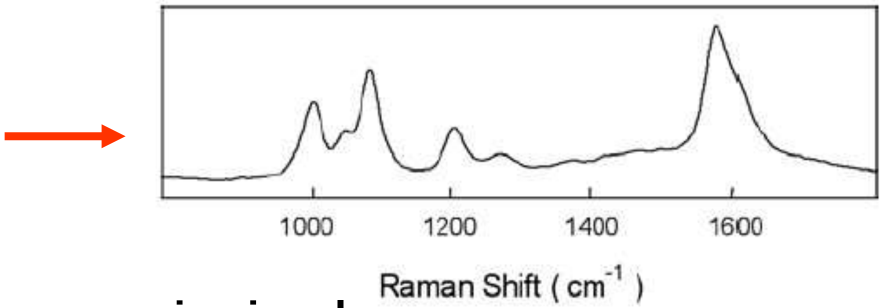


www.biacore.com

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

Surface Enhanced Raman Spectroscopy - SERS

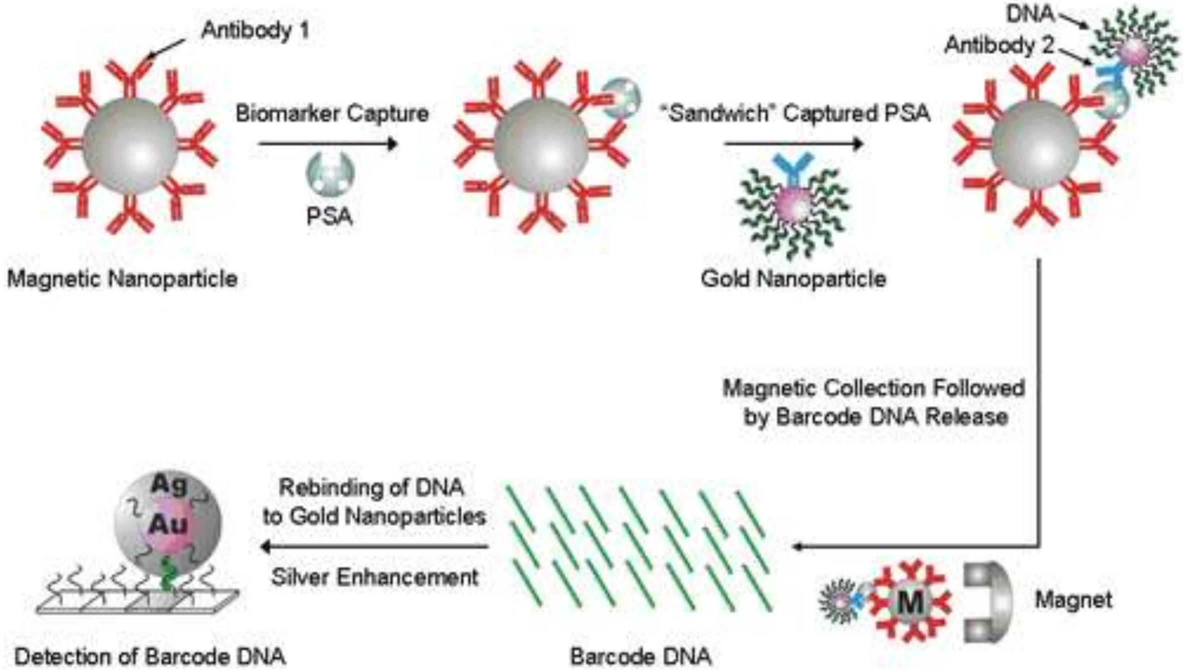




- Nanostructured surface gives 10^6-10^9 increase in signal
- High sensitivity, on par with heterogeneous, amplified systems
- SERS signal is photostable and, unlike fluorescence, cannot be “quenched”
- Signal is unaffected by ionic strength or temperature variations
- Does not work for all analytes

http://www.oxonica.com/

SERS example

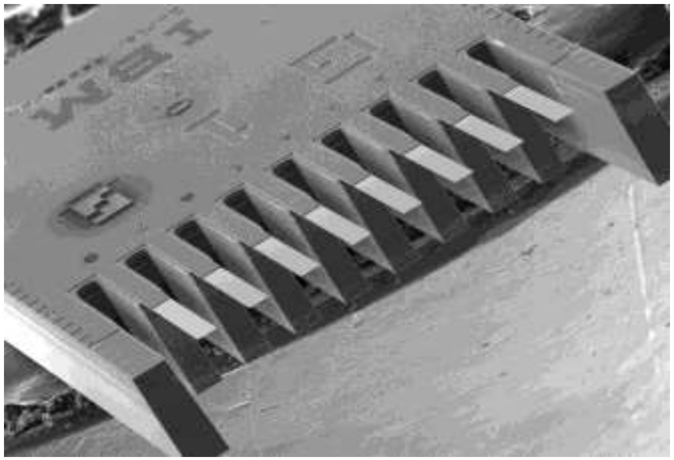


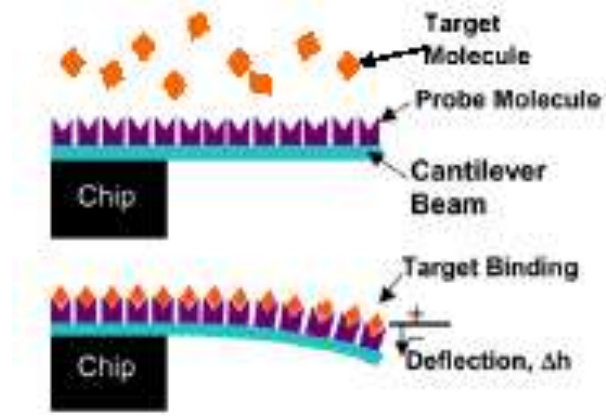
Amplification of protein through a reporter DNA

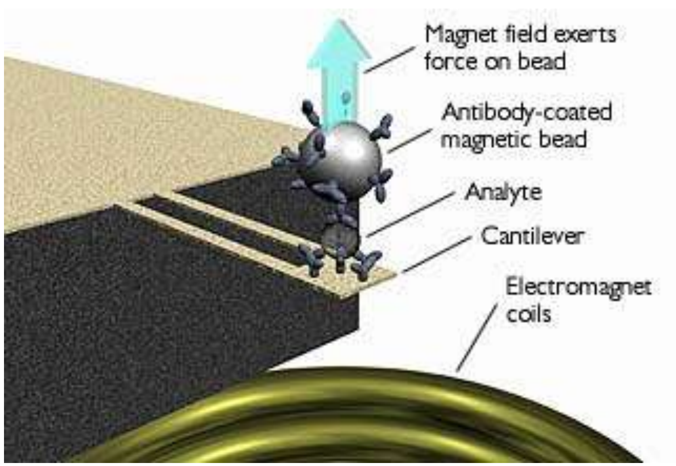
Mass sensors

- 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.

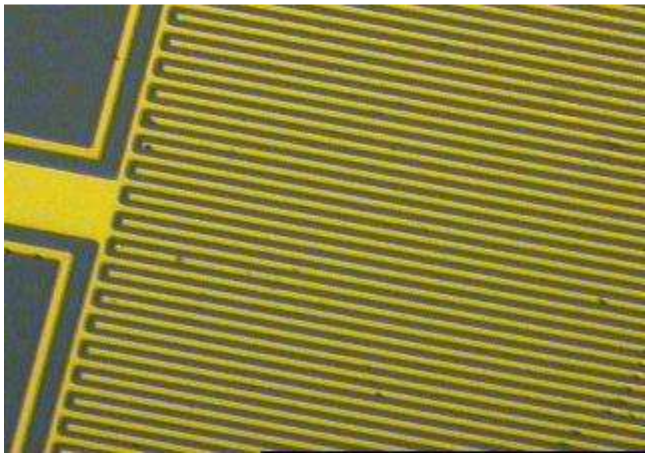
Mass sensor - cantilevers

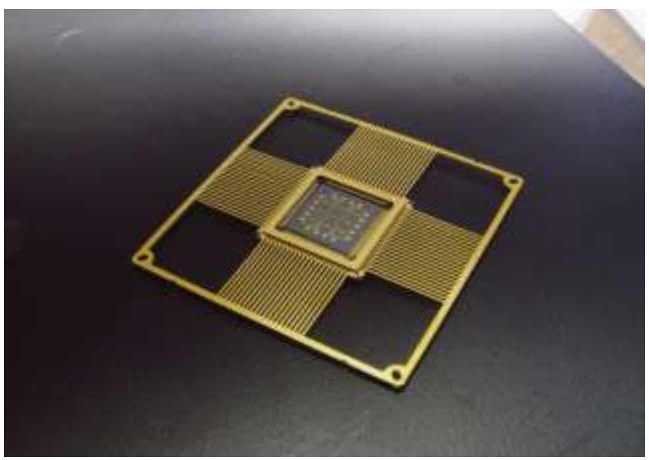






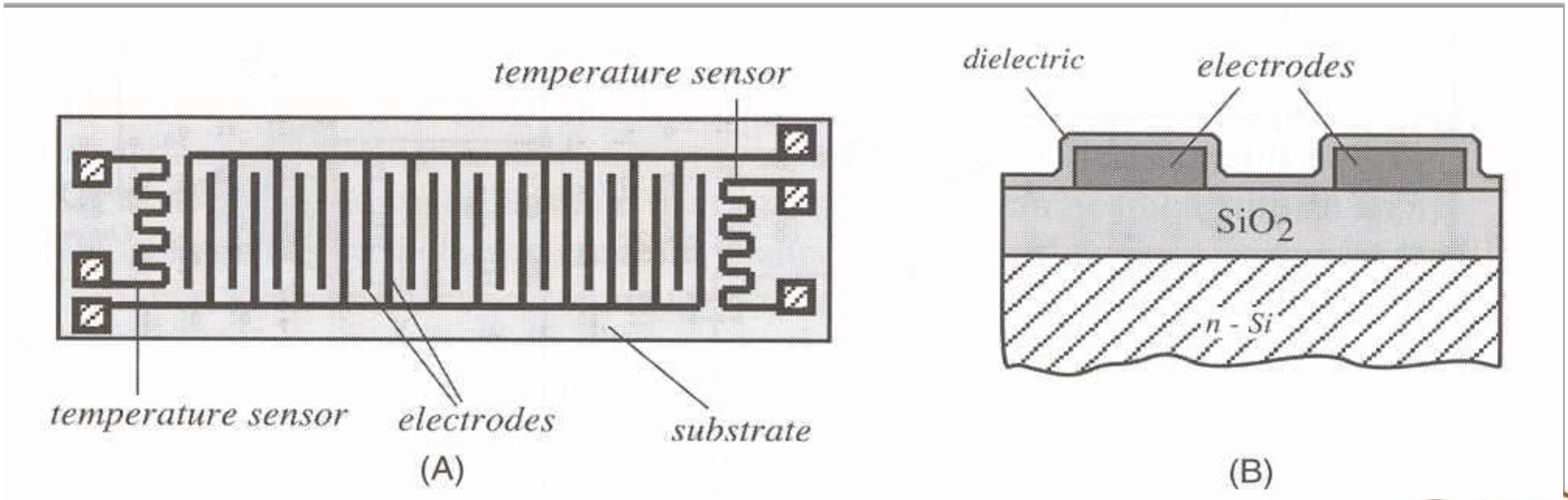
Using Interdigitated Capacitors as Chemical Sensors



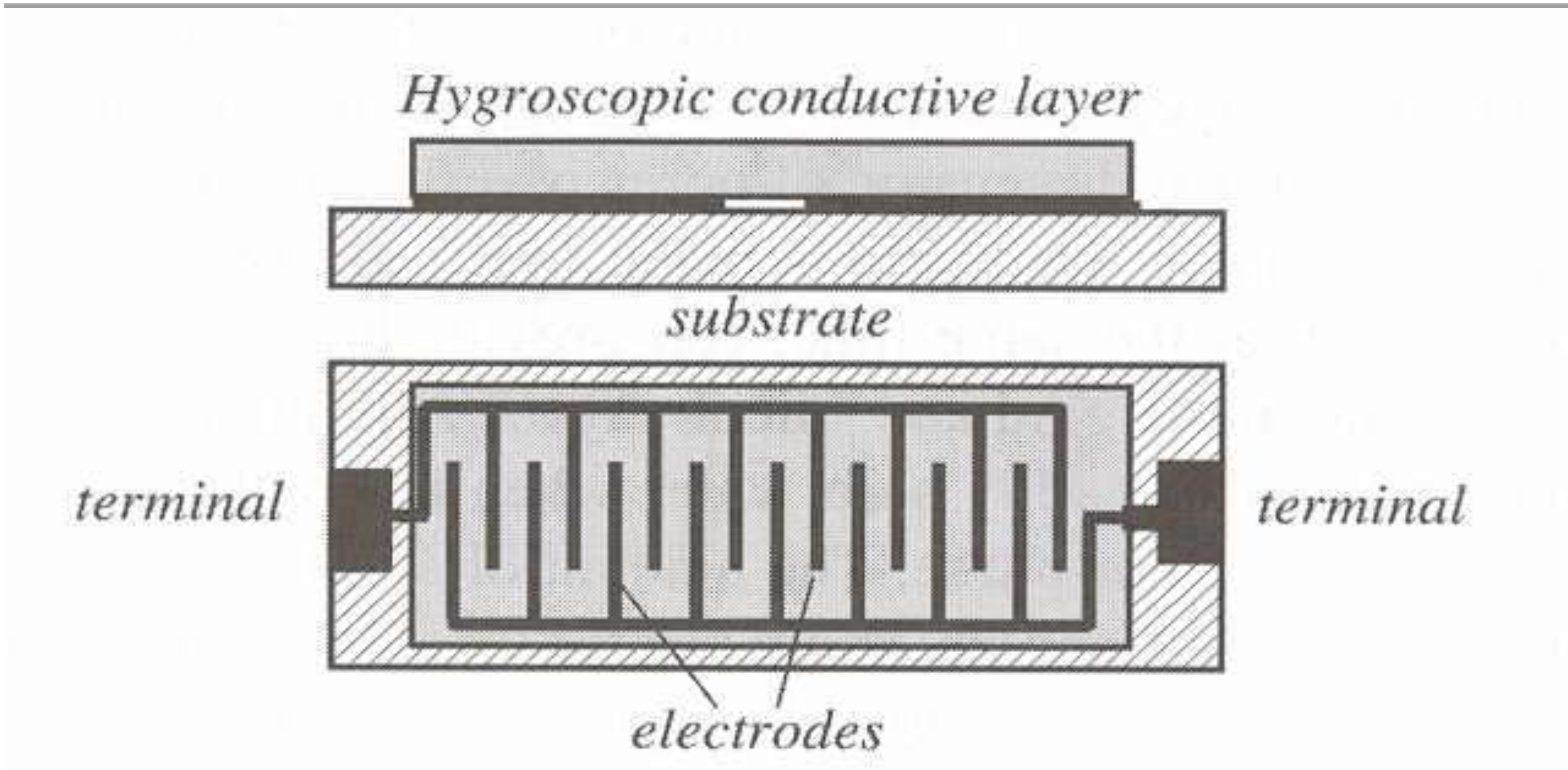


- **Interdigital geometry maximizes capacitance.**
- **Highly Sensitive to environmental changes.**
- **Arrays can be used to increase selectivity.**
- **Compatibility with MEMS fabrication Processes.**

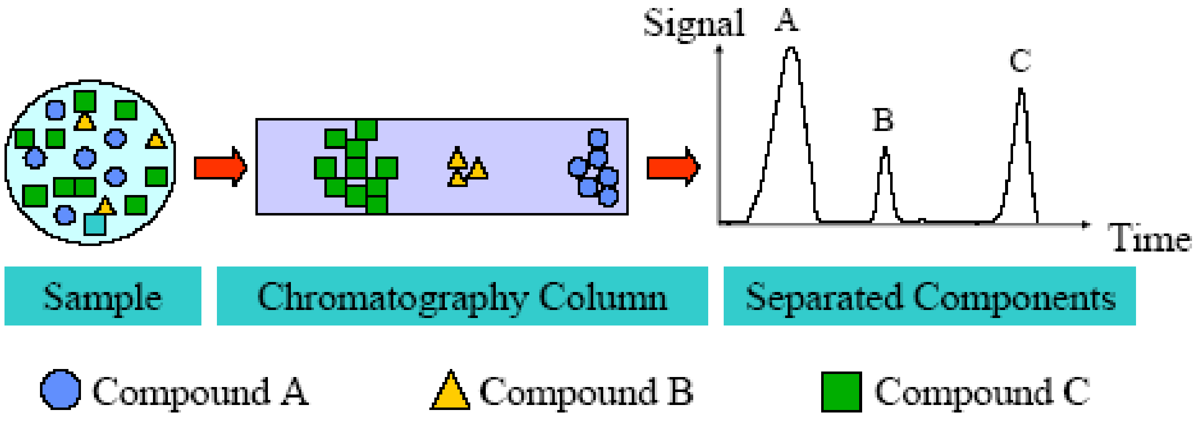
Capacitive moisture sensor



Resistive moisture sensor



Chromatography



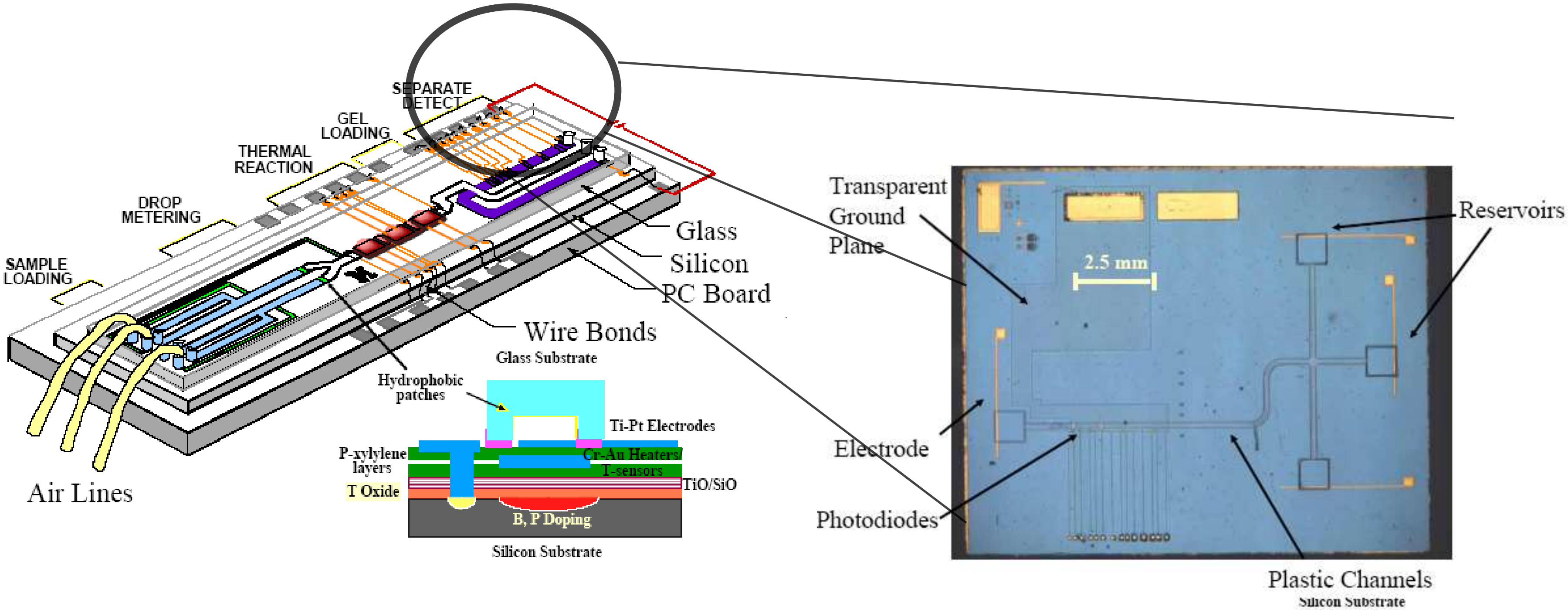
- **Multicomponent samples are separated in specially treated separation columns before measurement with a detector**
- **Samples are separated by different migration speed inside column due to differing adsorption characteristics**
  - **Liquid/Ion Chromatography (HPLC, IC)**
    - **Solid column, liquid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

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

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

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

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**

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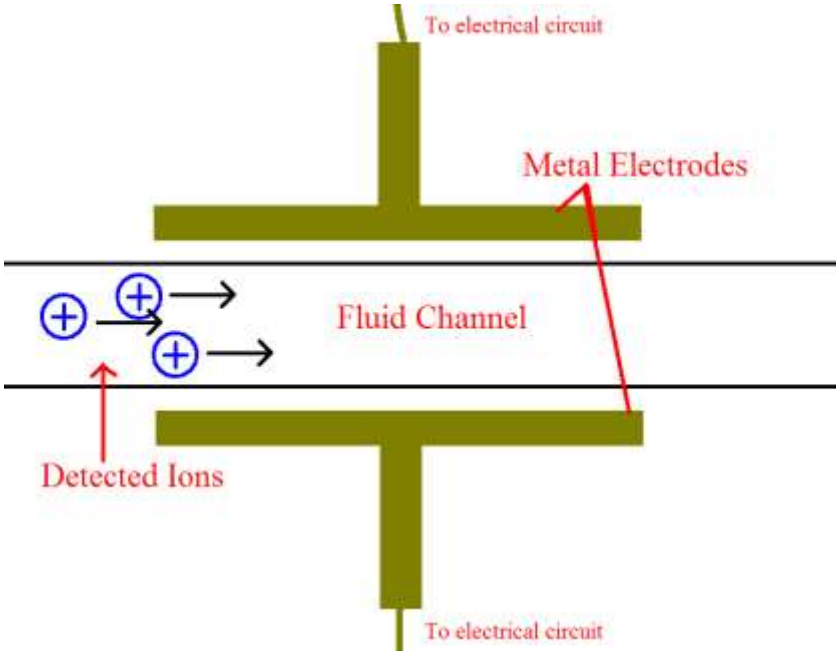
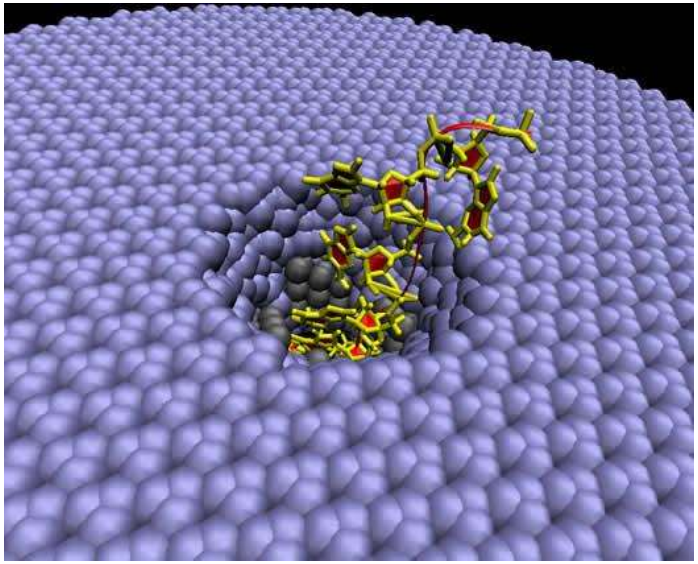


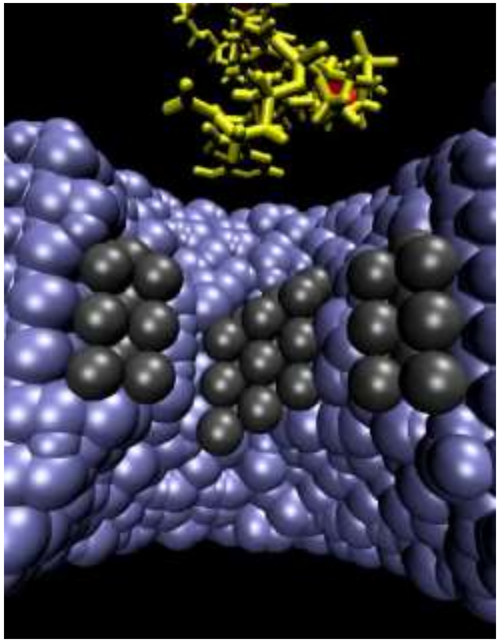
Lung-Ming Fu, National Pingtung University, Tawain

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

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.

Detection of Magnetic Beads

Giant MagnetoResistive (GMR) Sensor

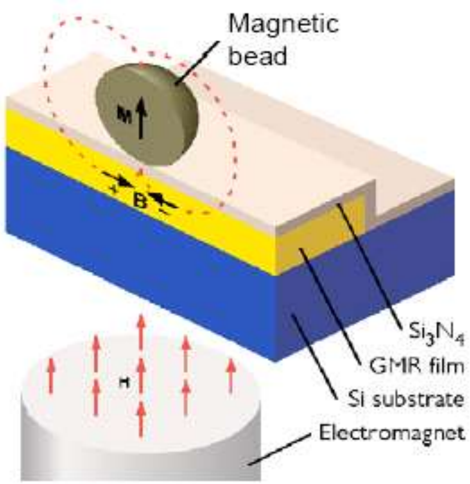
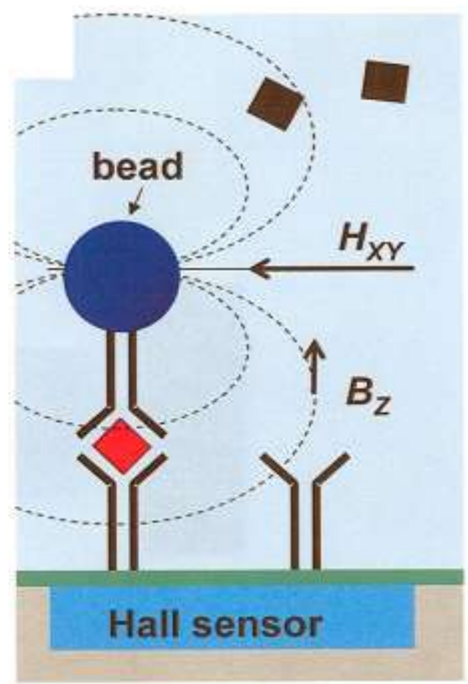


Fig. 5. Schematic of sensor magnetics. An external field induces a magnetic moment in the paramagnetic bead, and its induced field causes a decrease in the resistance of the GMR film.

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

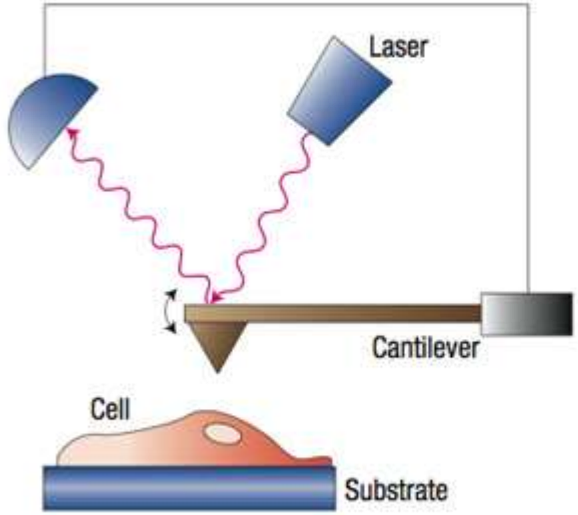
Hall Sensor



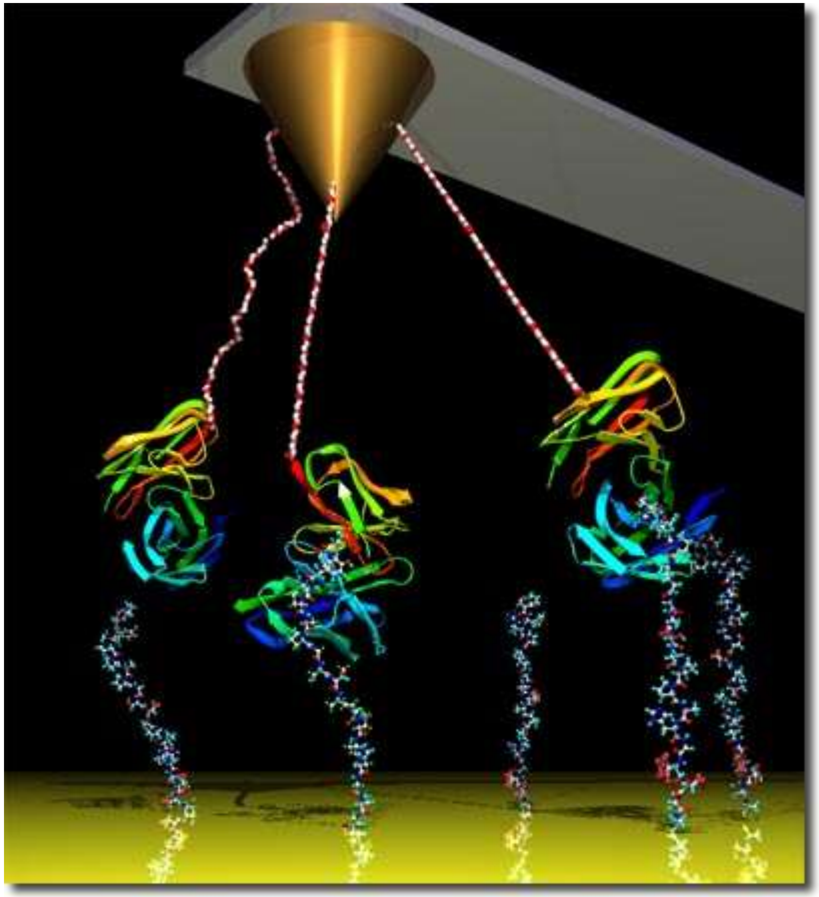
(Source: B. Boser, European IAB, 2004)

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).

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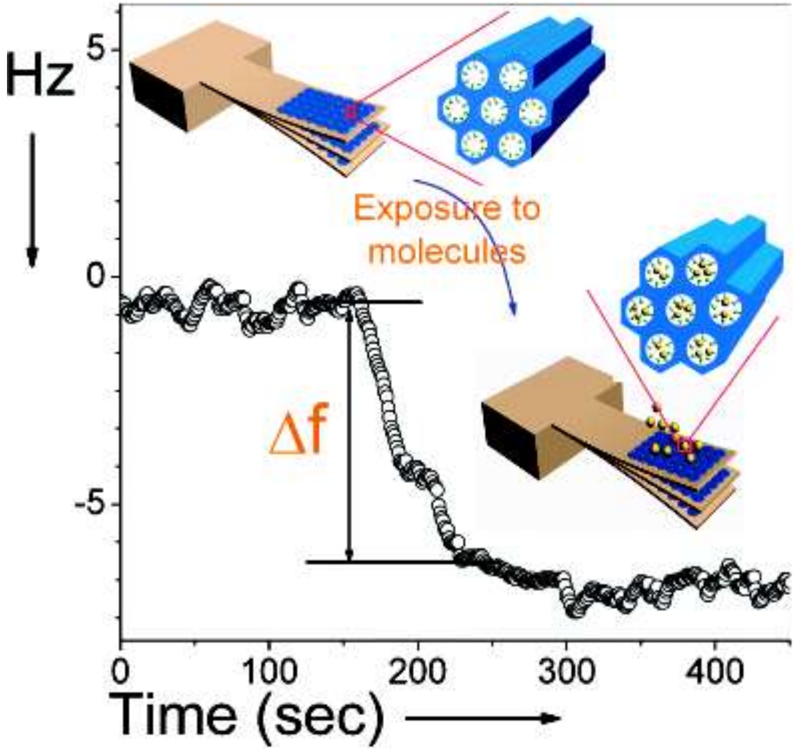
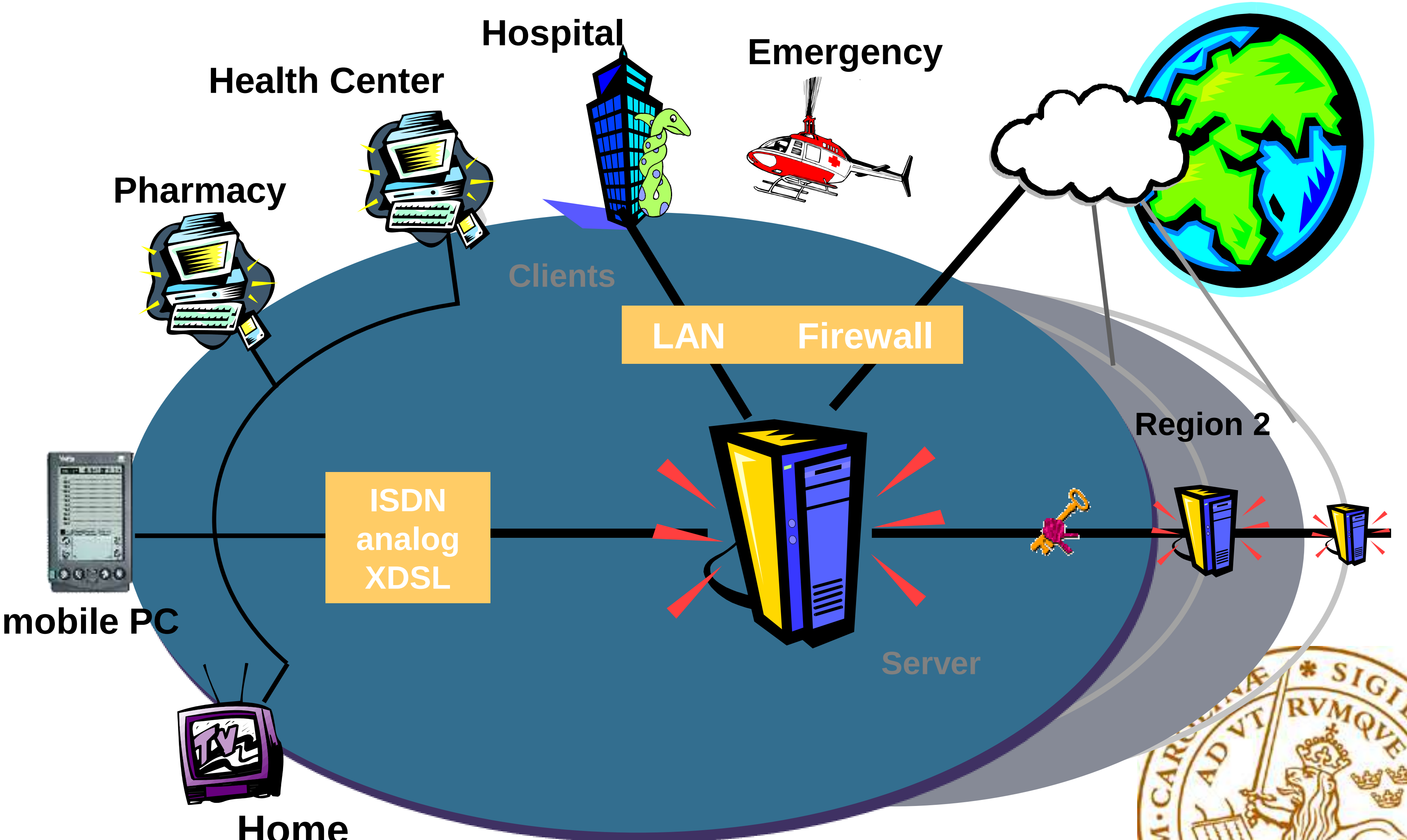


How does it work?

What can we detect?

Future scenario



End users for the technology

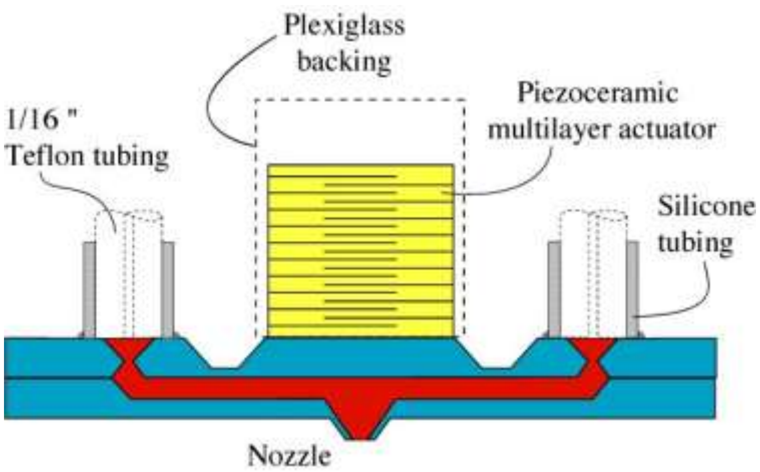
- **Research- discover new biology by faster and more sensitive analysis**
- **Diagnostics – biomarkers, POCT, personal medicine**
- **Biopharmaceuticals - screening, QA mm**
- **+ Food Industry, Environmental, forensic and military applications**

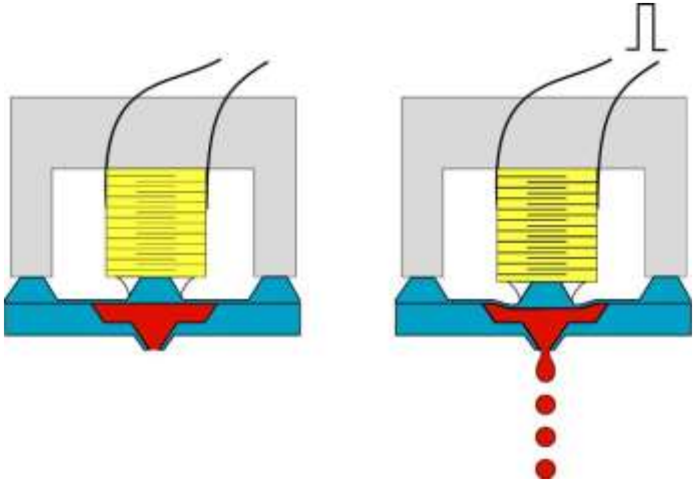
RVM·CAROLINÆ * SIGILL
AD VT RVMQVE

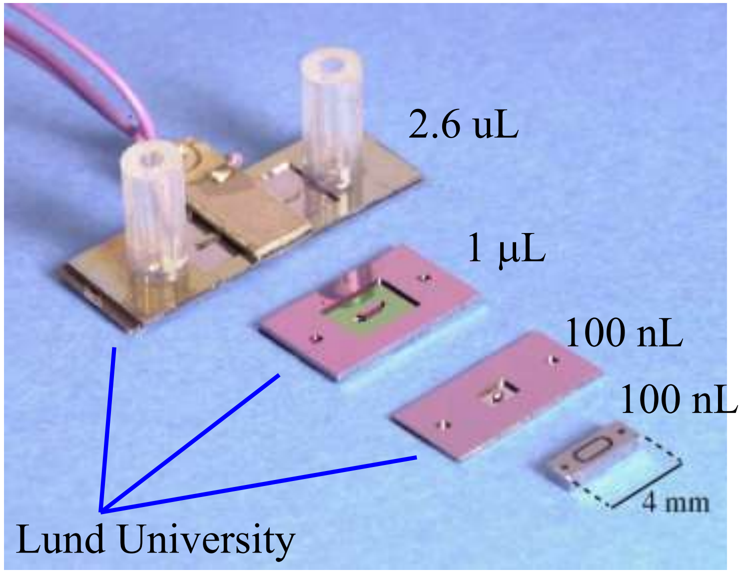
RVM·CAROLINÆ * SIGILL
AD VTRVMQVE

RVM·CAROLINÆ * SIGILL
AD VT RVMQVE

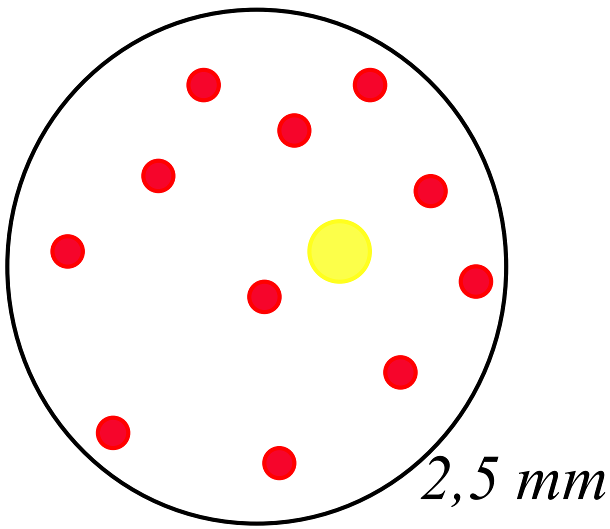
Microdispensing

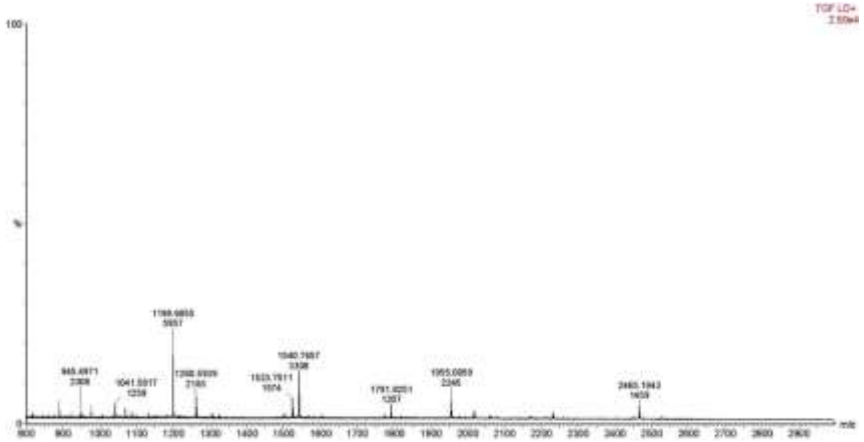


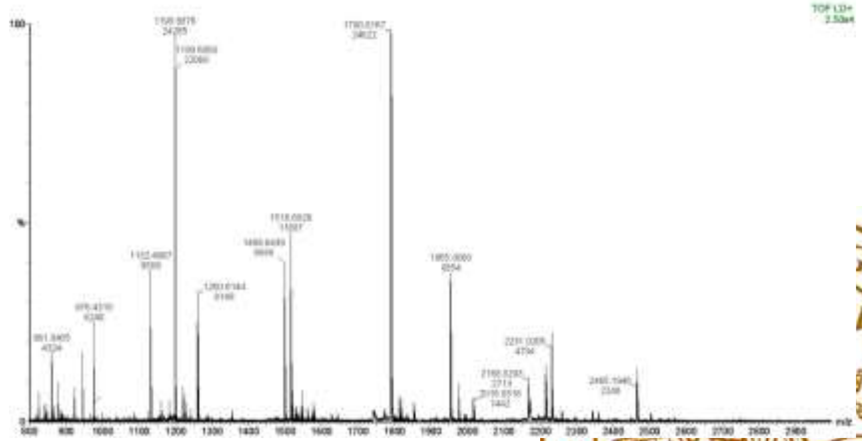




Small spots = higher MALDI MS sensitivity



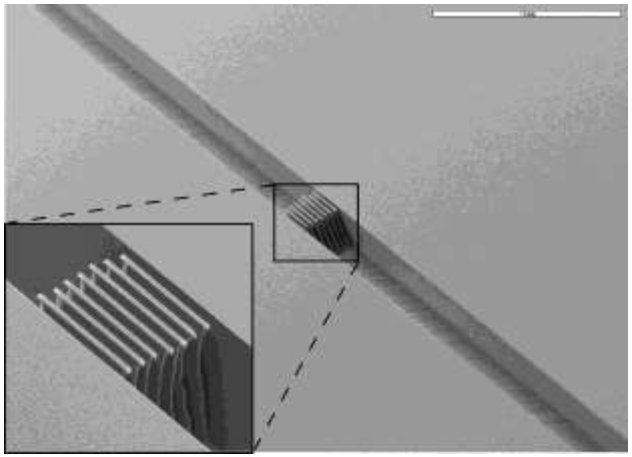




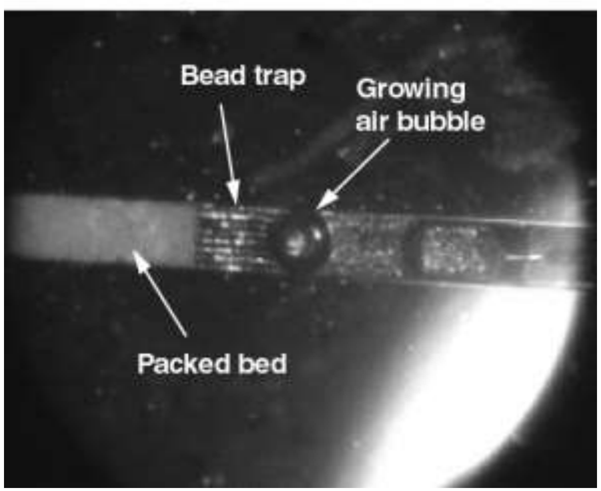
Analytical Chemistry, 73, 2001, 214-219

Chip integrated solid phase microextraction

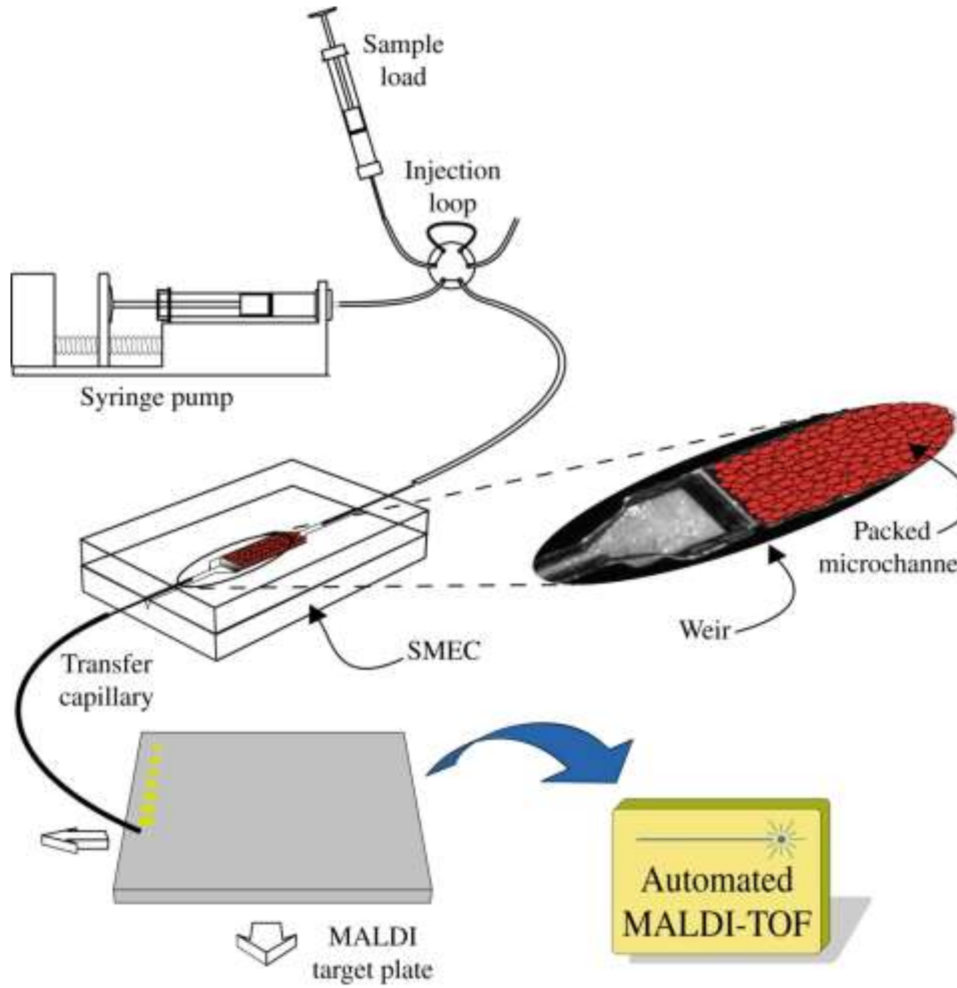
Bead trapping silicon microgrid
in a chip capillary



Problem

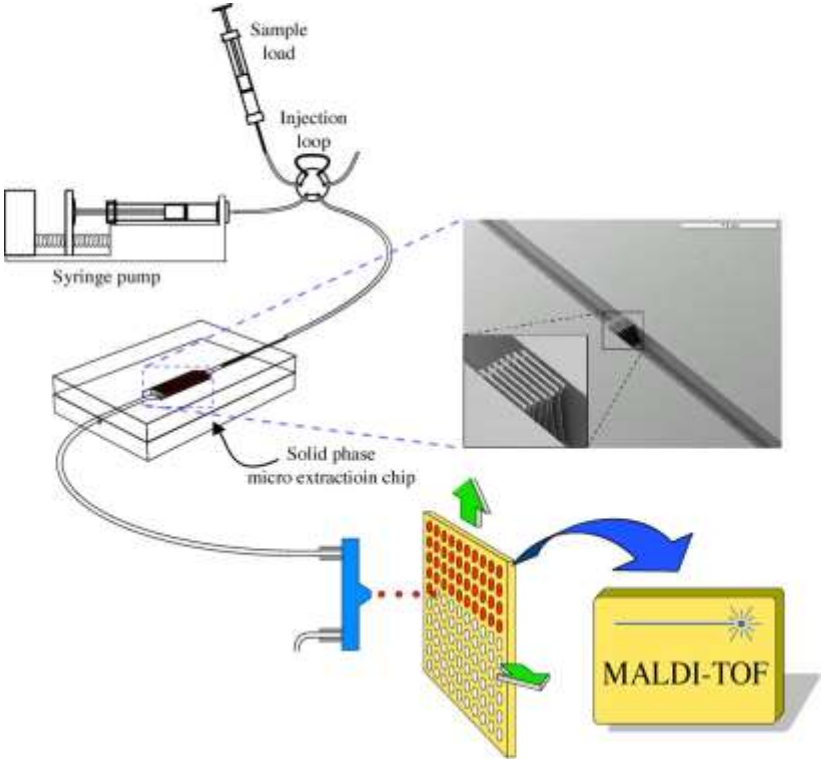


System set-up for solid phase microextraction



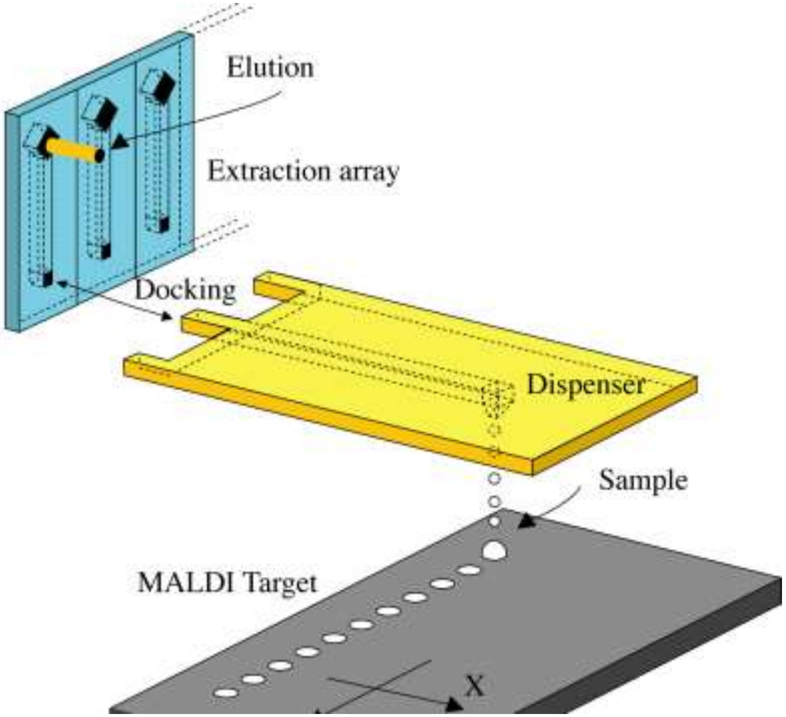
Solid-phase extraction

Pressure driven flow



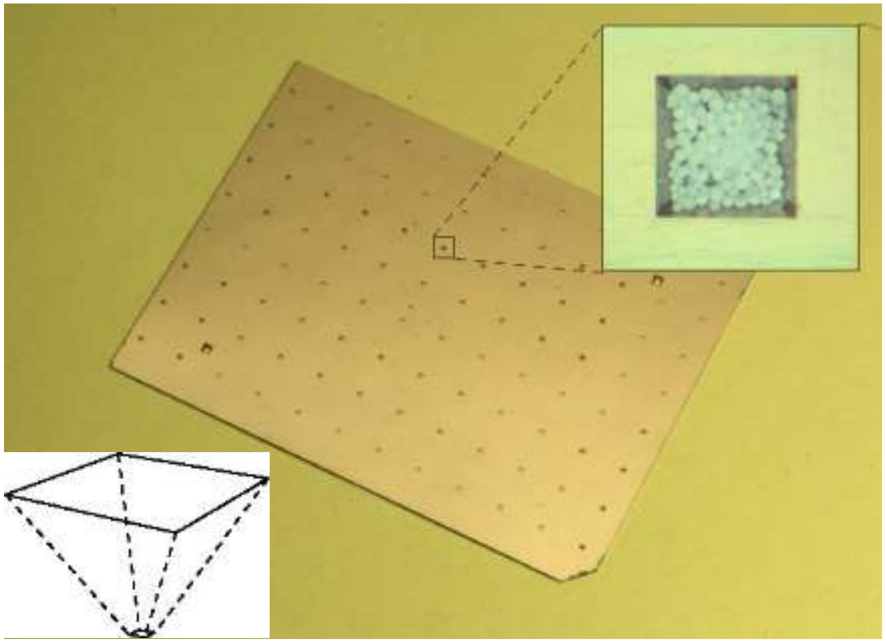
Proteomics, 2002, 2, 413–421

Capillary driven flow



Electrophoresis
2004, 25, 3778-3787

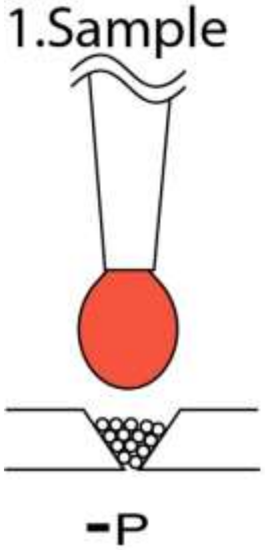
Integrated Sample Enrichment Target



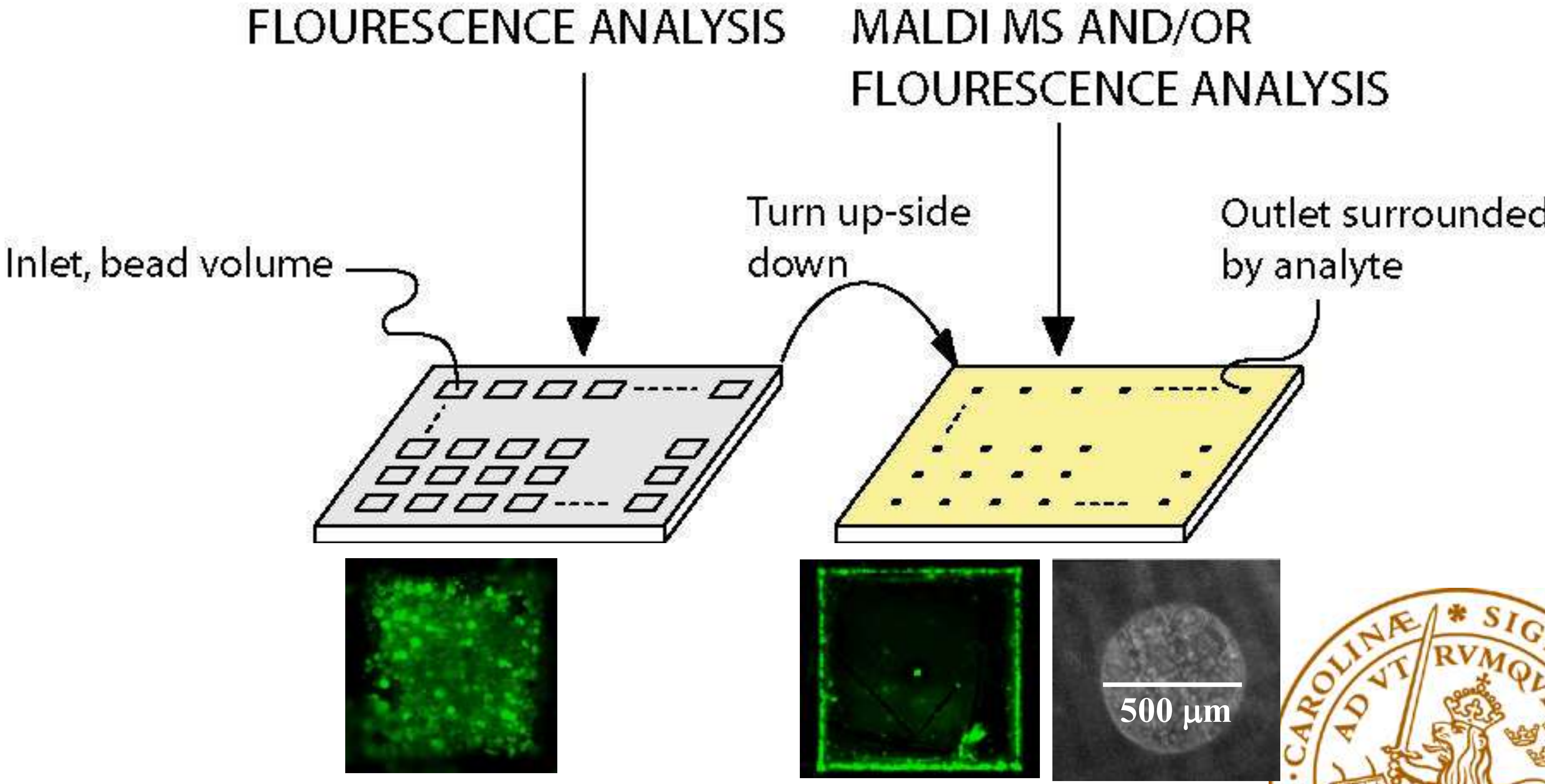
Same dimensions as the standard MALDI target. e.g. 5.5 x 5 cm and 96 perforated nanovials (30 nL volume)

- **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**

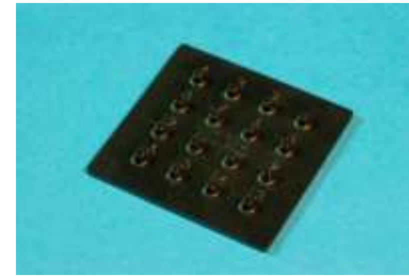
ISET- sample preparation and presentation

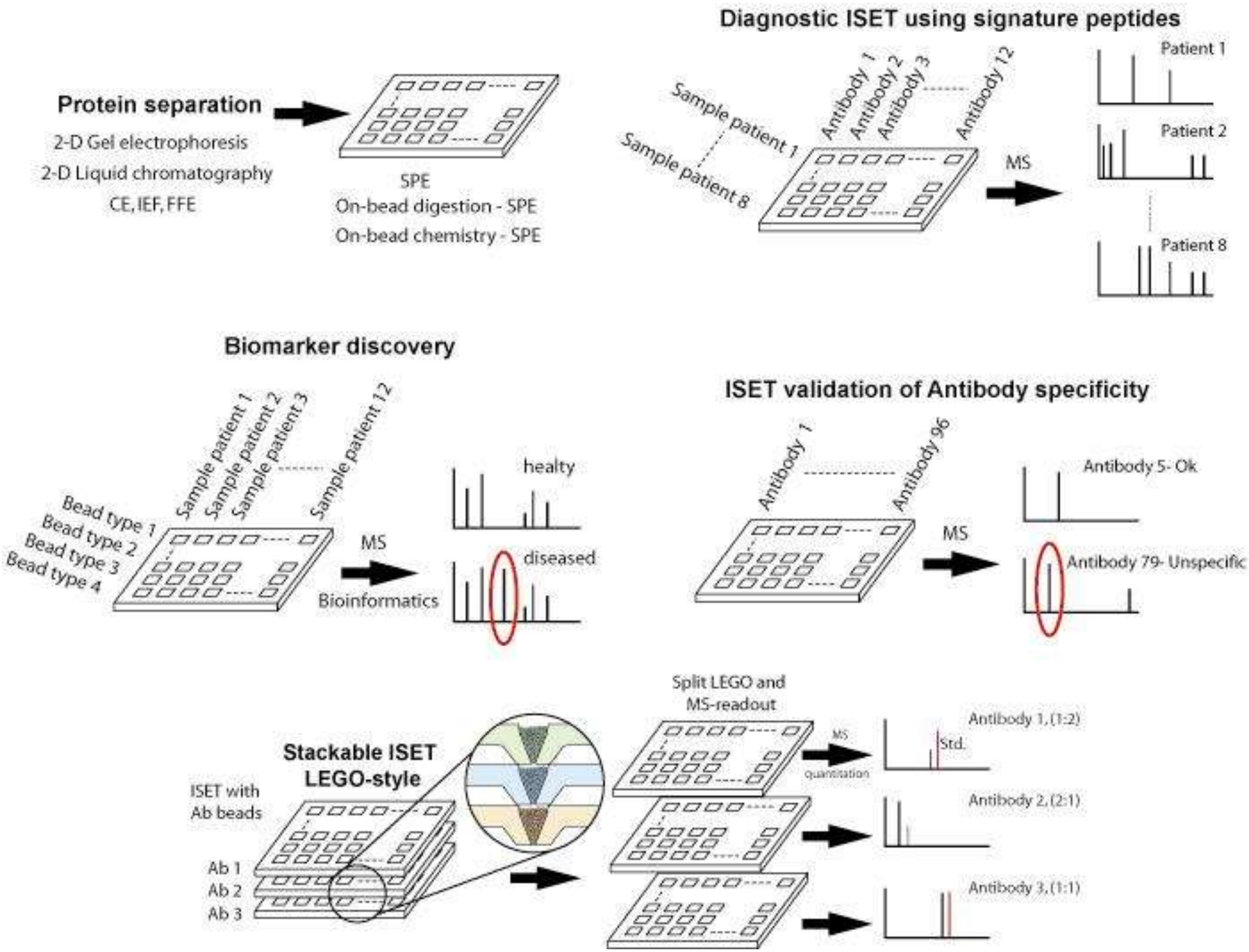


Detection of Analytes

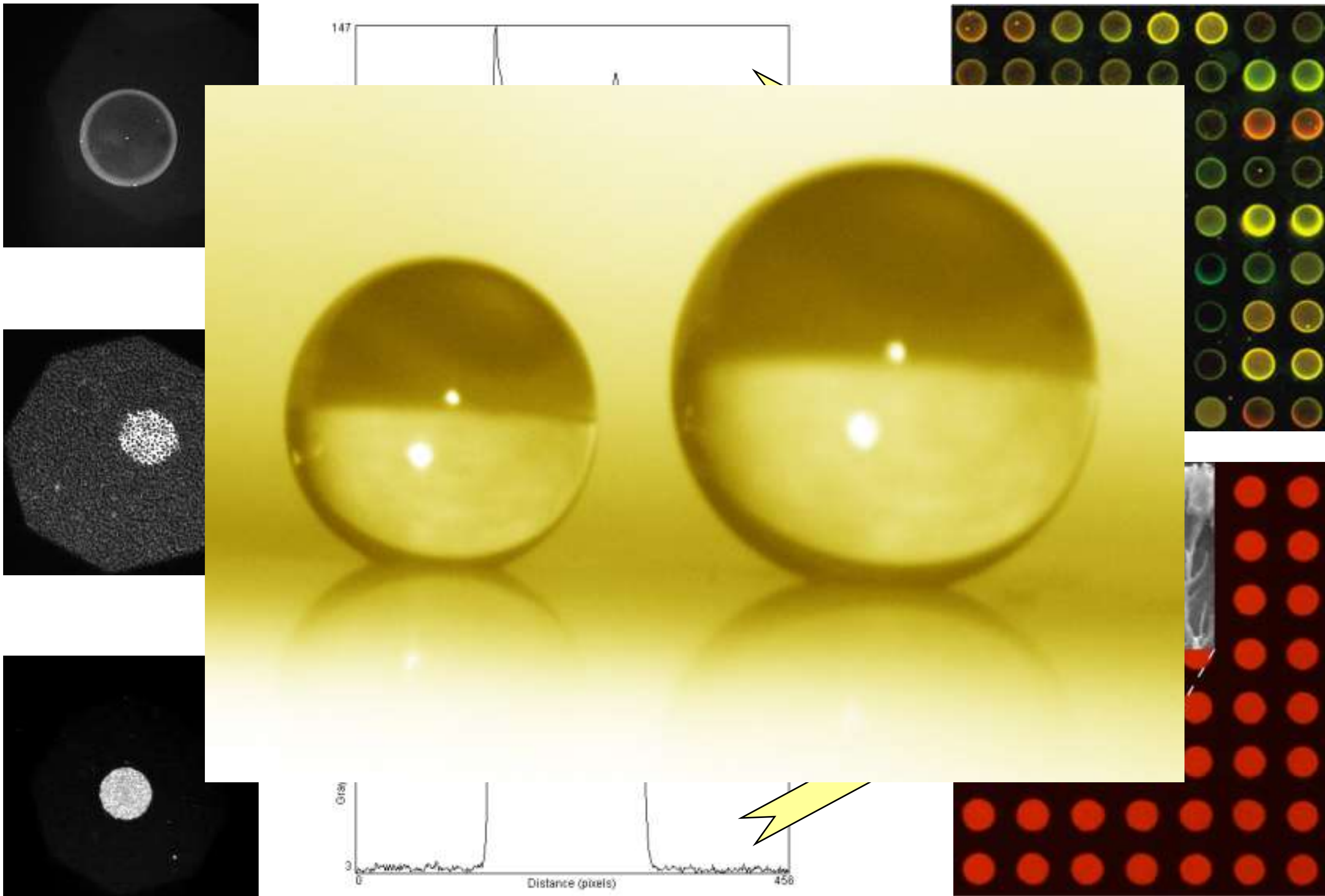


ISET Applications

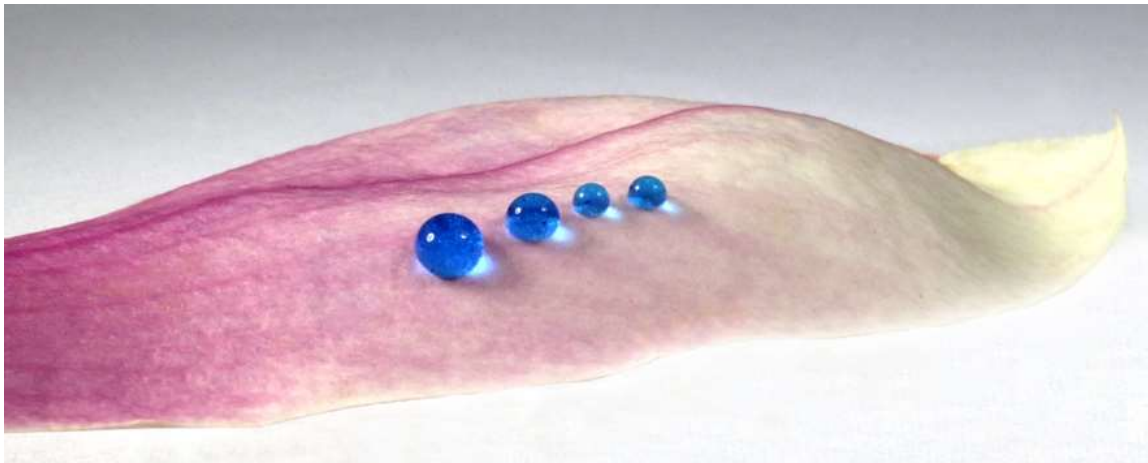


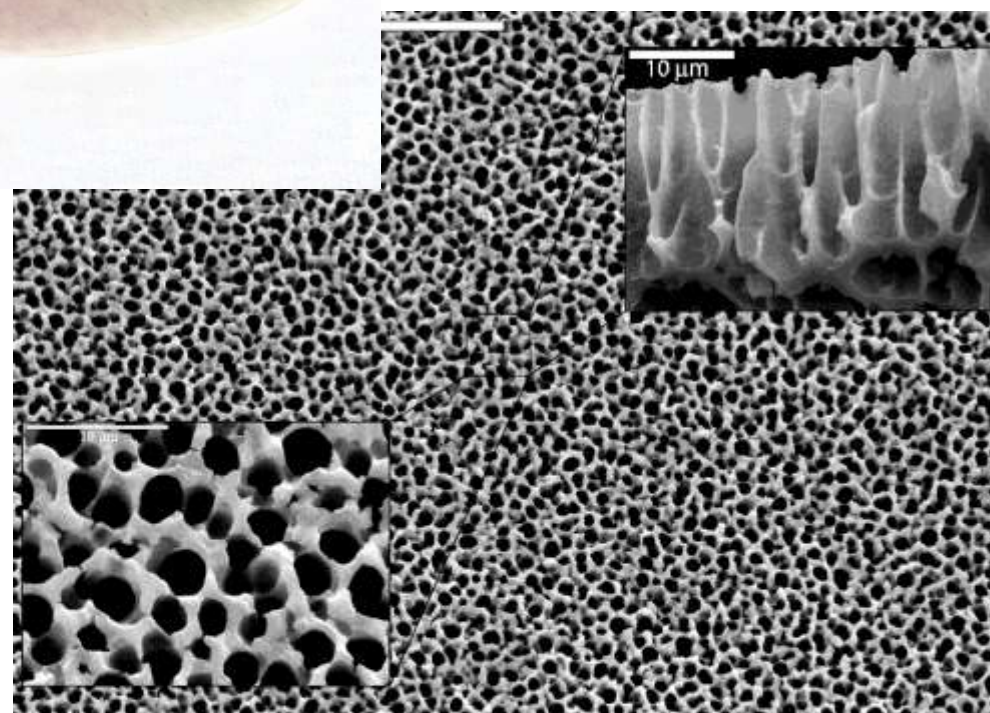


Spothomogeneity



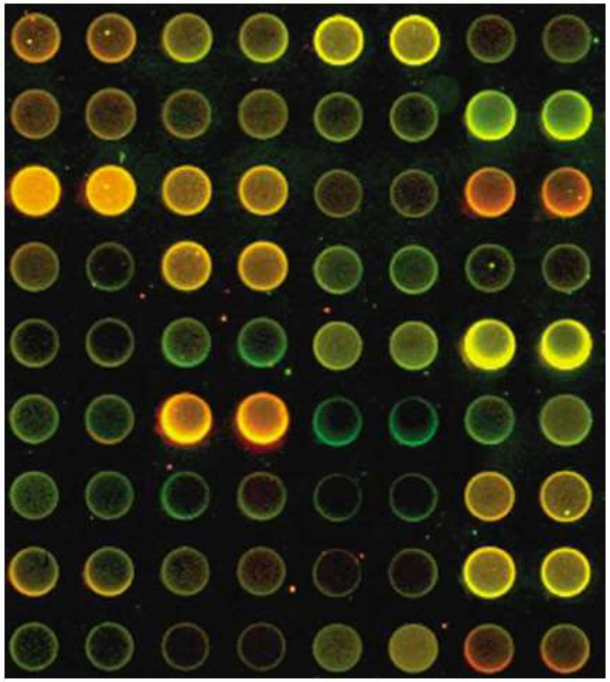
Protein chips based on porous silicon as substrate surface



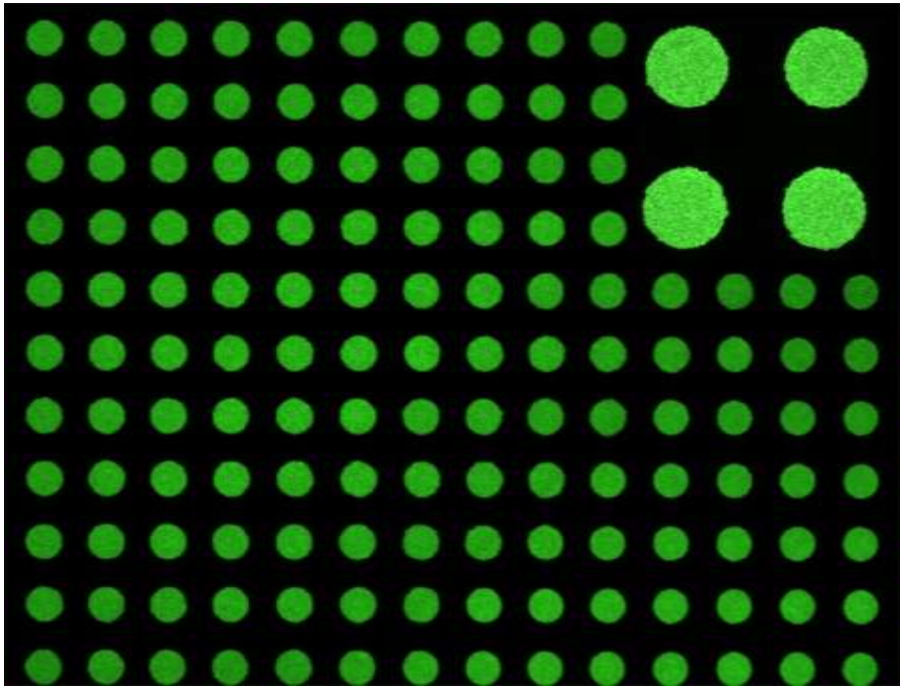


- Increased surface area
- Reduced spot size
- Homogenous spot profile

Non-homogenous spots
"coffee stain" effect



Silanized glass



Macroporous silicon