Advanced Training in understanding the Safety of Nanomaterials

NANOGENTOOLS

The new trends of nanomaterials applications for bionanosensors and nanomedicine

NANOGENTOOLS EU AUTUMN SCHOOL 2017

Dr Dumitru Ulieru, Oana-Maria Ulieru, Xavi Vila, Alex. Topor,

SITEX 45 SRL ,Bucharest Romania

ICCRAM-Burgos University

Table of Contents

Introduction

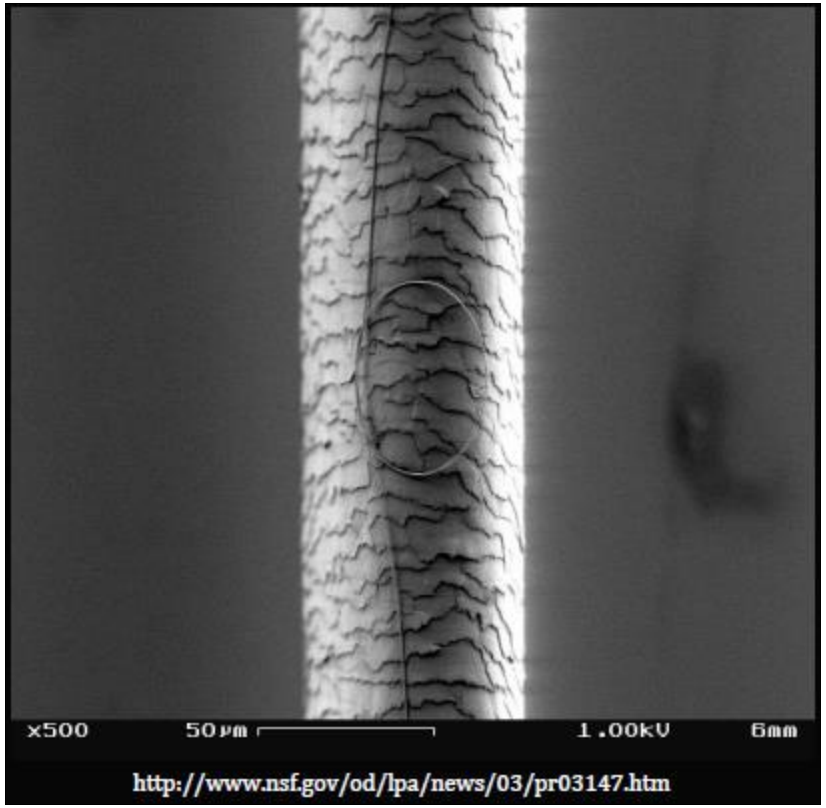
NANOGENTOOLS

- **Nanotechnology** =
- **the emerging technology** with enormous potential for
  - **Information and Communication ICT**
  - **Technology ,biology and biotechnology,**
  - **Medicine and medical technology**

- **Nanobiotechnology**= The convergence of recent advances in **nanotechnology with modern biology and medicine** has created the new research domain

- **Nanomedicine =**The use of nanobiotechnology in medicine

What is a nano



- What is **100,000** times thinner than a strand of hair &
20 times tougher than steel ?

A Carbon nano tube CNT

1x10-9 m

What is nanotechnolgy

NANOGENTOOLS

- **Nanotechnology** is not biology, physics or chemistry, its all sciences that deal with such a small scale

- **Best definition** : ncompesses the common unifying concept & physical laws that privail in the Nano scale

www.nanoscience- europe.org

What is nanomedicine

NANOGENTOOLS

Nanomedicine ***may be better defined as :***

„The monitoring, repairing and construction of human biological systems at the molecular level using engineered Nanodevices and Nanostructures"

Nanomedicine Roadmaps towards 2020 http//www.foresight.org/Nanomedicine

Definitions

- **Nanomaterials** and **biological structures** are of the **same size**, which allows for **unique interactions between biological systems and synthetic materials** for analytical, diagnostic and therapeutic applications
- **Nanomedicine** The use of materials whose components exhibit significantly changed properties by **gaining control of structures at the atomic, molecular, and supramolecular levels.**
- **Novel nano- and bio-materials** as well as **nanodevices** are fabricated and controlled by nanotechnology tools and techniques, **which investigate and tune properties,responses and functions of living and non-living matter at** ***sizes below*** **< 100 nm.**

Nanomedicine focused topics

NANOGENTOOLS

Engineering Topics including Peptide nanoparticles for medical applications, the Transition from semiconductors to biochemistry in the lithography ***industry;Topics in Clinical Applications*** *i.e.* nanomedicine and protein mis. diseases ***Topics in genetics*** (e.g. Nanostructured probes for gene detection in living cells, Detecting UV damage to individual DNA molecules with Atomic Force Microscopy, ***Topics in Diagnostics***, with its main focus on early diagnosis *in vitro* and *in vivo*; ***Policy and Commercialization Topics****,* including initiative in nanomedicine to focus efforts in research, development and applied nanotechnology for improving the diagnostics, therapeutics and treatment of cancer; ***Experimental Research Topics***,-main basis for preclinical study, like Nanodiagnostic ***imaging;Topics*** on Basic Nanomedicine, ***Topics*** on Pharmacology; ***Topics*** on Oncology and **Toxicology.**

Nanomedicine application domains(1)

- **Diagnostics** main objectives of development:
  -Devices for combined structural and functional imaging *in vivo*
  -Portable point of care devices (POC)
  -Devices for multiparameter (multiplexing) measurement
  -Devices for monitoring therapy and personalised medicine
- **Magnetic particles Imaging**
- **Magnetic particles for drugs targeting**
- **Targeted therapy and drugs release**
- **Molecular optical imaging**

Nanomedicine application domains(2)

NANOGENTOOLS

- **Drug delivery / Nanopharmaceuticals**
  - Noninvasive delivery of protein nanomadicine
  - Noninvasive delivery DNA based nanomedicine
  - Therapeutic nanaoparticles and polymers
  - Nanocarrrier and transporter molecules and particle
  - Computational tools
- **Nanodevices**
  - Focused ultrasound therapy system
  - Pressure and thermosensitive drugs
  - Targeted therapy in Oncology
  - Antiinflamatory diseases

Nanomedicine application domains(3)

NANOGENTOOLS

- **Regenerative medicine**
- **Smart biomaterials Nanorchitectured EMA**
    - **Synthetic prophorgens   High throughout nanoscreening devices**
        - **Cues delivery shapers**
- **Cells theraphy   Delivery vehicles**
- **Tissue Engineered Producvts (i.e Heart tissues !)**
    - **Cells (Parkinson ,Alzheimer,Huntington ds,cardiac,retinal,diabet,spinal cord)**
        - **In vitro assays and bioreactors**

Biomedical applications of Nanobiosensors

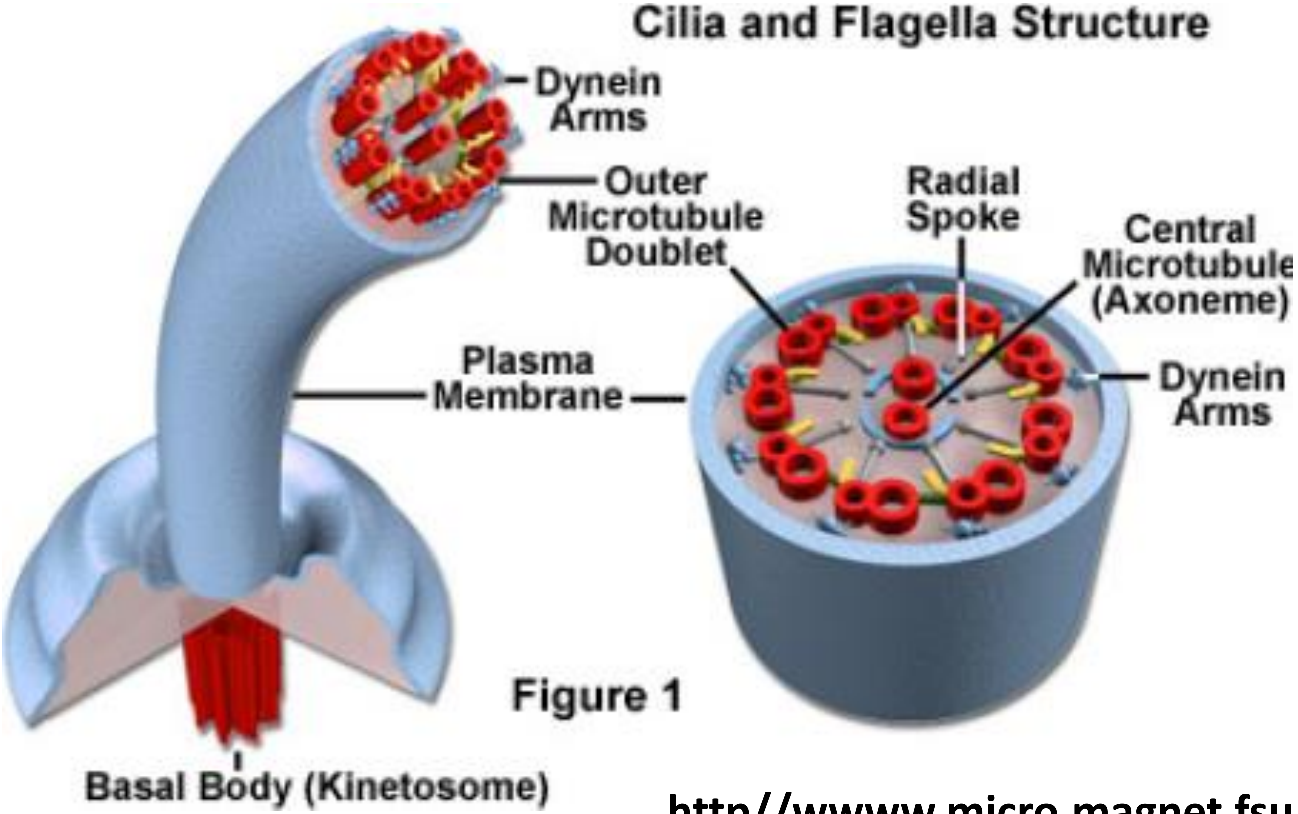
NANOGENTOOLS

- **The terms ''nanoscience'' or 'nanotechnology'' are best used for phenomenon associated with structures approximately 1-100 nm in size where the properties of interest are due to the size of the structure**

- ***„The design, characterization, production, and application of structures, devices and systems by controlled manipulation of size and shape at the nanometer scale that produces structures, devices and systems with at least one novel/superior characteristic or property"***

Nanotechnology in nature

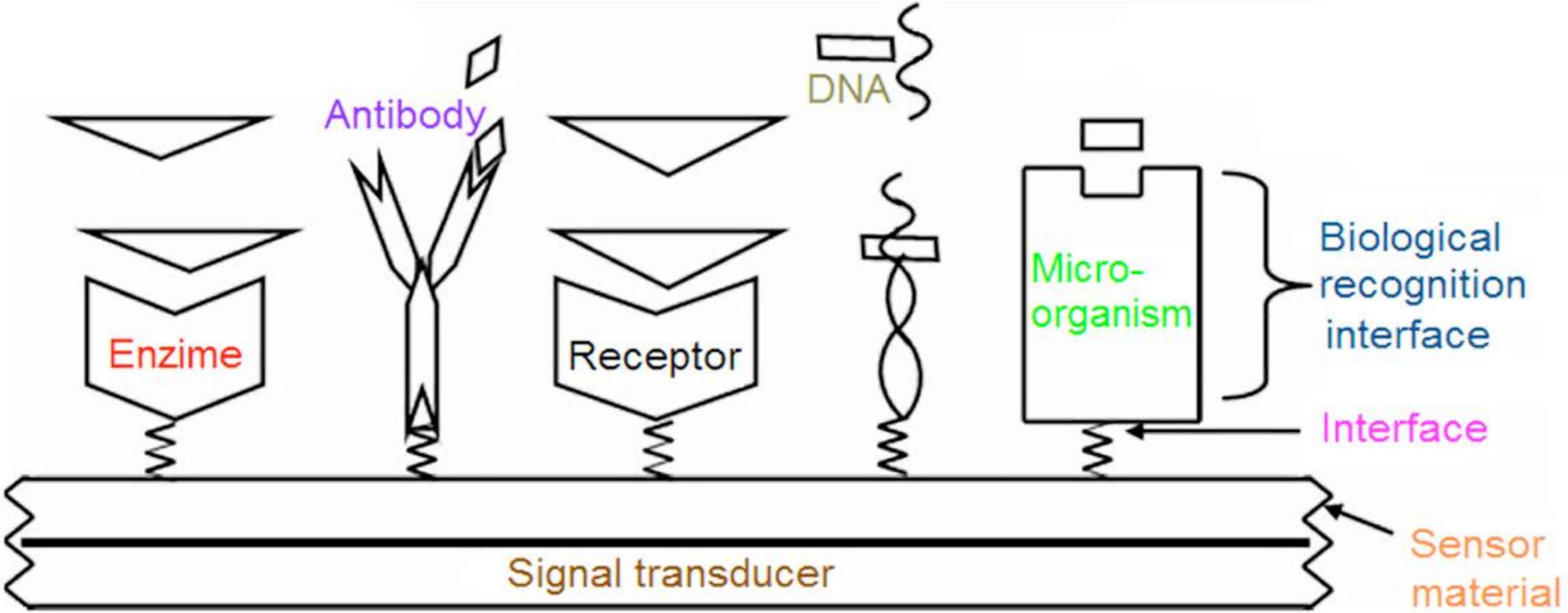
When it comes to nature,they are the king of nanotechnology



A flagelia structure is a complexity of nanorotors,motors tubes & arms that works better together, many of which we still try to decipher how they work

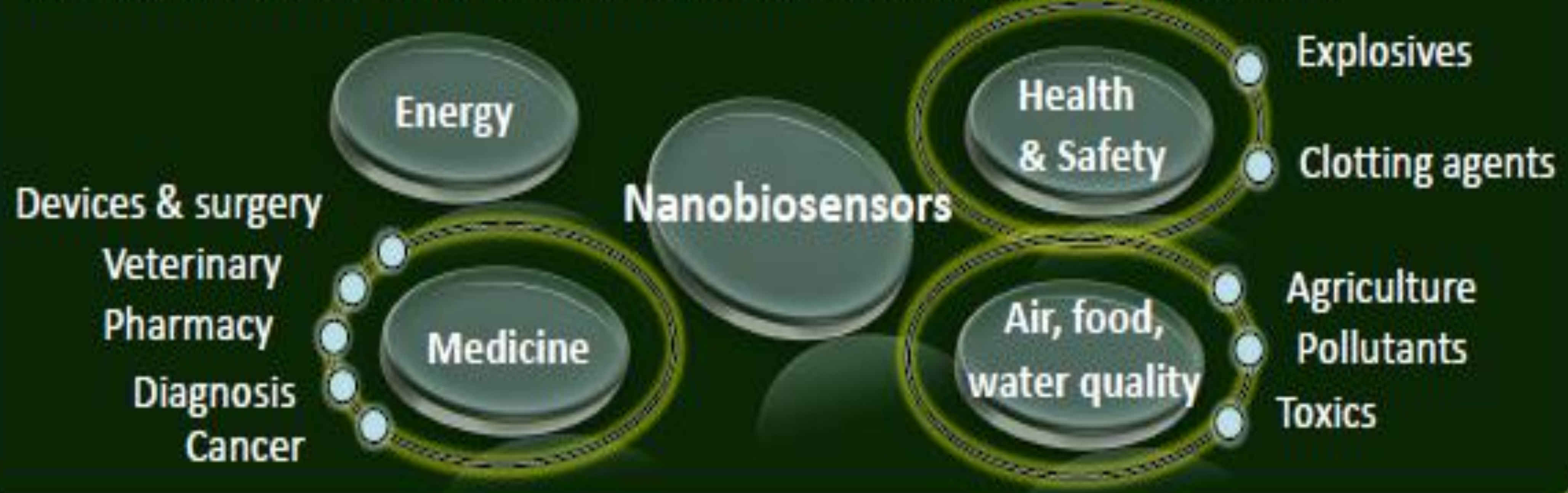
http//wwww.micro.magnet.fsu.edu//cells/cilliandflagella/ciliandflagella.html

Schematic representation of nanobiosensor components

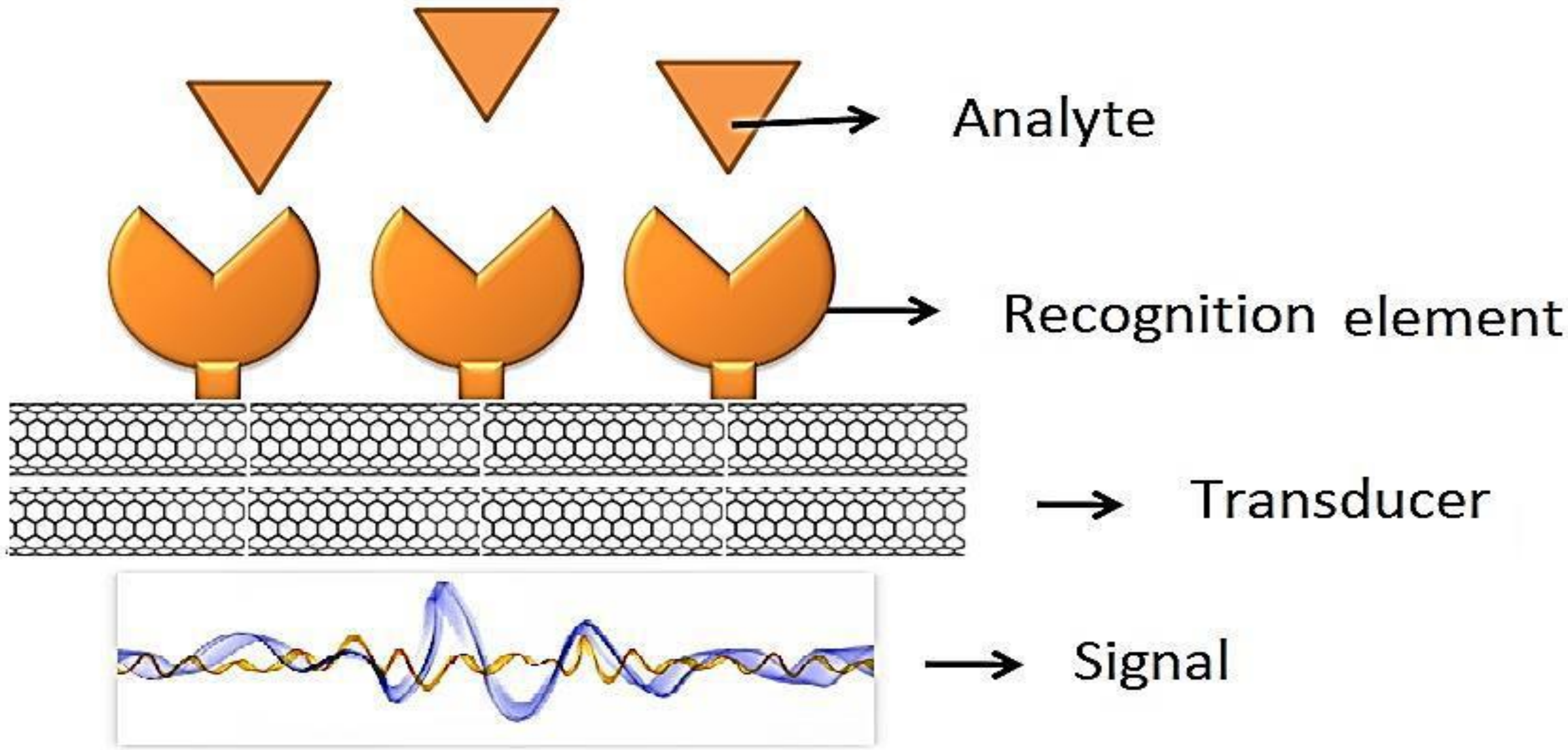


Potential fields

Nowadays, in spite of the fact that several areas benefit from nanobiosensors, the main field in which these tools have introduced and develop is medicine.



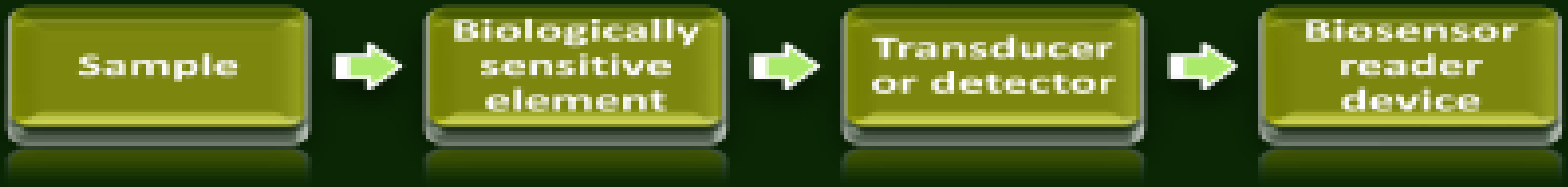
Schematic presentation of a biosensor.



Biosensors are the devices for detection of biological analytes which have wide applications, including biomarker dete-ction for medical diagnostics, and pathogen and toxin detection in a specimen by binding analyte on the reactive surface

The nanobiosensor principle of operation

Generally speaking, the principle of action is based on the signal detection produced by a physicochemical process of the recognized biological elements, that is converted, through the transducer, into measurable and quantifiable electrical output signals, folllowed by an optical or acoustic effect..



There has been a development of the technology in the fabrication , measurement and imaging at nanoscale; boosting the progress towards devices with action in real time, directly, in a portable small size and capable of detecting tiny amounts of analyte (nanounits).

Sensing techniques

NANOGENTOOLS

The sensing techniques can detect the interaction between bio-receptors and target compounds using different appropriate nanostructures

The two principal components of biosensors are :

biological element and a transducer.

The biological element interacts with an analyte to produce a detectable change.

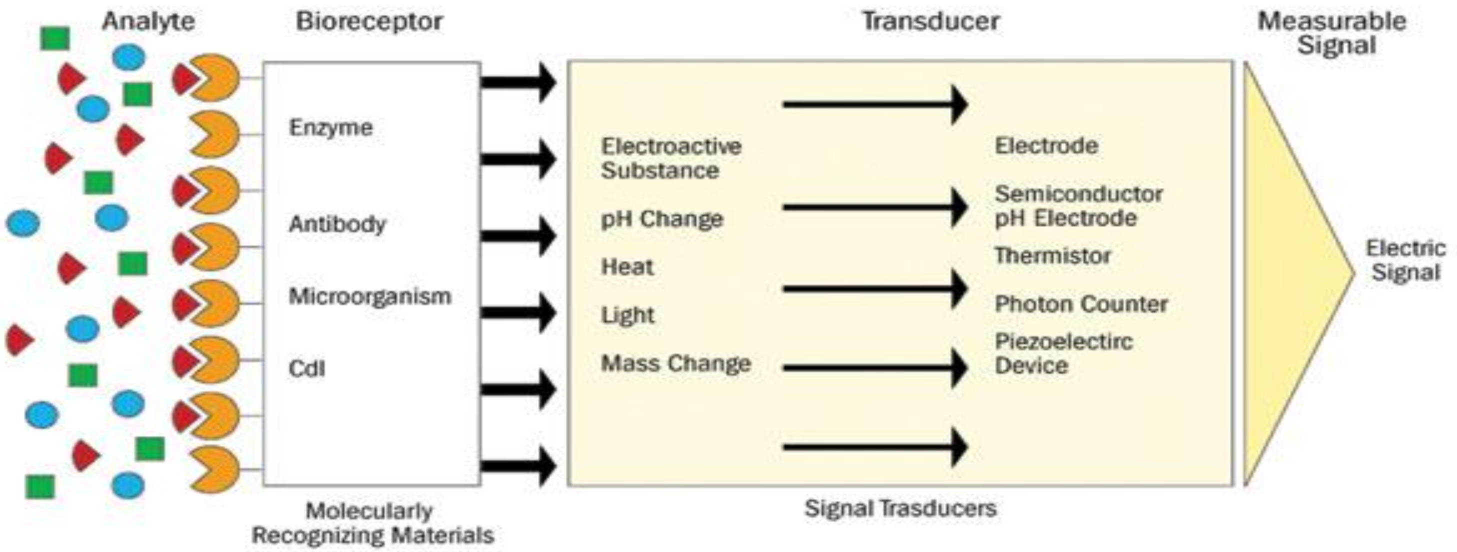
The transducer converts the physico-chemical change in the biologically active material resulting from the interaction with the analyte into an analytical useful / measurable signal

According to the transducers, the biosensors can be classified as

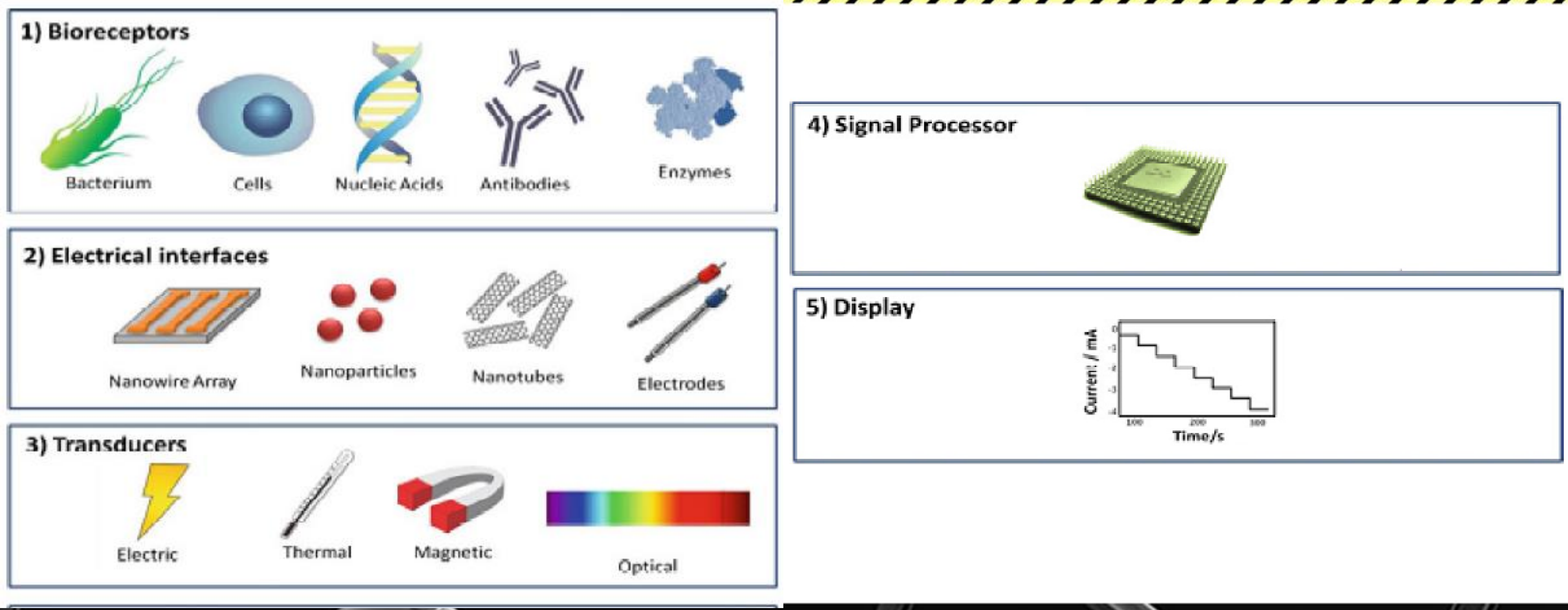
(i) electrochemical, (ii) optical, and (iii) piezoelectric biosensors.

What is a biosensor ?

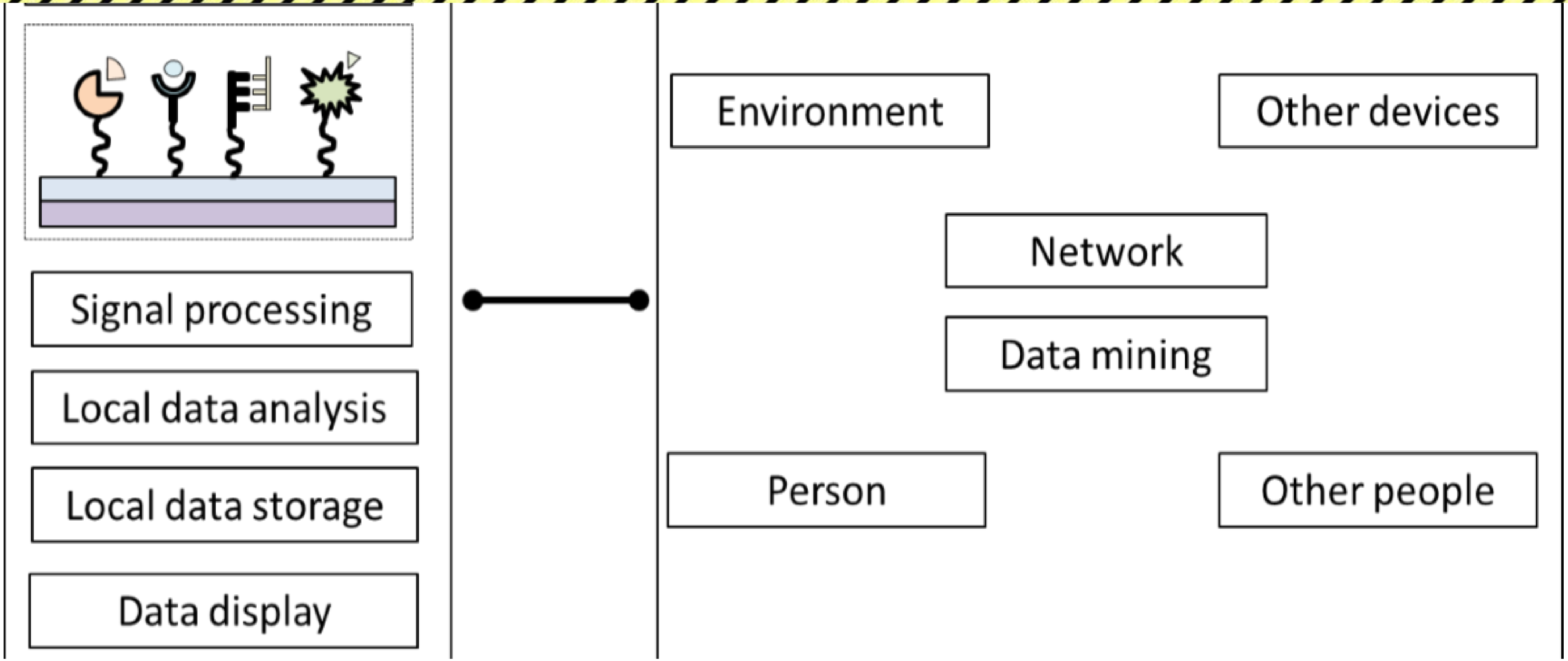
A biosensor is a self-contained integrated device that is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element which is in direct spatial contact with a transduction element (IUPAC, 1996)



The components of a typical biosensor.



Biosensing operation system



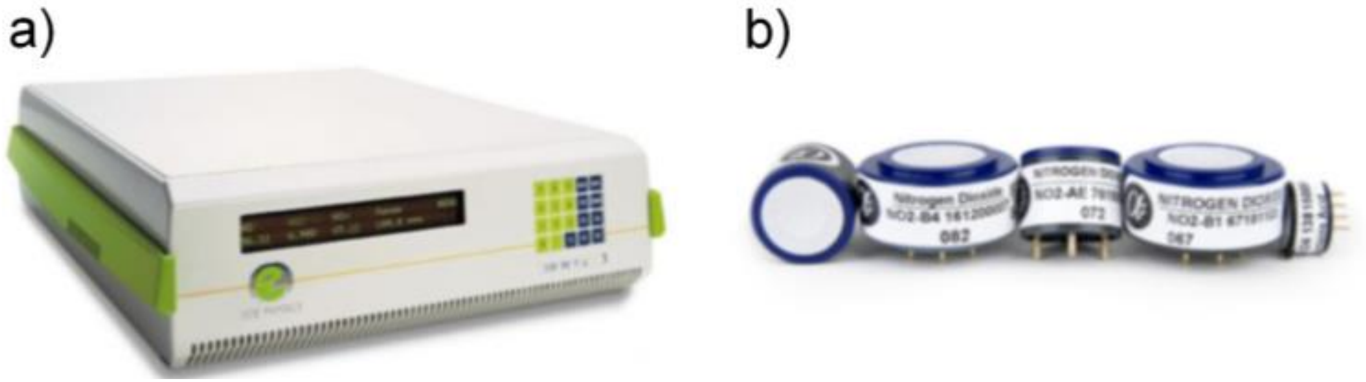
Electrochemical nanobiosensors

Electrochemical methods of interest worldwide and remarkable advantages:

- **high sensitivity,**
- **small dimensions,**
- **low-interference characteristics,**
- **low cost,** and **compatibility with microfabrication technology**

Depending upon the electrochemical property to be measured by a detector system, electrochemical biosensors can be divided into four sub-categories

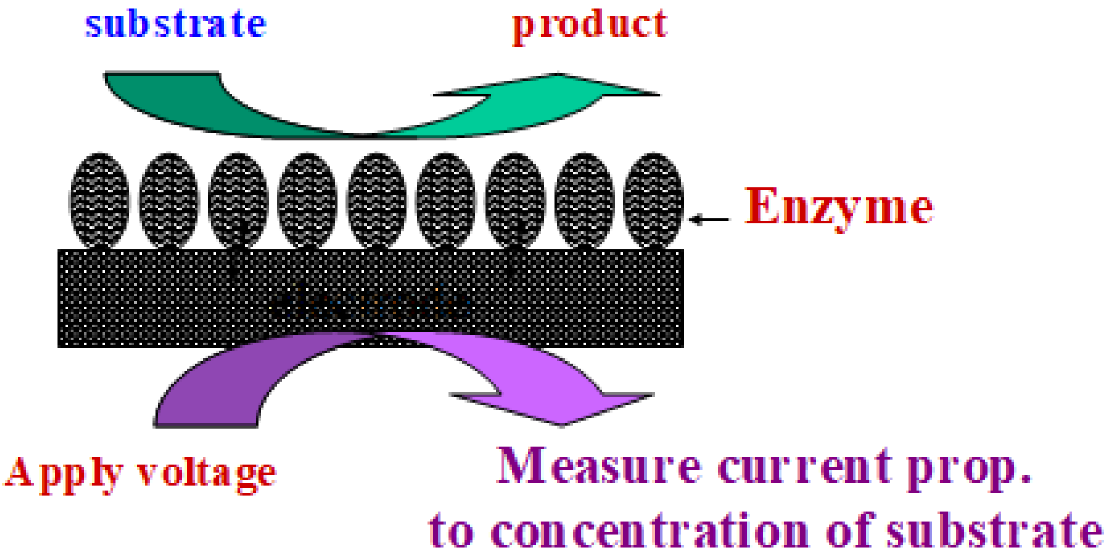
- **potentiometric,**
- **amperometric,**
- **conductometric,** and
- **impedimetric biosensors**



Electrochemical biosensors

NANOGENTOOLS

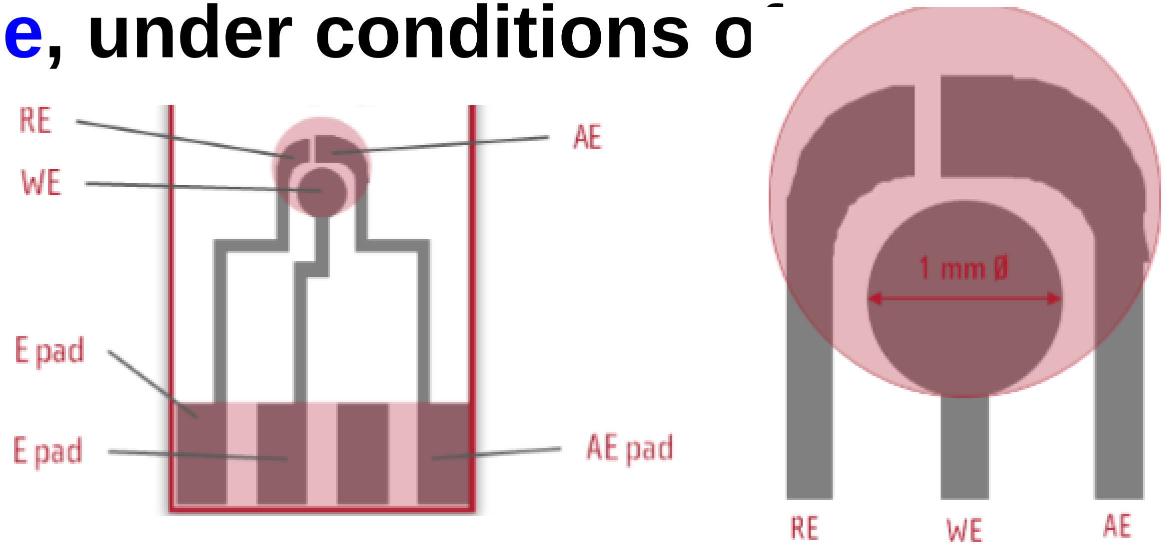
- **Electrochemical biosensors** are mainly based on the fact that **during a bio-interaction process, electrochemical species such as electrons are consumed or generated producing an physically readable electronic signal which can be recorded by applying different electro-chemical detections.**
- Electrochemical property to be measured by
  a detector system,
  allows to be divided into **four sub-categories**
- **potentiometric,**
- **amperometric,**
- **conductometric, and**
- **impedimetric biosensors**



Principle of Electrochemical Biosensors

Potentiometric nanobiosensors

- These bio-sensors are based on **analytical information obtained by converting the biorecognition process into a potential signal**
- Monitoring the potential of a system at a **working electrode**,
- An accurate **reference electrode**, under conditions o
essentially zero current flow



Amperometric nanobiosensors (1)

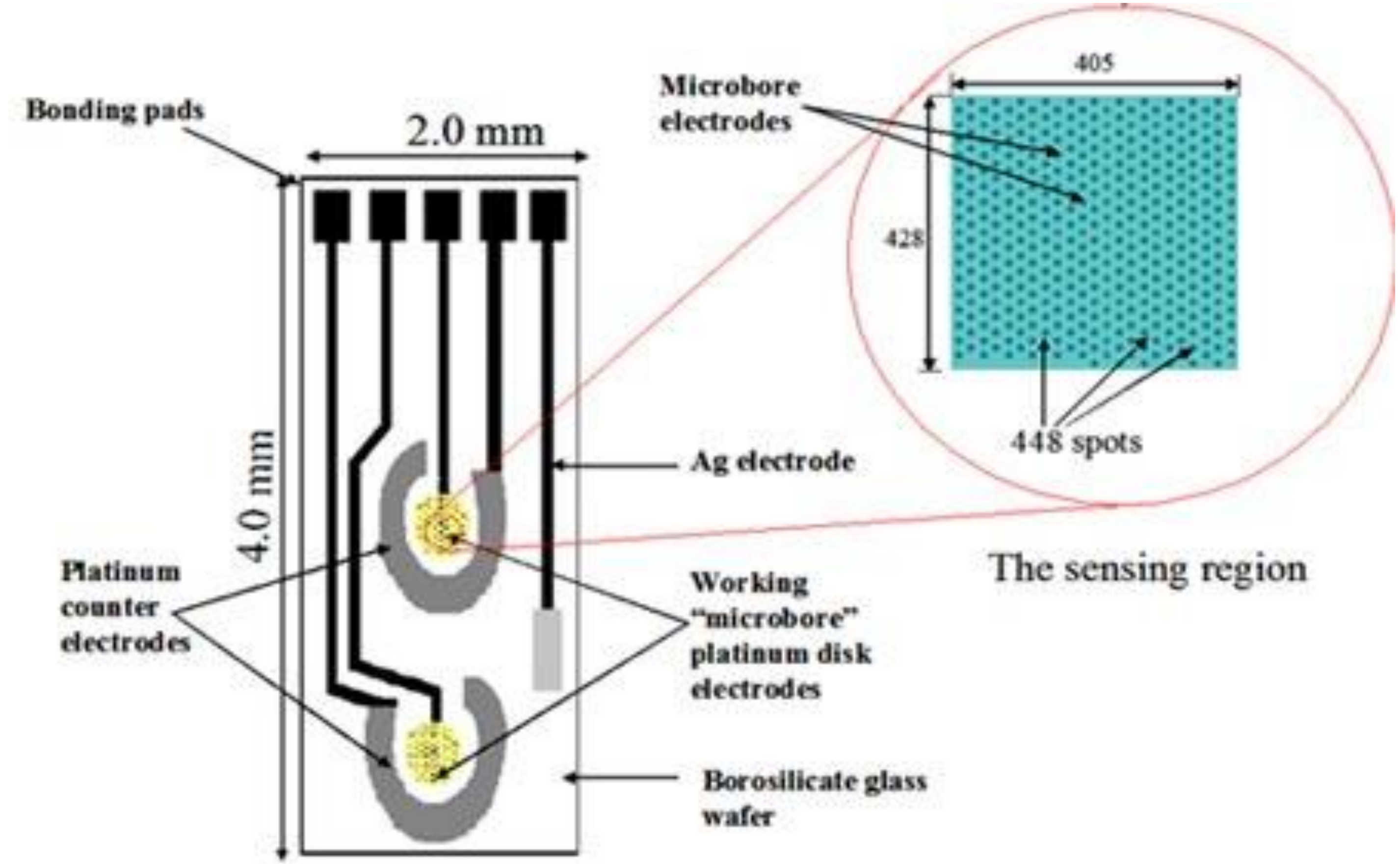
NANOGENTOOLS

- The amperometric biosensors **measure the current produced for the electrochemical oxidation or reduction of an electroactive species.**

- The amperometric biosensor is fast, more sensitive, precise and accurate than the potentiometric ones,

- Not necessary to wait until the thermodynamic equilibrium

Amperometric nanobiosensors (2)



Schematic of the microfabricated, implantable, amperometric biochip device

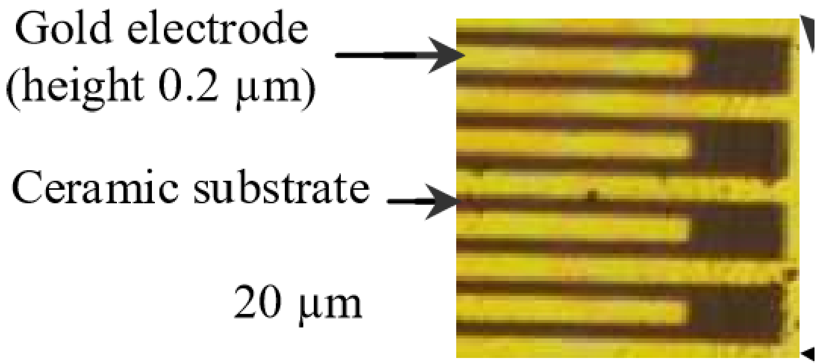
Impedimetric bionanosensors

- Impedance biosensors are less frequent compared to potentiometric and amperometric biosensors,
- Due to their all-electrical nature, they have significant potential for use as simple and portable sensors.
- Impedimetric biosensors measure the electrical impedance of a particular biological system in order to give information about that system

Layout for the structure of impedimetric sensor and pH sensor
the distance between electrodes is 50 μm

Conductometric bionanosensors

- In conductometric biosensors, **conductivity changes in the solution after the specific binding of the target to the immobilized partner,** can be detected.
- The principle of the detection is based on **the biochemical reactions in solution what produce changes in the electrical resistance between two parallel electrodes**



No	Source of changes in conductivity	Enzymes
1	Generation of ion groups	Amidases
2	Separation of different charges	Dehydrogenases and decarboxylases
3	Ion migration	Esterases
4	Change in level of ion particles association	Kinases
5	Change in size of charged groups	Phosphatases and sulfatases

Biosensors several exemples

- Cholesterol - based on cholesterol oxidase
- Antigen-antibody sensors - toxic substances, pathogenic bacteria
- Small molecules and ions in living things: H^+, K^+, Na^+, CO_2,H_2O_2
- DNA hybridization and damage
- Nano and Microarrays, optical absorbtion or fluor.

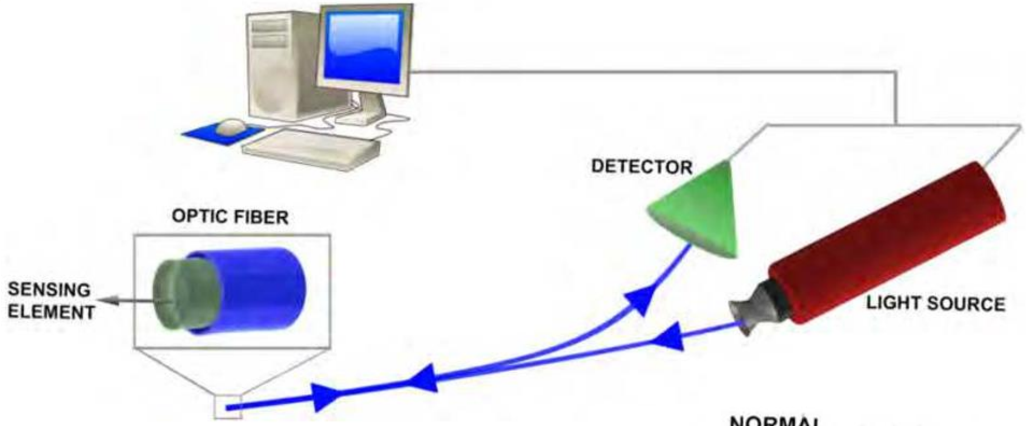
Optical biosensors

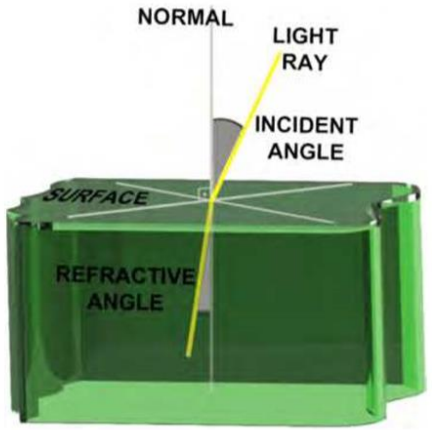
NANOGENTOOLS

- Optical biosensors are powerful detection instruments and versatile tools
- Highly sensitive to biomolecular targets,
- insensitive to electromagnetic interference,
- Real time response to biomolecular interactions.
- Optical methods in nanobiosensors include :
- surface plasmon resonance, localized surface plasmon resonance, fluorescence spectroscopy, interferometry,, total internal reflectance, light rotation and polarization,
- *impedance spectroscopy* .

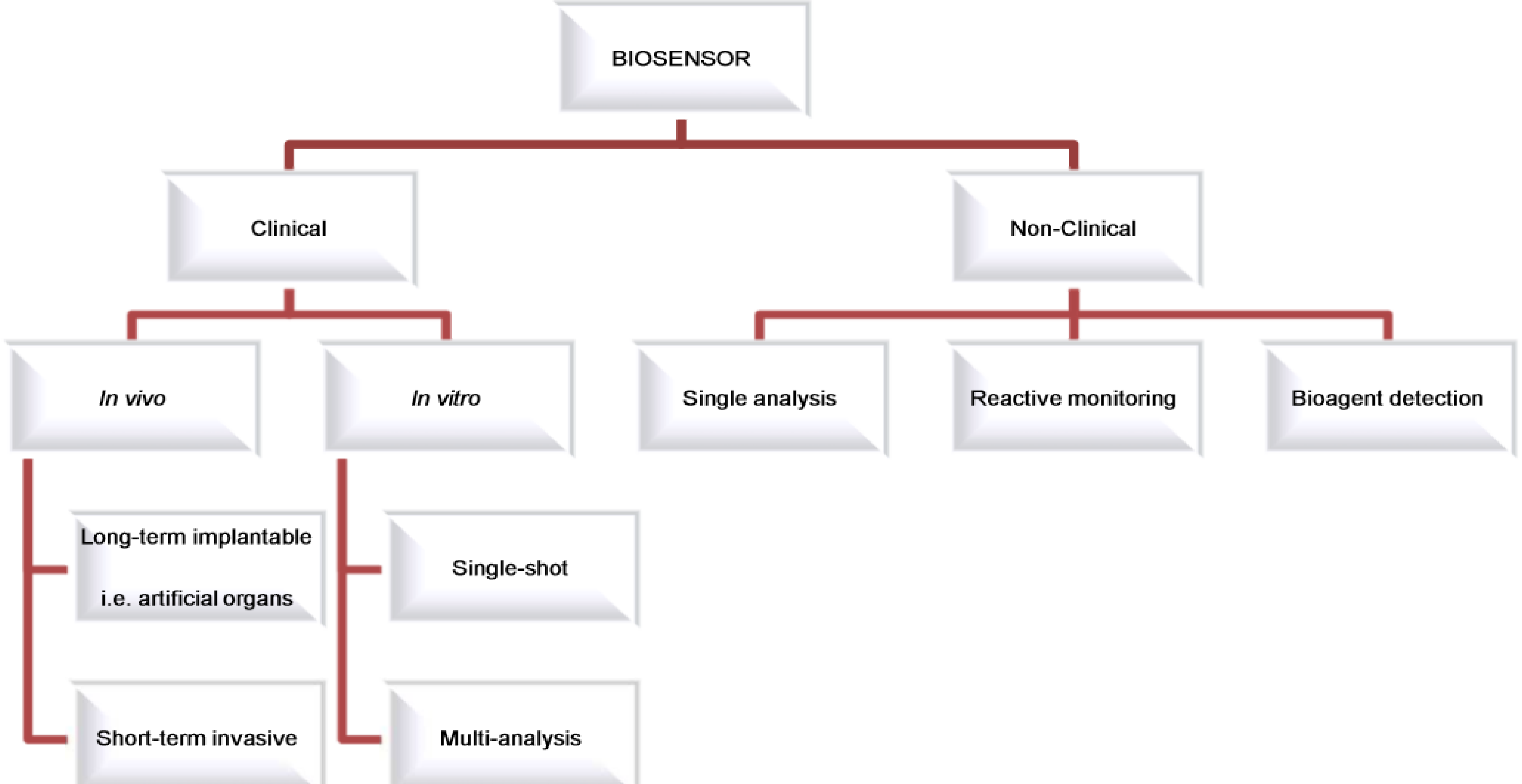
The advantages of optical biosensor

- Selectivity and specificity
- Remote sensing
- Compact design
- Fast, real-time measurements
- Isolation from electromagnetic interference
- Multiple channels/multiparameters detection
- Minimally invasive for *in vivo* measurements
- Choice of optical components for biocompatibility
- Detailed chemical information on analytes

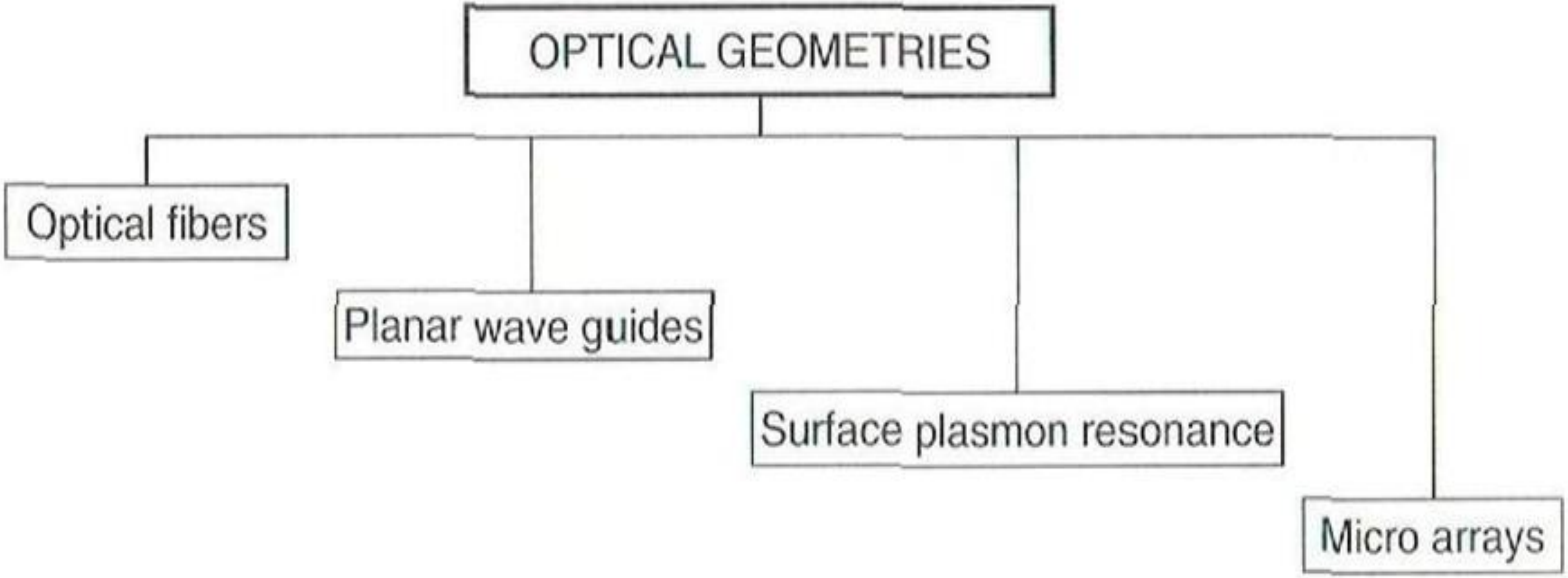




Nanobiosensors applications domain



Optical geometry of biosensors

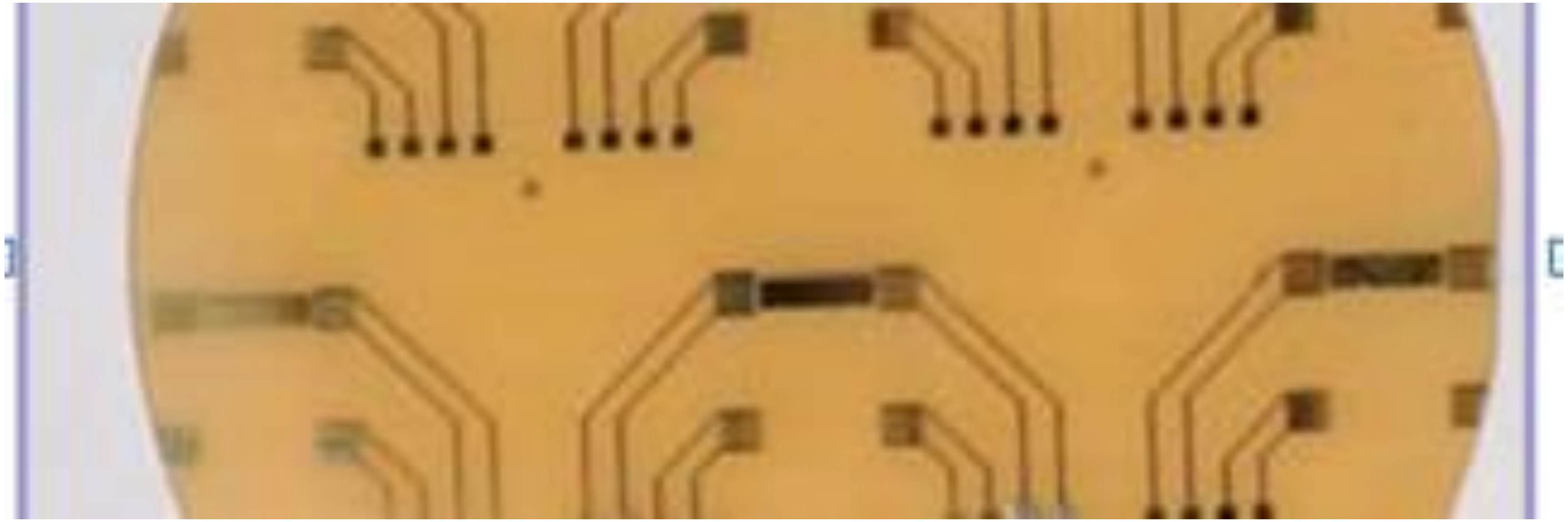


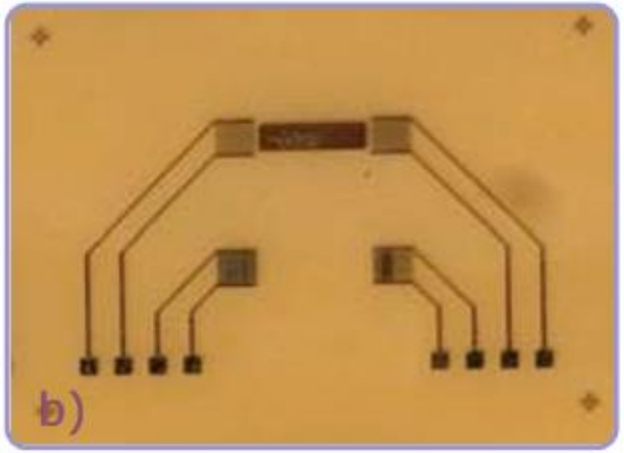
Piezoelectric nanobiosensors

NANOGENTOOLS

- Piezoelectric biosensors widely used to detect viruses, bacteria, proteins, and nucleic acids, because are extremely sensitive.
- Based on the measurement of the change in resonant frequency of a piezoelectric quartz oscillator in response to changes in surface adsorbed mass.
- The surface of crystal is coated with a layer containing the biorecognition element designed to interact selectively with the target analyte.
- Binding of the analyte on the sensing surface of crystals results in the mass change of the crystal which causes a measurable change in the resonance frequency

SAW TB Biosensor on quartz piezo substrate





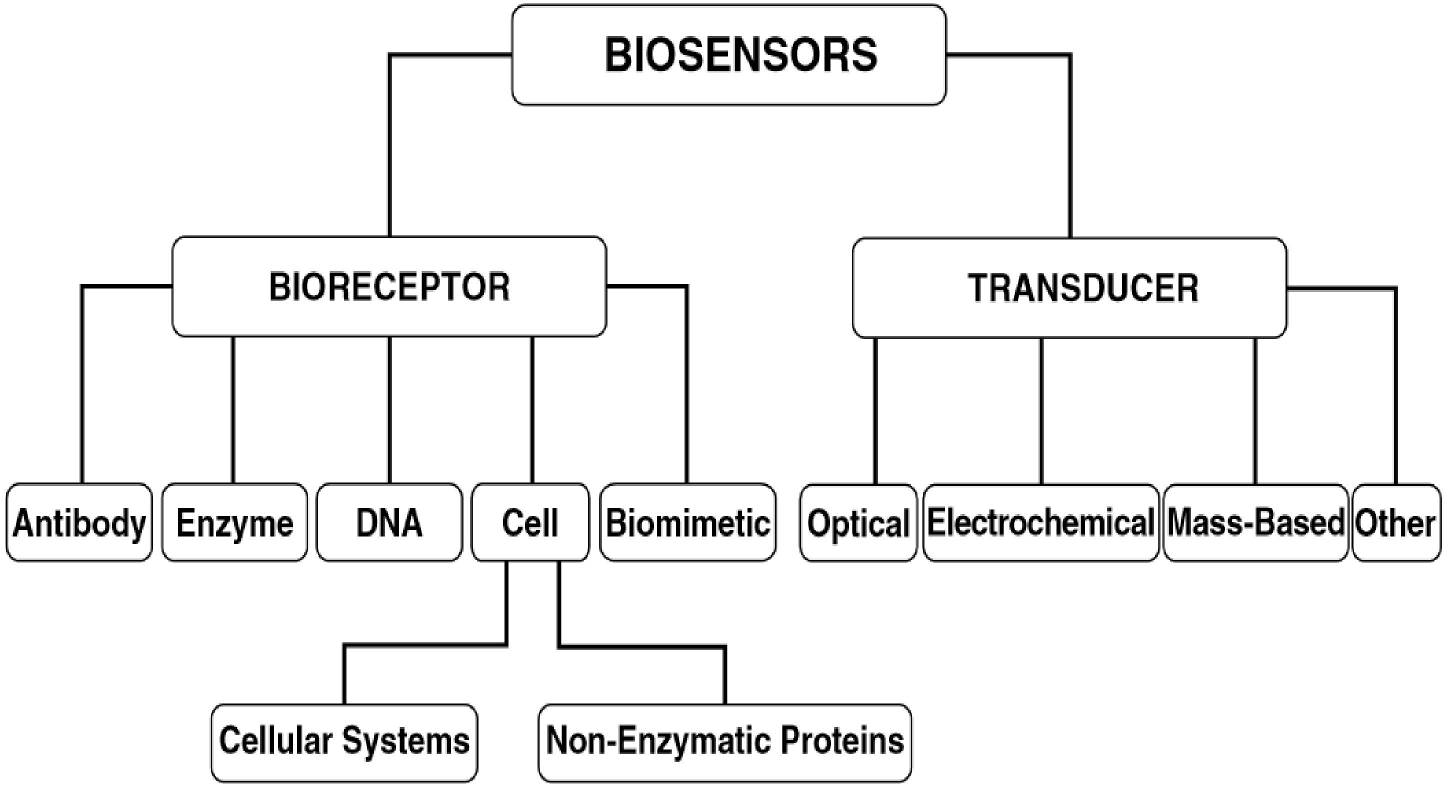
a) View of TB sensor for detection configuretions on langasite substrate;

a) Image of individual TB sensor
SITEX Project MICROBALERT
National Program PNII 2013-Romania

Nanobiosensors medical applications domain

NANOGENTOOLS

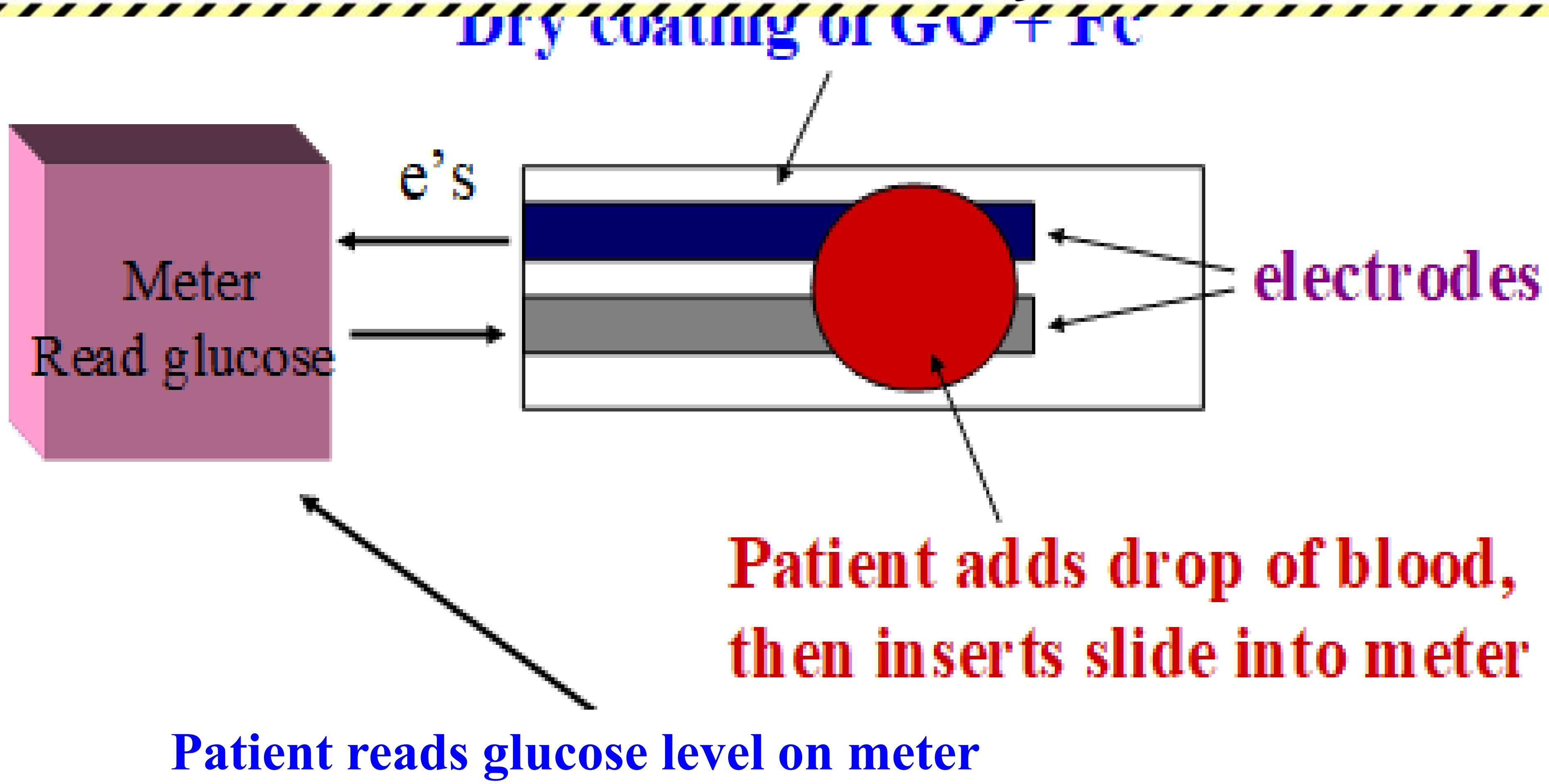
- Cellular Processes
- Viral Agents
- Human Immunodeficiency (HIV
- Bacterial Pathogens
- Cancer
- Parasites
- Toxins
- Blood Factors
- Congenital Diseases



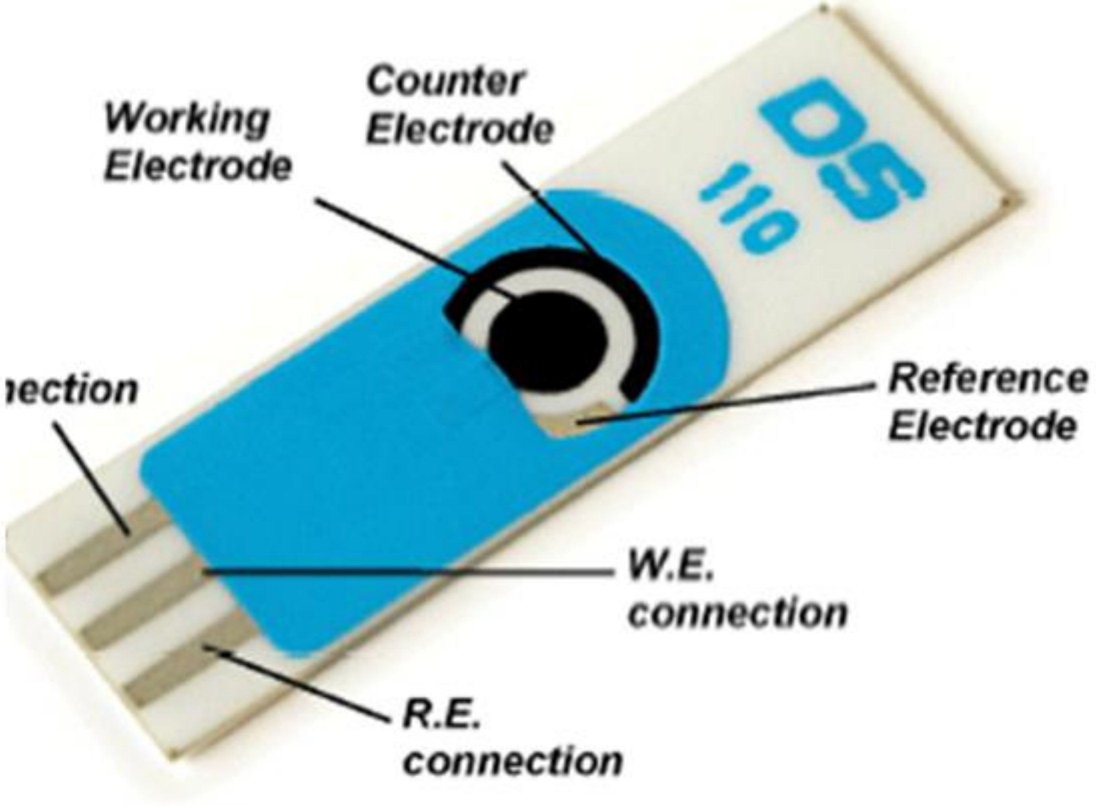
Research on glucose sensors

- Non-invasive biosensors - skin, saliva
- Implantable glucose sensors to accompany artificial Pancreas
- Feedback control of insulin supply
- Record is 3-4 weeks for implantable sensor in humans

Nanobiosensors applications exemples. Glucose test strip

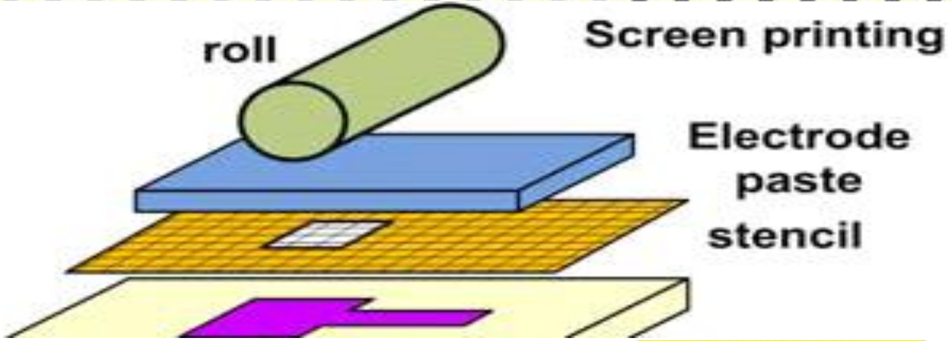


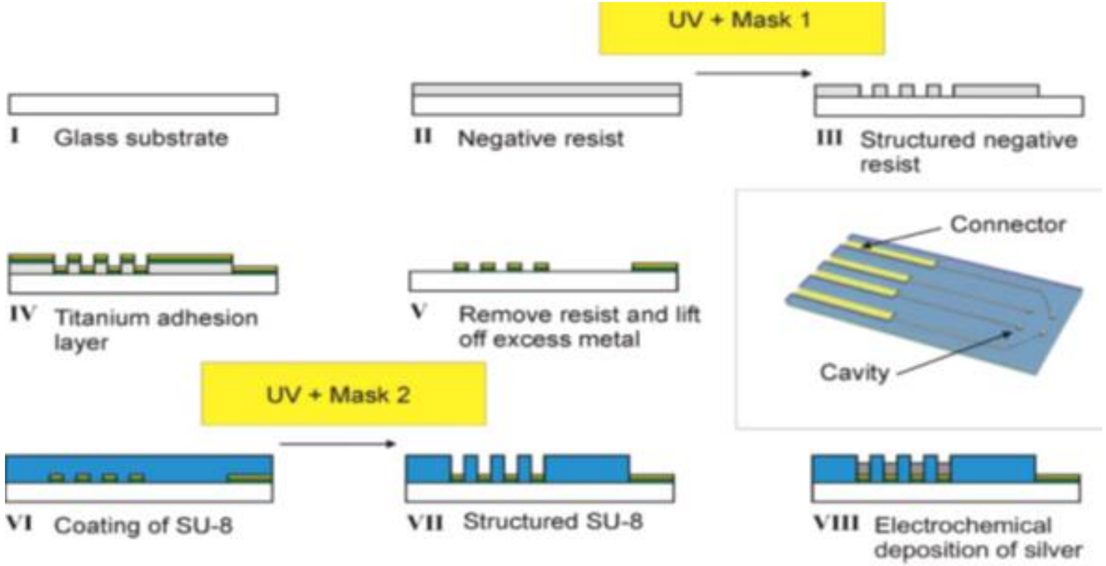
Electrochemical biosensors by printing technology



Electrochemical sensors based on Screen-printed electrodes based on carbon, gold, platinum, silver inks. Innovative strips manufactured for electrochemical analysis in environmental, clinical or agri-food areas.
(a DROPSENS product)

Printing technology for sensors patterning





Layer by Layer Film Construction

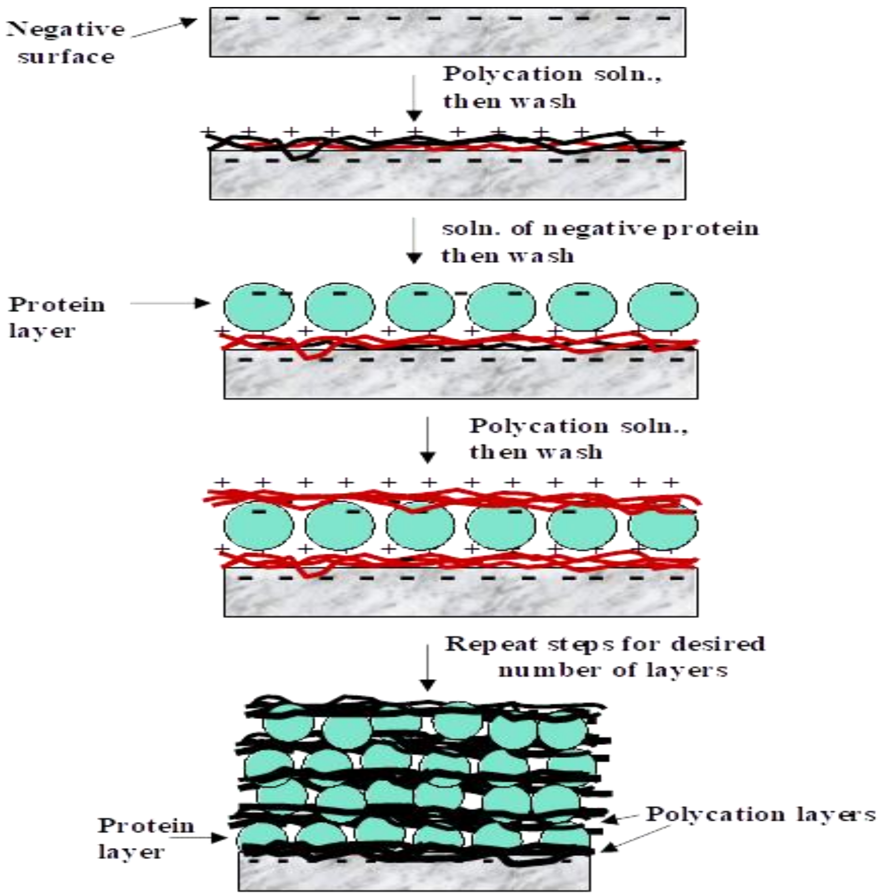
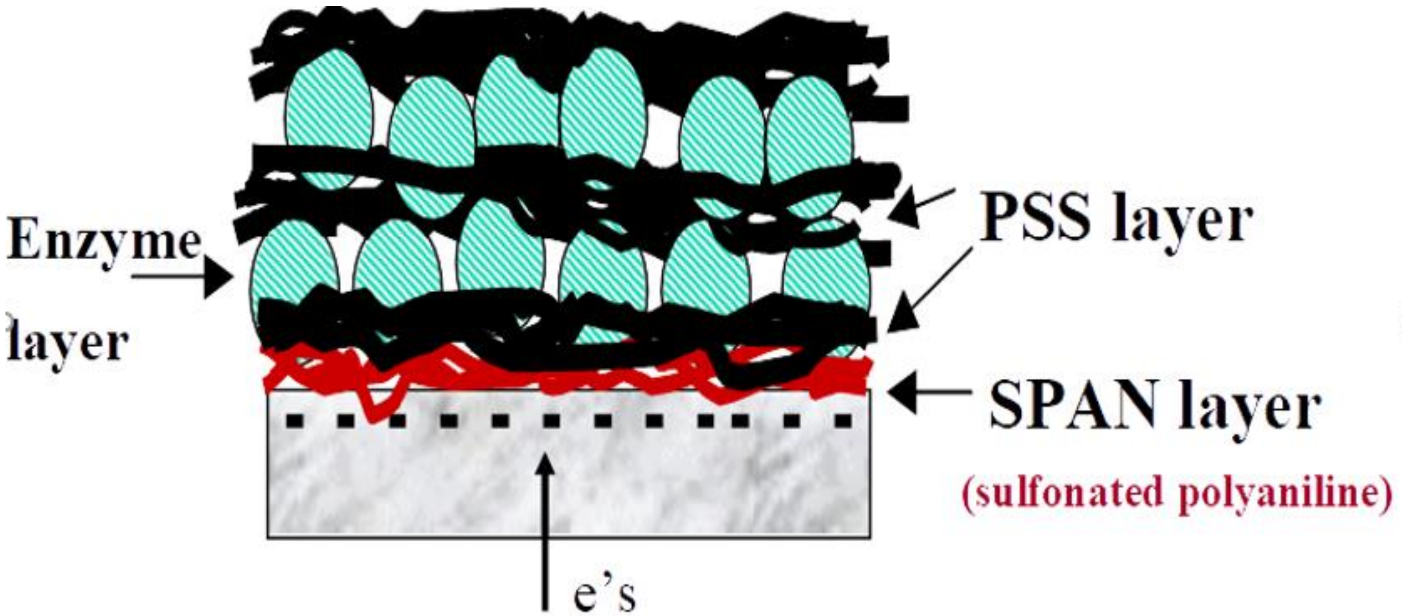


Figure 19

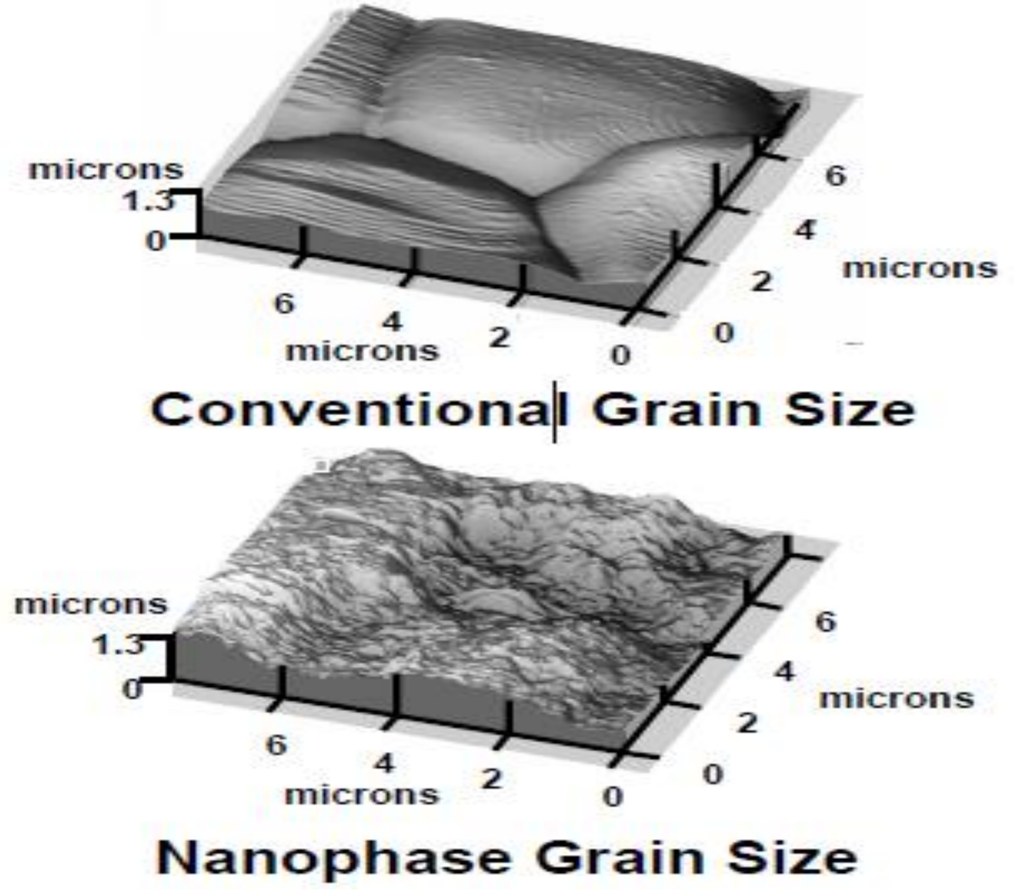
Detection of hydrogen peroxide



Conductive polymers efficiently wire peroxidase enzymes to graphite

Xin Yu, G. A. Sotzing, F. Papadimitrakopoulos, J. F. Rusling, Highly Efficient Wiring of Enzymes to Electrodes by Ultrathin Conductive Polyion Underlayers: Enhanced Catalytic Response to Hydrogen Peroxide, *Anal. Chem*., 2009, *75*, 4565-4571.

Closer Look at Nanotechnology in Medical Applications



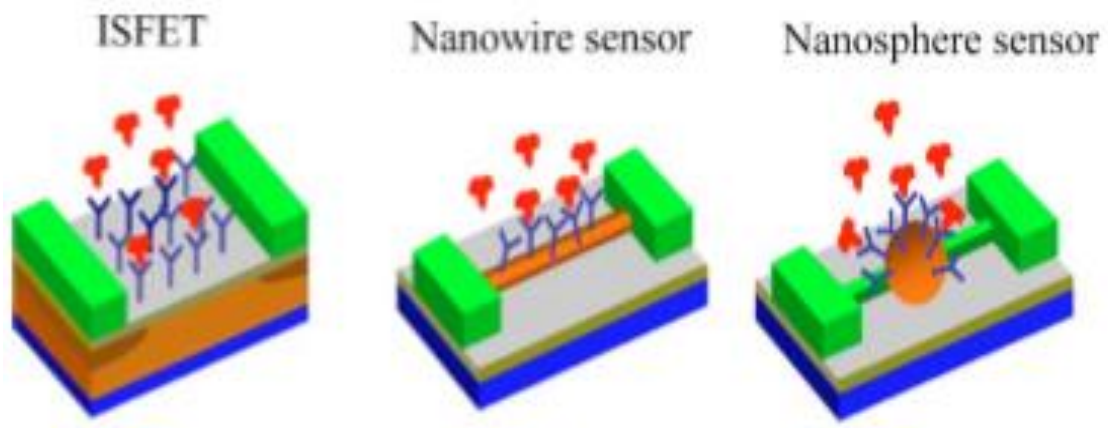
Compared to conventional grain size materials, nanophase materials possess enhanced:

- **processing,**
- **catalytic,**
- **optical,**
- **mechanical,**
- **electrical, and**
- **surface**

properties that may enhance existing biomedical implant applications

Nanomaterials for biosensing

- The nanomaterials are the used for manufacturing of all transducers that will be incorporated into the sensors
- The widespread interest in nanomaterials is driven by their many desirable properties; the ability to tailor the size and structure The properties of nanomaterials offers
- excellent rospects for designing novel sensing systems
- enhancing the performance of the biosensor



Overview of nanomaterials used for improving biosensor technology

NANOGENTOOLS

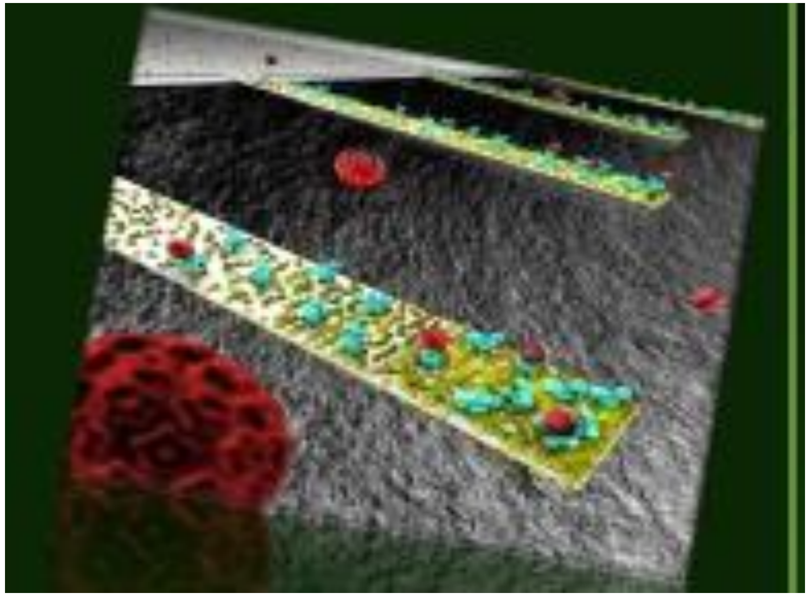
No	Nanomaterials	Key benefits
(1)	Carbon Nanotubes CNT`s	Improved enzyme loading,higher aspect ratios, ability to be functionalized, and better electrical communication
(2)	Nanoparticles NP	Aid in immobilization, enable better loading of bioanalyte, and also possess good catalytic properties
(3)	Nanowires	Highly versatile, good electrical and sensing properties for bio- and chemical sensing; charge conduction is better
(4)	Quantum dots	Excellent fluorescence,quantum confinement of charge carriers, and size tunable band energy
(5)	Nanorods	Good plasmonic materials which can couple sensing phenomenon well and size tunable energy regulation, can be coupled with MEMS, and induce specific field responses

Trends in biosensong systems

Nanobiosensor architectures are based on diverse principles of detection which provides different types of devices:

❖ ***Mechanical resonators*** *and* ***Static deflection devices*** **:**

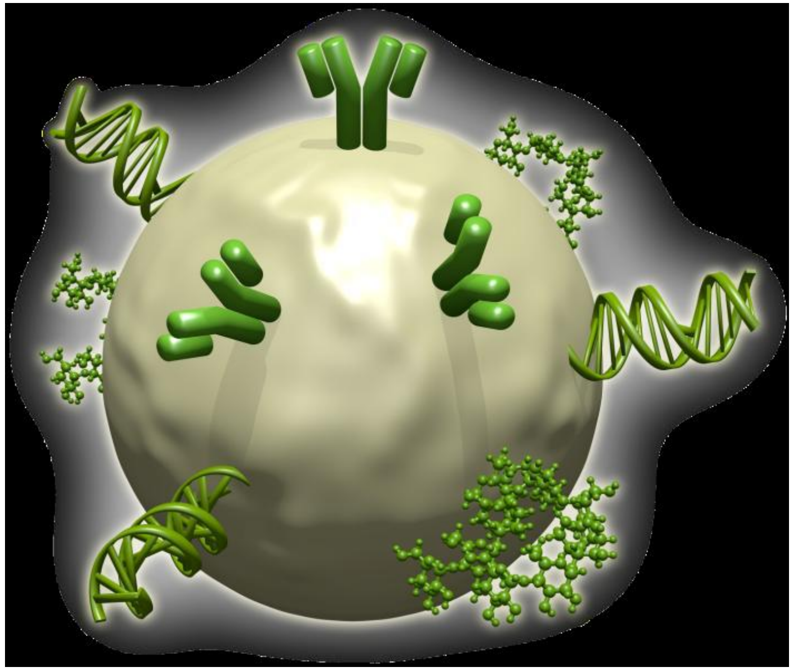
- **Cantielevers functionalized with specific receptors on top deflect suport down depending on the changes in surface stress.**
- **The detection is through a piezoresistive element reflecting a laser with a specific angle on the cantilever.**



Nanoparticles

•*Nanoparticles :*Extremely small size particles suspended in solution (during interaction with the analyte) show optical,conductive or magnetic properties,and form networks when interact with analyte through ligands that functionalized their surface.

Gold NP's are the most widely used.



The exemple of nanoparticles detection by combined optical biosensor (1)

NANOGENTOOLS

SEVENTH FRAMEWORK PROGRAMME

INSTANT

- **Innovative optical sensor for fast analysis of Nanoparticles detection in Selected Target Productsl INSTANT FP7 2012-2016**

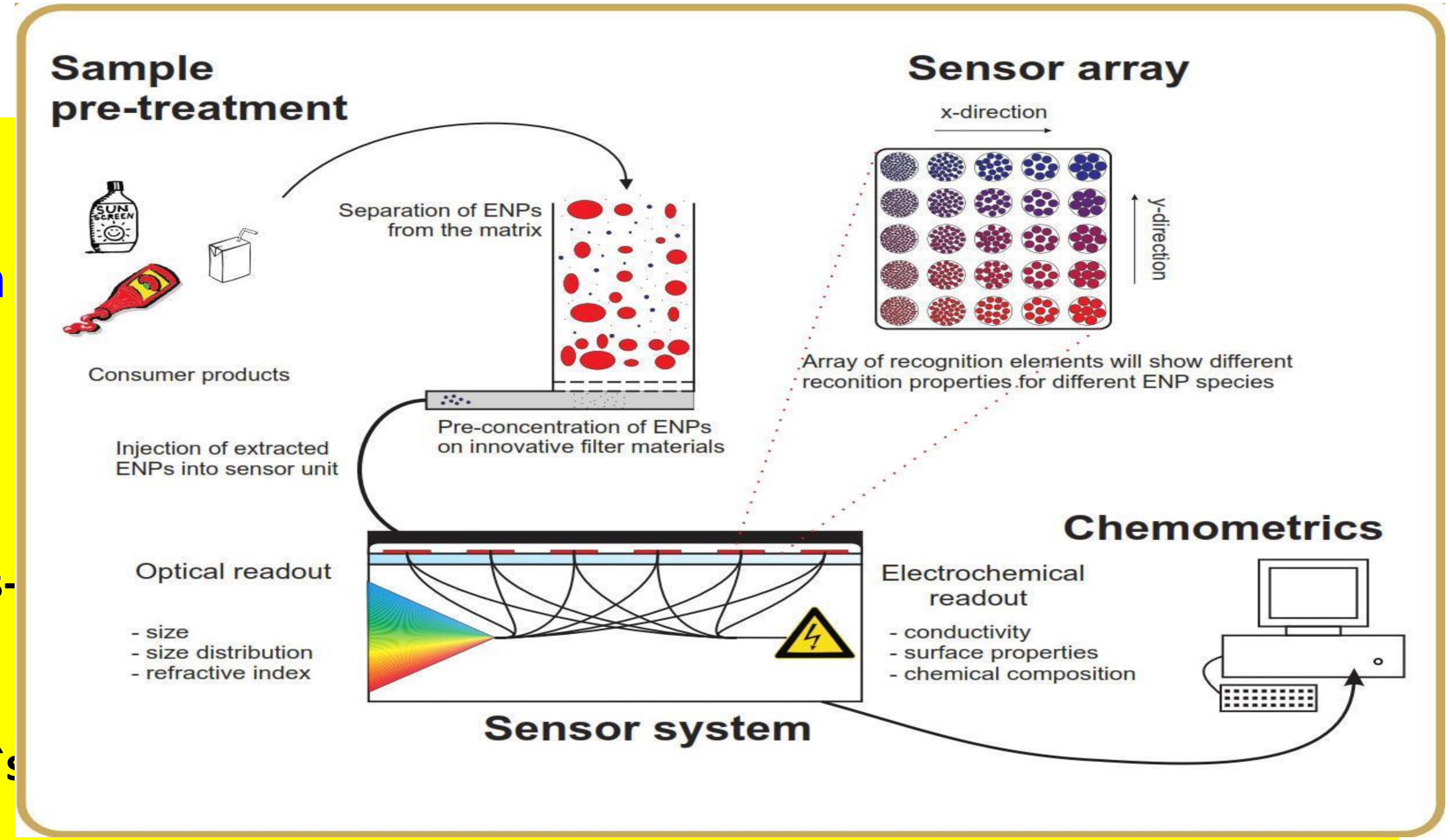
❖ **INSTANT analytical instrumentation**

Combines :

two complementary transduction principles-

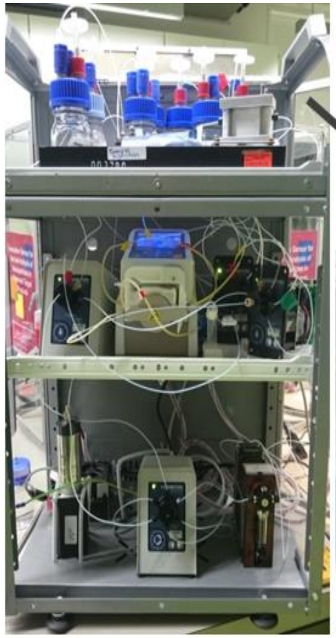
- **One optical and**
- **One electrochemical transducers.**

Different types of recognition elements (RE`s with complimentary selectivity for ENP`s.

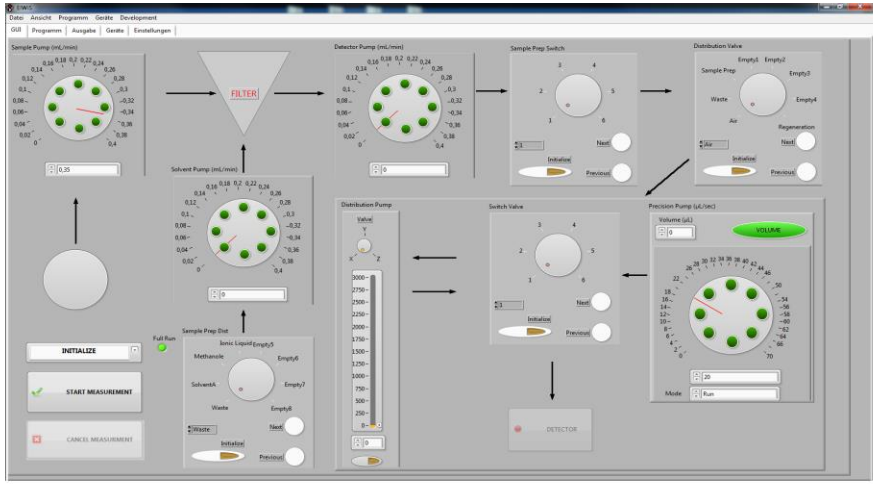


The exemple of nanoparticles detection by combined optical biosensor(2)

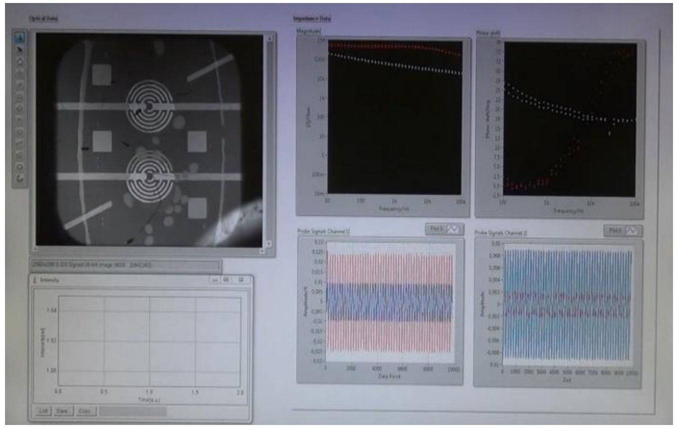
NANOGENTOOLS

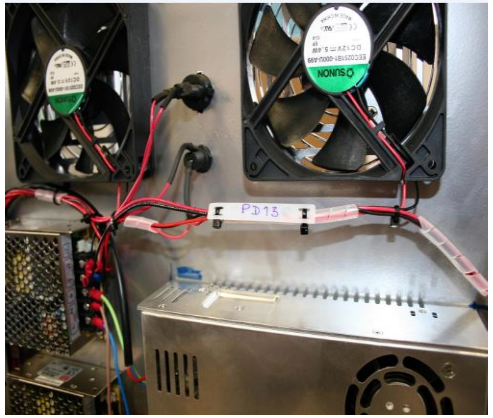


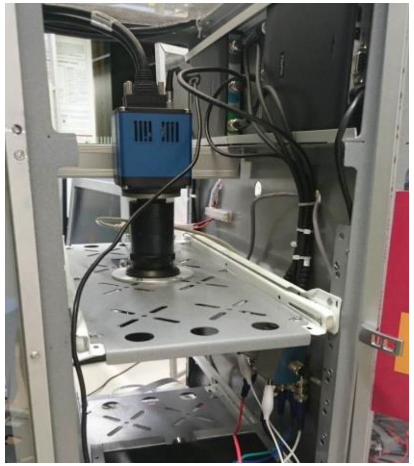
Sample preparation fluidics



Graphical User Interface (GUI) to monitor measurement sequence of the INSTANT device







EBERHARD KARLS UNIVERSITÄT TÜBINGEN

biametrics biomolecular interaction analysis

UMEÅ UNIVERSITET

universität wien

NANORDIC.COM a quality nanomaterials and services company

SITEX 45 SRL

BAM Federal Institute for Materials Research and Testing

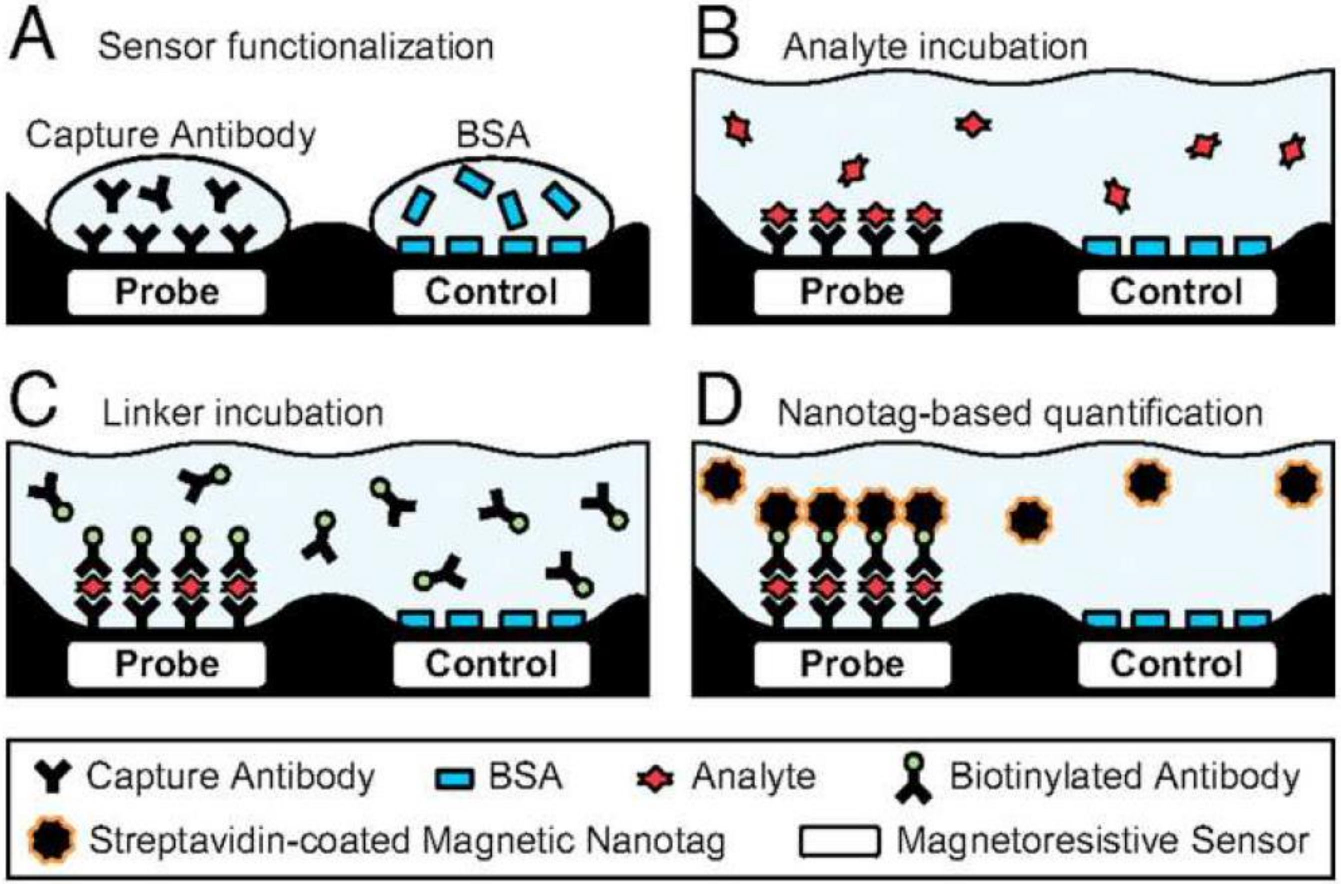
UNIVERSIDAD DE CÓRDOBA

Sinatec

CORPUS DATAMINING

Magnetic nanoparticles based biosensor

NANOGENTOOLS



Giant Magnetoresistive (GMR) sensor for an ELISA-type protein assay

Magnetoresistive sensors based on the binding of magnetic particles to sensor surface and the magnetic fields of the particles alter the magnetic fields of the sensor

- **result in electrical current changes within the sensor**

Biosensors semiconductor nanoparticles

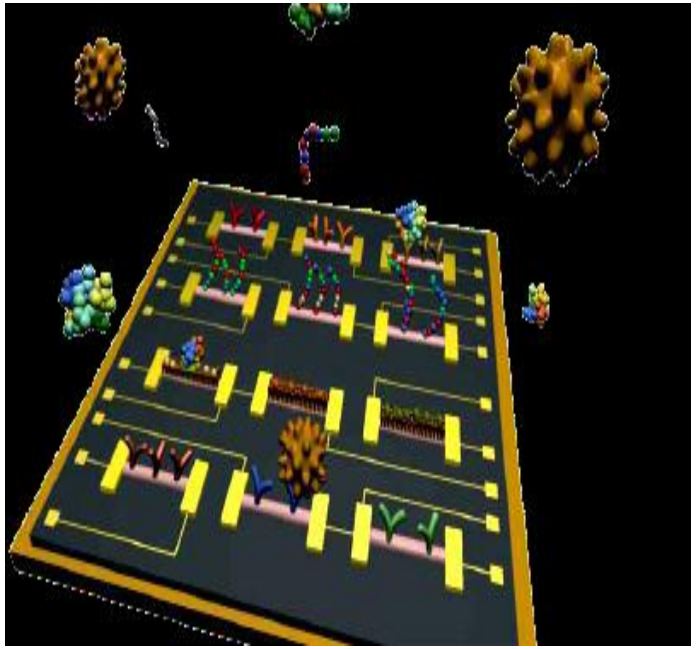
- **Biosensors semiconductor nanoparticles have wide application for detection of analytes.**
- **Semiconductor surface potential plays an important role in the performance and characteristics of semiconductor-based biosensors**
- **The unique optical, photophysical, electronic and catalytic properties of semiconductor nanoparticles directed to the use of semiconductor nanoparticles as fluorescence labels for biorecognition processes**
- **Zinc oxide (ZnO) and titanium dioxide (TiO2) nanoparticles are the most versatile semiconductor oxides with applications across a wide range from cosmetics to medical devices**
- **ZnO used for biosensor applications because of good biocompatibility, large surface area, good dispersing properties and fast electron transfer ability**

Carbon nanotubes CNT

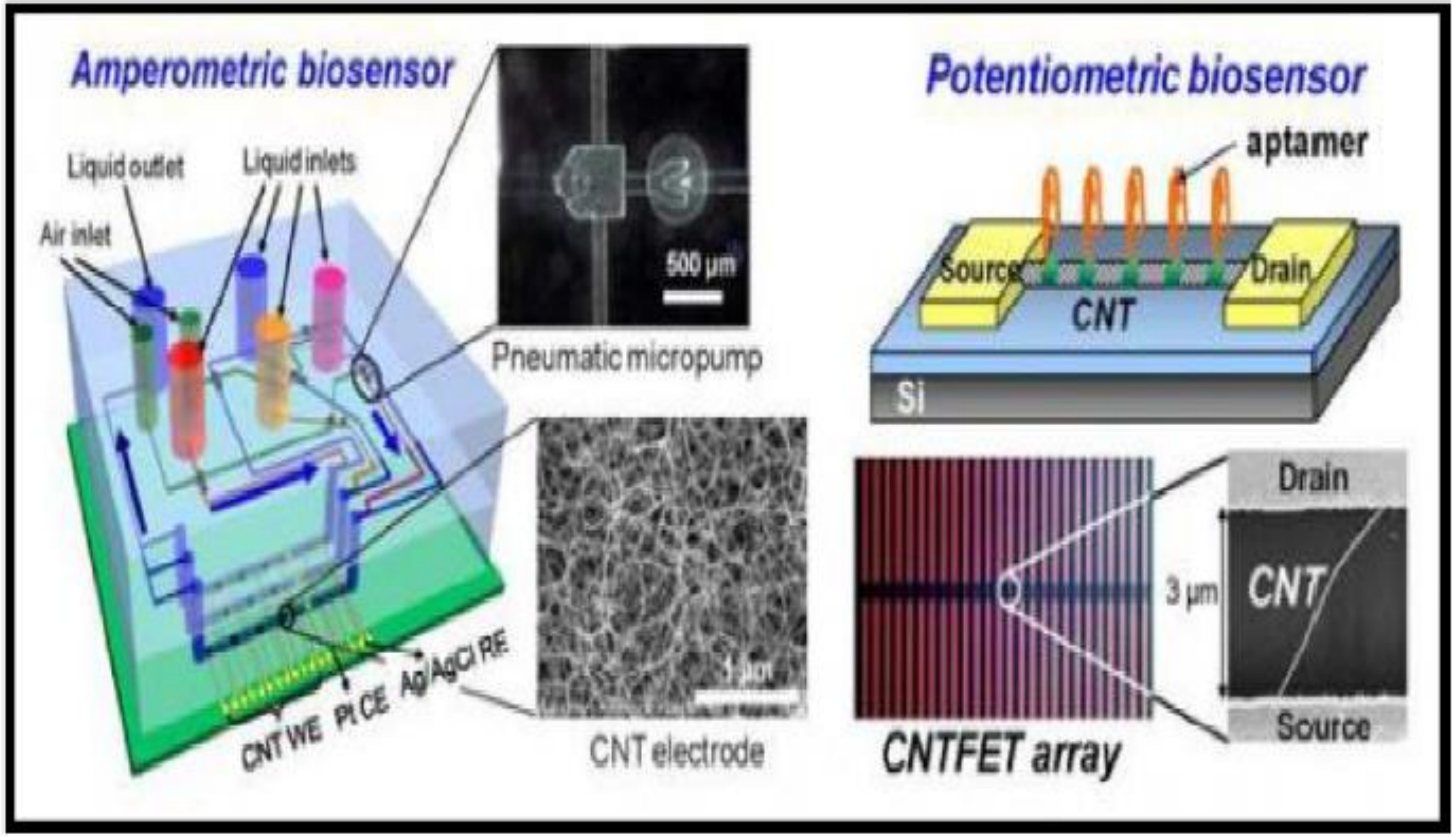
In a configuration of electrical field effect transistor,the molecules analized deplet or acummulate charge carriers, behaving as controler gate so electrical resistance.

- **The structures are located between metallic electrodes.**
- **CNT's have the ability of Increasing the speed of biosensing.**

Photos of GOx-grafted MWNTs (a) and MWNTs (b) in water (left)



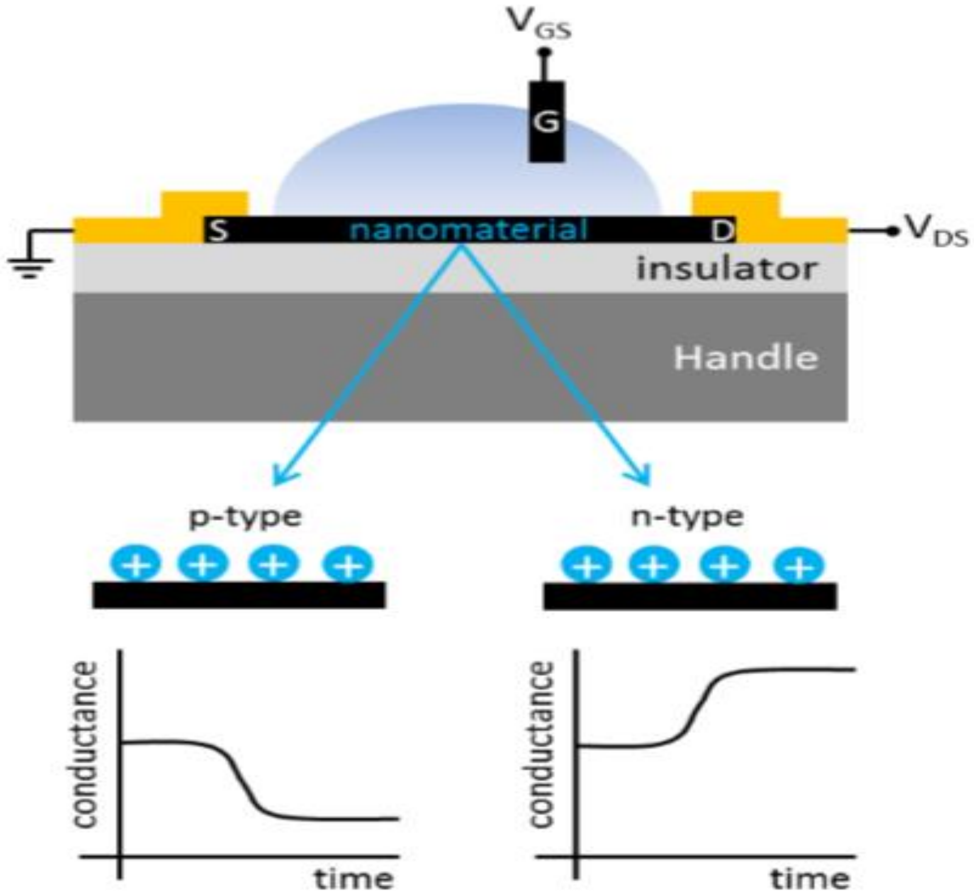
Carbon nanotubes CNT based biosensor.



Carbon nanotubes (CNT) are **single walled carbon nanotube (SWCNT)** or concentric carbon sheets of different diameters forming **multiwalled carbon nanotubes(MWCNT)** with sp2 bonding The particular cylindrical formof CNT is the principal aaspect provides the quantum confinement effect in the oriented 1D nanostructured materials .The characteristics possibility to **increase the chemical reactivity and electronic properties** which becomes a **crucial point for biosensing devices**

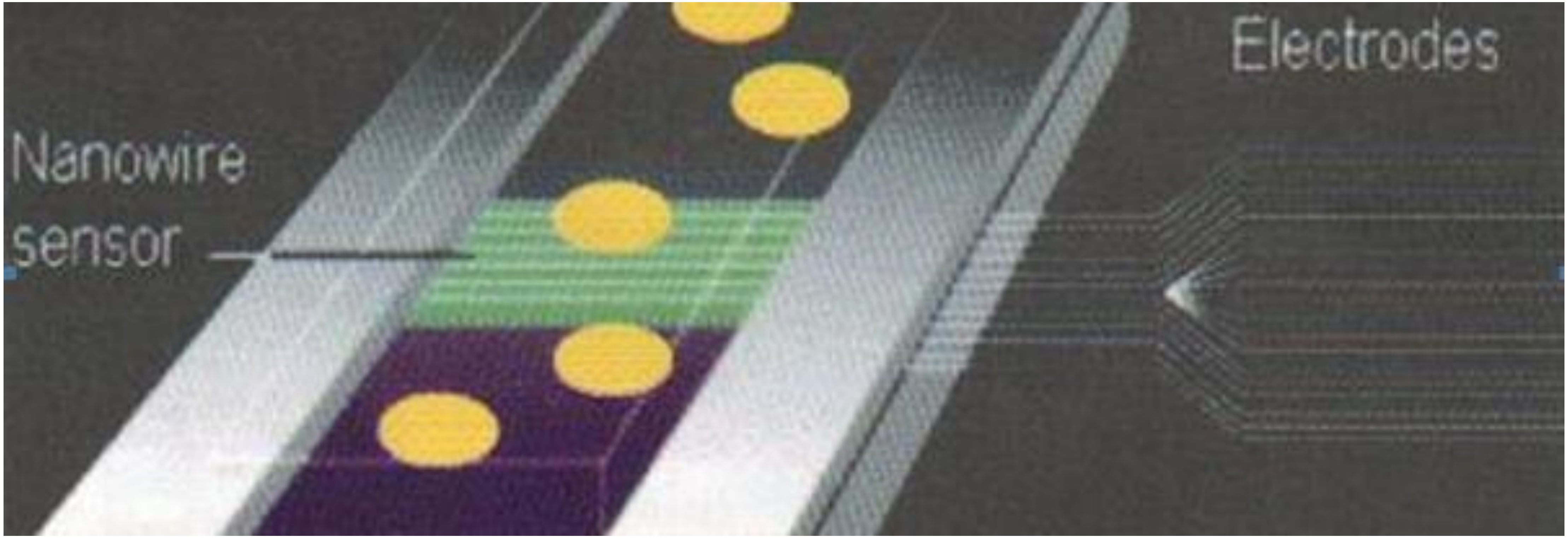
Nanowires based nanobiosensor(1)

NANOGENTOOLS



Biological FET (bioFET) sensors the gate(reference) electrode is a distance away from the dielectric, with an intervening sample fluid. Changes at the dielectric-solution interface alter the surface potential, which act as an additional gate voltage. A gate voltage(VGS) is applied using a reference electrode to set the operating point of the device, and the conductance of the channel is measured by apply in a drain(D) to source (S)voltage(VDS). P-type devices display a decrease in conductance with the binding of positive charges to the surface and n-type devices display an increase

Nanowires based nanobiosensor (2)



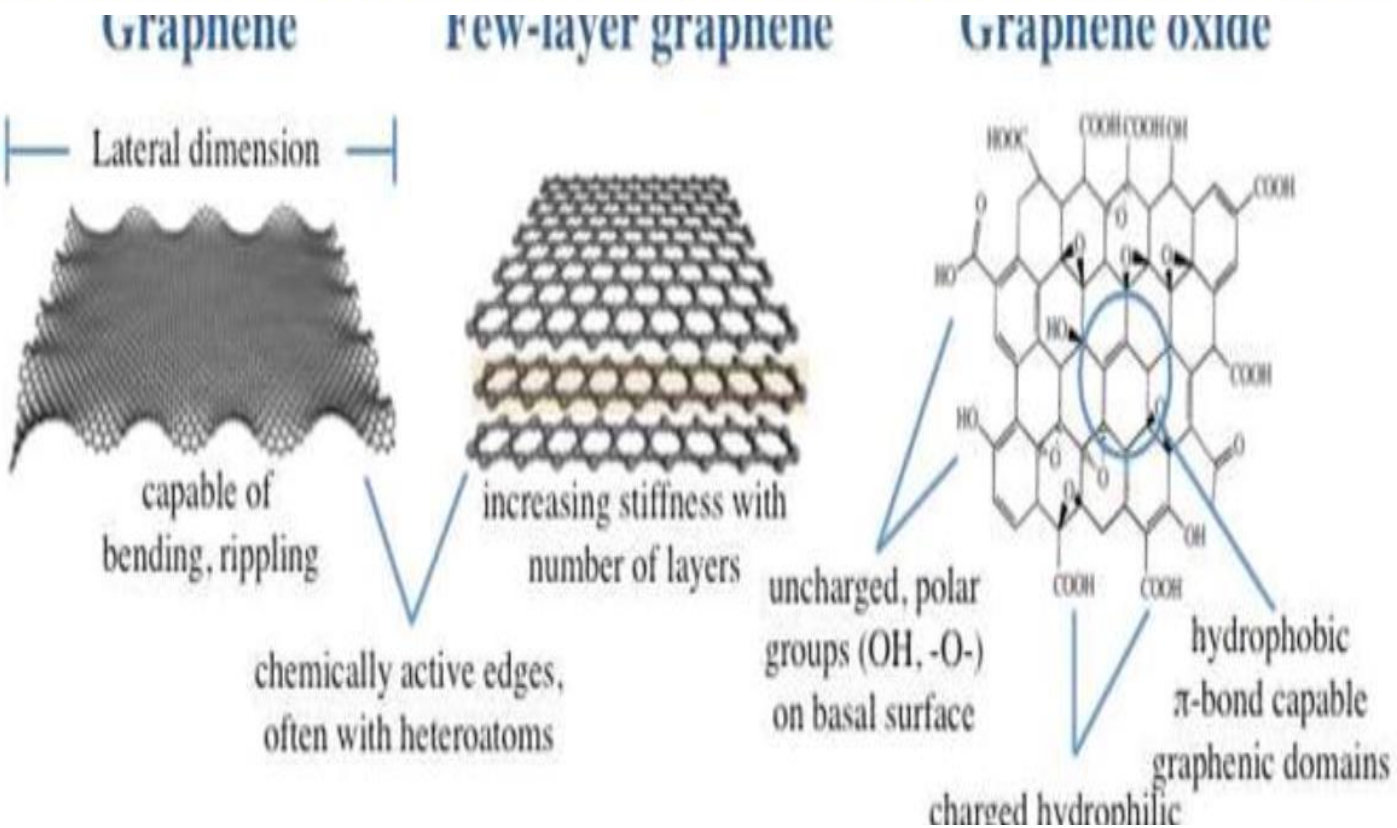
The nanowires sensor for detection of cancer biomarkers.

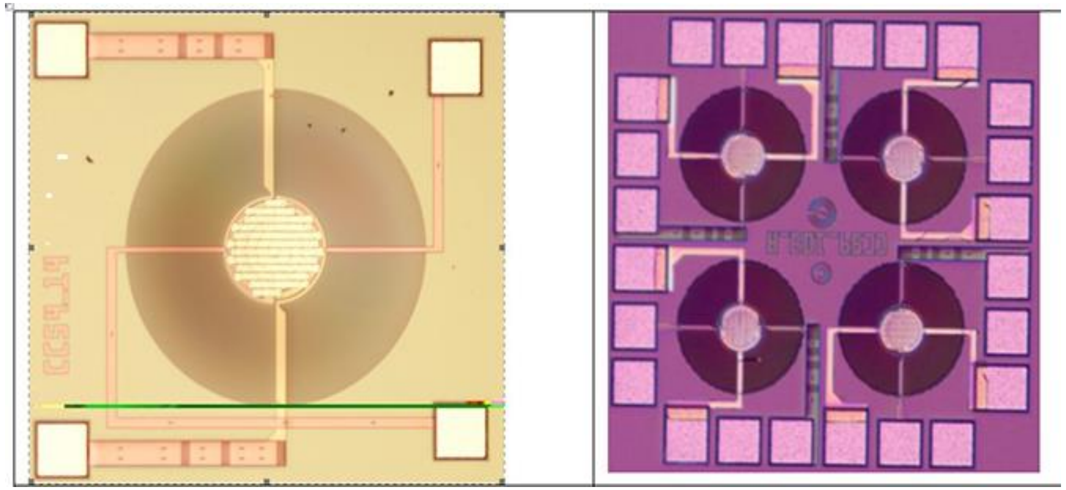
Graphene(1)

NANOGENTOOLS

- Graphene has unique physical properties considerable attention from both the experimental and theoretical scientific communities in recent years.
- Most of graphene used in nanobiosensors are produced with the last method of graphene oxide (GO) reduction
- The optical properties of graphene and GO, a topic of fundamental interest, unexplored could facilitate biological and medical research such as biosensing, and imaging.
- Graphene from GO reduction, as functionalized graphene sheets or chemically reduced graphene oxide, are advantageous for nanobiosensors and especially electrochemical base nanobiosensor applications
- Graphene an excellent electrode material for electroanalysis and electrocatalysis, development of graphene based theory, materials & devices

Graphene(2)





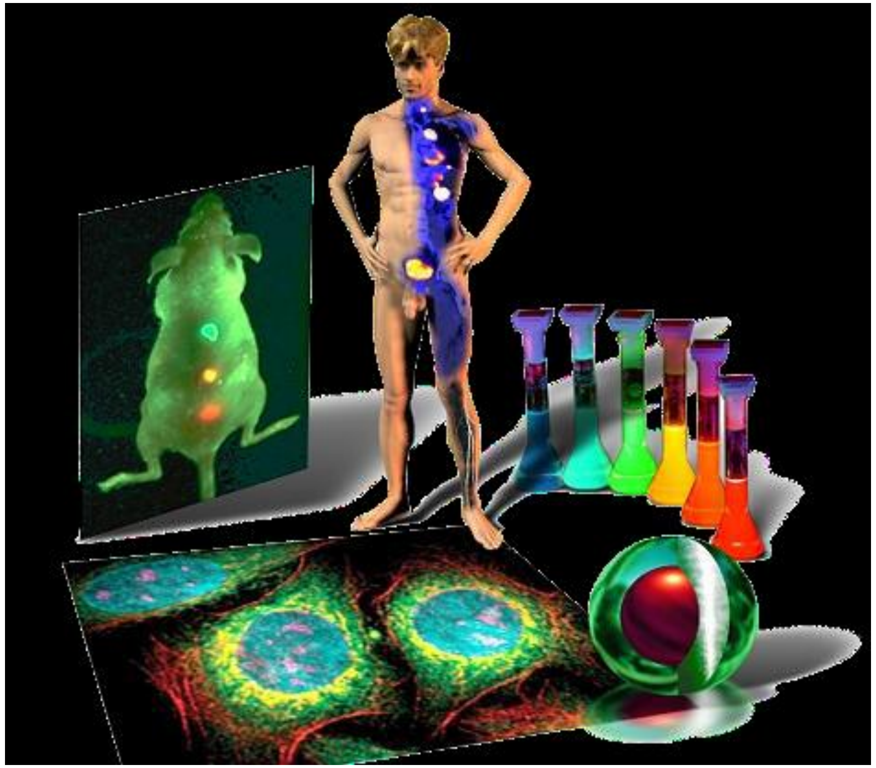
D.Ulieru,O.M.Ulieru,A Topor, Xavi Vila „Graphene based micro-sensors integrated into MEMS/CMOS platform for environmental monitoring applications” Poster at EuroNanoForum 2017 ,La Valetta,Malta 21/23 June 2017

Quantum dots(1)

NANOGENTOOLS

Optoelectronic (light related) properties specific for these semiconductor nanocrystals.

The specific features are as follows:



- **a high brilliance**
- **quantum yield ;giving**
- **quantum size effect tune in**
- **continuous maximun emission,**
- **broad absorption,**
- **do not show photo-bleaching**
- **narrow spectra emission.**

Quantum dots(2)

- **Quantum dots (QD), are colloidal nanocrystalline semiconductors having diameters between 1 nm and a few microns, which are composed of a combination of II–VI elements (CdS, CdSe, etc), or oxides, halides, tellurides and combinations of III–V elements, (InP and InAs).**

- **QD, have intrinsic electronic and optical properties including unique size-dependent tunable emission, resistance to photobleaching, high photochemical stability and high brightness.**

- **The disadvantage of QDs is their toxicity**

Gold and Silver nanoparticles (1)

NANOGENTOOLS

- Gold nanoparticles (GNPs) and nanorods are the most extensively studied nanomaterials for use in biosensors and bioelectronics because of their unique properties, such as
- Rapid and simple synthesis, large surface area, strong adsorption ability and facile conjugation to various biomolecules
- The application of GNPs in electrochemical and optical nanobiosensors.
- Gold nanoparticles (GNPs) and nanorods are the most extensively studied nanomaterials for use in biosensors and bioelectronics because of their unique properties, such as rapid and simple synthesis, large surface area, strong adsorption ability and facile conjugation to various biomolecules
- The application of GNPs in electrochemical and optical nanobiosensors.

Gold and Silver nanoparticles (2)

- ***Silver nanoparticles (SNP)*** ***a*****mong noble-metal nanomaterials, silver nanoparticles (AgNPs) are one of the most commonly used metal-nanoparticles, received considerable attention in biological detection.**

- **AgNPs can frequently be useful in electrochemical and SPR biosensors due to their attractive physicochemical properties including *the* surface plasmon resonance and large effective scattering cross section of individual silver nanoparticles**

- **Hydrophobic Ag–Au composite nanoparticles show strong adsorption and good electrical conducting properties, and can be used in biosensing**

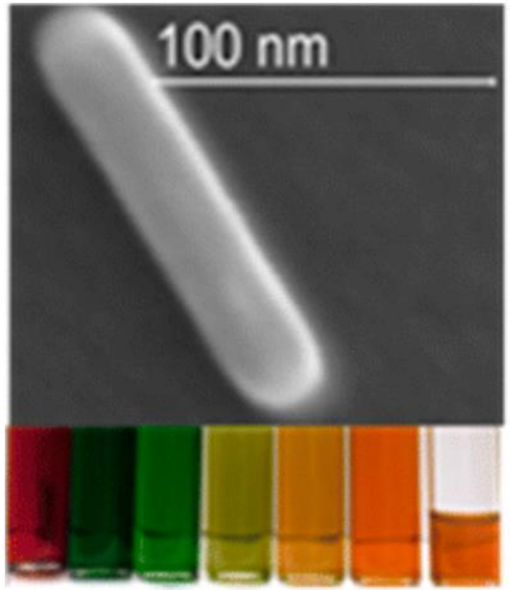
Gold and Silver nanoparticles (3)

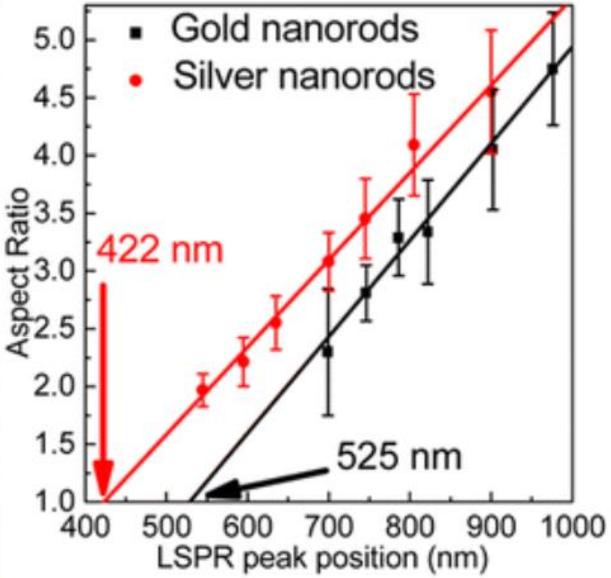
Silver nanorods (AgNRs) of ~20 nm diameter and different lengths, increased up to ~100 nm by increasing the reduction time, A linear relationship between the AgNRs aspect ratios and the LSPR peak position confirmed .

The Raman signal enhancement by silver nanorods is more efficient than by gold nanorods (AuNRs) because the plasmon field that of AuNRs,. The Rayleigh scattering by AuNRs is stronger than that by the AgNRs.

AuNRs are recommended for optical plasmon imaging, while

AgNRs are more efficient in plasmon sensing

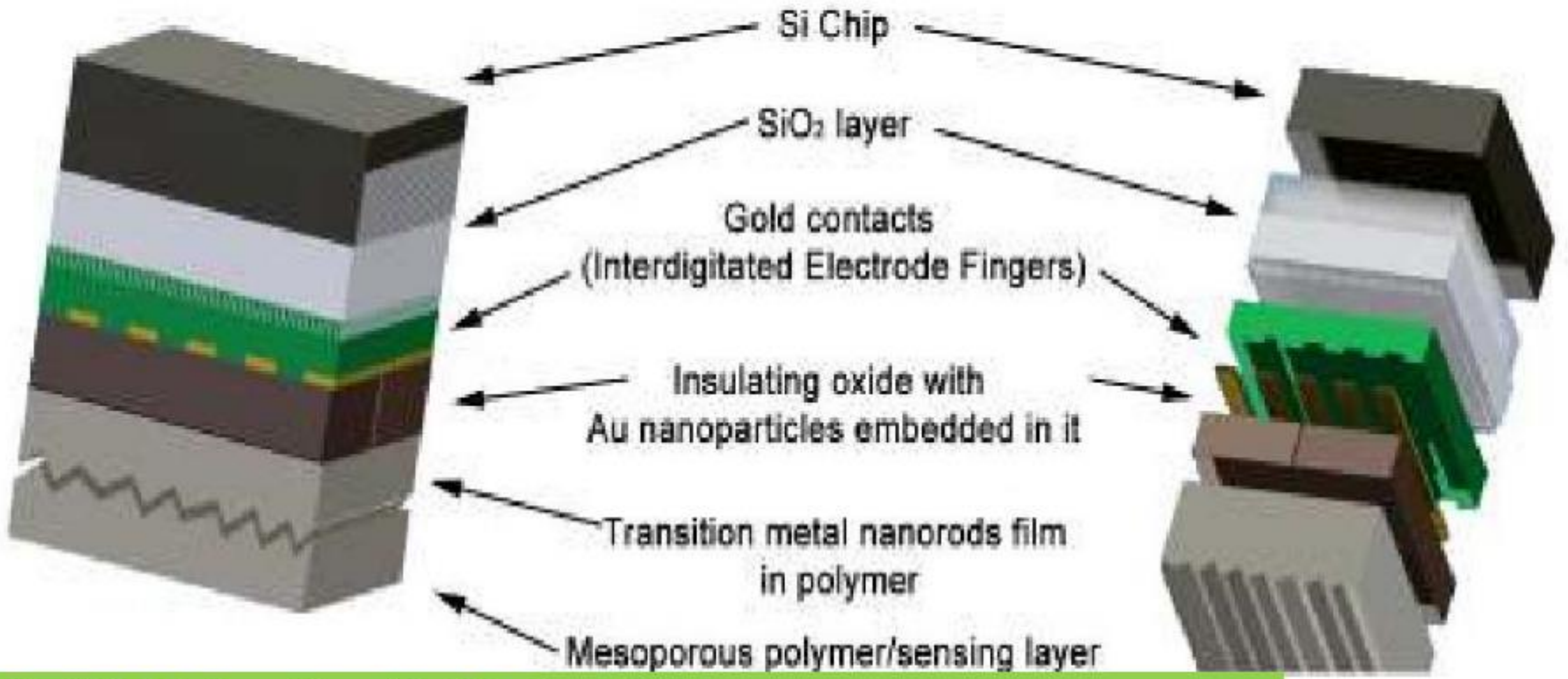




Gold and Silver nanoparticles (4)

NANOGENTOOLS

Nanosensing
E-nose device
EuroNanoMed
Project

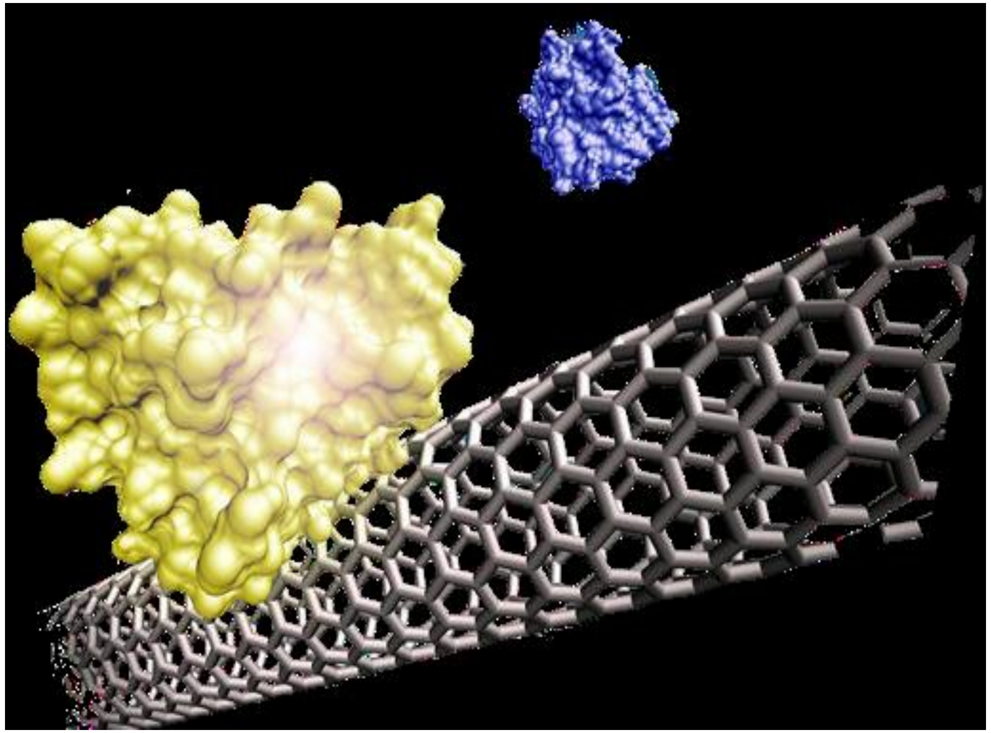


SITEX (CO) ,EuroNanoMed Project 2010
Lung Cancer Screening with Nanoscience Enhanced e-Nose Structures

DNA functionalized CNT'(3)

Single-walled carbon nanotubes field effect transistor (swNNFET) with a nanoscale layer of DNA adsorbed can be used for,depending on the sequence of DNA,detecting from“Sarin”gas or TNT
to *Salmonellatyphi*(bacteria).

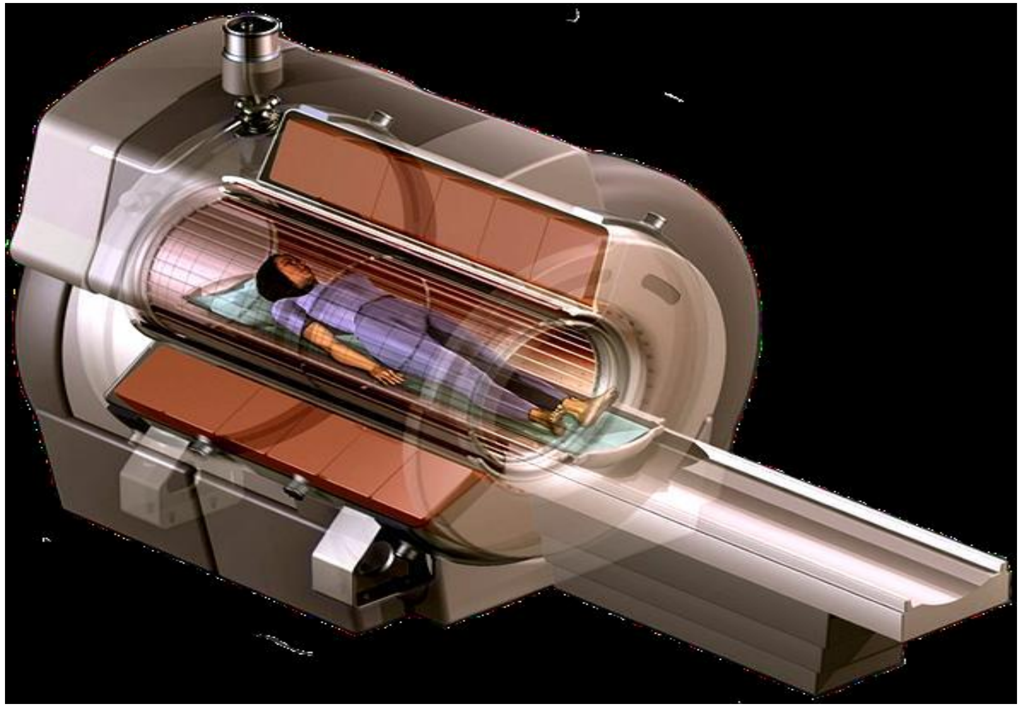
Extremely low amounts of analyte are needed,the speed and sensitivity is optimized,and the response and recovery times of the order of seconds.



Magnetic resonance imaging MRI(4)

NANOGENTOOLS

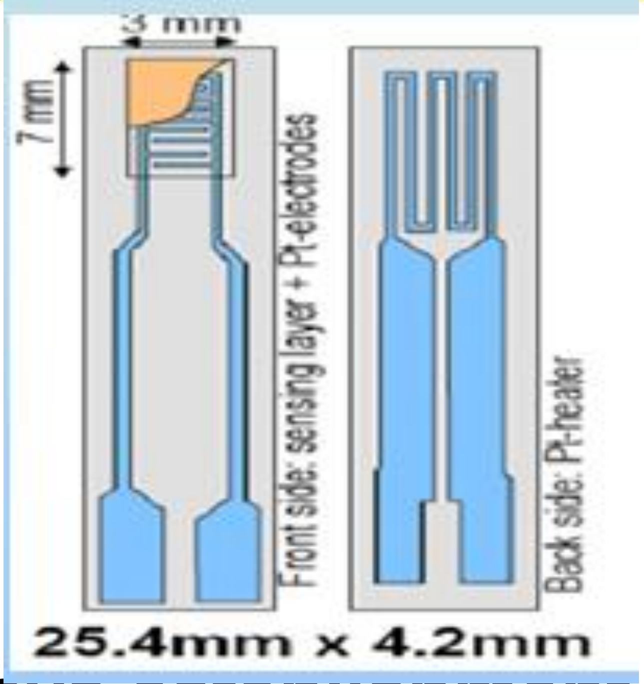
Gadolinium is toxic as contrast agent; however, since some nanoparticles,show superparamagnetic behaviour (only posible due to mono domain at this scale), the intensity signalis enhanced and
the relaxation velocity increased;
then low toxicity and higher affinity is reached.
The most used are Fe_3O_4 and γ-Fe_2O_3.



Future development of applications (1)

The main goals in research for creating
the next generation of nanobiosensors are:

- new immobilization strategies
- new technological approaches
- new types of nano and micromaterials
- new perspectives for exploiting properties at nanoscale



All these considered and comprehension of arrays establishment for potential uses,make nanobiosensing an area of research with multiple and challenging posibilities on the future.

Future development and exermples of applications (2)

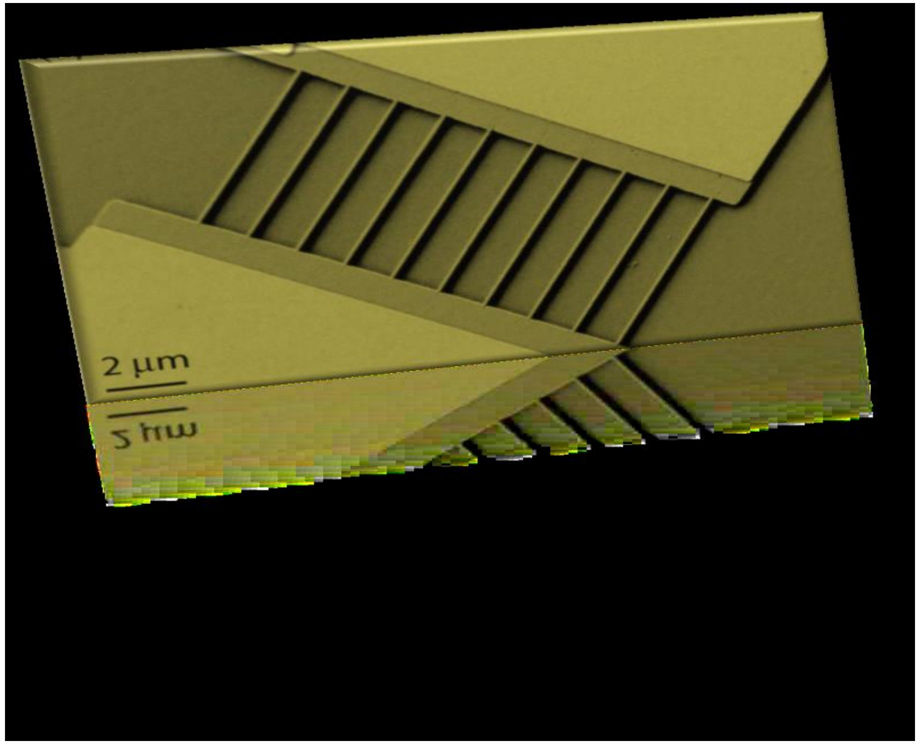
•*Glucose sensing devices*:

The 85% of the sold sensors are glucose determination.

System from silicon nanowires to test derived from conventional assay formats are used, In which signals,like colour,are obtained.

Similar devices are cancer tests or pregnancy tests

(this later commonly used).

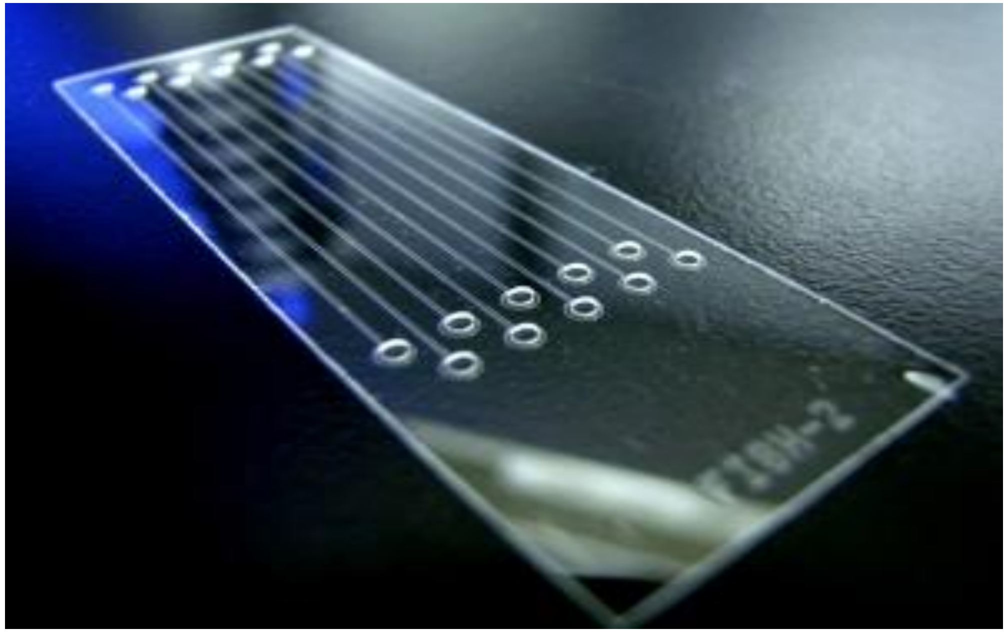


Future development of applications (3) -Lab on a chip (LOAC)

NANOGENTOOLS

- Recent trend confirm that it fall into nanofluidic field now in light of reducing the size of devices and response volume of fluidics.
- LOAC is a flow channels either in glass or silicon substrates and incorporated with stream infusion/pumping framework for liquid transport inside the chip and sample handling for detection
- LOAC is framework which do a complete bio-sample handling and investigation framework on a chip scale
- .A bio-sample little measure of liquid is on the chip,
- > blended with reagents and supports, >to frame items >by assembly >to a unit for investigation, on the same wafer.
- LOAC will significantly influence diagnostics business, regarding concentrated lab examination and the point of care POC testing.

Lab on Chip (models) (4)



Lab on Chips for glucose monitoring, HIV detection or heart attack diagnostics

Toxicity of Nanomaterials-Physicochemical Effects

NANOGENTOOLS

- Before employing of nanomaterials in biological and environmental and living systems, they should evaluate in terms of biocompatibility and distribution.
- Cellular uptake mechanisms and dispersion of nanomaterials in biological environments depend on their physicochemical properties
- The unique characteristics of nanomaterials and interactions of nanomaterials with biological systems, are important criteria for the safe use of nanomaterials
- Properties of nanomaterials such as size, shape, aspect ratio, density, and surface and structural defects and dissolving rate are the main cause of cytotoxicity and side effects of these materials in the body.
- Exposure to nanomaterials may be cause a range of acute and chronic effects, inflammation, exacerbation of asthma, metal fume fever, fibrosis, chronic inflammatory diseases and cancer.

Toxicity of Nanomaterials

NANOGENTOOLS

❖ Biological toxicity

- Nanomaterials can enter the body via intravenous, dermal, subcutaneous, respiratory, intraperitoneal and oral ways
- The absorption of nanomaterials may happen via first interaction with biological components (cells and proteins).
- Nanomaterials interactions with biological systems can cause toxic effects including allergies ,fibrosis ,metal fume fever, deposition in organs (causing defects and insufficiency in organs), inflammation, cytotoxicity ,tissue damage, producing reactive oxygen species ,DNA, damage.

➢ Environmental toxicity

- Working with nanomaterials cause transfer of some of these materials to the environment finally leads to a kind of pollution known as nanomaterials related environmental pollution.
- Prior to release of large amounts of nanomaterials into the environment, their solubility and degradability in soil and water should be investigated and basic information on their safety, toxicity, and compatibility of nanomaterials with soil and aquatics be acquired.

Possible nanomaterials effects as the basis for pathophysiology and toxicity.

NANOGENTOOLS

Experimental nanomaterials effects	Possible pathophysiological outcomes
ROS generation	Protein, DNA and membrane injury, oxidative stress
DNA damage	Mutagenesis, metaplasia, carcinogenesis
Oxidative stress	Phase II enzyme induction, inflammation, mitochondrial perturbation
Mitochondrial perturbation	Inner membrane damage, permeability transition (PT), pore opening, energy failure, apoptosis, apo-necrosis, cytotoxicity
Inflammation	Tissue infiltration with inflammatory cells, fibrosis, granulomas, atherogenesis, acute phase protein expression (e.g., C-reactive protein)
Uptake by reticuloendothelial system	Asymptomatic sequestration and storage in liver, spleen, lymph nodes, possible organ enlargement and dysfunction
Protein denaturation, degradation	Loss of enzyme activity, auto-antigenicity
Nuclear uptake	DNA damage, nucleoprotein clumping, autoantigens
Perturbation of phagocytic function "particle overload," mediator release	Chronic inflammation, fibrosis, granulomas, interference in clearance of infectious agent
Endothelial dysfunction, effects on blood Clotting	Atherogenesis, thrombosis, stroke, myocardial infarction
Altered cell cycle regulation	Proliferation, cell cycle arrest, senescence

Reasons of toxicity

NANOGENTOOLS

- Toxicity of nanomaterials may occur in a cellular or system level. Nanomaterials toxicity is relevant to the following features:
- Size and surface to volume ratio (factors increasing nanomaterials reactivity with other molecules).
- Chemical composition (reactivity factor) Surface charge (electrostatic interactions factor).
- Hydrophobicity and the existence of lipophilic groups.
- Nanomaterials connecting to biomolecules (the factor inhibiting enzyme activities in a competitive or non-competitive way).
- The large surface of nanomaterials.
- The presence of metallic species or toxic components in nanomaterials.

Conclusions

NANOGENTOOLS

- Biosensors are widely used in biomedical research, health care, pharmaceuticals research via spatially separated molecular probes Immobilized on a solid surface to scrutinize or detect biomarker for diagnosis of various diseases

- Discussed the fundamental differences of the different types of nanobiosensors based on different transduction approaches, such as electrochemistry, optic, and piezoelectric measurements

.

- Working principles, constructions, advantages, and applications of nanomaterials in biosensors were presented.

- Recent advances in application of nanomaterials such as carbon (graphene, CNT), gold, silver, and semiconductors in nanobiosensors, and nanomaterials toxicity were reviewed briefly.

- it can be stated that nanobiosensors offer the possibility of diagnostic tools with increased sensitivity, specificity, and reliability for in vivo and in vitro analytical applications.

Referencies

1.D.Ulieru, R.Calavia,A.Topor Towards a Cancer Detection by Integrated NanoSensing Devices as Electronic Nose: A Review" Swiss&Romania Workshop,"Trends in nanomaterials field for cancer detection / therapy" ,Buchaerest 11.09.2015

2.D.Ulieru,O.A.M Ulieru,Xavi Vila Raports 2015/2016 project Development of a non-invassive breath test for early diagnosis of tropical diseasesH TROPSENSE H2020-MSCA-RISE-2014,Rovira I Virgili University,Tasrragona,Spain.

3.D.Ulieru New technologies achieving microbiosensors for real time detecting an monitoring tuberculosis in group with high potential risk" Workshop 2016,Polytechnica Gdansk,Poland 16.02.2016

4.D.Ulieru,Elena Ulieru,Integrated microfluidic systems for in vitro analysis of biological fluids with applications for diagnosys and medical treatment,CAS/IEEE Conference 2011,Proceeding pp 85/90 ,Sinaia Romania

5.D.Ulieru,Elena Ulieru,The micro/nanosensors arrays for real time detection of acquatic environment contamination with chemical agents
CAS/IEEE Conference 2012,Proceeding pp123/127,Sinaia Romania

6.D.Uliertu,O.M.Ulieru,Xavi Vila,A.Topor, Graphene based micro-sensors using an innovative MEMS/CMOS platform for environmental monitoring applications,Poster 88,EURONANOFORUM Conference 2017,21/23 june 2017,La Valetta,Malta.

7) D. Ulieru, "The ubiquitous technology for prototype and disposable biochemical sensors packaging" Biosensors IMCS Conference 2012 Nürnberg, Germany

8. D. Ulieru, O.M. Ulieru, V. Vila, A. Topor,"The modern concept of microsensors/microsystems integration at wafer level by high accuracy micromanufacturing processes", 4M Conference 2015 Proceeding pp. 374-377, 30 March-2nd may 2015, Milan Italy

9. D. Ulieru, G. Gauglitz, F. Kolarov, D. Furin, J. Widmeier, G. Proll et al., „Innovative sensor for the fast Analysis of Nanoparticles in selected Target Products", 11th International Conference on Nanosciences and Nanotechnologies Conference NN2014, July, 710/2014,Thessaloniki, Greece.

10.D.Ulieru, Xavi Vila, Oana-Maria Ulieru, A.Topor, "Wireless innovative sensors network applications for health monitoring Industrial Technologies Conference April 9-11,2014,Athens,Greece

11.D.Ulieru,Oana-Maria Ulieru ,A.Topor, Xavi Vila, „A thinner technology from thin to thick films microprocessing of microelectronics circuitry by laser precision trimming",4M/IWMF 2017 Conference Proceeding pp 195/198,Danish Technical University, DTU, Lyngby/Copenhagen 13/15 september 2016.

Thank you!

The research leading to these results has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 691095.