Middlesex University London

EIS Biosensors

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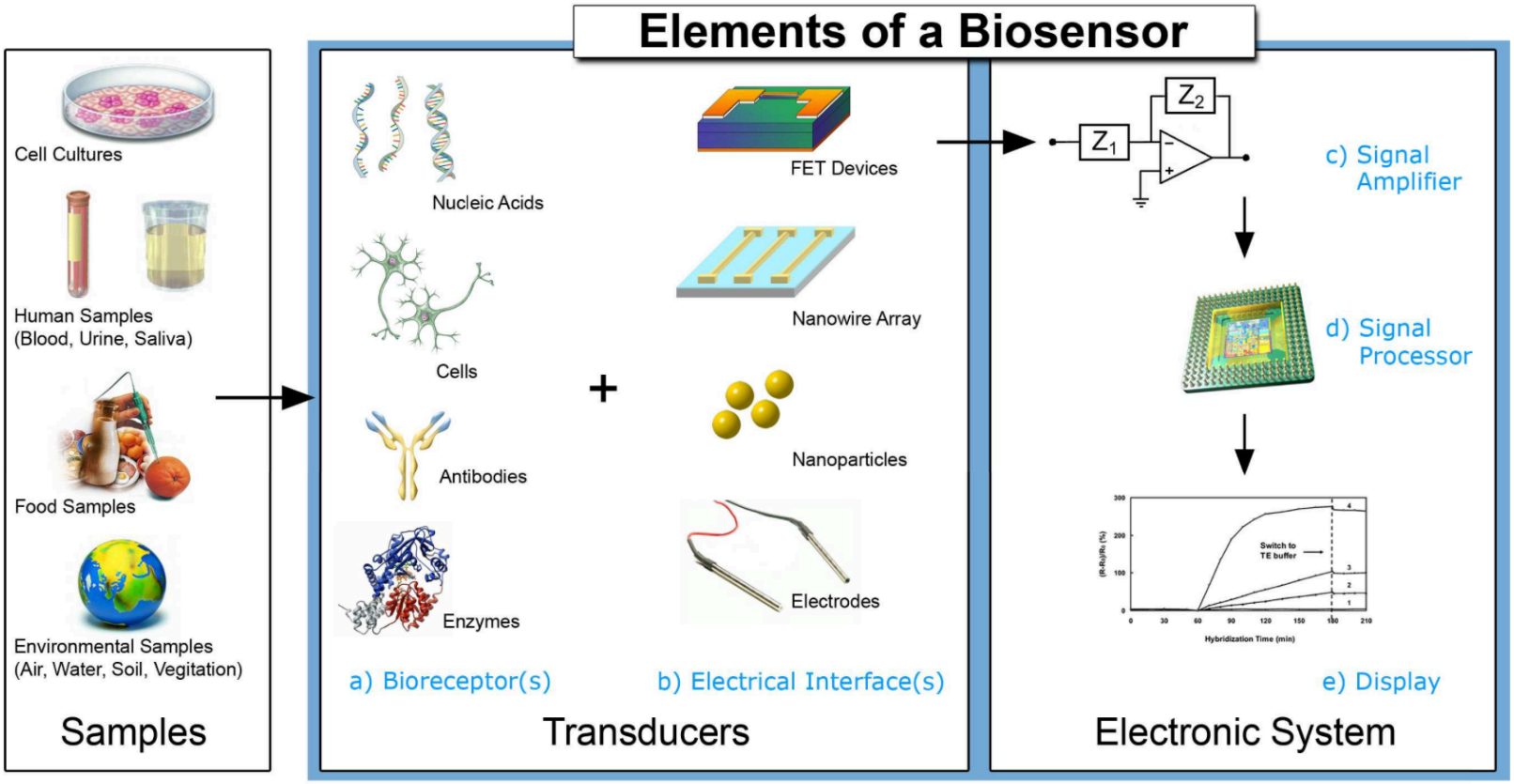
Biosensors

The device is made up of a transducer and a biological element that may be an enzyme, an antibody or a nucleic acid.

The bioelement interacts with the analyte being tested and the biological response is converted into an electrical signal by the transducer.

Biosensors


Elements of a Biosensor
Cell Cultures
Human Samples
(Blood, Urine, Saliva)
Food Samples
Environmental Samples
(Air, Water, Soil, Vegitation)
Samples
Nucleic Acids
Cells
Antibodies
Enzymes
a) Bioreceptor(s)
+
FET Devices
Nanowire Array
Nanoparticles
Electrodes
b) Electrical Interface(s)
Transducers
Z2
Z1
c) Signal Amplifier
d) Signal Processor
Switch to TE buffer
Hybridization Time (min)
e) Display
Electronic System

Point of Care

MALDI-TOF-TOF MS

Soft-Tact

Need for Point-of-Care Device

- Fast economical diagnostic devices providing multiple answers for use in doctors' clinics and field stations
- Enable immediate clinical decisions to be made without the need to wait for distant laboratories' answers.

Potential:

Allergy, where 26 different allergens are pricked into the skin to see which elicits an inflammatory response.
Incidence of allergy in developed world now nudging above 30%.

Autoimmune disease in particular the need to recognise rheumatoid diseases, type I diabetes, pernicious anaemia and thyroid disorders at an early stage where treatment is efficacious. The advantage of multiplexing is that associated autoimmune diseases related to the presenting condition but unexpected, can be revealed by the multiplex arrays.

Cancer biomarker signatures for early detection of cancer are now being recognised. Also good for monitoring treatment.

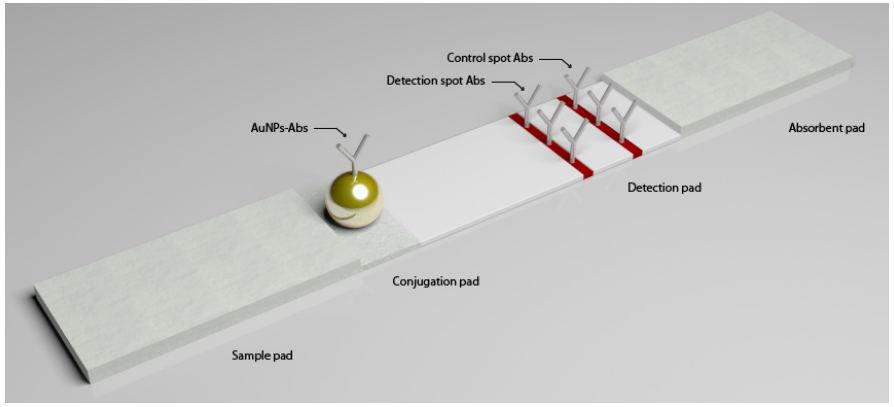
Infectious diseases*:* There is an obvious advantage in diagnosing the wide variety of infectious diseases encountered in world-wide clinics but particularly relevant for distant field stations. The sort of infections we could diagnose with multiplexed arrays include HIV, TB, malaria, candida, CMV, leishmania, typhoid, legionella and Chlamydia.

Neurodegenerative diseases: e.g. Alzheimer disease

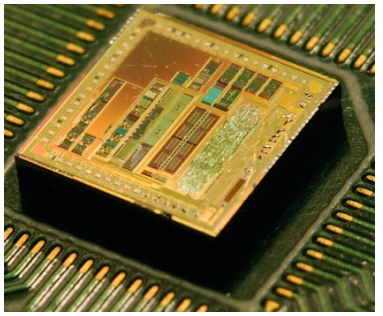
Typical Sensing Techniques for Biosensors

- Fluorescence
- DNA Microarray
- SPR Surface plasmon resonance
- Electrochemical/Impedance spectroscopy
- SPM (Scanning probe microscopy, AFM, STM)
- QCM (Quartz crystal microbalance)
- SERS (Surface Enhanced Raman Spectroscopy)

Chip-Sensor Interfacing



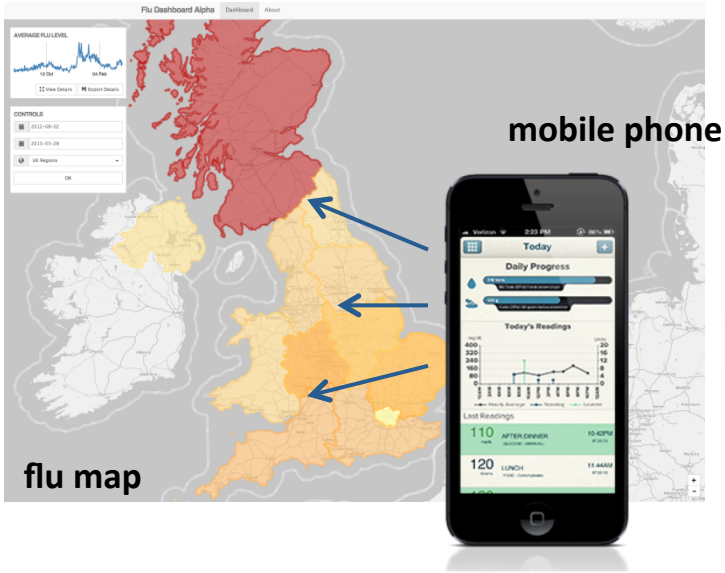
Lateral-flow immunoassay (LFIA)



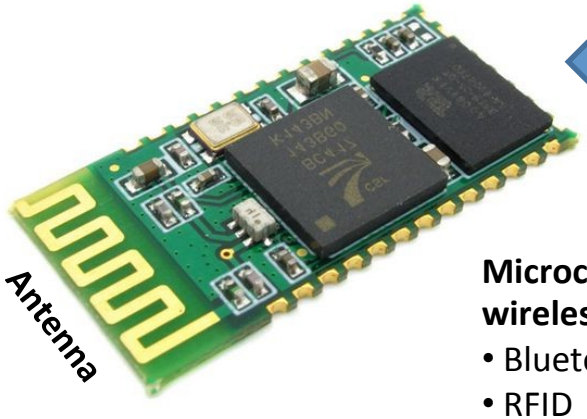
CMOS readout chip
- Electrical
- Optical

Integration

data tx/rx

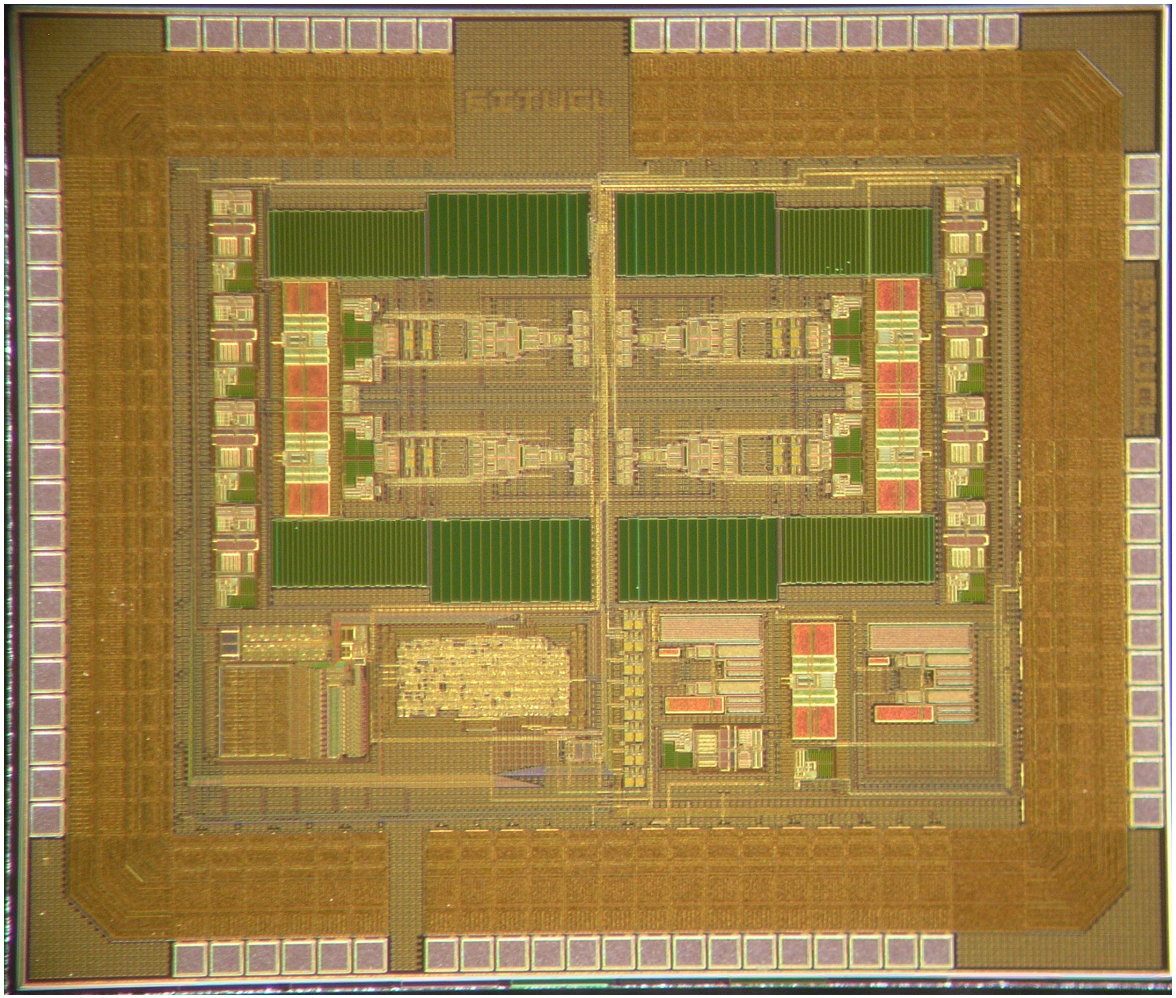


mobile phone app



Microcontroller-based wireless link
- Bluetooth
- RFID

Chip Implementation



- 0.6 μm CMOS
- 5-V operation
- 4-channel system
- 4mm^2 active area
- DC to 1MHz operation
- Fully programmable via a digital SPI
- On chip 10-bit ADC

Basic Characteristics of a Biosensor

LINEARITY: Maximum linear value of the sensor calibration curve. Linearity of the sensor must be high for the detection of high substrate concentration.

SENSITIVITY: The value of the electrode response per substrate concentration.

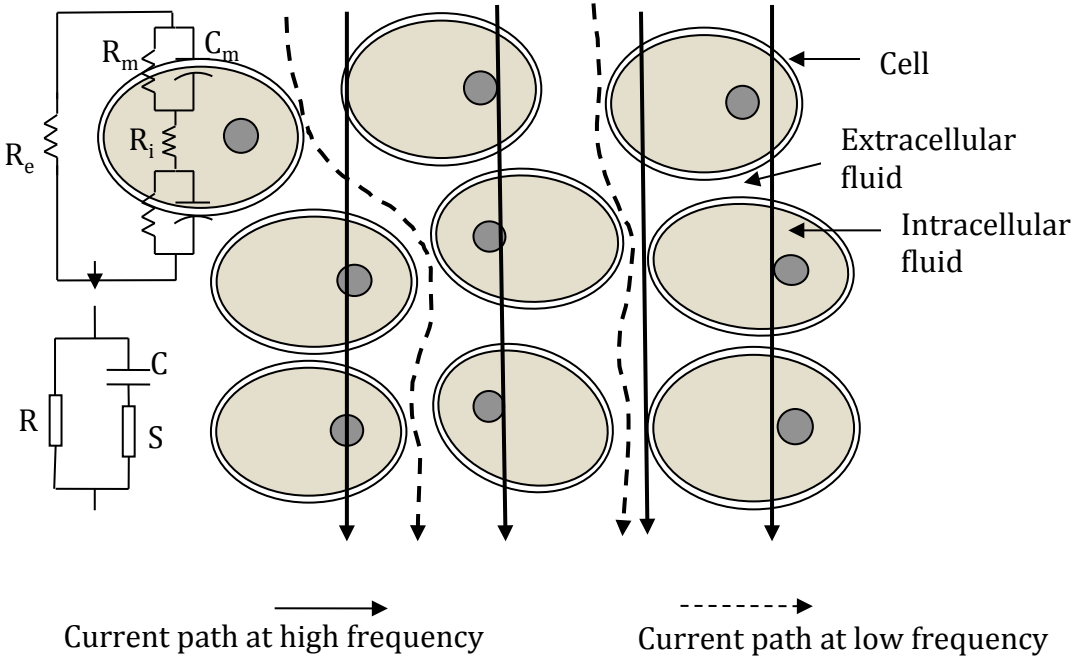
SELECTIVITY: Interference of chemicals must be minimised for obtaining the correct result.

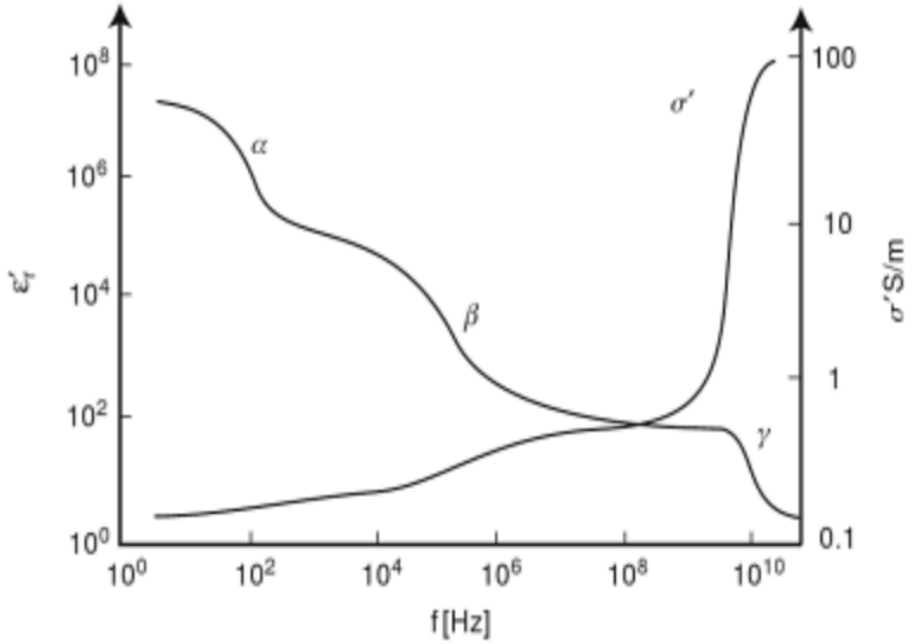
RESPONSE TIME: The necessary time for having 95% of the response.

The majority of these sensors are affinity-based, meaning that the biosensing molecules (the capture probes) are immobilized on a solid support.

This may be gold (Au), platinum (Pt), carbon (C), titanium (Ti), chromium (Cr), indium tin oxide (ITO) and glass and one important selection-condition for the material is its immobilization biochemistry with the capture system used.

Bio impedance



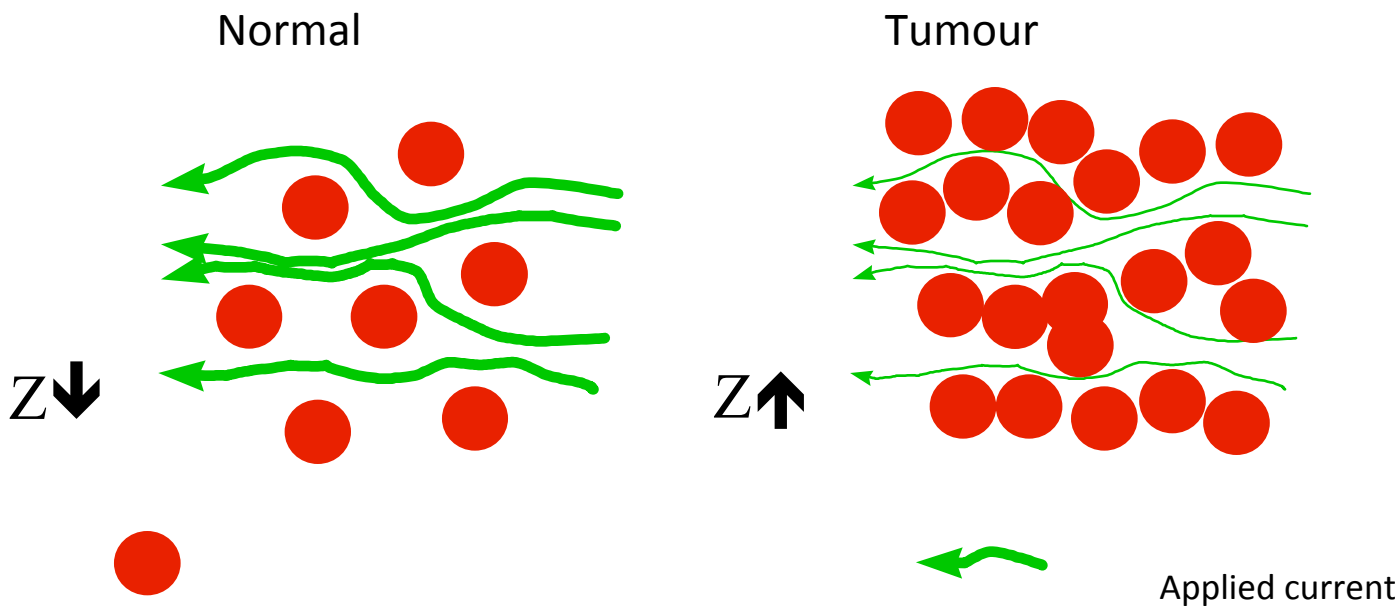


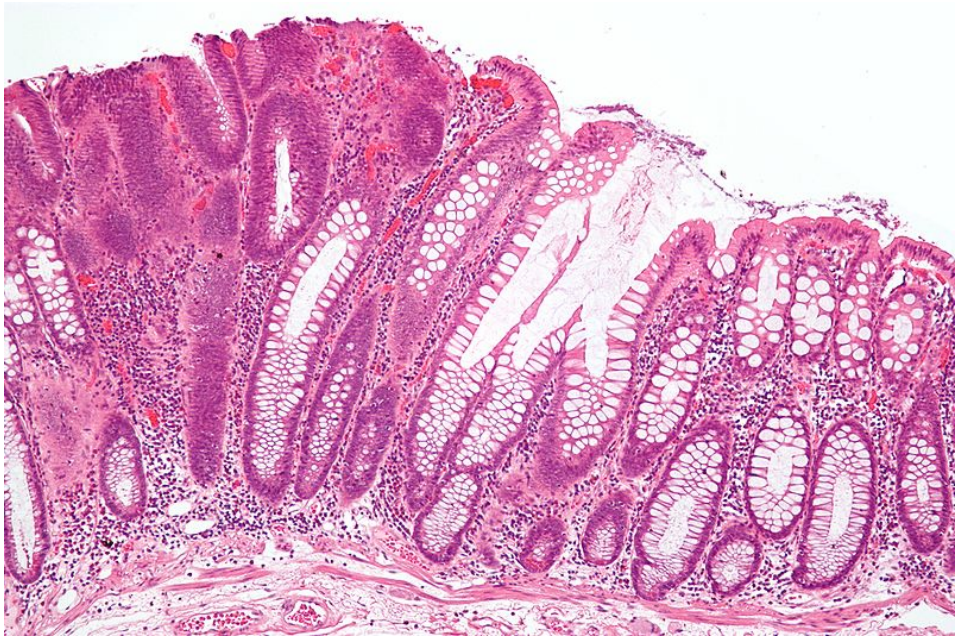
Dispersion regions, idealized. Source. Modified from Schwan (1988)

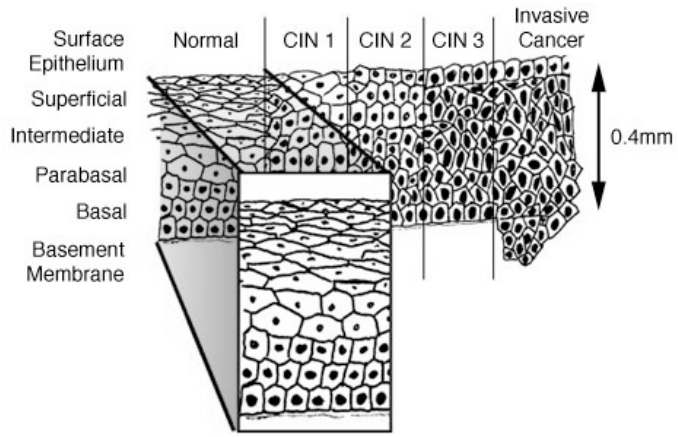
Dialect Dispersions

Type	Characteristic frequency	Mechanism
α	mHz–kHz	Counterion effects (perpendicular or lateral) near the membrane surfaces, active cell membrane effects and gated channels, intracellular structures (e.g. sarcotubular system.), ionic diffusion, dielectric losses (at lower frequencies the lower the conductivity).
β	0.001–100 MHz	Maxwell–Wagner effects, passive cell membrane capacitance, intracellular organelle membranes, protein molecule response.
γ	0.1–100 GHz	Dipolar mechanisms in polar media such as water, salts and proteins.

Bio impedance

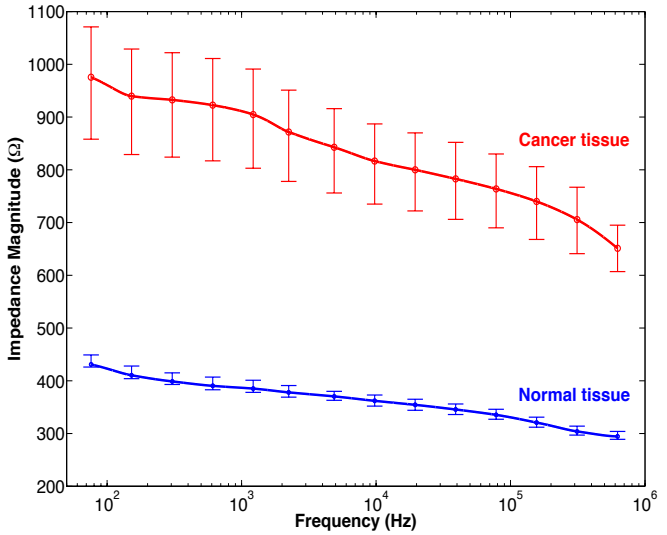




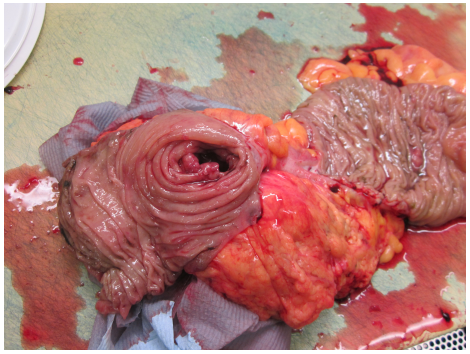


http://www.zilico.co.uk/research_development/electrical_impedance_spectroscopy

EIS measurement of tissue



Plot of impedance vs. frequency taken from fresh tissues sample within ½ hour of the patient undergoing CRC surgery.



Total of 27 samples at present, results from 10 non chemo with Zilico system in test mode

Cancer Biosensor

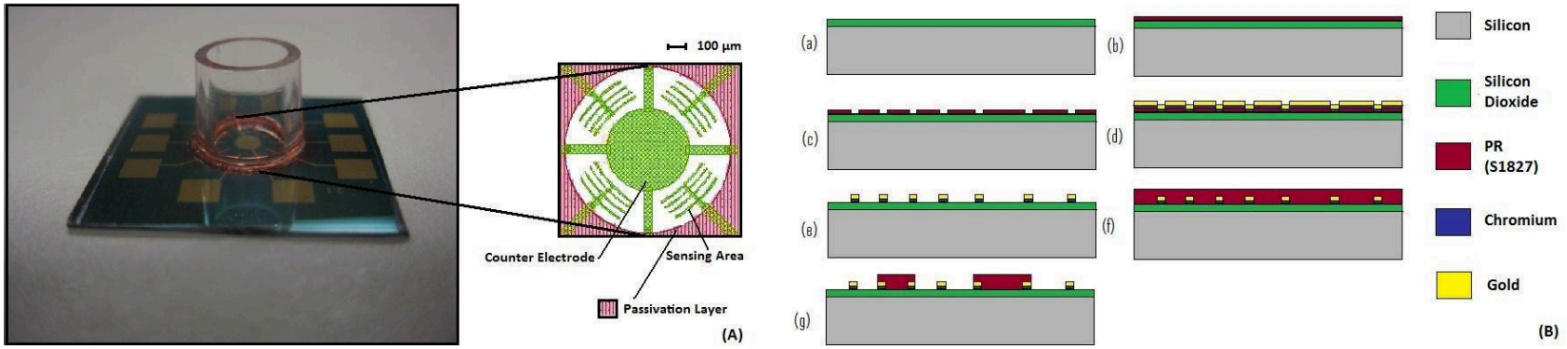
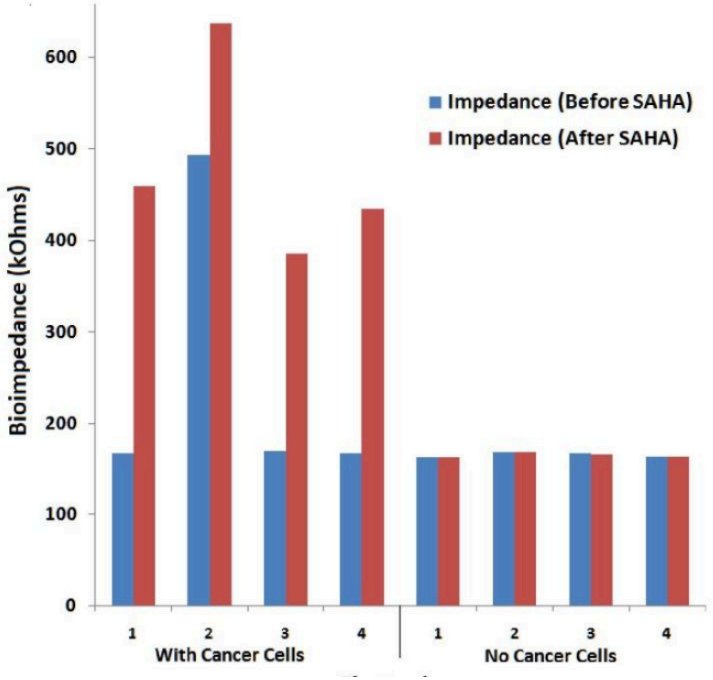
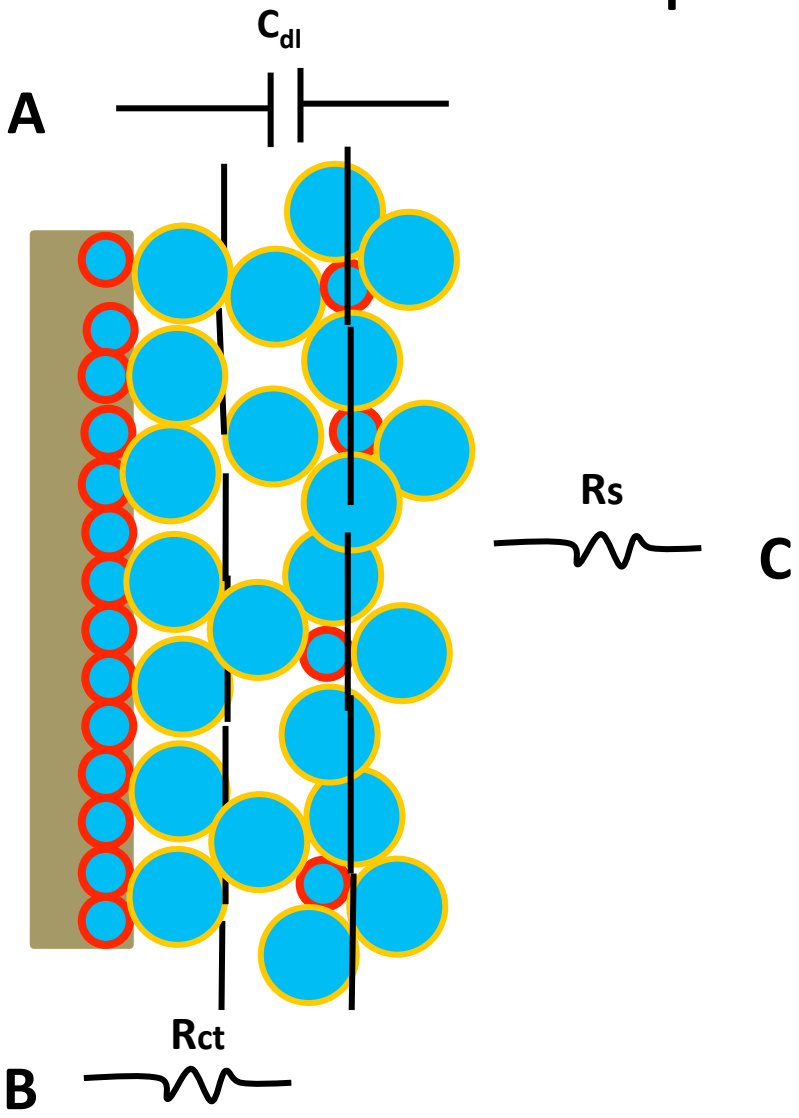


Figure 1: (A) The bioimpedance sensor with an enlarged view of the electrode design. (B) Process flow for the fabrication of the biosensor.



DETECTION OF BREAST CANCER CELLS IN TRI- CULTURE USI-NG IMPEDANCE SPECTROSCOPY Vaishnavi Srinivasaraghavan , Jeannine Strobl, Masoud

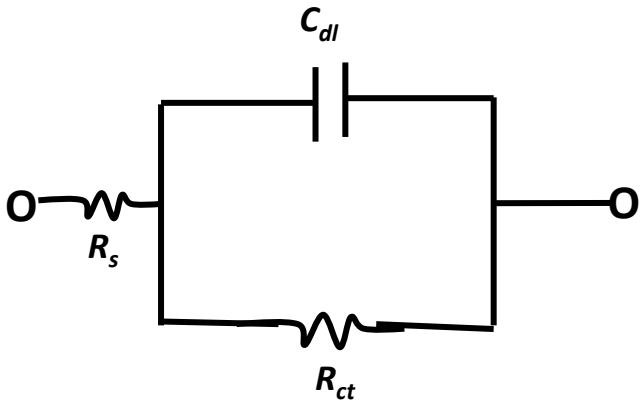
Electrochemical impedance spectroscopy



A (C_{dl}) is the double layer capacitance

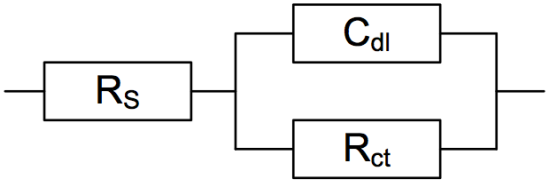
B (R_{ct}) electron transfer resistance

C (R_s) uncompensated electrolyte/solution resistance



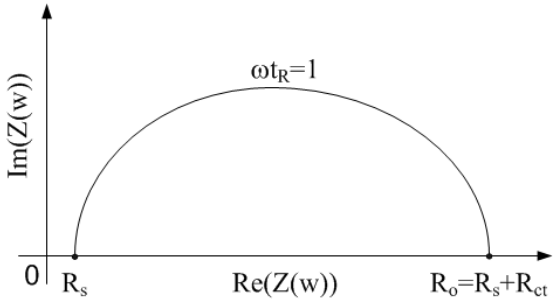
Electrochemical activity modelled into different electrical circuit elements and the Randle's circuit.

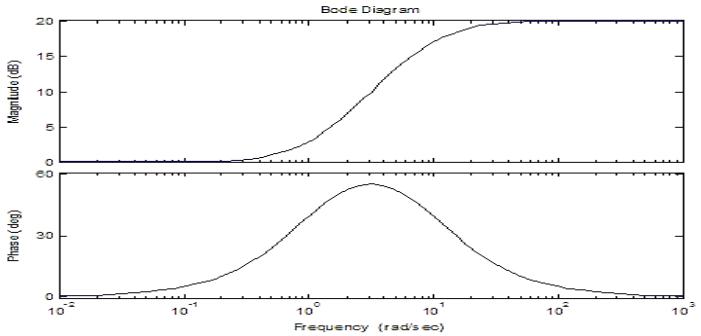
Circuit models



Randles equivalent circuit model of the electrode/electrolyte interface.

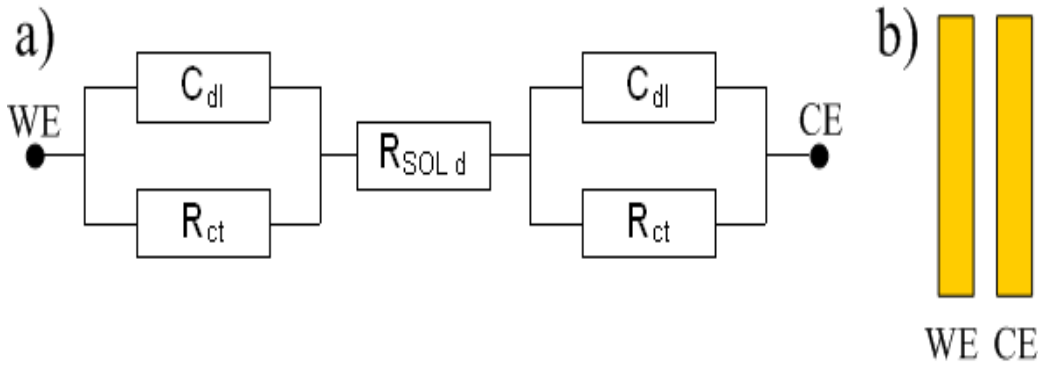
$$Z = R_S + \frac{R_{ct} - R_S}{1 + (j\omega\tau_R)^{\psi_z}}$$





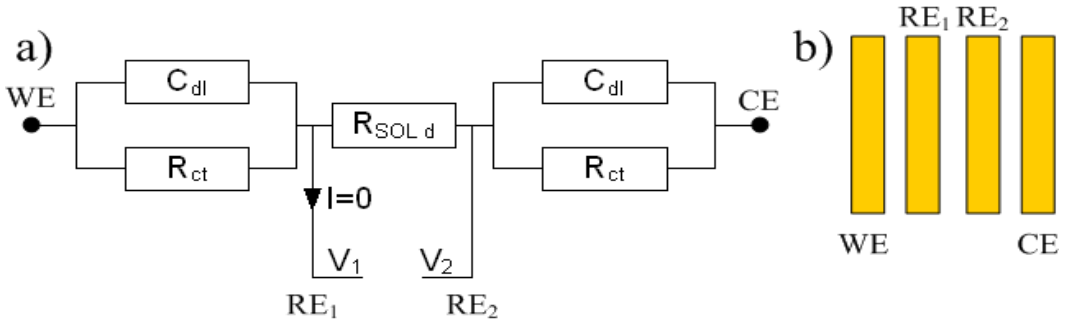
Typical Nyquist plot illustrating a depressed semi-circular EIS response

Electrodes

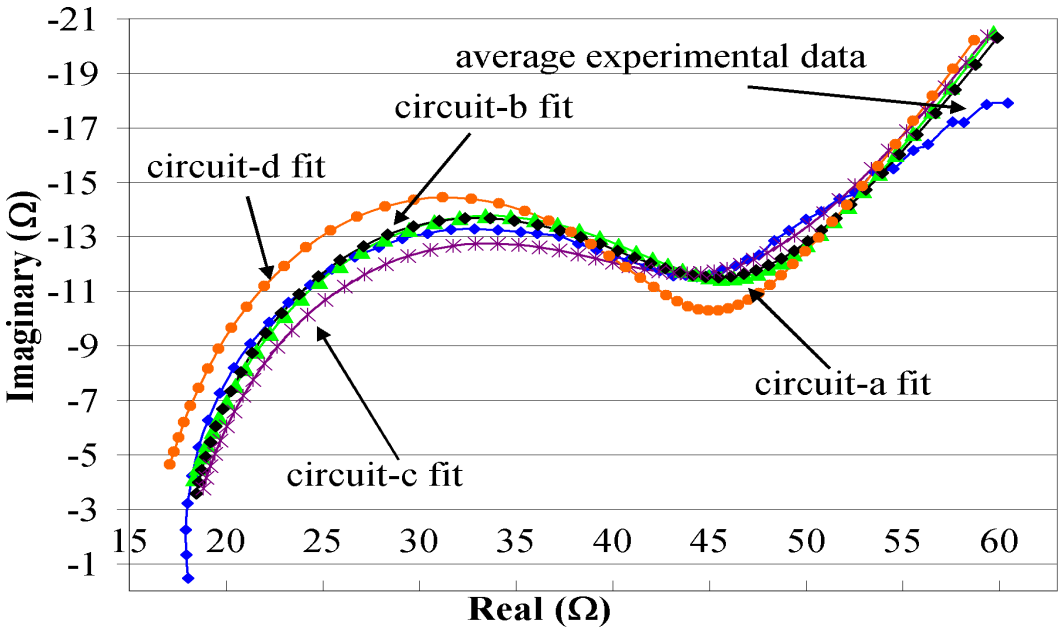


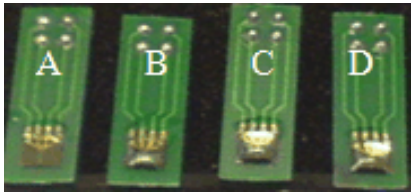
a) Two electrode system equivalent circuit model. b) An example of two parallel coplanar gold electrodes acting as the working (WE) and counter electrodes (CE).

Electrodes

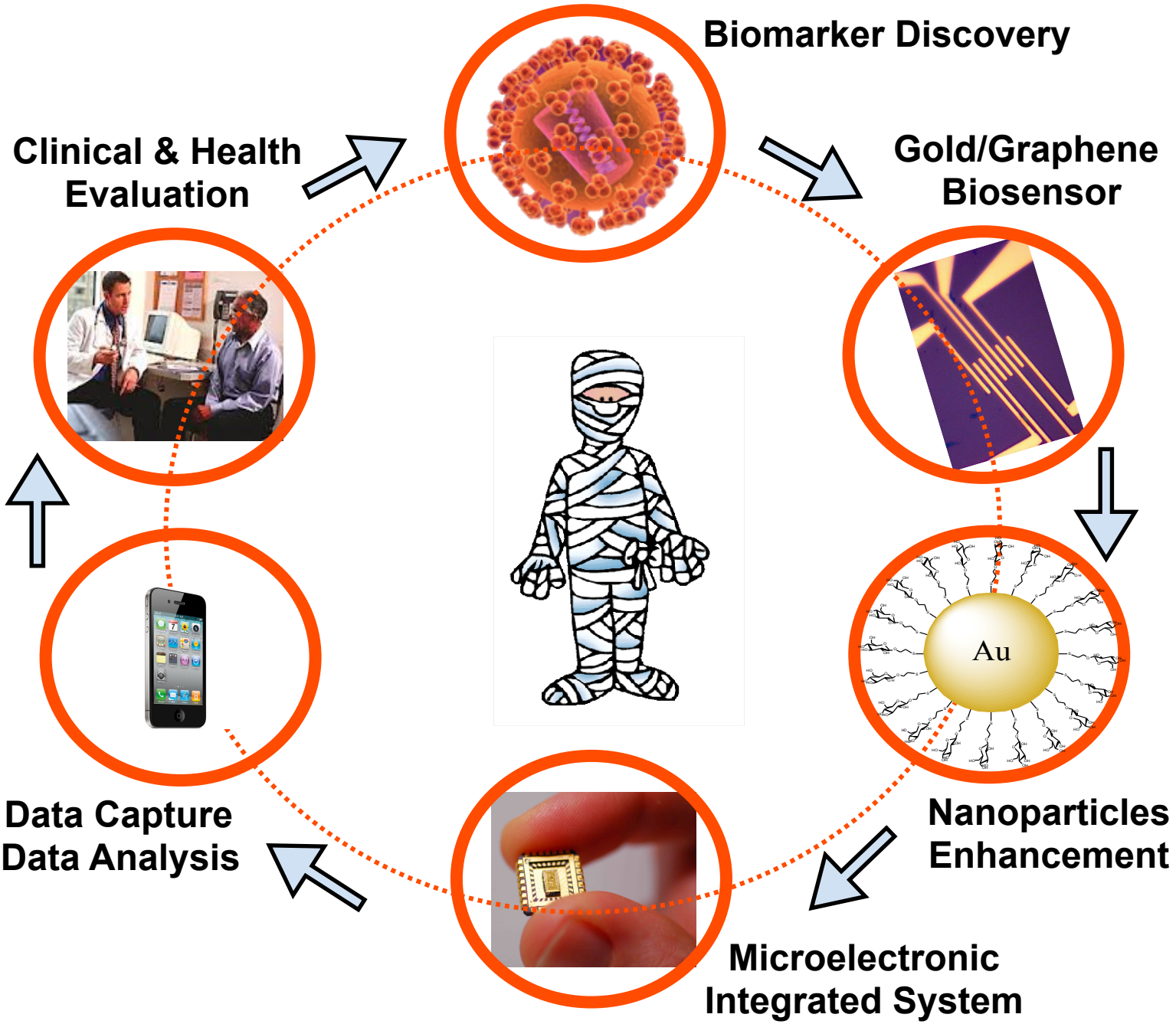


a) The four electrode measurement system equivalent circuit model. b) An example of four parallel coplanar gold electrodes acting as the working (WE) counter (CE) and voltage measurement reference electrodes (RE).

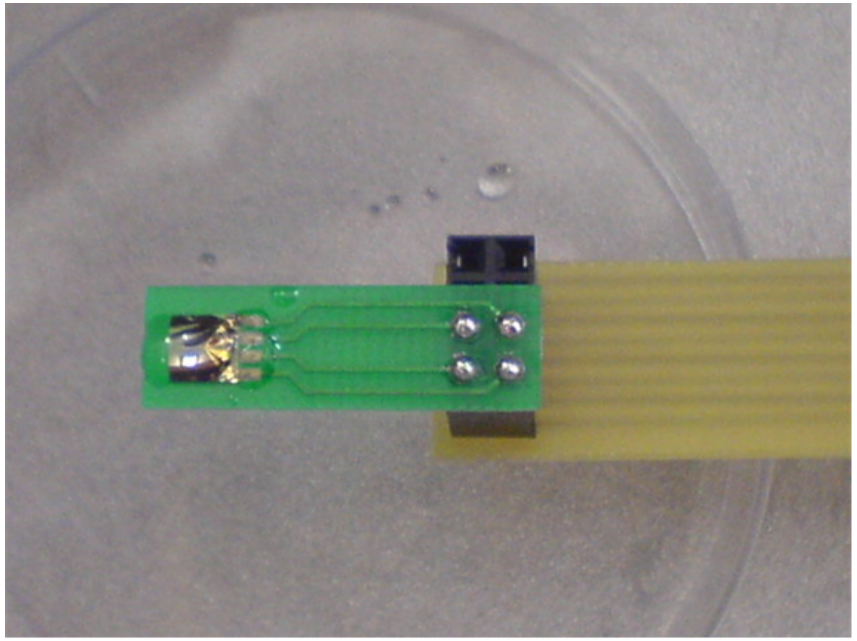




Comparing experimental average data obtained from the sensor with the SAM layer only, with the data obtained from the equivalent circuit fitting process.

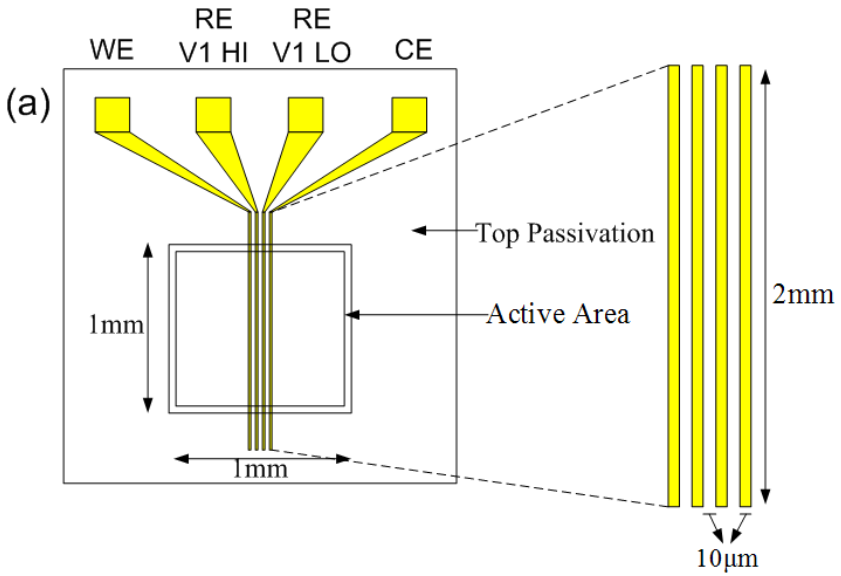

Biomarker Discovery
Gold/Graphene Biosensor
Nanoparticles Enhancement
Microelectronic Integrated System
Data Capture Data Analysis
Clinical & Health Evaluation
Au

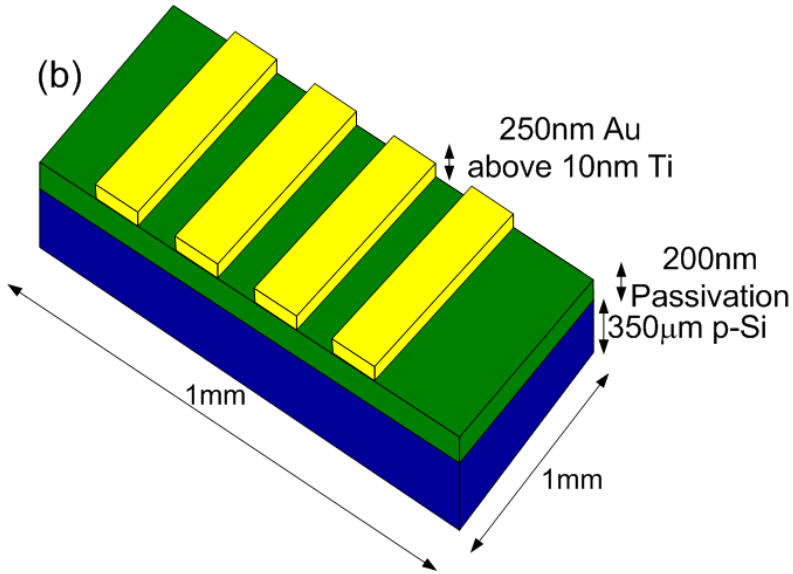
Materials and Methods:
EIS Biosensor



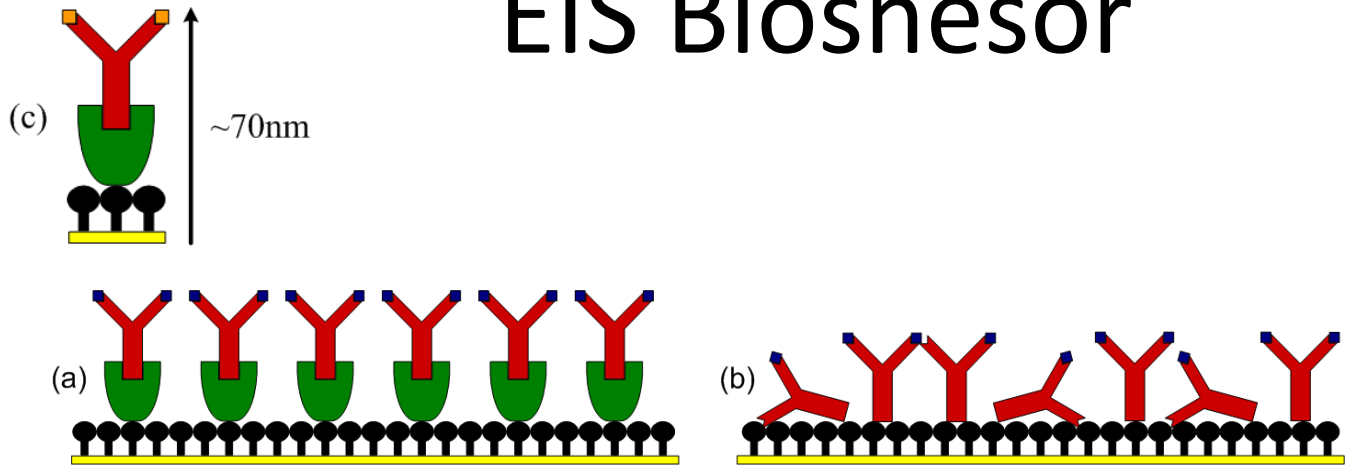
We have constructed a NON-optical assay biosensor system based on the change in electrical impedance as a result of hCG being bound by immobilized anti-hCG antibodies.

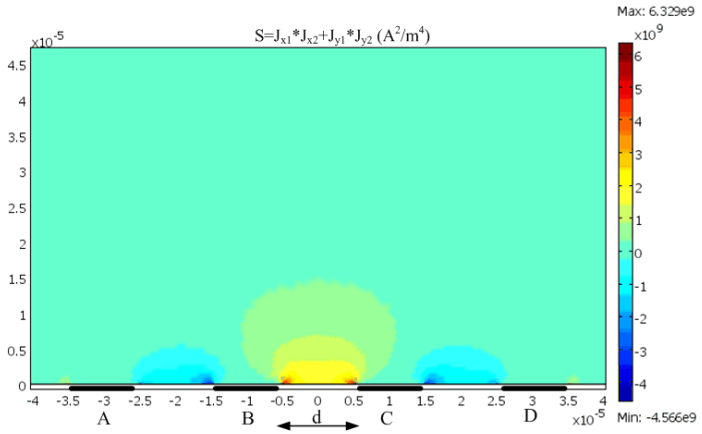
EIS Biosensor



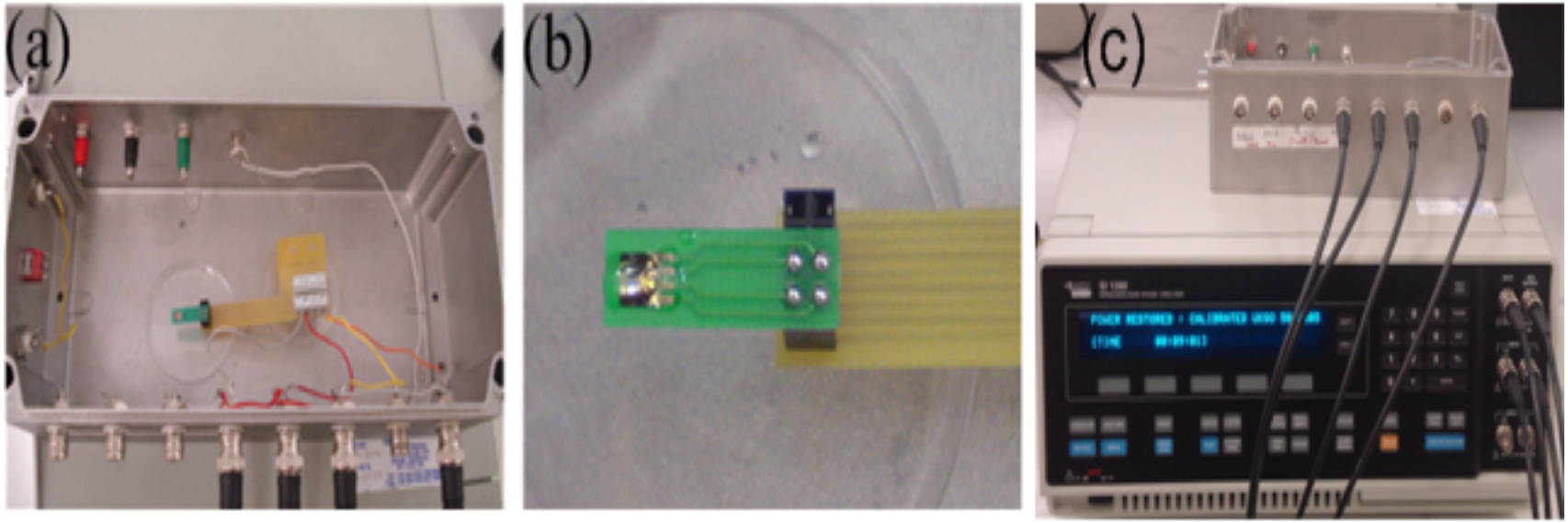


EIS Biosnesor



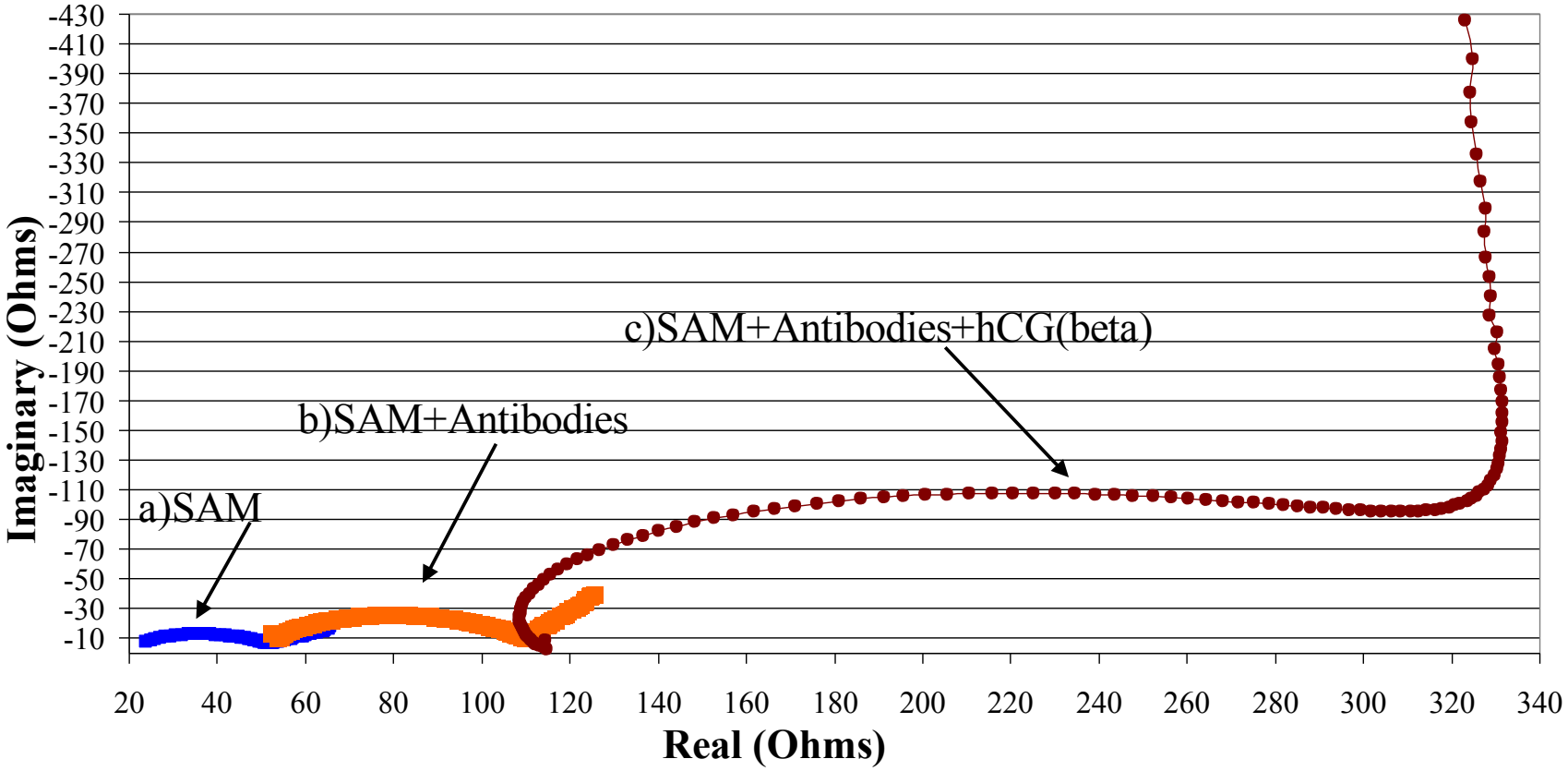


(a) With the protein G layer. From bottom to top: The golden substrate, SAM layer, protein G layer and antibodies with attached hCGb, (b) the sensor without the protein G layer illustrating its reduced detection-ability. c) The approximate total height of the biomolecular complex under investigation



Solartron Impedance Gain/Phase Analyzer 1260: 5mV 10mV and 15mV, 5mHz-1MHz

Impedance change due to hCG binding to the sensor

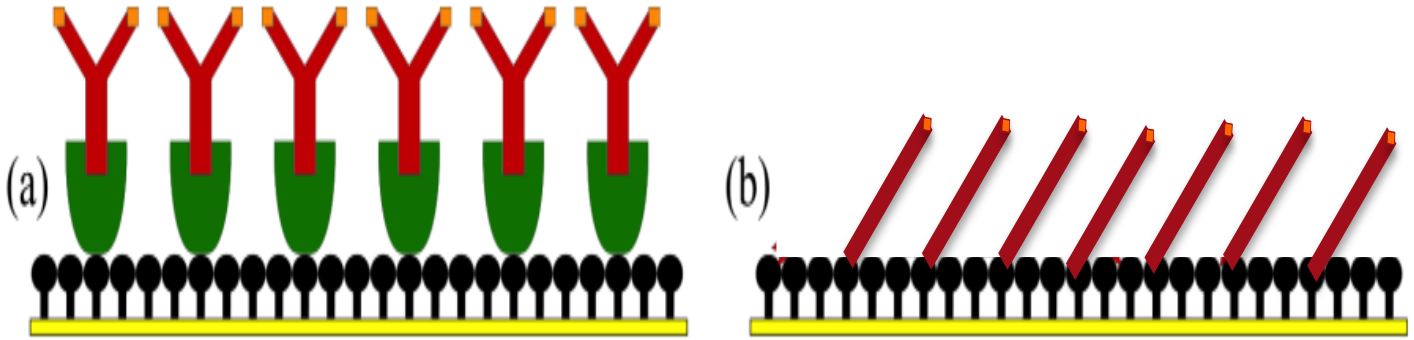


Kassanos P, Iles RK, **Bayford RH** and Demosthenous A (2008) Towards the development of an electrochemical biosensor for hCGβ detection. *Physiol. Meas.* 29

Antibody capture biosensors

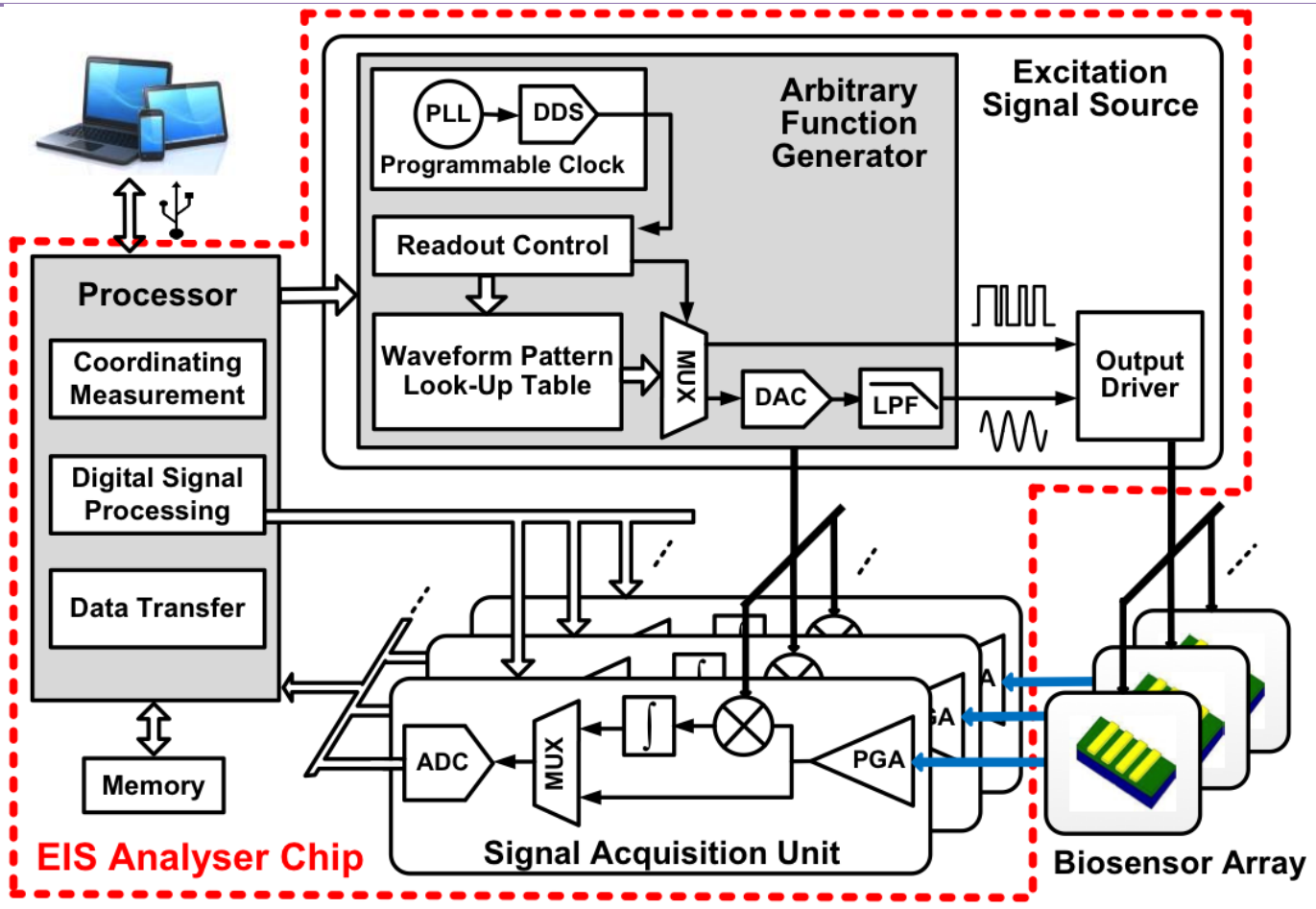
IgG coating

Fab coating

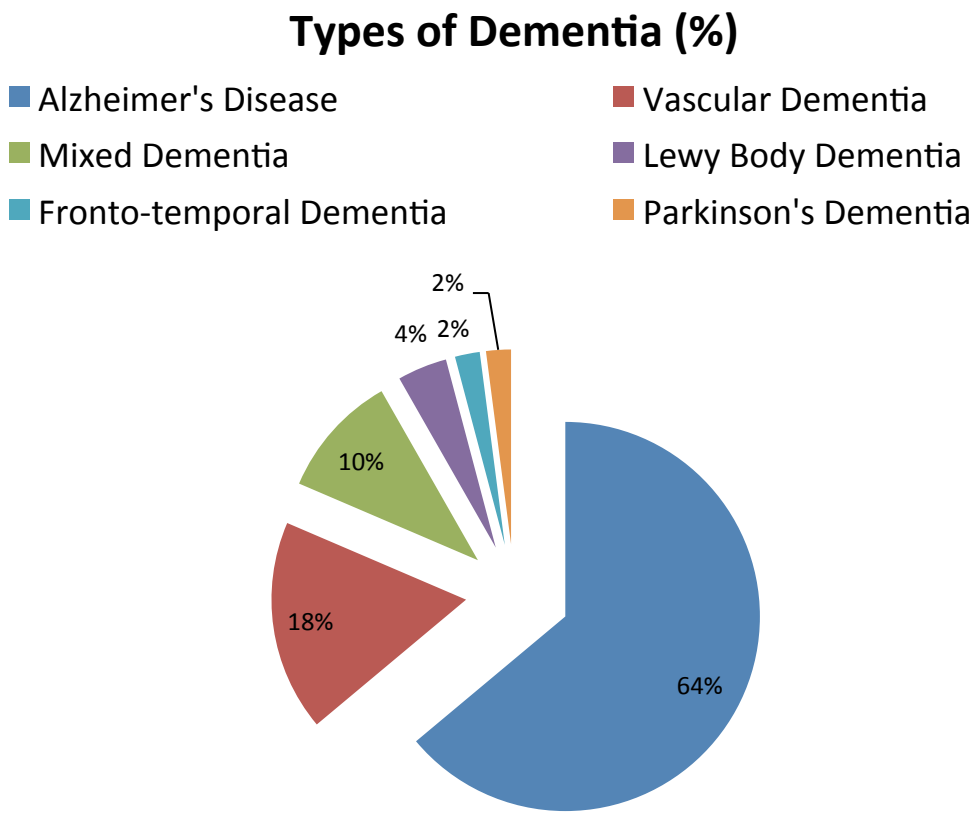


Electrodes

Architecture of an EIS analyser chip.

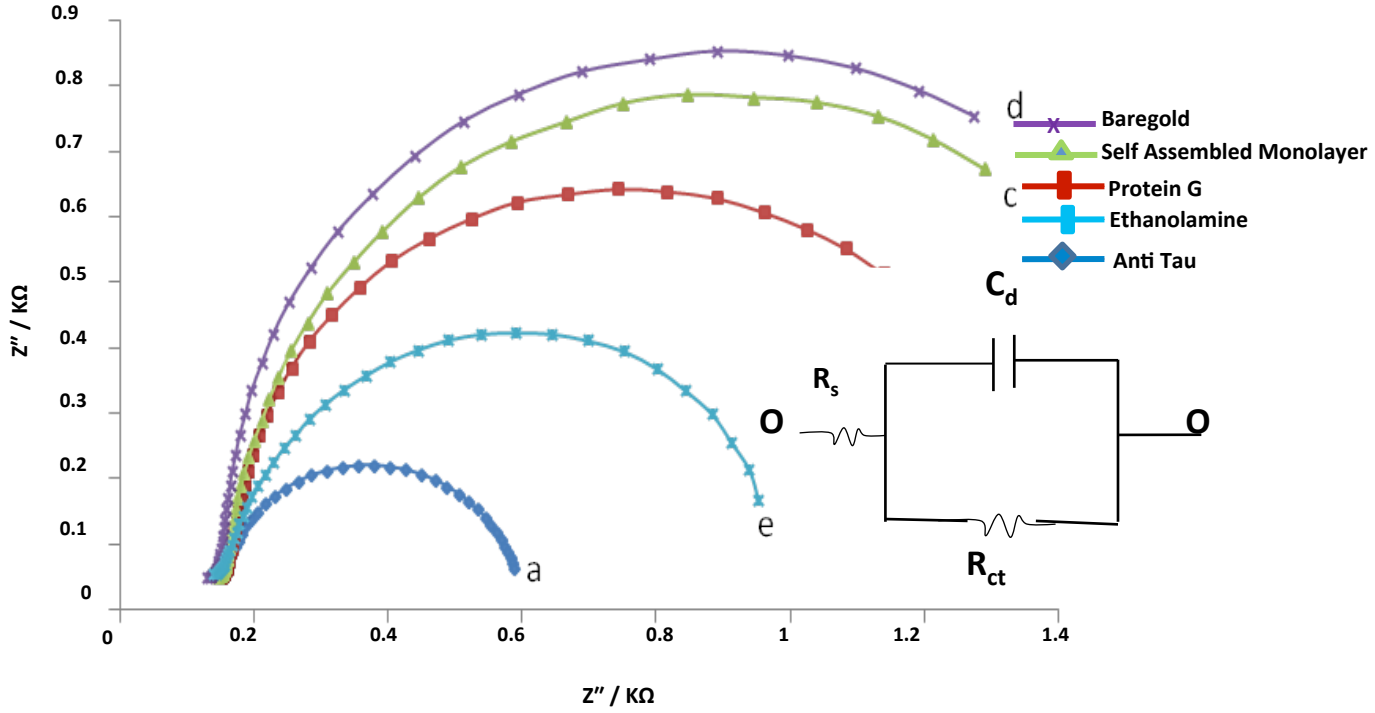


Types of dementia



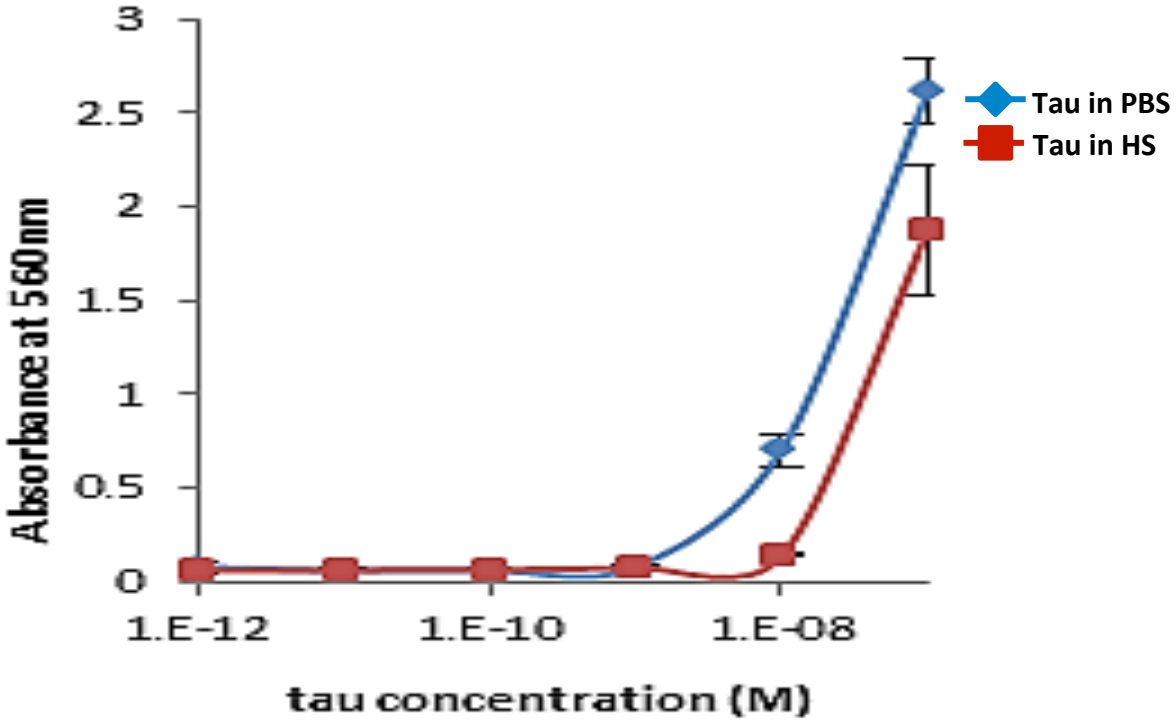
Percentages of the different types of dementias

Verification of construction of sensor



Construction and assembly of the biosensor ; layer by layer development of the biosensor verified by EIS, imaginary impedance plotted against real

Confirming the detection of Tau by ELISA compared to EIS



ELISA results showing detection of different concentrations (from 10^{-12}M to 10^{-7}M) of tau in PBS or tau spiked in human serum (HS).

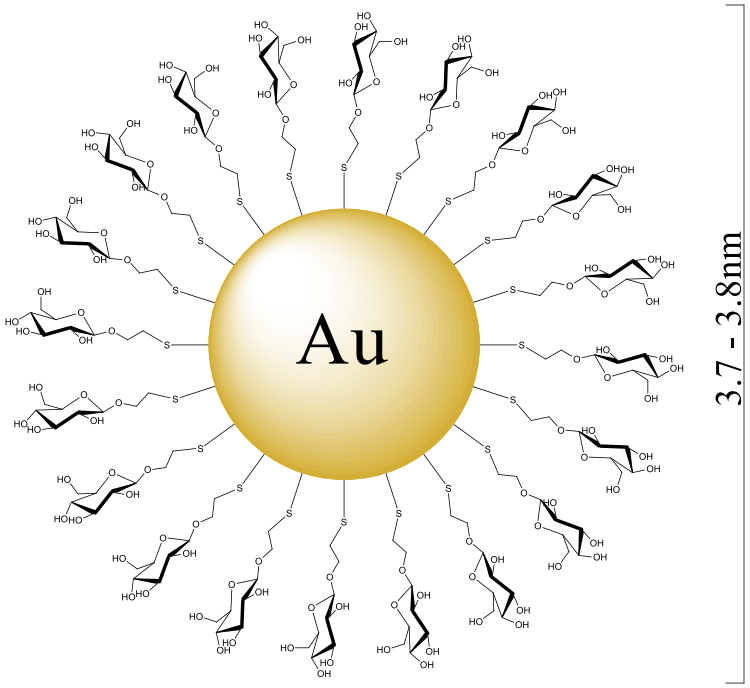
Table : Comparison between ELISA and EIS biosensor detection limit.

Assay method	Limit of detection (M)	Assay range
Biosensor	10^{-14}	10^{-14}~10^{-7}
ELISA	10^{-8}	10^{-12}~10^{-7}

Advantages of the biosensor

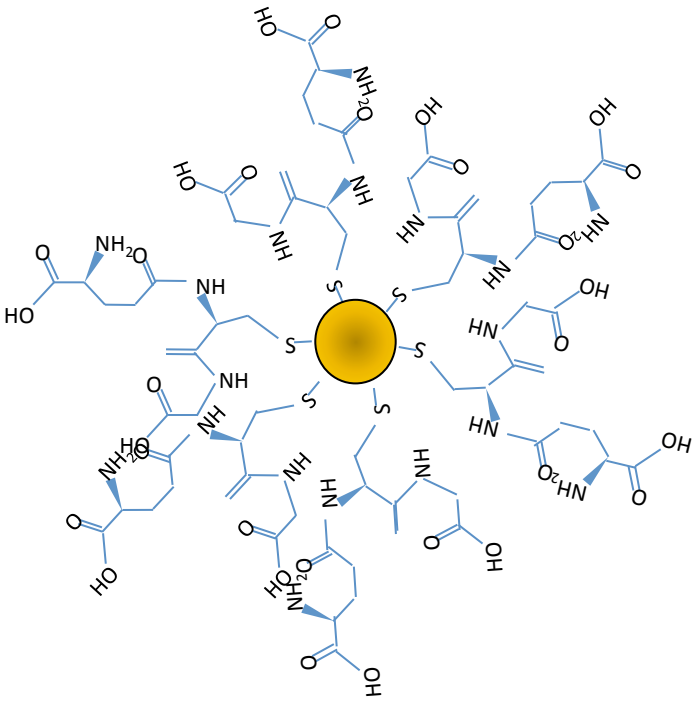
- Compared to other methods such as the ELISA and mass spec it gives real time measurements
- Easier to use
- Less laborious and less time consuming
- Cost effective
- More sensitive

Nanotechnology



C2 beta glucose
estimated Volume 26.5-28.5nm³

Nanoparticles

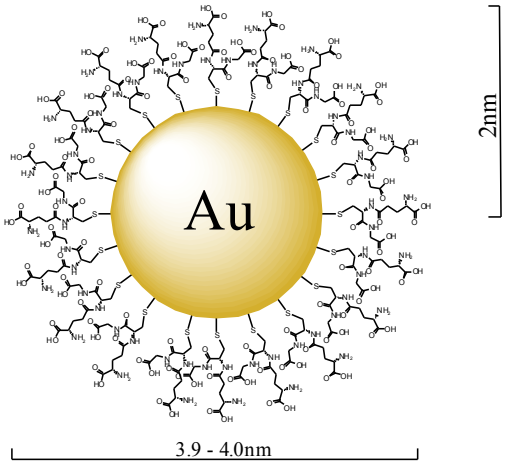


~ 1.6nm Core

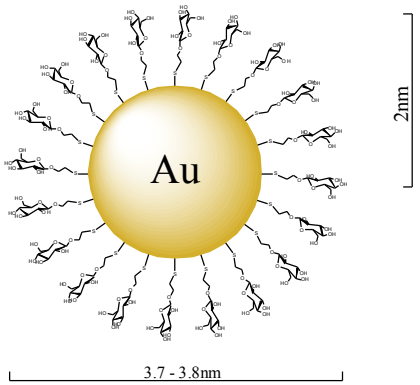
~ 5nm Nanoparticle

Example: Glutathione Coated Gold Nanoparticle (gsh-GNP)

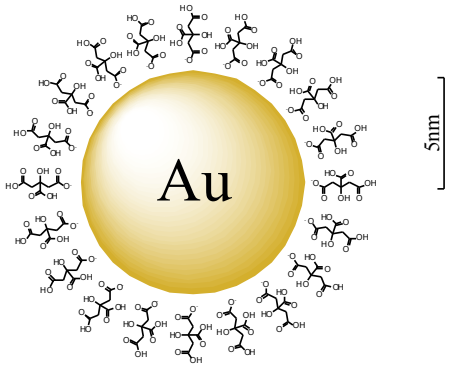
Types of particles investigated



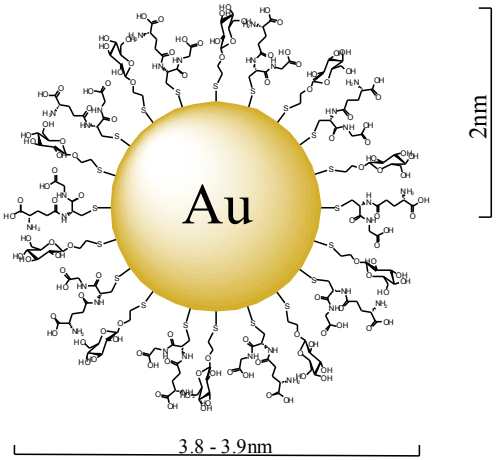
Glutathione NP
Estimated Volume 31.1 - 34.0nm³



C2 Glucose
Estimated Volume 26.5 - 28.7nm³

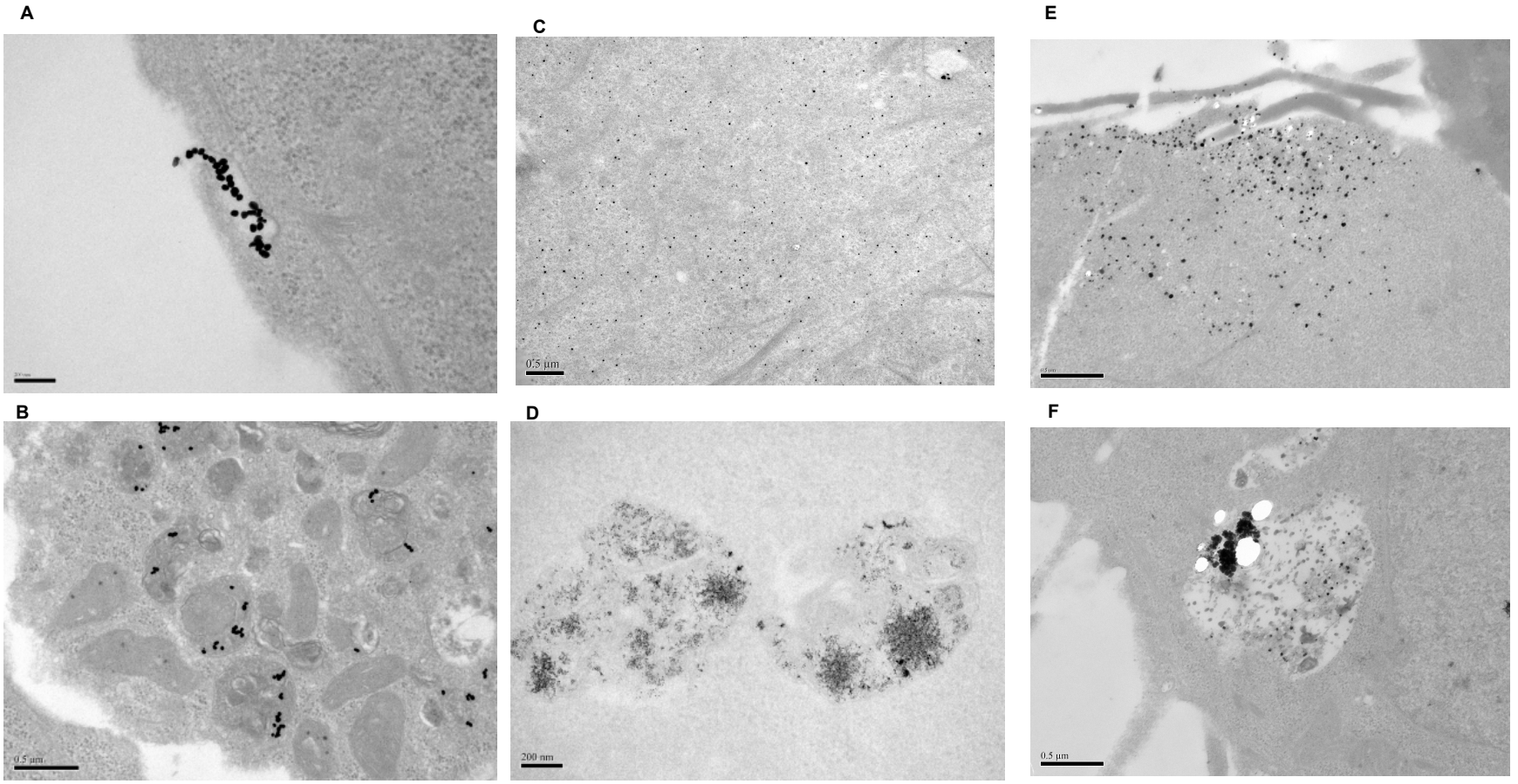


Citrate passivated
Estimated Diameter 10 - 12.5nm³
Estimated Volume 500 - 1000nm³



Glutathione & C2 Glucose
Estimated Volume 28.7 - 31.1nm³

Uptake of GNPs in HCT-116 colorectal cancer cell line

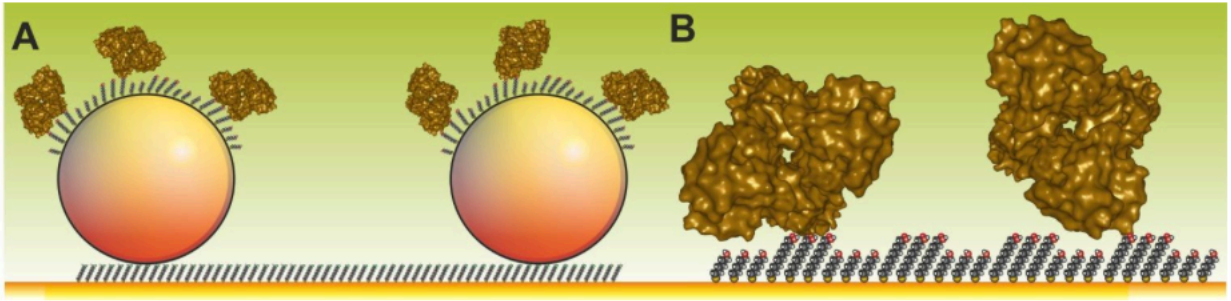


40 nm Citrate-colloidal GNP

5 nm Glutathione-GNP

5 nm Glucose-GNP

A surface area of bare and AuNPs modified electrodes



A graphical representation drawn to scale of interfacial layers applied to build up the 3D biosensor based on integrated 20 nm gold nanoparticles (A) or the 2D biosensor (B). The 3D biosensor was build up on a planar gold surface by chemisorptions of 11-aminoundekanethiol, functioning as a linker for attachment of 20 nm gold nanoparticles, represented in a form of a sphere. On every gold nanoparticle a mixed SAM composed of 11-mercaptoundecanoic acid (MUA) and 6-mercaptohexanol (MH) was formed for covalent immobilisation of lectin (A). The 2D biosensor was formed by incubation of a planar gold with MUA and MH for covalent attachment of a lectin.

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Future

Mobile device, test strip and blood sample

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