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Current trends in nanobiosensing towards lab-on-a-chip devices for ultrasensitive analyte detection

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Abstract

The development of nanobiosensors has been at the forefront of research considering their importance for the future of health and maintenance of wellbeing. In particularly they harness the exquisite sensitivity and specificity of biology in conjunction with physicochemical transducers to deliver complex bioanalytical measurements with simple, easy-to-use formats. This paper introduces the basic concept of a nanobiosensor providing an overview of the different types available and their basic working principles including numerous applications. The investigation of nanomaterials such as gold nanoparticles, carbon nanotubes, magnetic nanoparticles and quantum dots are discussed within the frame of improving their sensitivity and performance. Nanobiosensors have the potential to lead to highly specific and accurate lab-on-a-chip devices for the rapid screening of a wide variety of analytes at a low cost, making health care available at a low cost across the globe.

1. Introduction

Biosensors are compact analytical devices converting biological responses to electrical signals with the ability to detect a wide range of target molecules such as proteins, viruses, bacteria, cell components, DNA, etc. in biological fluids as well as water samples [1-3]. They are composed of a biological recognition element, i.e. the receptor that is directly interfaced to a signal transducer relating the concentration of the analyte to a measurable response [4,5] (Figure 1).

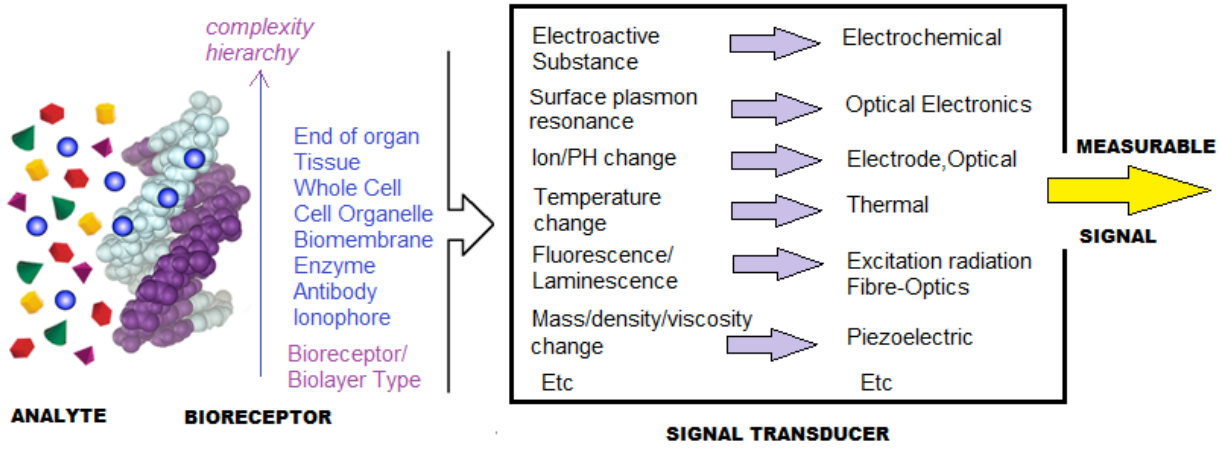

Figure 1. Biosensor operating principles [6]

The first biosensing device was the *Clark electrode* in 1956 [7] made from a thin layer of the enzyme glucose oxidase (GOx) entrapped over an oxygen electrode. It was used to measure glucose based on the oxygen

consumed by the catalyzed enzyme (GO_x +*glucose* + *oxygen* → *gluconic acid* + H_2O_2). The *Clark electrode* was the simplest form of an *amperometric* biosensor, i.e. a class of electrochemical sensors measuring the current resulting from the oxidation or reduction (*REDOX*) of an electroactive species in a biochemical reaction. Other electrochemical biosensors included the *potentiometric* urea detector based on ammonia ions obtained after urease (enzyme) catalyzed the hydrolysis of urea. It involved an urease electrode made by polymerizing a gelatinous membrane of immobilized urease enzyme over a cationic glass electrode which is responsive to ammonium ions [8,9]. The signal was measured as the potential difference between the working electrode and a reference. [10] also introduced the microbial biosensor that used the rate of microbial respiration as a specific signal on the total amount of oxidizable organic matter in water. In particular, the authors reported a BOD sensor based on a microbe fuel cell using the hydrogen produced by Clostridium butyricum immobilized on the electrode. Optical biosensors (*optodes*) were introduced by Opitz et al, in 1978 [11] who determined the surface pO_2 (partial pressure of oxygen) of an isolated guinea pig heart using a fiber optic sensor to measure fluorescence quenching of pyrenebutyric acid (fluorescence indicator) by oxygen. The concept was then extended to make an optical biosensor for alcohol by immobilizing alcohol oxidase at the end of a fiber optic oxygen sensor [12]. In 1973 Aoyagi also introduced the *pulse oximeter* that determines oxygen saturation in blood (SpO2%) and heart rate (pulse) by measuring the absorbance spectra of hemoglobin through the human tissue, usually the finger [13].
Piezoelectric biosensors have also seen significant growth [1,14]. Recently piezoelectric immunosensors involving the construction of crystal electrodes coated by receptor molecules, e.g. antigens have been particularly successful in registering biochemical interactions, utilizing the fact that the resonant frequency of an oscillating piezoelectric crystal (e.g. alpha quartz) can be affected by changes in the mass on the crystal surface.

2. Main biosensor types and operating principles

The main biosensor types based on the *transducer* element are summarized in Figure 2 below, i.e. electrochemical, piezoelectric, optical as well as calorimetric/thermistors [15]. Additionally, based on the *biorecognition* element we can have antibody-based biosensors, enzyme or DNA biosensors device, etc.

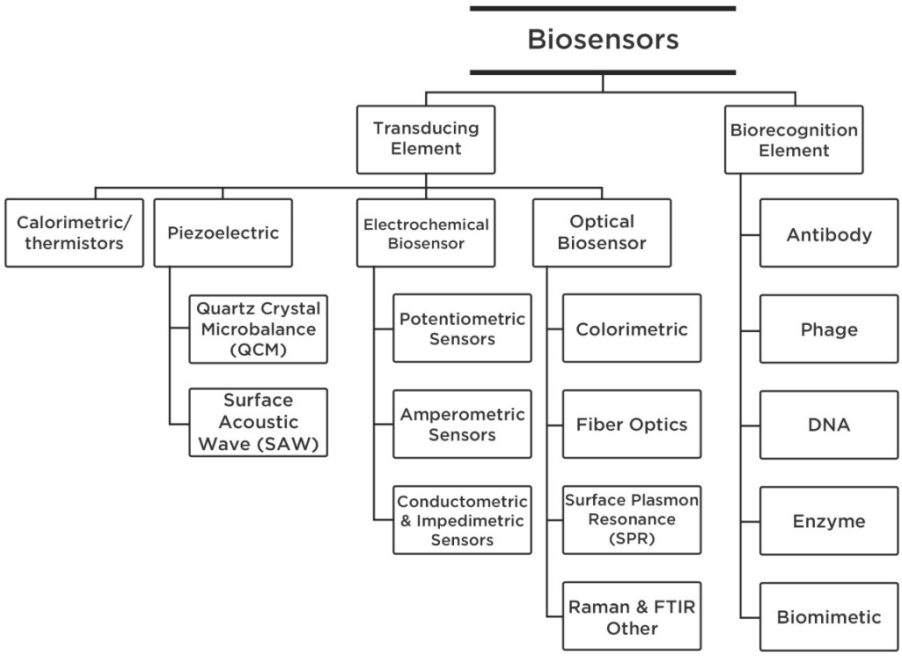

Figure 2. Main types of biosensing devices according to the transducing and biorecognition element

Biosensors have experienced rapid development in recent years [16,17]. In particular electrochemical biosensing has undergone significant advances since the Clark electrode. Currently amperometric detection which is the main route of electrochemical sensing is based on the measurement of the current generated by the reduction/oxidation processes of electro-active substances in intimate contact with an electrode system [18]. In

order to allow these processes to happen, an appropriate potential must be set between the electrodes, depending on the characteristics of the reaction and the electrode's materials. In general, three electrode systems are preferred utilizing a working electrode (WE), a reference electrode (RE) and an auxiliary or counter electrode, (CE). In particular the 3-electrode system for biosensors is normally implemented by screen-printed electrodes as seen on the right side in Figure 3. These are built by the deposition of different "ink" layers over a number of substrates such as PVC, ceramics, aluminum bases, etc. [19]. Such screen-printed electrodes have an important advantage being low cost, as they are intended to be disposable with an easy automated production, and small size. Within this frame one of the most successful achievements in electrochemical sensing was the introduction of the home-based glucose biosensor in 1984, which revolutionized portable blood analysis for the quantitative detection of glucose in diabetes patients [20]. In general, electrochemical sensors are considered some of the most robust routes towards quantitatively measuring both catalytic and affinity reactions and currently there is increased interest towards microfluidic paper printed devices for the simultaneous detection of various analytes in biological samples.

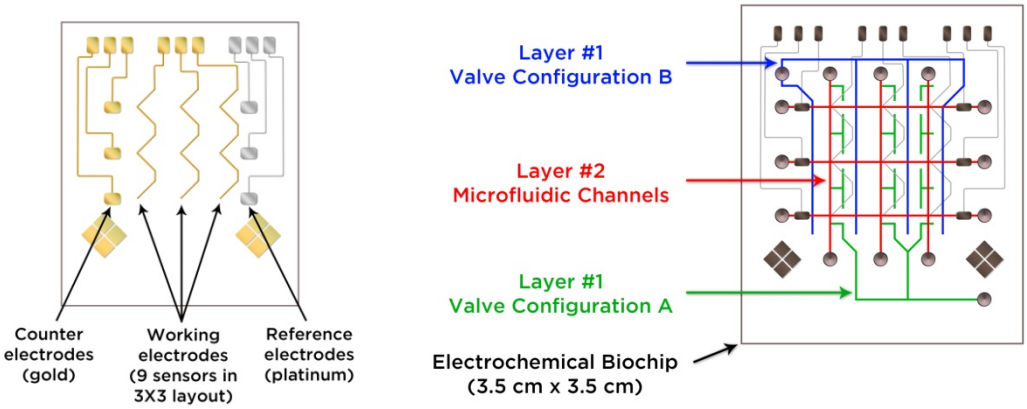

Figure 3. *Recent advances in electrochemical sensing*: an electrochemical sensor as a screen-printed electrode and a sample package of a microfluidic valve actuated electrochemical sensor [21]

Optical biosensors are a powerful alternative to electrochemical sensing and may involve direct detection of the analyte of direct or indirect detection through optically labeled probes. Their basic operation principle involves the coupling of bioreceptor molecules to the transducer either by physical entrapment or chemical attachment allowing the conversion of the binding event to a measurable optical signal [22]. In general, the optical transducer [1] may detect changes in the absorbance, luminescence, polarization, or refractive index (Figure 4).

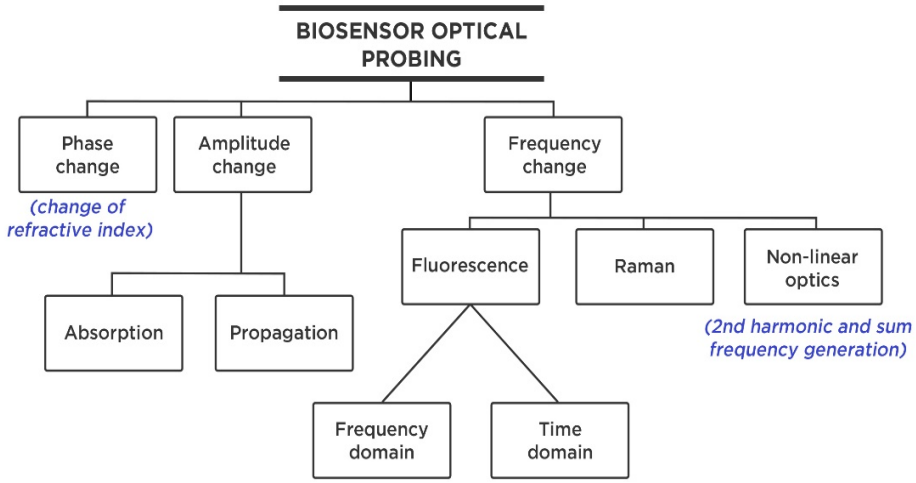

Figure 4. Various parameters used in optical biosensing

Colorimetric biosensors [23,24] which are a class in optical biosensing, change color when exposed to the target analyte and detection is performed through changes in absorption at a specific wavelength, e.g. colorimetric test strips which are single-use cellulose pads impregnated with enzyme and reagents (colorimetric test strips). In

particular the use of paper-based [28] colorimetric array test strips have allowed the simultaneous detection of multiple analytes both qualitatively and semi-quantitatively in a cost-effective manner offering ease of use, simple fabrication and biocompatibility [29]. Notable examples of colorimetric biosensors include the Whiteside's group glucose and protein assay with photoresist borders [25], multiple indicator systems for glucose, lactate, and uric acid [26] and the Ketone test [27].

The use of optical fibers in biosensing, as discussed in the case of *optodes* is depicted in further detail below (Figure 5.) It involves light signals generated by a sensing laser usually composed of biorecognition molecules and dyes, coupled to the fiber end. Light is transmitted through the optical fibers to the sensing layer where different optical phenomena such as absorption, luminescence, etc. are used to measure the interactions between the analyte and the sensing layer. Optical fiber biosensing can be used for remote analytical applications including clinical, environmental, and industrial process monitoring.

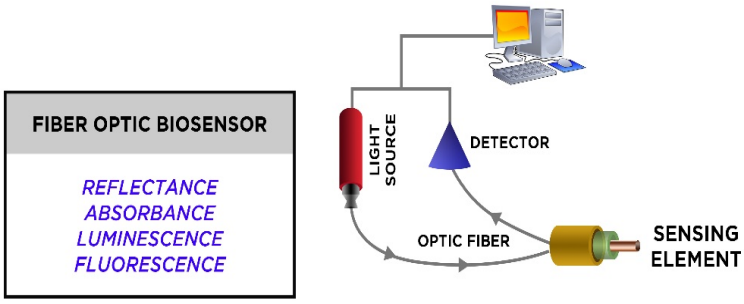

Figure 5. The Fiber Optic Biosensor [30]

Below in Figure 6, there is an example of an evanescent wave fiber optic bionsensor that is utilized in fluoro-immunoassays [31]. Generally, such biosensors use the evanescent field emitted in a waveguide to determine changes in the refractive index at the sensing surface.

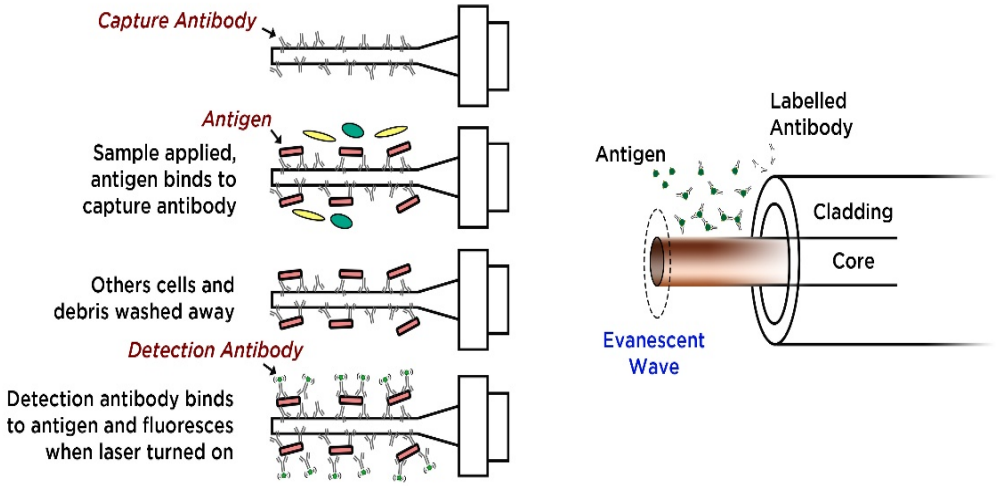

Figure 6. The fluorophore (Cy5) antibodies form a sandwich assay by capturing the target antigen. Furthermore, the fluorescent molecules are excited as a result of the evanescent wave and part of their emission energy recouples with the fiber [32].

Amongst other transducer types piezoelectric systems are attractive due to their simplicity and low instrumentation [14,33-34]. The quartz crystal microbalances which are typical example of piezoelectric systems were first introduced by Sauerbrey [35] in 1959, following the initial prediction in 1880 by Jacques and Pierre Curie [36] that as a result of mechanical stress to materials such as quartz there is resulting voltage proportional to the stress. Sauerbreys work led to the use of quartz plate resonators as sensitive microbalances for thin films. In particular according to Sauerbrey's equation (1) below the change in mass (Dm) on the quartz surface is directly related to the change in frequency Df of the oscillating crystal, times a coefficient C:

$$Dm = -C * Df \quad (1)$$

Below in Figure 7 a piezoelectric biosensor based on the quartz crystal microbalance (QCM) is depicted conducting a measurement based of an immune reaction where the change of mass D_m (mass of antigen) $=m_0$(before antibody-antigen reaction)-m_1(after antibody-antigen reaction) leads to a change in oscillating frequency.

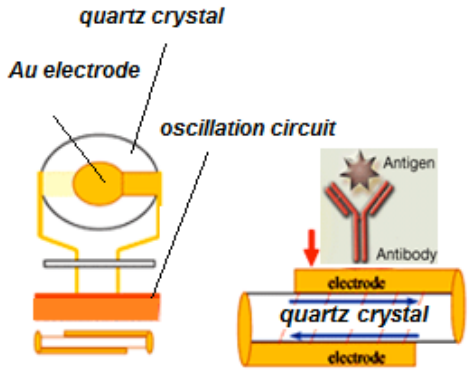

Figure 7. Operational principle of a quartz crystal microbalance

QCM sensors and QCM arrays were employed to accurately determine biomolecules as well as volatile organic compounds (VOC's) and other gases [37,38]. Moreover, they were recently used to determine the concentration of nanoparticles in a colloidal suspension dropping the nanoparticle suspension in a volatile substance [39]. Recently major improvements in QCM sensing were reported [40] by removing electrodes and wires attached on the quartz surfaces and performing non-contacting measurements using wireless antennas. In general, some of the critical parameters for QCM sensors are sensitivity, stability, response time and reusability as well as environmental factors including the role of temperature and humidity in measurements.
Finally, calorimetric, i.e. thermistor- based biosensors monitor changes in temperature; if an enzyme catalyzed reaction is exothermic two thermistors may be used to measure the difference in resistance between the reactant and product and hence the analytic concentration [41]. They can be used to monitor biocatalysis, fermentation systems, enzyme catalyzed synthesis as well as in clinical and food technology.

3. Nanobiosensors: classification and applications

Nanobiosensors including implanted and integrated biosensors are currently at the forefront of research especially due to recent advances in nanotechnology. In particular the integration of a wide range of nanomaterials in biosensing devices such as nanoparticles, nanotubes, nanorods and nanowires have significantly improved precision, accelerate detection times as well as enhancing result reproducibility due to their unique properties. In particular nanomaterials can exhibit high electrical conductivity, better shock bearing ability, response sensitivity such as piezoelectric and versatile color-based detection mechanisms. Nanobiosensors are usually classified according to the nanomaterial they utilize to improve sensing, as listed in Table 1 along with some of their key benefits.

Table 1. Nanomaterials in biosensing and key benefits [42].

Nanomaterial	Key benefits
Carbon nanotubes	Improved enzyme loading, higher aspect rations, ability to be functionalized and better electrical communications
Nanoparticles	Aid in immobilization, enable better loading of bioanalyte and also possess good catalytic properties
Quantum Dots	Excellent fluorescence, quantum confinement of charge carriers and size tunable band energy
Nanowires	Highly versatile, good electrical and sending properties for bio and chemical sensing, charge conduction is better
Nanorods	Good plasmonic materials which can couple sensing phenomena well, can be coupled with MEMs and induce specific field responses

3.1 Carbon nanotube sensing technologies

Carbon nanotubes (CNTs) are promising candidates for highly sensitive and ultrafast detection as an alternative to conventional solid-state biosensors [43,44]. Their average diameter is between 1.2-1.4 nm, they have a thermal conductivity of approximately 3000 W/m*K and a resistivity of 10^{-4} Ω·cm at room temperature, making them the most electrically-conductive fibers known [45,46]. Furthermore, their tensile strength is almost 100 times larger than that of steel of the same diameter [47]. CNTs can be either single walled (SWCNTs) or multiwalled (MWCTs), having three distinct geometries as can be seen in Figure 8 below:

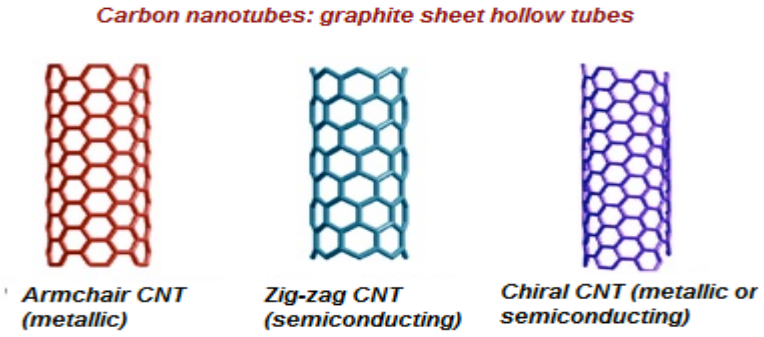

Figure 8. Carbon nanotubes: graphite sheet hollow tubes

Once SWCNTs are oxidized they form carboxylic ends allowing their functionalization with the amine groups of biomolecules such as DNA, proteins and enzymes as well as enhancing their dispersability. Table 2 provides a summary of the most important sensing mechanisms in carbon nanotube biosensing:

Table 2. Overview of the most important mechanisms in carbon nanotube biosensing [48].

Transduction Mechanism	Explanation
Electrical/FET	Binding of the analyte changes the dielectric environment/charge carriers of the carbon nanotube and transduces this event.
Electrochemical fluorescence	Redox-reaction (electron transfer) of the analyte on the carbon nanotube surface. Change of the fluorescent spectrum due to the interaction between analyte and SWCNT/wrapping (intensity or wavelength shift)
Quenching Raman scattering	Carbon nanotube quenching of other organic fluorophores. Carbon nanotubes are used as tag that exhibits extremely high Raman scattering

In particular due to their high surface to volume ratio and surface events, e.g. binding of a protein or ion can result in a significant change in bulk electronic properties leading to electrical detection of binding events.

Additionally, due to their luminescent properties, excellent wavelength conversion function and tunable near-infrared emission that responds to changes in the local dielectric function they are excellent candidates also in optical biosensing. Recently Barone et al. developed near-infrared optical sensors based on SWCNTs that modulates their emission in response to the adsorption of specific biomolecules. Efforts have also been made towards incorporating carbon nanotubes in temperature sensing [49]. Some further example of carbon nanotube biosensors include single walled carbon nanotubes that can be employed in glycose biosensing as immobilizing surfaces of the enzyme glucose oxidase. These yield significant increase in enzyme activity due to enhanced enzyme loading and better electrical conductivities of the nanotubes [50]. CNTs have also been coupled with other materials such as nanogold or polymers immobilized on glassy carbon electrodes to enhance catalytic activity and improve glycose detection limits [51,1].

Interest has also been shown in modulating single-walled carbon nanotube (SWNT) fluorescence in response to glucose to create a biomedical device that exploits the near infrared (NIR) emission of SWNT, where blood and tissues are most transparent. Below in Figure 9, a glucose binding protein (GBP) is covalently conjugated to a fluorescent single-walled carbon nanotube (SWNT) acting as an optical switch. Hinge-bending response to glucose causes a reversible exciton quenching of the SWNT fluorescence with high selectivity [52].

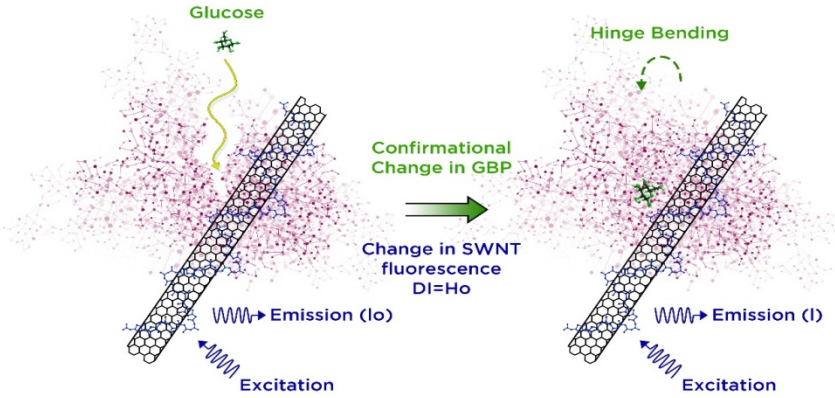

Figure 9. Glucose sensor: using GBP to mechanically actuate a fluorescent SWNT, resulting in reversible exciton quenching in response to glucose [52].

3.2 Nanowire and nanorod based biosensors

Nanowires and nanorods are classed as 1D nanostructures in a similar manner to carbon nanotubes and can be synthesized from metallic or semiconducting materials. In particular nanowires and nanorods are very similar, and during most synthesis produced together. In general, 1-D nanostructures, such as nanowires can be used for both efficient transport of electrons and optical excitation with minor perturbations strongly influencing their electrical properties [53-55]. In particular especially in uses such as MOSFETs they have the advantage that binding to a 1-D nanowire leads to depletion or accumulation in the 'bulk' of the nanowire as opposed to only the surface in the 2-D thin film case. There have been a number of studies on nanowire surface functionalization. Cui Y. et al, 2001 [56] used non-covalent affinity to immobilize peptic nucleic acid (PNA) on silicon nanowires [57], while in segmented nanostructures, it is possible to achieve selective functionalization along the nanowire length. For example, on Au/Pt/Au nanowire, based on the differential reactivity of Pt and Au towards thiols and isocyanides [58]. In this case a butaneisonitrile monolayer on the Au /Pt/Au wire surface is replaced by a SAM of 2-mercaptoethylamine (MEA) only on Au, and not on Pt. In this case the MEA-bearing gold portion of the nanowires can be tagged with a fluorescent indicator molecule to image the spatially localized SAMs along the length of the nanowires.

Nanowires are readily applicable in field effect transistor biosensors (FET) which is a very promising area of biosensing especially as large arrays of such nanobiosensors could lead to broad biomarkers screening. The "sensing element" of a Field Effect Transistor (FET) in this case is a *nanowire or could be a carbon nanotube.* Once the nanowire-based transistor has been coated with a specific recognition group, the device is ready to function as a nanobiosensor. In Figure 10 below a FET nanobiosensor was fabricated using a single indium oxide nanowire and functionalized in order to detect the presence of PSA, i.e. a prostatic specific antigen, which is a marker for prostate cancer [59,60].

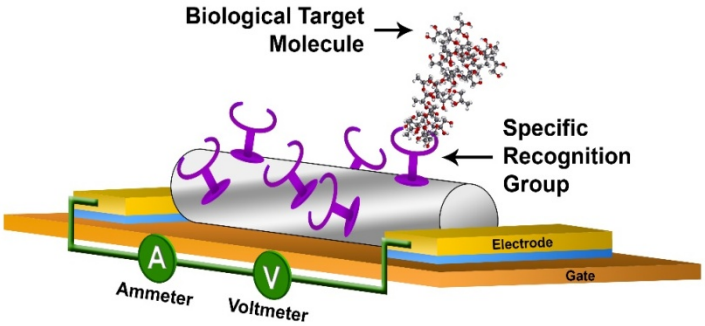

Figure 10. A schematic representation of a FET nanowire biosensor

In the presence of a physiological solution, but in the absence of the target molecule, a voltage was applied between the transistor's source and drain with the resulting current registered as the baseline signal. The target molecules are usually charged molecules in an aqueous media acting as a chemical gate for the transistor and modifying its electrical properties. Once the target molecule interacts with the surface of the nanowire the current flowing through the nanowire either decreases or increases, depending on the type of charge injected. In general, ideal conditions for immunoFET sensors include good antibody coverage and highly charged antigens, capacitive interface and low ionic strength buffers. However, in real conditions issues in sensitivity and performance can arise due to rich levels of salts and species of non-interest.

Multianalyte biosensing has also been explored in the context of photonic crystal fibers coated (PCF) or infiltrated with gold or silver metallic nanowires. Luan et al, 2014 [61] introduced a 6-hole *photonic crystal fiber with a silver nanowire for temperature sensing*. The photonic crystal fiber holes were filled with a liquid mixture displaying a high thermo-optic coefficient, i.e. ethanol and chloroform. In the presence of temperature variations, the refractive index of the mixture was altered shifting the resonance peaks of the silver nanowires. The measurement of the peak shift could detect temperature changes.

3.3 Nanoparticle Biosensing

One of the most common method in detection and quantification of biomolecules remains fluorescence with colloidal luminescent semiconductor nanocrystals, i.e. quantum dots (QDs) presenting unique opportunities due to the advantages they present compared to conventional organic based fluorophores, such as rhodamine 6G and fluorescein [62-63]. In particular quantum dots have a broader excitation and sharply defined emission peak. Additionally, they are brighter compared to organic dyes by almost 20 times, as well as exhibiting a higher signal to noise ratio. Furthermore, as quantum dots are inorganic they are resistant to photobleaching as well as metabolic degradation.

Below in Figure 11 the main routes of conjugating biomolecules to quantum dots are schematically represented:

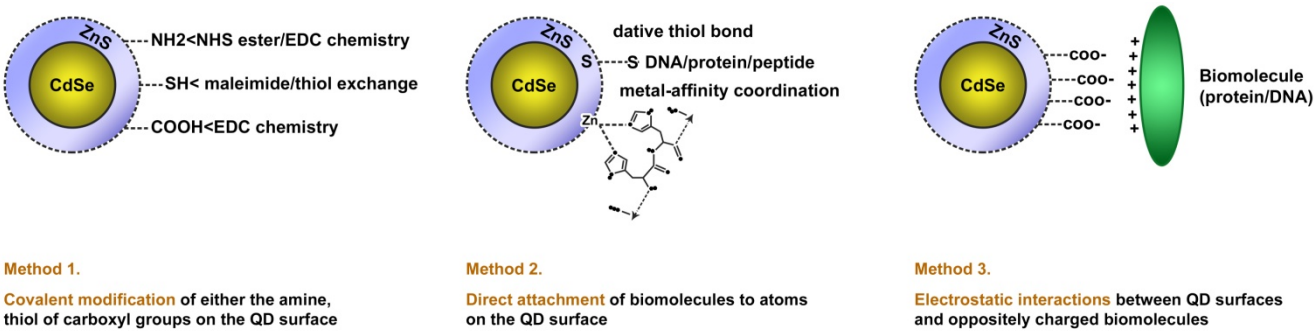

Figure 11. Methods of Conjugating Biomolecules to QDs [64]

Apart from quantum dots the unique spectral and optical properties of noble metal nanoparticles combined with ease in surface functionalization have encouraged their use in various biosensing platforms. Below in Table 3 various types of conjugations between biomolecules and noble metal NP's can be seen:

Table 3. Types of conjugations between biomolecules and noble metal NP's [65]

Type of conjugation	Pros	Cons
Electrostatic interactions e.g. adsorption of negative charged DNA to positive charged gold NP	- Very simple and straightforward to perform	-restricted to opposite charged biomolecules and NPs -very sensitive to environmental properties, eg. PH ionic strength etc - weak functionalization
Chemisorption e.g. quasi-covalent binding of thiol functionalized biomolecule to gold NP	-Allows oriented functionalization -Very robust functionalization	-requires NPs with capping agents with weaker adsorption than the derivatization moiety -usually requires modification of the biomolecule -subject to interference by other chemical groups available for adsorption within the biomolecule -affected by chemical degradation and surface oxidation of some NPs eg. silver
Affinity based Eg. His-tag protein binding to Ni-NTA derivatised gold NP	-Allows oriented functionalization -Very straightforward binding between affinity pairs	-Requires modification of both NPs and biomolecules with an affinity pair -Limited to availability of suitable binding affinity pairs

The unique physicochemical properties of the *noble metal NPs*, such as Localized Surface Plasmon Resonance LSPR, fluorescence enhancement/quenching and surface-enhanced Raman scattering (SERS) have led to a number of highly sensitive optical biosensing methods. As a result of LSPR noble NP's are good candidates for colorimetric biosensing considering the color changes generated by the plasmon coupling between NPs upon aggregation, while other methods have used the LSPR properties of the noble metal NPs just as a colorful reporter (*i.e.*, making use of their superb scattering and/or absorbance properties).

Recently a colorimetric Au-enzyme nanoparticle-based biosensor was developed in a strip of filter paper [66], with a color change from yellow to red in about 10 minutes as a result of the bacterial level detection. In this case cationic gold nanoparticles (NPs) featuring quaternary amine headgroups are electrostatically bound to an enzyme (β-galactosidase) inhibiting its activity. Once the analyte bacteria which in this case was *E.coli* bind to the NP the (β-Gal) is released restoring its activity and providing an enzyme-amplified colorimetric readout of the binding event.

Magnetic nanoparticles can also be used in biosensing as magneto resistive sensors, utilizing the property of materials to change the value of their electrical resistance when external magnetic fields are applied. In particular Srinivasan et al, 2009 [67] introduced a highly sensitive giant-magnetoresistive chip that can detect stray magnetic fields from magnetic labels on the sensor surface. In this case it was used along with FeCo nanoparticles to linearly detect 600–4500 copies of streptavidin. The particular system also has the ability to detect human IL-6 with a sensitivity 13-times higher than that of standard ELISA techniques (Figure 12)

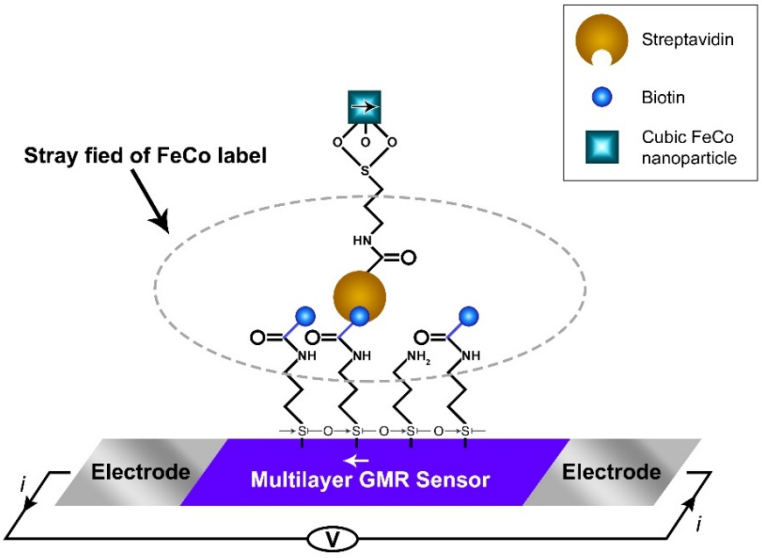

Figure 12. A highly sensitive giant-magnetoresistive chip and FeCo nanoparticles used to linearly detect 600–4500 copies of streptavidin [67]

Additionally, *magnetic nanoparticles* have also been used in biosensing based on magnetic resonance effects using diagnostic magnetic resonance (DMR). In particular DMR uses magnetic nanoparticles as proximity sensors that modulate the spin-spin relaxation time of neighboring water molecules, which can be quantified using clinical MRI scanners or benchtop nuclear magnetic resonance (NMR) relaxometers. Using DMR technology a wide range of targets including DNA/mRNA, proteins, enzymes, drugs, pathogens, and tumor cells can be detected. Moreover, the development of highly sensitive chip-based NMR (microNMR) detector systems has allowed for measurements on microliter sample volumes and in multiplexed format [68].

Furthermore, a novel implanted nanobiosensor consisting of polyethylene glycol (PEG) nanobeads has also been developed for the continuous monitoring of glycose levels of patients [69]. The sensor changes its fluorescent properties with glucose concentration, allowing its' optical detection without blood draws. The process employed in this case is FRET, i.e. fluorescence resonance energy transfer, a useful technique utilized frequently in studying molecular interactions inside cells involving two proteins at a distance of less than 10nm apart tagged with different fluorophores often referred to as the *donor* and the *acceptor*. FRET can be detected by the appearance of fluorescence of the acceptor or by quenching of the donor's fluorescence as a result of energy transfer between them. In general, the donor and the acceptor are autofluorescent proteins, called GFPs, with carefully selected spectroscopic properties such that there is both an overlap (>30%) between the emission spectrum of the donor and the excitation spectrum of the acceptor to obtain efficient energy transfer, as well as a

reasonable separation in emission spectra between donor and acceptor to allow for independent fluorescence measurements of each fluorophore. In the sensor described above two molecular compounds- dextran, a carbohydrate derivative and concanavalin (conA) a plant lectin that has (4) binding sites for glucose are encapsulated in polyethylene glycol (PEG) where they bind to each other. The nanobeads, which are tissue compatible, are injected just under the skin and remain in the interstitial fluid that surrounds the tissue cells. The glucose levels of the interstitial fluid are comparable to the ones in blood and once the glucose enters the picture it competes with dextran displacing it (Figure 13). Now if conA is covalently labelled with allophycocyanin (APC) as a fluorescent donor and dextran with malachite green (MG) as the acceptor then upon displacement of dextran by glucose the distance between acceptor and donor increases and the fluorescence resonance energy transfer (FRET) signal is lowered as can be seen in Figure 13 [70-72]. Fluorescence levels could be measured using a device, such as a watch, that could also give users a readout of their glucose level.

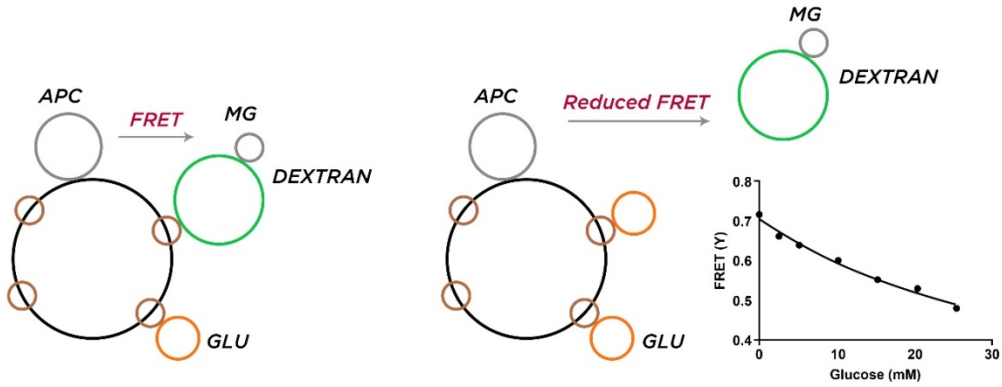

Figure 13. A FRET based assay for glucose using ConA [70]

Conclusions

Biosensing has been around for since the 1950's and saw great advances during between the 1960's and 90's where a plethora of biosensing devices based on electrochemical, optical, piezoelectric and calorimetric transducers became a reality. Since the advancement of nanotechnology there has been a significant shift in miniaturization of devices as well as creating ultrasensitive devices that can perform an array of biosensing measurements. Additionally, there is a need for robust portable, disposable and inexpensive biosensing platforms for health monitoring, which is especially appealing in countries with limited resources. Potentially the future of diagnostics could be based on non-invasive wearable sensors with wireless capabilities providing continuously human health monitoring as well finding considerable use in sports and military applications.

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