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# Manufacture of modern electrochemical sensors based on organic and inorganic nanoparticles and decorated with multi-walled carbon nanopipes

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***Abstract:*** *One of the reasons for the rapid development of electrochemical sensors for nanomaterials is because of the rapid international development and manufacture, a variety of dangerous chemicals are currently being released into the atmosphere in terms of Airborne, water, and solid waste. Thus, a sensitive, robust, and cost-effective sensor network Make very important pollutants from the atmosphere. Significant progress has been made ineffective electrochemical sensors and biosensors platforms for environmental-based applications of nanomaterials. The current review assesses recent trends in developing an electrochemical sensor platform based on the latest nanomaterials such as metallic nanoparticles, metal oxide nanomaterials, carbon nanomaterials, polymers, and biomaterials. Special synthetic methods, properties, integration techniques, specific sensor applications and development prospects for advanced sensor platforms from these nanostructured materials were also highlighted. The great development of nanomaterial-based electrochemical sensor platforms is driving new momentum to develop new technologies to ensure human health and the environment in days gone by nanotechnology has played a crucial role in upgrade biometric sensors. The sensitivity, accuracy, and reproducibility of the biometric sensors have improved greatly due to the incorporation of nanomaterials into their design. In general, nanomaterial-based electrochemical immune sensors improve sensitivity by allowing wider activation with broader surface recognition molecules for biological recognition as well as enhancing the electrochemical properties of the transformer.*

***Keywords:*** *Electrochemical sensor, functionalized multi-walled carbon nanopipes, nanomaterials of organic and inorganic materials, biomaterials, ions of organic and inorganic heavy metals, modified electrode, electrochemical sensors, Graphene, voltammetry.*

## I. Introduction

Since the discovery of carbon nanotubes (CNTs) by Iijima in1991, researches on CNTs have created an active field covering their synthesis and purification, physical/chemical properties and potential applications [1, 2]. As a new allotrope of carbon, CNTs are mainly classified into two types: single-wall carbon nanotubes (SWCNTs) and multi-wall carbon nanotubes (MWCNTs), which are cylindrical tubes of $sp^2$ carbon,

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conceptualized by seamlessly rolling up single- or multi-layered Graphene, respectively, Sensors are instruments that register, and transform, a physical, chemical or biological change into an observable signal. The sensor contains a recognition feature allowing selective response to a particular analyte or group of analytes, thereby minimizing interference from other sample components (Fig. 1) [3, 4].

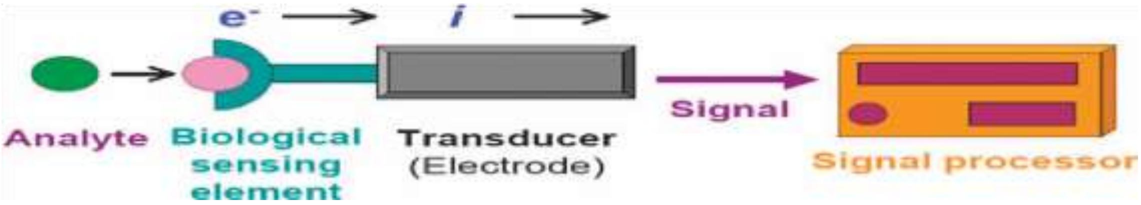


Fig. 1. A schematic of a biosensor with an electrochemical transducer.

Another key component of a sensor is the transducer or the signal-producing detector. A signal processor collects, amplifies, and displays the signal. Electrochemical biosensors, a subset of chemical sensors, combine the sensitivity of the electrochemical transducers with the high ones as shown by low detection limits specificity of biological recognition processes. These instruments are biological electrochemical biosensor can Are split into two major groups according to the essence of the phase of biological recognition i.e. Affinity sensors rely on a selective binding interaction between the analyte and a biological component such as an antibody, the combination of reconnaissance elements with electronic elements to build electrochemical sensors and biosensors has been given considerable attention. Various electrochemical devices, such as aerometric sensors, electrochemical impedance sensors[5]. Significantly, comprehensive work on the design of practical electrode materials, combined with various electrochemical methods, is advancing the wide use of electrochemical instruments. Such as (Walcarius et al). Highlighted the recent developments in the logical design of biofunctionalized electrodes and associated (bio)sensing systems of nano-objects and nanoengineered and/or nanostructured materials [6].

The development of analytical methods based on nanomaterials has attracted rising attention for various applications in recent years; including basic biological research, health monitoring, clinical diagnostics, pharmaceutical analysis, food safety. And its outstanding physicochemical properties, the large proportion between surface and volume, high adsorption and reactive capacity and other beneficial properties that are not present in bulk materials, nanomaterials have served as analytical possibilities probe for not only offering enhanced sensitivity but also providing a change in stairs for the study of the single molecular realm [7]. Our group's general overview recently introduced paper-based nanomaterial-enhanced biosensors such as lateral-flow test strips and microfluidic paper devices. The biosensor in paper systems exhibited tremendous potential for different forms of Nanoparticles (NPs) in enhancing sensitivity and specificity to the Diagnosis of disease in developed countries [8]. In a world where technical developments require detailed information about various categories [9, 10], sensors are becoming increasingly relevant now. They have been widely applied in fields such as industrial manufacturing, aerospace, ocean exploring, environmental protection, resources investigation, medical diagnosis, and bioengineering [11-14]. Recent developments in new materials have opened up a new age of analytical techniques, particularly the production of nano- and bio-materials. In particular, due to their specific electronic, physical, chemical and mechanical properties, the broad applications of nano- and biomaterials in electrochemistry have been explored. [15]. Normally electrochemical detection is performed with a three-electrode device comprising a working electrode (WE), a reference electrode (RE), and a count electrode (CE) (Fig.2). The WE can be changed to particular metal ion detection or/and concentration with different materials[16, 17].

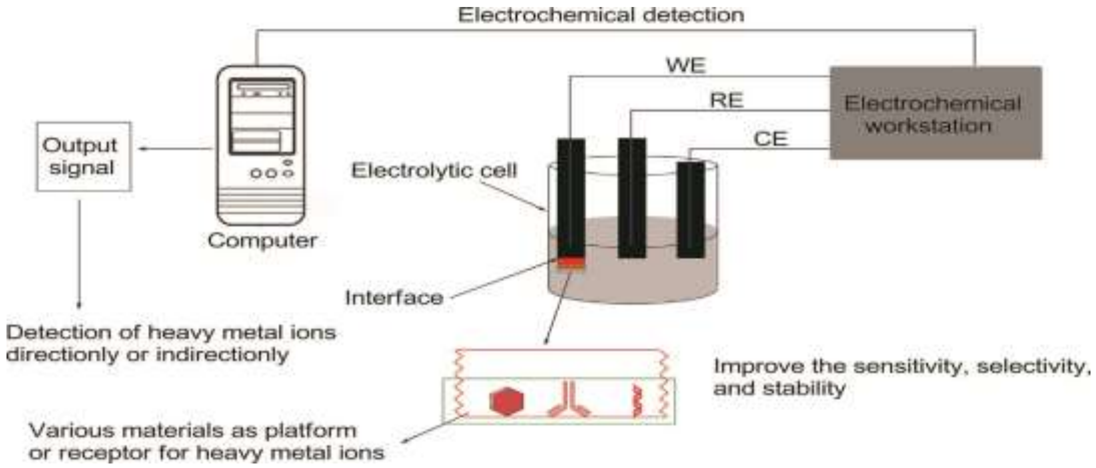


Fig. 2. Schematic illustration of the general principle of electrochemical sensing of heavy metal ions.

## II. Chemicals

Multi-walled carbon nanotubes with >95% purity, 20–30 nm outer diameter and 5–10 nm inner diameter were purchased from US research nanomaterials (USA). All chemicals were of analytical grade and used without further purification. Deionized water was used for preparation of solutions throughout the work. The working solutions were prepared by diluting of this solution with phosphate buffer (PBS) to the desired concentrations.

### 2.1. Electrochemical detection

Many biosensors use the transducer's electrochemical detection due to the low cost, ease of use, portability and simplicity of construction [4, 5]. The reaction is controlled electrochemically produces a measurable current (amperometry), an accumulation or potential of measurable charge (potentiometry), or changes Medium conductive properties (conductometry) between electrodes. It also getting more popular to use electrochemical impedance spectroscopy by measuring both the resistance and reaction in the biosensor[13]. In general, electrochemical techniques are grouped into three major measurement categories: current, potential, and impedance. This article focuses on those techniques which measure current since they are the most commonly used in biosensors. The detection step is one of the biggest challenges of transferring well studied chemical reactions from the macroscopic scale to the micro- and nanoscale. These methods may also require a fair amount of the sample and may give false positive or negative results due to coloured, turbid, and complex sample matrices. Also, the interferences from other sample components are easier to eliminate in electrochemical methods, for example by carefully choosing the detection potential in amperometry, and the detection can be done in complex coloured or turbid samples and can be used in homogeneous immunoassays that are typical in the clinical analysis[18].

### 2.2 Voltammetry/amperometry

Voltammetry and amperometric techniques are characterized by applying and calculating the current Potential for an Electrode working (or indicator) versus a reference electrode. The current is the result of electrolysis at the electrode in use using electrochemical declines or oxidations cycle. The current of electrolysis is constrained by the rate of mass transfer of molecules towards the electrode. The term voltammetry is used for those techniques where the potential is checked over a given range of potential. Typically, the current response is a peak or trough Ratio with any concentration of an analyte. Voltammetric methods include linear sweep voltammetry, cyclic voltammetry, hydrodynamic voltammetry, differential pulse voltametry, square-wave voltammetry, ac voltammetry, polarography, and voltammetry stripping. These methods have a vast range of dynamics available and are useful for quantitation at low levels [19].

### 2.3. Devices

Voltmetric measurements were performed using µ-Autolab TYPE III potentiostat / galvanostat (Netherlands). A wire of organic and inorganic materials was used as electrodes, countermeasures, reference and working, respectively. The pH scale (Metro, Form 827) with a glass electrode (Corning) was used to control the pH of the solutions. Morphological characterization of modified electrodes was performed using an electronic scanning microscope (LEO 1450 VP, Germany).

### 2.4. Preparation of the modified electrode

At first, in order to increase the edge sites and better dispersion of the carbon nanotubes, the multi-walled carbon nanotubes were functionalized under concentrated nitric acid treatment process[20]. 0.3 g of crude MWCNTs was added in to 50 mL nitric acid and homogenized by ultrasonication. The resulting mixture was refluxed at 120 °C under stirring for 24 h. After cooling to room temperature, it was filtered and washed with deionized water ultrasonicated in water and ethanol for 2 min, respectively. After that, the electrode surface was cleaned through immersing it in piranha solution (1:3 mixture of 30% $H_2O_2$ and concentrated $H_2SO_4$) and then washed with water. For preparation of f-MWCNTs suspension, 1.0 mg of f-MWCNTs was dispersed in 1.0 mL of dimethylformamide (DMF) solvent under sonication for 15 min. Then, 7 µL of this suspension was dropped directly on the electrode surface by a micropipette and the solvent was evaporated under an infrared lamp. Successively until the pH of the filtrate solution was reached to 7.0 and then dried under vacuum. Then, the gold electrode surface was polished with a slurry of alumina and then.

### 2.5. Graphene

Graphene is another material that offers great prospects for the future of analytical chemistry, consisting of a one-atom-thick sheet of $sp^2$ hybridized carbon atom composed of six-member rings that provide a surface area that is nearly twice as large as that of SWCNT. This material has high mechanical strength, high elasticity and high thermal conductivity but also has a significant disadvantage: its low aqueous medium dispersion[21]. Stable dispersions of graphene sheets were achieved using, among other things, amphiphilic polymers, alkylamines, and hydrophilic carboxyl groups as dispersing agents[22]. Graphene functionalization is regarded as an essential route to increase its dispersion. Many scientists have therefore attempted to manufacture graphene oxide, a graphite derivative covalently attached to its layers with hydroxyl, epoxy, and carboxyl groups, with a stronger dispersion in certain solvents. Graphene can be interlinked with CNT for the manufacture of transparent high-performance electrodes, and the resulting films pose features comparable to indium tin oxide[23]. Crystalline graphene 's electrochemical behaviour is distinct from that of the reduced graphene oxide flakes[24]. A large variety of graphene processing methods, first published in 2004[25], are available and consist of Mechanical exfoliation (repeated peeling) of highly concentrated small patches ordered pyrolytic graphite. Many other manufacturing Methods were developed including the removal of MWCNT to form ribbons of graphins [26], with nuclease for interferon-gamma further improving the technique, resulting in a LOD of 0.065 pM [27]. Other authors [28], Graphene oxide Nanoplatelets (GONPs) used as electroactive markers for the identification of thrombins. Graphene was used in various biosensor fields, especially for electrochemical sensing platforms. Graphene has the same physicochemical intrinsic properties as graphite and CNT, including large surface area and numerous functional locations. As seen in Table 1, this is superior to other carbon based goods Nanomaterials based on the following physicochemical characteristics: exceptional electron transfer; Improved thermal, mechanical and biocompatible conductivity[29].

Table 1 Summary of representative carbon-based nanomaterials used in electrode and label of electrochemical biosensor

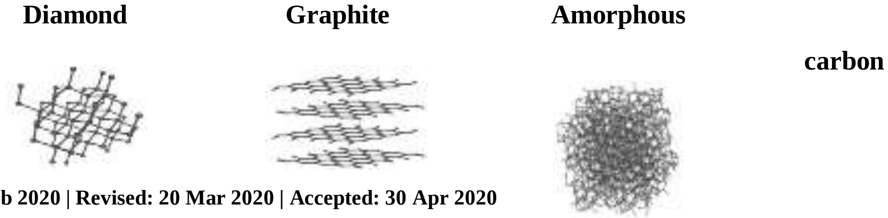
| Materials | Advantage | Limitations | Feature | Limit of detection | ef. |
|---|---|---|---|---|---|
| SWCNT | Large surface area to volume ratio (S/V)<br>Low charge-carried density<br>Delocalized π-orbitals Electrical conductivity improvements | Limited surface to interface with large biological components Nonspecific adsorption of protein Difficult manipulation during the sensor fabrication process<br>Difficult chemical functionalization | Electrode | DeoxyriboNucleic acid (DNA) 71 pM | 30] |
| | | | Electrode | Glucose 7.06 μA/mM | [31] |
| | | | Electrode | aflatoxin B1 (AFB1) 0.01 nM | 32] |
| | | | Electrode | Anti-IgG 0.2 pM | 33] |
| MWCNT | Excellent conducting and electrocatalytic properties | Need to functionalize surface for increasing biocompatibility Irreversible agglomerates in aqueous solution | Electrode | Carcinoembryonic antigen (CEA) 0.0055 FM | 34] |
| | | | Electrode | Transforming growth factor beta 1 (TGF-β1) 0.05 pM | [35] |
| | | | Electrode | Prostate specific antigen (PSA) 0.11 fM | 36] |
| | | | Electrode | Mouse IgG 0.066 pM | 37] |
| | | | Label | PSA 0.13 pM | 38] |

| | | | | | |
|---|---|---|---|---|---|
| Graphene | High S/V<br>Large active sites<br>Fast electron transfer<br>High thermal conductivity<br>Better mechanical flexibility<br>Good biocompatibility | Hard to dissolve in water | Electrode | dibutyl phthalate (DBP) 0.025 μM | 39] |
| | | | Electrode | PSA 0.33 pM | 40] |
| | | | Electrode | Cystatin C 0.002 nM | 41] |
| | | | Label | Cry1C 0.02 pM | 42] |
| | | | Label | CEA 0.003 pM | 43] |

## III. Carbon-based nanomaterials

Carbon nanomaterials deliver specific advantages spanning many domains, Requires a high volume to surface ratio, High electrical conductivity, chemical stability, mechanical strength and biocompatibility [44]. Therefore, they are also integrated as components of sensation. Sensors based on carbon nanomaterials are generally more sensitive and have lower detection limits than their conventional counterparts. The morphologies of carbon-based nanomaterials constitute an additional critical factor that enables their functionality and stable operation in the design of efficient electrochemical sensors; all of which impart influences on their electron transport kinetics [45]. Biosensors based on carbon nanotubes supply a major biomolecular detection avenue for both in vivo and in vitro Application performance [46]. Electrochemical biosensors that integrate enzymes into nanomaterials (which combine enzyme recognition and catalytic properties with the electronic properties of different nanomaterials) have novel constructions with synergistic properties that derive from hybrid composite components. Graphene, as a truly two-dimensional material, has received increasing attention Because of its special look physicochemical properties and has attracted considerable scientific and technological interest in recent years [47, 48].

A comprehensive overview of the fundamental concepts related to graphene electrochemistry has been conducted recently by Banks and co-workers, thus the potential biomedical applications of graphene-based electrochemical sensors are not covered in this review. In the following sections, we provide a broad snapshot of the applications of several carbons based nanomaterials in the development of electrochemical sensors, to conduct a critical evaluation of their characteristics and performance [49]. The carbon nanomaterials (Figure 3) cover a broad range of structures, beginning with zero-dimensional structures (fullerenes, diamond clusters), continuing with single-dimensional (nanotubes), two-dimensional (graphene), and three-dimensional structures (nanocrystalline diamond, fullerite).



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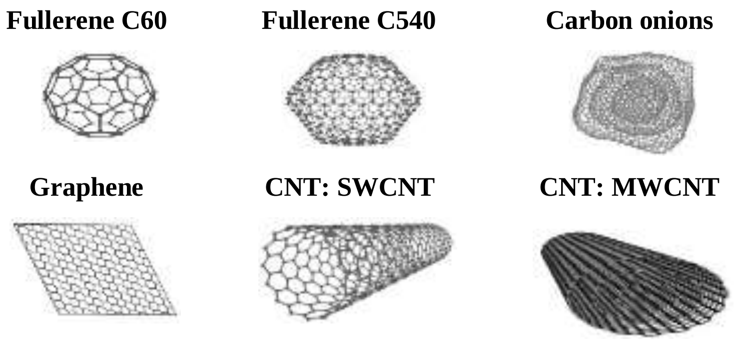

**Figure .3.** Main carbon entities at the nanoscale level

### 3.1. Single-walled carbon nanotubes

Carbon nanotubes (SWNTs), single-walled, consisting of single graphene sheets that are seamlessly wrapped into cylindrical tubes with diameters of between 0.4 and 2.5 nm, offer excellent physical and chemical properties that enable a wide collection of biomedical applications. Their high electrical conductivity in conjunction with diminutive size makes them suitable as individual nanoelectrodes; many studies have shown that SWNTs can efficiently promote electron-transfer reactions. This capability avoids the requirement of expensive electronic devices and is likely to improve The noise-signal ratio, leading to ultrasensitive electrochemical sensors for the detection of chemical and biological analytes. Here, we briefly outline some recent advances in SWNT based electrochemical sensors. The distinctive physical and chemical features of SWNTs Have paved the route to new and improved sensing devices in general and electrochemical sensors in particular. Functionalized carbon nanotubes exhibit unique properties that may facilitate a variety of clinical applications Infectious for cancer diagnosis and treatment diseases, central nervous system disorders and enable applications in tissue engineering [50]. The therapeutic efficacy of these potential applications may be further enhanced as they also can penetrate biological membranes for uptake by cells and are relatively non-toxic. Diabetes is a collection of metabolic diseases that affects B150 million people worldwide; it is one of the leading causes of death and disabilities such as blindness, nerve degeneration and kidney failure. Diabetic patients diagnosed and treated need careful monitoring and regulation of the body's glucose levels. The repeated monitoring of physiological glucose levels is therefore important to confirm the efficacy of the procedure, preventing long-term complications and preventing diabetes emergencies, such as hypoglycaemia (low blood sugar, 3 mM) [51].

### 3.2. Multi-walled carbon nanotubes

Multi-walled carbon nanotubes (MWNTs) are comprised of multiply-nested graphene sheets, having variable diameters of up to 100 nm. The lengths of these nanotubes can range from a few nanometers to several micrometres. With chemically modifiable surfaces that possess large surface areas, unique physical properties and tunable lengths, MWNTs are strong candidates for biomedical applications. These were used to build electrochemical DNA sensors use cyclic voltameter for identification of calf thymus DNA molecules. The detection of genomic DNA sequences and the identification of mutations are vital in the treatment of inheritable and infectious diseases. Carbon nanotube-based DNA sensors have been well covered in recent reviews; therefore, the focus here will be on the general characteristics of these sensors. They can be produced by loosening single-stranded DNA (ssDNA) onto an electrode, enabling the hybridization of complementary DNA sequences to be detected via a change in the current [52].

### 3.3. Nanomaterials involved in biosensor construction

Advances In nanotechnology this has contributed to the recent development of many nanomaterials, including carbon nanomaterials, magnetic and metallic nanoparticles [53]. Nanomaterials, commonly described as feature-size materials of less get an impressive 100 nm, the effect on different applications Because of its assets, (increased Electrical conductivity, tensile strength and chemical reactivity) imparted by its decreased Surface area by mass per unit. Nanomaterials have already been used in devices such as batteries, food, cosmetics, telecommunications, drug production, and sensing.

The use of nanomaterials, in particular nanoparticles and nanostructured films, provides advantageous properties that can be exploited to optimize interactions with different bioelements, preserve their activity, reduce structural changes and improve Catalytic process. An emerging trend which spans many disciplines is the analytical exploitation of these protein-nanomaterial interactions in the biosensor field[54]. Metal-based nanomaterials, semiconductors and organic compounds contribute to the enhancement of the optical, electrical, chemical and magnetic properties related to sensing devices and, because of these details, have been frequently used in this research field[55, 56]. Nanomaterials are used mainly for the construction or modification of electrodes and as tracers of biomolecules. Nanoparticles (NPs) are very stable (as opposed to enzyme labels), providing high sensitivity (thousands of atoms can be released from one nanoparticle), and a wide variety is available on the market. Nanoparticles are used nowadays as electrochemical labels or as vehicles containing several hundred or thousands of electroactive labels, pushing detection limits down to several hundreds of biomolecules. Various nanomaterials Were commonly employed for bioelement immobilization, For example, metal nanoparticles, carbon or copper nanotubes; Magnetic beads lined with nanosilver, magnetic particles, functionalized conductive polymers, etc. [57].

### Sensors’ Design

The design of the sensors influences the reliability of the analytical information. Matrix composition and the ratio between electroactive materials used as matrix modifier influence the response characteristics of the electrode. Electroactive material has an essential role in the electrode response; therefore, it will be attentive to choose according to selectivity, sensitivity, and detection limit. Another issue that must be considered in the construction of the sensors is the biocompatibility of the materials used for sensors’ design[58]. Characteristics of the electrode can be adjusted by the appropriate designs and architectures. New nanostructured materials were designed and used as a modifier on different substrates like carbon or metal substrates. Carbon materials such as nanotubes and graphene, nanoparticles, and nanowires, and also conducting polymers engineered as nanowires, have been synthesized, characterized, and applied for the design of sensors. The use of nanomaterials increased the current intensity by increasing the active surface area concerning a flat substrate where the sensor reaction can occur [59]. Solid-state electrodes based on noble metals and different forms of carbon have been used intensively in the past years. The Coal, Platinum, Gold, Nickel, Silver-based Electrodes and copper were used for many applications due to their characteristics like Potential flexibility, low background current, low cost, and chemical inertness. Chemically modified electrodes represent a modern approach in sensors' technology. Modification of the sensor surface is achieved with Utilizing a suitable surface modificator. Chemical alteration of the active sensor surface; it can boost the sensor characteristics. The interest for modified surfaces of sensors is motivated especially by the increase of selectivity and sensitivity for many potential applications.

There is significant progress in the synthesis and characterization of nanostructured materials using surface characterization techniques which helped the evolution of the design and surface characterization of sensors. Special properties of carbon nanotubes (CNTs) modified with functional groups improved the properties of CNT and made possible its application in high-tech sensors' design[60, 61]. The sensors based on nanotube include also metal oxide-based tubes such as Co3O4, $Fe_2O_3$, $SnO_2$, and $TiO_2$ and metal tubes such as Pt nanosensor. The sensors based on nanomaterials present improved sensitivity and selectivity, fast response, high recovery, and potential for integration in arrays on a massive scale. All these properties represent an improvement from classics sensors. These advantages are helping the detection of biomolecules at a molecule level[62].

### Types of Sensors

Electrochemical sensors had fast progress in the term of electroactive materials, matrix materials, and size [63, 64]. Compared to the other instruments, electrochemical sensors are attractive due to screening capabilities, easy and reliable design, short time of analysis, and low cost. They are leaders among the other types of sensors. Many of them reached the commercial process and found A broad choice of essential health applications, manufacturing and food sectors, and research on biomedicine[65]. Recent developments in nanomaterials used for the design of chemically modified sensors have opened new fields of applications such as Whole blood screening early detection of diseases. The response of them converts chemical information in analytical signals and the chemical information can come from a chemical reaction of the target analyte or a physical property of the system investigated [66]. Optical sensors based on nanomaterials progressed due to utilization of nanomaterials in their design.

## IV. Inorganic and organic nanoparticles

Major environmental, pharmaceutical and biomedical nanoparticles include magnetic nanoparticles, quantum dots, metal nanoparticles, silica nanoparticles and polymeric types with intrinsic properties which contribute to their use in specific applications. Usually, nanoparticles are categorized into Magnetic nanoparticles (taking hold of a center of Fe3O4) Commonly used in the distribution of medications and most recently in immunosensing; semiconductor/QDs (CdS-Based, CdSe)used in bio- and immunosensing; metal nanoparticles (Ag, Au, Pd) used in biosensing and drug delivery; polymeric nanoparticles (polystyrene) primarily used in drug and gene delivery; hybrid nanoparticles [67].

### 4.1. Organic functionalization

Numerous researches on organic functionalization of CNTs (the edges or ends) with chemical groups that enable the binding of CNTs to other units or surfaces have been reported. Oxygen functional groups, small organic molecules, polymers and biomolecules (primarily including DNA, proteins and enzymes) are also used for organic modification of CNTs.In the following section, the electrochemical behaviours of organic functionalized CNTs are discussed based on their modifiers.

### 4.2. Inorganic functionalization

Similar to organic modification, inorganic nanomaterial functionalized CNTs have also received great attention. Generally, two kinds of inorganic nanomaterials have been employed to modify CNTs. One is noble metal nanoparticles, including Au, Ag, Pt, Pd, etc. The other is metal oxide nanostructures such as ZnO, CuO, SnO2 and so on. Besides, many different compounds have also been proposed as electrochemical sensing materials to modify the electrode surfaces for detection. However, owing to the effects of size and dispersion for noble metal particles and poor electrical conductivity for metal oxides, their electrochemical activity has been inhibited. To decrease their particle size and improve electron transport on modified electrode surfaces, CNTs were commonly used as a strong carrier and as conducting pathways. For preparing the hybrid composite of CNTs with Metal and oxide nanoparticles, two main pathways have been addressed. One is that nanoparticles are performed with linkers and are bound to CNTs. Naked nanoparticles are grown and/or deposited directly onto The surface of CNTs in an alternative method. CNTs here most likely play the role of models in tailoring the size of An oxide of metal or metal particles, in addition to serving as supporting material. Inorganic nanoparticles were homogeneously dispersed on the surface of CNTs due to the addition of CNTs, which significantly expanded their active surface area. Furthermore, the unique properties of both components for such a formed hybrid may be integrated and even greatly enhanced. Thus, the hybrid composite of CNTs with inorganic material modified electrochemical electrodes could be expected to present great catalytic activity and sensitivity [68].

### 4.3.Organic-inorganic hybrids functionalization

Besides the above mentioned organic and inorganic functionalization of CNTs, Organic-inorganic hybrid composite functionalized CNTs have also received great attention and been applied to modify electrodes for electrochemical sensors. Up to now, numerous research works have demonstrated that various organic-inorganic hybrid composites, including noble metal or metal oxide nanoparticles incorporated with polymers, metal nanoparticles with proteins or enzymes, etc., Was used to functionalise CNTs. For these composites, synergistic effect arising from organic materials and inorganic materials have also been sufficiently presented for their electrochemical activities. For example, using molecularly imprinted polymer-modified CNTs-gold nanoparticles, a tetracycline sensor has been developed [69]. Here Polymer with molecular imprint offered many recognition sites and CNTs decorated with gold nanoparticles greatly improved the electron transferability on the electrode surface. Through a combination of the above two advantages, this led to Evolution of A highly selective, sensitive person sensor for tetracycline. Furthermore, through immobilizing glucose oxidase on a nanocomposite matrix On electrostatic basis adsorption of negatively charged Au nanoparticles and CNTs with a positively charged poly (diallyldimethylammonium chloride) polymer membrane, a biosensor They were designed for amperometric glucose determination[70]. Recently, Wang and colleagues proposed Electrochemical novel immunosensor Assessment of the casein-based on gold nanoparticles and composite poly(L-arginine)-MWCNTs [71]. The above examples highlight the potential application of noble metal nanoparticles incorporated with polymer-modified CNTs in electrochemical sensors. And for proteins or enzymes combining with metal nanoparticle functionalized CNTs, they could be also employed as electrochemical sensing materials.

### 4.4.Nanomaterials Applied for Nanosensors

For chemiresistive sensing applications, nanostructures from silicon, silicon oxide Get, graphene, carbon nanotubes recently been extensively explored. The size is small and the high volume-to-volume ratio of nanomaterials have multiple sensing advantages for more than the conventional bulk films. Sensors made from metal nanoparticles have strong potential by increasing Sensitivity both and selectivity by tuned amplification of the signal. Metal nanoparticles, biofunctionalized nanoparticles, and nanocomposites architecture have attracted nanosensor-focused work. Numerous advanced analytical methods have been developed for use in environmental control and food safety[72]. Noble metals with excellent corrosion and oxidation resistance even at high Temperatures include VIIb, VIII and 1b metals of the second and third transitions sequence From periodic table i.e. rhodium (Rh), ruthenium (Ru), palladium (Pd), silver (Ag), osmium(Os), iridium (Ir), platinum (Pt), and gold (Au) [73].

## V. The Advantages of Using Nanomaterials

Due to their advantages: rapidity, usability, and low-cost electrochemical sensors based on nanomaterials have been used very much in chemical analysis over the last years [74]. Utilization of nanomaterials and nanosensors improved the response characteristics of the sensors due to the high surface area/volume ratios as well as enhanced optical properties (quantum dot fluorescence, gold nanoparticle quenching[75, 76]. For example, nanoscale materials have a higher mechanical resistance compared with macroscopic samples of the same material. Substructures of the materials about a host of scales influenced the fracture strength and character, ductility/ flexibility, as well as various mechanical modules. Downsizing of the materials used for sensor design influenced the properties of the materials with direct effects on sensor behaviour and reliability. Few examples related to this point are as follows: materials at the nanometer scale have a lower melting point and reduced lattice constant [77, 78]. Nanomaterials may show different elastoplasticity compared with the macro materials [79]. Functionalization of the nanostructured materials is essential in many cases for the design of new sensors and biosensors. Using these materials, new stable and reliable solid-state sensors and biosensors offering compatibility of inorganic materials with the chemical/biological agents were designed for reproducible screening of biological fluids[80]. Many processing methods have been developed for producing bulk nanostructured materials with a size of less than 100 nm[81]. Typical sizes were known at electrochemical interfaces at the nanoscale. Three aspects deserve attention regarding the use of nanoscale materials in the electrochemical field [82]: (Downsizing of microelectrodes, Utilization of materials with pores or surface roughness in the nanometer range, Utilization of materials with Large number of defects caused by crystallized amorphous or non-crystalline materials of extremely small size).

### 5.1. Conducting Materials and Fabrication Methods

Many materials including both organic and inorganic have been used to fabricate CP. The inorganic materials (metal, metal oxide, etc.) provide better electrical signal but are costly, and difficult to process. Besides this, cracks during bending / sintering can lead to these films. By contrast, Organic materials (polymer conductive materials, carbon nanomaterials, etc.) deliver excellent flexibility, low cost, and processability of the solution, but suffer from low conductivity and/or stable in the long term. Perhaps a solution can be achieved by using a composite material to solve those limitations. Siegel et al. used a variety of metals (Al, Zn, Cu, Pb, Ni, Sb, Sn, Ti, Ag, Bi, In, Au, and Pt) to produce electrically conductive pathways on paper and studied its electrical conductivity, mechanical properties, melting point, and cost, etc.[83]. Besides this, organic materials can be utilized to make paper conducting. A variety of techniques (depending on the material behaviour) Was used to deposit conducting materials over the paper. These include dip coating, printing, sputtering, spin-coating, etc. (Figure 4). Most of these Processes allow materials or its models to be performed. Dip coating technique was widely used for fabricate A CP conducted with an ink or sol-gel precursors. In this process, the substrate is submerged and removed [84].

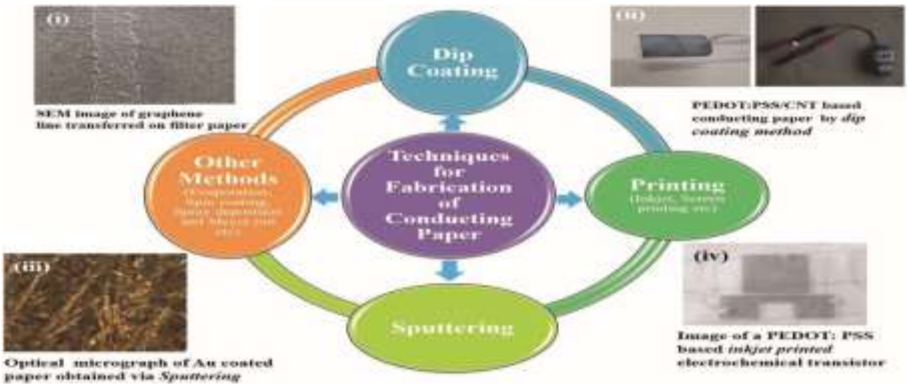

**Figure .4.** Fabrication of CP via different technique. Reproduced with permission. a) Copyright 2016, AIP Publishing. b) Copyright 2017, IOP Publishing. c) Copyright 2013, Wiley-VCH. d) Copyright 2015, RSC Publishing [85, 86].

### 5.2. Conductometric Sensors

Different groups directly studied conductometric immunosensor for the identification of tumor markers[87]. A simple conductometric transducer detects changes in the sample solution's electrical conductivity, or a nanomaterial containing a medium such as nanowires resulting from changes in the solution / medium composition during a chemical reaction[18]. Such detectors are made of an insulating material filled with graphite, gold, stainless steel or other metallic pieces that serve as the sensing elements[88]. The metal contacts are positioned apart from each other a fixed distance to make contact with a sample solution, in which variations in conductivity are calculated as the signal. The change in conductivity is observed in immunosensor with enzyme labels as a result of charged products from enzyme-catalyzed reactions that increase the ionic strength, and ultimately the microenvironment conductivity. Biosensors based on conductometric detection can be very quick, sensitive, have low power demands, low cost, and are compatible with advanced micromachining technology without needing a reference electrode[87]. This detection method is also amenable to miniaturization of the biosensor device as well as automated detection strategies. In addition to biomarkers of clinical interest such as AFP, conductometric immune sensors have been developed for the detection of toxins such as aflatoxin B1[89], viruses such as hepatitis B[90], and foodborne pathogens such as enter hemorrhagic Escherichia O157 coli: H7 and Salmonella spp[91].

### 5.3. Electrochemical characterization of nanoparticle-modified electrodes

#### 5.3.1 Methods

Compared to bulk electrodes, the presence of NPs on the electrode surface allows for strong electron-transfer kinetics, reduces over potential, increases the electroactive surface area and makes kinetically feasible redox reactions. From electrochemical studies of NP-modified electrodes, the amount of NPs deposited on the electrode surface, capacitive charging effects or special underpotential deposition (UPD) effects can be determined. Many NPS's are electrochemically active materials, including Au-NPs and Pt-NPs. Thanks to their unique electronic structures, they possess distinct electrochemical properties. Illustration.2A shows a typical cyclic voltammograms of an Indium oxide to tin (ITO) electrode before and after Pt-NPs were grown onto the surface[92-95]. Due to the simple, well-defined responses, redox models (e.g., the $[Fe(CN)_6]^{-4}/[Fe(CN)_6]^{-3}$ or

$Ru(NH3)_6^{3+}/Ru(NH3)_6^{2+}$couples) have been widely used to characterize the surface properties of different NP modified electrodes (see Fig. 2B). The voltammetry of these two standard redox processes is examined to investigate how the NP-surface coverage and electron-transfer kinetics are compared to unmodified electrodes. The electrochemical properties of NP-modified electrodes significantly depend on their surface properties. In cyclic voltammetry experiments, the peak-to-peak separation and electron-transfer kinetics of NP modified electrodes have been shown to change with the amount of NPS. However, there is an optimal coverage for the amount of NPs on the surface. An excess amount of NPS usually gives no further improvement or increases the resistance and the double-layer capacitance of the modified electrode, leading to a decrease in electrochemical sensitivity[96-98].

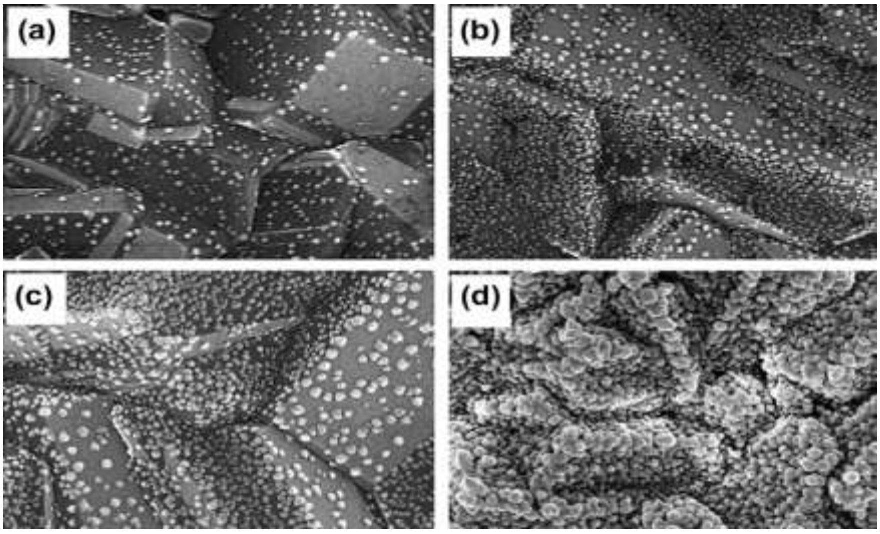

Figure.1.SEM images of a polycrystalline boron-doped diamond (BDD) electrode surface after direct electrochemical Au-NP deposition time of (a) 10 s, (b) 30 s (c) 60 s and (d) 600 s (86) reprinted with permission from Elsevier.

### 5.3.2. Enzymatic sensors

A combination of enzymatic reactions with electrochemical methods allows the development of selective enzyme-based electrochemical biosensors for determination of environmental pollutants. These sensors, although less robust, exhibit good selectivity, sensitivity, rapid response, and have miniature size. In environmental monitoring, enzyme-based or protein-based NP sensors have mostly been prepared for detection of pesticides (e.g., phenolic compounds) or NOx compounds. A major challenge to develop such sensitive and stable sensors comes from the effective immobilization and ‘‘electrical connection’’ of enzymes to solid electrode surfaces. The most promising areas for the use of enzyme electrodes in environmental monitoring are pesticide biosensors. Enzyme electrodes have been investigated as emerging sensors for faster, simpler detection of pesticides. However, their sensitivity is not yet adequate for application in detecting very low concentrations of pesticides. The external supply of substrate is often required to measure the changes in enzyme activity[99].

### 5.3.3. Non-enzymatic sensors

The sensing ability of NPs in non-enzymatic sensors is directly related to their catalytic property. For example, using a seed-mediated growth technique, Cui et al. deposited Au-NPs (mean size 4 nm) on glassy carbon (GC) electrode [99], which showed excellent catalytic activity towards the oxidation of nitrite in a real wastewater sample without any major interference. However, the catalytic properties of NPs depend on the protecting groups or the presence of additives (e.g., cysteine or tannic acid). Controlling NP size, it is possible to change the catalytic activity of NPs so that it becomes sensitive to different oxidation states of one species. For example, controlling the size of Au-NPs allows Cr(VI) to be measured electrochemically in the presence of an excess of Cr(III), offering benefits over the commonly-used diethylenediamine-pentaacetic-acid (DTPA) method. The stability and activity of this electrode depended on the size and the density of the NPS. Larger NPs were shown to cause not only a negative shift in peak potential and lower peak current but also deterioration in the stability due to the blocking electron transfer between solution species and electrode. This sensor was applied to measure Cr(VI) in tap water, stream water, and seawater[100].

## VI. Novel Devices Designed by Top-Down Nanofabrication

### 6.1. Introduction to the Top-Down Approach

The top-down approach is a process where the structure is removed from a larger substance. In particular, in the area of macro-electronics, the top-down approach is more desirable because various materials can be produced by conventional lithographic processes [101, 102] and etching techniques[103-105]. The lateral dimensions of this method can range from tens of nanometers to the millimetre scale. Additionally, freestanding single-crystal sheet types can be created from wafers by employing an embedded release layer to yield flexible systems. Thus, nanostructures are synthesized by etching the layers on a substrate. However, it is impossible to conduct the entire procedure on a flexible substrate, because certain processes, such as the doping process and chemical vapour deposition (CVD), require high temperatures that significantly deform flexible substrates[106]. To resolve this issue, a transfer-printing process and a method of releasing from the rigid substrate are integrated to form flexible electronics[107-114]. Here, various flexible electronic devices that are fabricated using the top-down approach, are introduced.

### 6.2. Transfer-Printed Graphene Lines for Flexible Transistor

Recent work demonstrates that graphene-based electrolyte-gated transistors (EGTs) can be introduced as a platform via transfer printing with a silicon stencil, to produce graphene lines[115]. The transfer printing process, which is conducted with a viscous graphene-flake ink, enables transistors to maintain their great electrical performance while achieving a high printing resolution with flexibility and scalability at low cost; such results are not easily achieved by the conventional rigid substrate-based fabricating processes. Figure 1a shows the schematics of the detailed fabrication steps, starting with the spin-casting of a Cytop film on the micro-lithographically patterned Si wafer to design a mould. Then, graphene ink is squeezed through the line-holes of the Cytop/Si stencil, forming five groups of graphene lines using the differences in surface energies and wetting properties at the interface of the mould and ink. After the annealing of the graphene film, the graphene lines are ready to be transferred onto a flexible substrate. Figure 1b shows the specific procedures for transfer printing graphene lines onto a polyethene terephthalate (PET) substrate. A liquid Norland Optical Adhesive (NOA73, Norland Products, Inc., Cranbury, NJ, USA) is coated on the graphene lines, and then the ultraviolet (UV) light is illuminated at the backside of the $O_2$plasma-treated PET substrate. The graphene lines are subsequently peeled-off from the Cytop/Si mould by the UV-cured NOA73 adhesive layer. Figure 1c shows the flexible aerosol-jet printed transistors, which are fabricated based on poly(3-hexylthiophene) (P3HT, Sigma-

Aldrich, Saint Louis, MO, USA) as the semiconductor, ion gel for the gate dielectric and graphene lines for the source-drain contact pads. Figure 1d, e presents the transfer characteristics and output characteristics of the device, respectively. These two graphs show the operation of the transistor with negligible drain current ($I_D$) hysteresis and clear $I_D$ saturation. This unconventional fabrication process of graphene transistors provides benefits for circuit design, and by increasing the packing density with transfer printing, assures compatibility for the scalable manufacturing of the flexible devices.

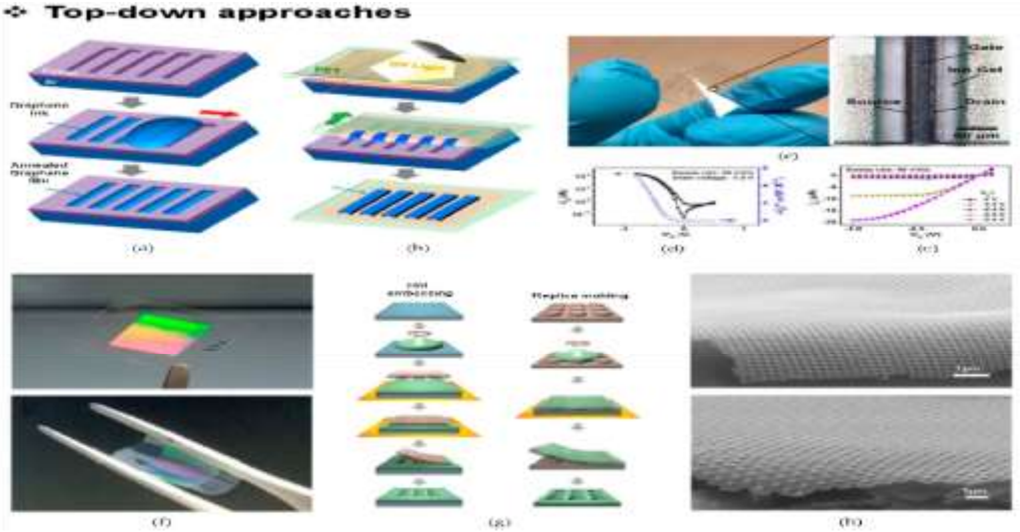

Figure 1. Graphene lines-based flexible transistor/hydroxypropyl cellulose (HPC) photonic thin film with a hexagonal nanopillar structure: (**a**) a schematic of the fabrication of the Cytop/Si mould; (**b**) simple procedures for transferring graphene lines from the Cytop/Si mould to the polyethene terephthalate (PET) flexible substrate; (**c**) an image of flexible electrolyte-gated transistor (EGT) arrays, the magnified picture shows the composition of each transistor; (**d**,**e**) the transfer and output characteristics of the graphene electrodes, Reproduced with permission from 2017 ACS NANO[115]; (**f**) images of an HPC photonic crystal (top) and its mechanical flexibility with a free-standing property of the design (bottom); (**g**) schematics of two fabrication processes to make HPC photonic films-hot embossing and replica moulding methods. The blue-coloured slide indicates the glass substrate, the green one for HPC, and the brown one for hard polydimethylsiloxane (h-PDMS); (**h**) special hexagonal nanopillar images obtained by scanning electron microscopy (SEM) in the lateral view. Paper substrates are used to imprint the predesigned nanopattern. Reproduced with permission from 2018 Nature [116].

### 6.3. Classification of Sensors According to its Applications

#### 6.3.1Chemical nanosensors

—This type can be applied to analyze a single chemical or molecule. Several different optical chemical nanosensors were used for measuring some properties such as pH, and various ion concentrations. Deployable nanosensors.

—This type is used in military or other forms of national security such as Sniffer STAR. It is characterized by a lightweight, portable chemical detection system that combines a nanomaterial for sample collection and a concentration with a microelectromechanical detector. Electrometers.

—It consists of a mechanical resonator, a detection electrode, and a gate electrode which are used to couple charge to the mechanical element. Biosensors.

—It is one of the most common sensors used due to the possibilities of early cancer detection and detection of other various diseases. It can also be used to detect a specific type of DNA[117]. The biosensor can usually be considered a subset of chemical sensors because the transduction methods or the so-called sensor platforms are similar to those for chemical sensors[64]. Within different kinds of developed biosensing technologies, field-effect transistor (FET) has many advantages such as; ultra-sensitivity detection, mass production capability, and low-cost manufacturing[119]. The major FET-based biosensing devices are ion-sensitive field-effect transistor (ISFET), silicon nanowire, organic FET, graphene FET, and compound-semiconductor FET[120].

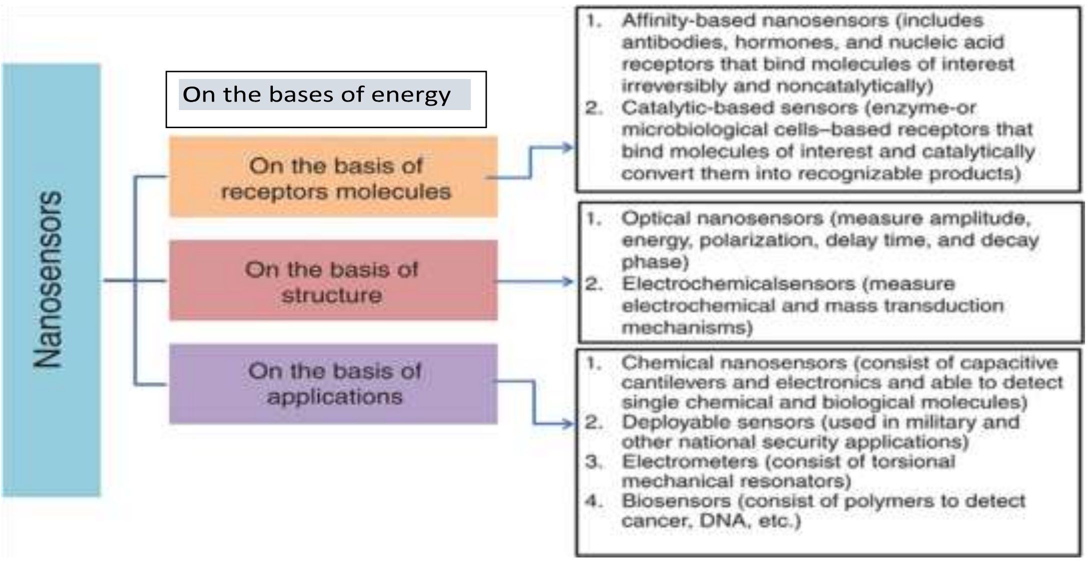

Figure 1. Classification of nanosensors[118].

### 6.3.2. Risks of Real-time Biosensors

As with any new technology, there are risks associated with nanomaterial-mediated biosensors. Implantable devices suffer from some challenges including postimplantation complications and insufficient miniaturization to reduce trauma from implantation[121]. To reduce traumatic effects on the implant patient, indirect glucose monitoring through subcutaneous implantation has been generally favoured over the direct method of vascular bed implantation[122]. Hydrogel platforms have also been shown to be more biocompatible and reduce protein adsorption which subsequently reduces postimplantation effects[123, 124]. The cytotoxicity of carbon nanomaterials such as single-walled CNTs, MWCNTs, and graphene is still unclear[125, 126]. This is a particular concern for implantable devices that depend on the catalytic action for highly sensitive detection of glucose. Sohaebuddin et al. have investigated the effects of various nano metal oxides and MWCNTs on physiologically different cell types and concluded that the nanomaterial toxicity was highly dependent on the type of nanomaterial, size, concentration and the function of the target cell [127]. However, this study exposed cell lines to a constant dosage of free nanoparticles which differ from most electrochemical sensing applications where the nanomaterials are immobilized on an electrode (i.e., nanoparticle leaching is expected to be minimized) and the expected concentration exposure of cells is expected to be much less. Au nanoparticles have shown cytotoxicity in some studies of mammals, but in other studies, the nanoparticles are benign and are excreted through urine[128]. The toxicity of quantum dots is well known and is a major deterrent against mainstream use for fabricating implantable devices [129-131].

### 6.3.3. Nanomaterials and the Use of Nanotechnology for Clinical Diagnostic Purposes

The use of nanotechnology and the variety of unique nanomaterials with favourable electrochemical and surface properties that were described above, has helped: (1) maximize the detection capabilities by improving the signal-to-noise ratios; (2) improve selectivity and minimize interference from biological specimens; and (3) increase the stability of the biosensors and related reagents to a standard where they meet the demands for detection of biomarkers at extremely low concentrations (typically pg/mL to ng/mL). Known nanomaterials and their application in the detection of cancer and disease management in other fields of medicine are summarized in Table 3 below.

| **Nanomaterials** | **Potential Applications in Cancer Detection** | **Ref.** |
|---|---|---|
| Au-Ag-graphene hybrid nanosheets | Detection of alpha fetoprotein (AFP) | [132] |
| Au-nanowires dopes Sol-Gel film | Detection of testosterone | [133] |
| Au-$TiO_2$ nanoparticles with Pt nanosphere bioconjugates | Detection of carcinoembryonic antigen (CEA) in breast cancer | [134] |
| $[Co(bpy)_3]^{3+}$ in MWNTs-Nafion composite film and Au NPs | Detection of ovarian and uterine cancer by CA125 biomarker | [135] |
| Chitosan-CNTs-AuNPs nanocomposite film | Detection of carcinoembryotic antigen (CEA) | [136] |
| CNTs and core-shell organosilica@chitosan nanospheres | Detection of ovarian cancer by CA125 biomarker | [137] |
| Graphene | Detection of breast cancer by CA 15-3 biomarker | [138] |
| Graphene sensor platform with colloidal carbon nanospheres | Detection of alpha fetoprotein (AFP) | [139] |
| QD-based microfluidic protein chip | Multiplexed detection of CEA and AFP | [140] |
| NanoAu-functionalized magnetic beads on Au NP-dispersed graphene | Detection of thyroid-stimulating hormone (TSH) | [141] |
| SWCNT conducting polymer-metal nanocomposites | Detection of cortisol | [142] |
| SWNT forests | Detection of oral cancer biomarker Interleukin-6 (IL-6) | [143] |

| | | |
|---|---|---|
| Silica nanoparticles with silver nanoparticles | Detection of prostate specific antigen (PSA) | [144] |

## VII. Conclusions

In this research work, nanoparticle decorated multi walled carbon nanotubes (f-MWCNTs) modified gold electrode was developed for determination of pharmaceutical and biological samples. The proposed electrochemical sensor showed a good electrocatalytic activity towards the DS oxidation due to the synergetic effects of nanoparticles and multi walled carbon nanotubes which are presented at the surface of the electrode.

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