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Progress in Carbon Nanotube-Based Electrochemical Biosensors – A Review

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Abstract

The use of carbon nanotubes (CNT) for fabrication of sensors and biosensors has increased considerably over the past decade. This review covers the progress and advances made during the years (2014-2018) in the utilisation of carbon nanotubes for fabrication of electrochemical biosensors. The focus of the review is on reported CNT-based biosensors for detection of, important substances, such as glucose, H_2O_2, (DNA), ascorbic acid, uric acid, dopamine, metal ions, and pesticides. The review starts by first discussing the structures and properties of CNTs, followed by discussion of some of the synthetic methods for CNTs preparation. The working principles and performances of CNT-based biosensors are then discussed. Considerations for future developments in CNT-based biosensors are also outlined.

Keywords: Biosensors, Carbon nanotube, Functionalisation, Glucose, Nanomaterials

Introduction

Biosensors are increasingly becoming a critical part of modern life, because these devices can be used for a diverse range of applications, ranging from diagnosis of life-threatening diseases (Son, Kim *et al*., 2016; Caglayan, 2017; Chen *et al*., 2017; Han *et al.*, 2017; Pan *et al*., 2017; Syedmoradi *et al*. 2017; Thapa, *et al*., 2017; Wang *et al*., 2017; Wang, *et al*., 2017) to detection of biological agents in warfare or terrorist attacks (Bahadır & Sezgintürk 2015). Recently, materials science has boosted the advances in the development of biosensors and has attracted huge interest due to its ability to greatly enhance biosensors performances and applications by incorporation of various nanomaterials (Campuzano *et al*., 2017; Hasanzadeh *et al*., 2017; Liu *et al*., 2017; Medyantseva *et al.*, 2017; Reshetilov *et al*., 2017; Syedmoradi *et al*., 2017; Wang *et al*., 2017; Zhang & Chen 2017; Zhang *et al*., 2017). Rapid and intense advances in the field of materials science have led to the synthesis of many new nanomaterials with unique physicochemical properties and these have driven the rapidly growing developments in nanomaterial-based electrochemical biosensors.

Among the various nanomaterials that have been synthesised and used to date, carbon-based nanomaterials such as CNTs (Lawal, 2016; Wahab *et al*. 2016; Dervisevic *et al*., 2017; Yang & Shimizu 2017; Dervisevic *et al*., 2018), graphene (Cui *et al*., 2017; Terse-Thakoor *et al.*, 2017; Xu *et al*., 2017; Yardım *et al*., 2017; Zhang *et al*., 2017; Zhu *et al*., 2017; Lawal 2018), buckypaper (Papa *et al*., 2014, Chatterjee *et al*., 2015) and nanohybrids (Gu *et al*., 2016, Ko *et al*., 2017; Shuai *et al*., 2017, Wang *et al.,* 2017) have attracted enormous

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attention due to their widely recognised application to chemical and biochemical sensors which have led to the increasing use for the electrochemical sensing of various compounds (Bai *et al*., 2016; Hamidi & Haghighi, 2016; Pandey *et al*., 2016; Saxena & Das 2016; Wu *et al*., 2016; Xu *et al*., 2016; Wu *et al*., 2017; Yang *et al*., 2017, Yang *et al*., 2017; Zhao *et al*., 2017; Zhou *et al*., 2017).

Carbon based nanomaterials have received special attention because of their remarkable mechanical and electrical properties. These nanomaterials offer diverse advantages due to their unique properties, such as a high surface-to-volume ratio, high electrical conductivity, chemical stability, biocompatibility, and robust mechanical strength. Carbon-based nanomaterials have been found to be advantageous for construction of electrochemical biosensors because they increase the electroactive surface area, enhance electron transfer, and promote adsorption of molecules (Tiwari *et al*., 2016; Wang *et al*., 2016; Zhang & Yuan 2016; Jaiswal & Tiwari 2017). CNTs are one of the most innovative nanomaterials because of their exceptional physical, chemical, and electrical characteristics, which offer unique electronic, optical, mechanical, thermal, chemical and electrochemical properties (Soleymani 2015). CNTs also offer a large edge plane/basal plane ratio, and rapid electrode kinetics. Therefore, there has been a considerable progress in recent years in the synthesis and use of single and multi-walled carbon nanotubes (CNTs) for the design and construction of novel biosensor (Luo *et al*., 2017; Sharma *et al.*, 2017; Wu *et al*., 2017). The use of CNTs offers to the biosensing platforms exceptional optical, electronic and magnetic properties. These nanomaterials are capable of increasing the surface area of the chosen transducer for the sensors and, in turn, results in substantial increase in catalytic and sensor performances. CNTs have been used in construction of biosensors which operated in various transduction modes, ranging from electrical and electrochemical to optical detection (Zhu & Lee, 2017). Their excellent fluorescence quenching ability has been exploited in optical sensors (Jain *et al*., 2015; Kim *et al*., 2015, Budhathoki-Uprety *et al.*, 2017). Among the exceptional properties of CNTs, its large surface area, high electrical conductivity and their very efficient electrocatalytic behaviour are the most relevant for electrochemical applications. Therefore, CNT-based biosensors generally achieve higher sensitivities, lower limits of detection, and faster electron transfer kinetics than traditional carbon electrodes. Other utilisation of CNTs for fabrication of sensors, include uses for chemical sensors (Wang *et al*., 2017), gas sensors (Chen *et al*., 2017; Żelechowska *et al*., 2017), mechanical sensors, resonant sensors, humidity sensors, biofuel cells (Bandodkar *et al*., 2016; Ouyang *et al*., 2016; Shoji *et al*., 2016; Shu *et al*., 2016; Qu *et al*., 2017), environment sensors (Arduini *et al*., 2016; Piro *et al*., 2016; Ramnani *et al*., 2016) and optical sensors (Jain *et al*., 2015; Kim *et al*., 2015).

Due to the unique properties of electroanalytical techniques, CNTs have received enormous attention for construction of electrochemical sensors and biosensors (Uwimbabazi *et al*., 2017; Yoo *et al*., 2017). Different electroanalytical techniques have been employed for the development of CNTs electrochemical biosensors for the detection and quantification of many biomolecular species (Dervisevic *et al*., 2017; Uwimbabazi *et al*., 2017; Yang *et al*., 2017), chemical compounds, inorganic ions in environmental and biological samples (Braga *et al.,* 2015; Cui *et al*., 2015). Various CNTs electrochemical biosensors have been developed for detecting and quantification of medically and pharmaceutically important compounds such as glucose (Shrestha *et al*., 2016; Song *et al*., 2017; Surucu & Abaci, 2017; Termehyousefi *et al*., 2017, Uwimbabazi *et al*., 2017; Zhou *et al*., 2017; Jiang *et al*., 2018), acetaminophen (Alam *et al*., 2018), methylglyoxal, H_2O_2 (Hamidi & Haghighi, 2016; Dramińska & Bilewicz, 2017; Sánchez-Tirado *et al*., 2017), metal ions (Moyo *et al*., 2014a; Shi *et al*., 2017; Somayeh, *et al*., 2017), DNA (Fu *et al*., 2017; Hien *et al*., 2017; Huang *et al*., 2017) (Chiorcea-Paquim, *et al*., 2017; Unal *et al*., 2017), ascorbic acid (Deb *et al*., 2016; Hu *et al*., 2016), uric acid (Erden *et al*., 2015; Ghodsi *et al*., 2015; Sun *et al*., 2015; Hu *et al*., 2016; Yang *et al*., 2016), Nicotinamide Adenine Dinucleotide (NADH) (Eguílaz, Gutierrez *et al*., 2016; Mutyala &

Mathiyarasu 2016; Atta *et al*., 2017), acetaminophen (Cernat *et al.,* 2015; Moretti *et al*., 2016), herbicides (Szabó *et al*., 2017) and pesticides (Zhang *et al*., 2015; Zhang *et al*., 2015; Liu *et al*., 2016; Miao *et al*., 2016) .

Biomolecular detection with CNT-based biosensors has attracted considerable applications in many areas of health care, screening of new drug molecules (Karimi-Maleh *et al*., 2016; Yue *et al.*, 2016), HIV screening (Ma *et al.*, 2017), cardiac biomarker (Prakash *et al*., 2017), malaria biomarker (Paul *et al.*, 2017), clinical medicine (Janegitz *et al*., 2014; Revathi *et al*., 2015; Zribi *et al.*, 2016), pharmaceutical products (Adhikari *et al*., 2015; Alpat *et al*., 2016; Koteshwara *et al.,* 2017), food safety (Abdalhai *et al*., 2015; Zeng, *et al*., 2016; Kitikul *et al*., 2017) and environmental monitoring (Kim *et al*., 2016). The high surface- to -volume ratio of CNTs makes it possible to obtain ultrafast detection of biomolecular species at low temperature. CNTs-based biosensors are ultra-sensitive, have fast response time, lower redox reaction potentials and less fouling effect. These devices have high stability and longer life than the commercial metal oxide, silicon and other material sensors (Sharma *et al*., 2017). These enhanced characteristics have stimulated a lot of research interest in utilisation of CNTs as components for electrochemical biosensors. The advantages of CNT-based electrochemical biosensors include: (i) high sensitivity due to the large surface area ratio and hollow pipe which enables immobilisation of enzyme or other biomolecules to maintain a high biological activity; (ii) fast response time due to the outstanding ability of CNTs to mediate fast electron-transfer kinetics and, hence, promote electron-transfer reactions like NADH and H_2O_2; (iii) lower potential of redox reaction and less surface fouling effects; and (iv) high stability and longer lifetimes.

Two types of CNTs are commonly used for fabrication of biosensors. As these carbon nanomaterials may comprise of either a single graphitic layer, or multiple coaxial layers, they result in the formation of two distinct types of CNTs: (a) single-walled carbon nanotubes (SWCNTs) and (b) multiple-walled carbon nanotubes (MWCNTs) (Yang *et al*., 2015). SWNTs consist of a single graphite sheet seamlessly wrapped into cylindrical tubes, having diameters of between 0.4 nm and 2.5 nm (Fig.1b), while MWCNT is composed of more than two layers of curly graphite sheet, and its diameter is at the range of 2–30 nm and some even more than l00 nm (Fig. 1b), the distance between each layer is approximately 0.42 nm. MWCNT have shown the most promising appearance to the market place in recent times. Both SWCN and MWCNT equally used as electrode materials. The small size of SWCN and a corresponding large active surface area of MWCNT, the easy functionalisation with carboxyl or amino were the advantages, which were exploited by CNT for electrochemical applications.

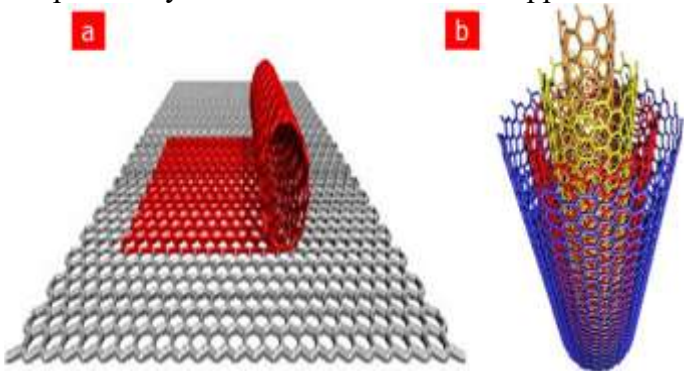

Figure 1: (a) Schematics of SWCNTs which composed of a single layer of curly graphite. (b) Schematics of MWCNTs. (Yang *et al*. 2015)

Scope of this Review

This review highlights recent progress made in the utilisation of CNTs for fabrication of electrochemical biosensors. Considering the numerous reports and reviews (Malhotra *et al.*, 2014; Sagadevan & Periasamy, 2014, Tiwari & Turner 2014; Barsan, *et al*., 2015; Soleymani, 2015; Yang *et al*., 2015; Yang *et al*., 2015; Barsan & Brett 2016; Lawal, 2016; Shanta *et al*., 2017; Zhu, 2017, Gupta *et al*., 2018) that have been published on CNT-based biosensors, this review has been limited to the recent progress made in the years (2014-18) on the utilisation of CNTs for fabrication of electrochemical biosensors. More specifically, this review considers three aspects of the utilisation of CNTs for construction of CNTs-based enzymatic, CNTs-based non-enzymatic and CNTs-based nanoelectronic devices. For the CNT-based enzyme biosensor, the focus will be on the electrochemical

detection of glucose, NADH, and cholesterol. For CNTs-based non-enzymatic electrodes, the detection of glucose, H_2O_2, Ascobic acid (AA), Uric Acid (UA) and Dopamine (DA) will be considered. Lastly, the CNT-based nano-electronic devices will focus on detection of DNA, organophosphate compounds and heavy metal ions.

Synthesis and Functionalisation of CNTs

Synthesis

The increase in momentum in research on CNTs has resulted in the high demand of CNTs in industry and recently it is becoming increasingly urgent in demand. There are three basic methods for synthesis of SWCNTs and MWCNTs: electrical arch discharge, laser ablation (laser vaporization) and chemical vapour deposition (CVD) (or catalytic decomposition of hydrocarbons). Research on CNTs is more and more extensively pursued and the synthetic methods of CNTs have been improved. In arc discharge the current through two graphite electrodes creates a deposit of CNTs on the cathode. By altering conditions either SWCNTs or MWCNTs can be synthesised. Laser vaporization of graphite in a silica tube lined, high temperature furnace generally results in MWCNTs, but with the use of catalytic metal nanoparticles, SWCNTs can be synthesised. MWCNTs are produced by CVD during the pyrolysis of hydrocarbon gases at high temperatures. Table 1 shows the lists of various methods for preparing various kinds of CNTs in recent years.

Functionalisation

CNTs have poor solubility in most solvents and this limits their applications. The outer walls of pristine CNTs are chemically inert. CNTs are required to functionalise in order to provide biocompatibility and solubility. Functionalisation of CNTs with other functional materials, such as enzyme, proteins or nanomaterials, is a rational way to regulate their properties to fulfil different biosensing requirements. Noncovalent and covalent surface functionalisations are two commonly used methodologies to modify CNTs. Their poor solubility in aqueous and organic solvents and limited compatibility with polymer matrices are major drawbacks, rendering these materials incapable of achieving their full potential. Consequently the functionalisation of nanotubes is extremely important, as it increases their solubility and process ability. Functional CNTs have attracted much attention for analytical and biomedical applications. Functionalisations of CNTs can be achieved by physical and chemical methods. CNTs can be functionalised with different chemical groups using covalent and non-covalent procedures which will enhance and enrich their functions in electrochemical biosensors. Most of the current functionalisation methods follow covalent or chemical approach. Through this method, a strong covalent bonding is formed between CNTs and coupling agent.

Physical methods includes the mechanical means such as ultrasonic, milling, crushing and friction to activate CNTs surface to change their surface physical and chemical structure. This method increase CNTs' internal energy and surface activity and then make the tubes react with or attached to other materials, to attain the purpose of the surface modification. At present, the large shear force or ultrasonic processing is often used to disperse CNTs. Some other physical surface modifications include ultraviolet, plasma beam, electron beam, high-energy corona discharge and μ-ray.

Chemical methods mainly have two approaches: covalent modification (Emami & Haghjoo, 2014, Eguílaz *et al*., 2016a, Eguílaz *et al.,* 2016b, Bensghaïer *et al*., 2017; Costa, *et al*., 2017, Dagar & Pundir 2017) and non-covalent modification (Eguílaz *et al.,* 2016c; Kangkamano *et al*., 2017) (Figs.2 and 3). Non covalent modification can retain the original structure and properties of CNTs, and does not damage the system while the structure of covalent modification is more stable. In Non-covalent modification, the highly delocalised electron via sp2 hybridization of carbon atoms in CNTs can be combined with other compounds containing Pie electrons through the Pie-Pie non-covalent bonding effect. Non-covalent bond is much weaker than covalent bonding. Non-covalent modification generally uses conjugated polymers, bioactive molecules (e.g. DNA, enzyme, protein)

Table 1: The synthetic methods of CNTs.(Yang, Chen et al. 2015)

Method	Progress	Consequence	Refs.
Arc discharge	Synthesized between two graphite rods in water bath at different voltage	Good quality and high yield CNTs are obtained	(Lakshmi and Khan 2014)
	Two graphite electrodes submerged in different liquid media	Yielding various dimensional nanocarbon structures	
	Using strong oxidizing agent HNO_3/ H_2O_2 instead of metal catalyst and vacuum devices	Improving purity of MWCNTs	
	The discharge is maintained in a magnetic field	High quality MWCNTs are obtained	
	Using physical forces both during synthesis	Relatively straight and defect free MWCNTs are obtained	
Laser ablation	Dynamic light scattering, micro-Raman and high-resolution transmission electron microscopy were used	Controlling their nanostructures	
	Using binary catalysts combining the transition metals Fe, Co and Ni	Different carbon nanostructures can be obtained	
	Direct synthesis using pulsed laser ablation	SWCNTs show fast and strong photo-response (as high as 1350% at 405 nm)	
	Irradiating of a CO2 laser in continuous wave mode onto a boron-containing graphite target at room temperature	The fine crystalline structure of MWCNTs can be obtained	
	Ablating a nickel/carbon composite target in ethanol or ambient air	MWCNTs	
CVD	Growing on iron catalyst film using plasma enhanced chemical vapour deposition (PECVD) system	Vertically aligned single wall carbon nanotubes of diameter 0.8-1.5 nm can be obtained	(Ali, Kumar et al. 2014)
	Co was used as catalysts, at 700 °C using hydrogen to acetylene gas ratio at 25:25 Sccm	High yield of MWCNTs	
	Using NiO powder as catalysts and LPG as carbon source	The yield of CNTs increased	

	AlPO4 was used as catalysts	Y-shaped CNTs	
	Taking iron nanoparticles as catalyst	SWCNTs	
	Taking Co-Mo as catalyst and using CH4 at 900 °C	SWCNTs	
	Metal catalyst-free mist flow	SWCNTs can be synthesized without any treatments	(Fu, Cui et al. 2014)
	Ni over Cr layer as a catalyst at 600 °C	CNTs	
	Taking Ni/MgO as catalyst and using CH4 in micro-fluidized bed	CNTs exhibited relatively small and mean outer diameter, less defect, and high purity	(Fu, Cui et al. 2014)
	Photochemical deposition	MWCNTs	
Low-temperature plasma	The plasma causes the dissociation of carbon resource	CNTs with highly distributed active species and catalyst activation	
Low-temperature plasma reduction	Facile glow discharge plasma reduction operated at room temperature	CNTs	
Solvothermal	At the low temperature of180 °C	MWCNTs bundles	
Low-temperature solvothermal	Dichlorobenzene as a carbon source was catalyze by a solvothermal approach at 200 °C	Well-aggregated carbon nanotubes are achieved	
Solvothermal	At the temperature of200 °C and a reaction for 10 h	Magnetic MMWCNTs with alterable structure	
Sol-gel	The mixed solution was evaporated at 80 °C for 8 h	MWCNT-LiMn2O4	

and conjugated polycyclic aromatic hydrocarbons (e.g. pyrene and its derivatives) to disperse and functionalise CNTs. Proteins are often used material to disperse CNTs efficiently in aqueous medium. Covalent modification occurs in tip defects as well as side wall of CNTs. The principle of the method is that the CNTs are first oxidised by high concentration acid and this is followed by introducing functional groups (e.g. carboxyl) onto in the terminal or the defect sites of lateral wall of CNTs. Therefore, CNTs can be functionalised with different functionalities by covalent modification to meet the different requirements of biosensing applications. Covalent modification in tip mainly includes carboxylation and subsequent derivatisation, such as amidation and esterification reaction (Fig. 2). But in covalent modification in side wall includes fluorination, alkylation reaction, cycloaddition which can improve the properties of CNTs and to a certain extent it will destroy the sp2 structure of the CNTs there by influencing their

stability. Covalent modification of CNTs is much more desirable when stronger interaction

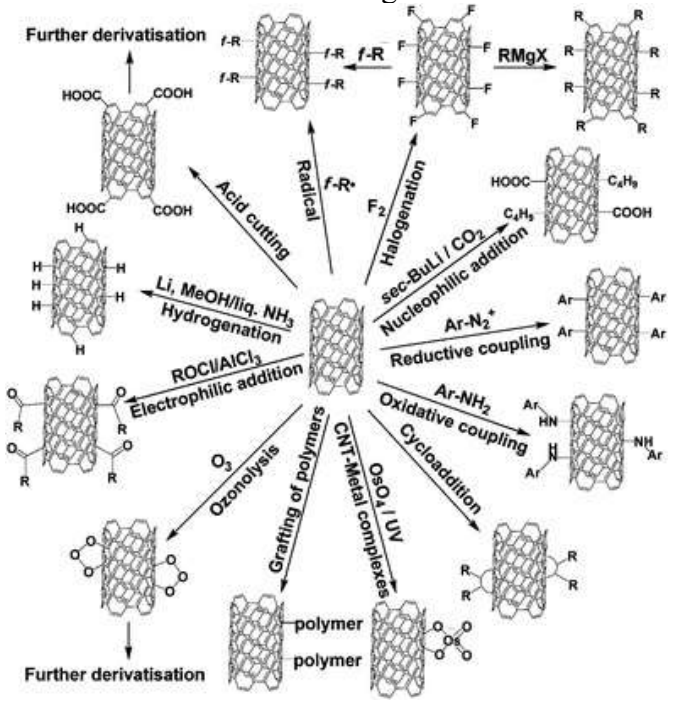

Figure 2: Covalent functionalisation (Yang *et al*., 2005).

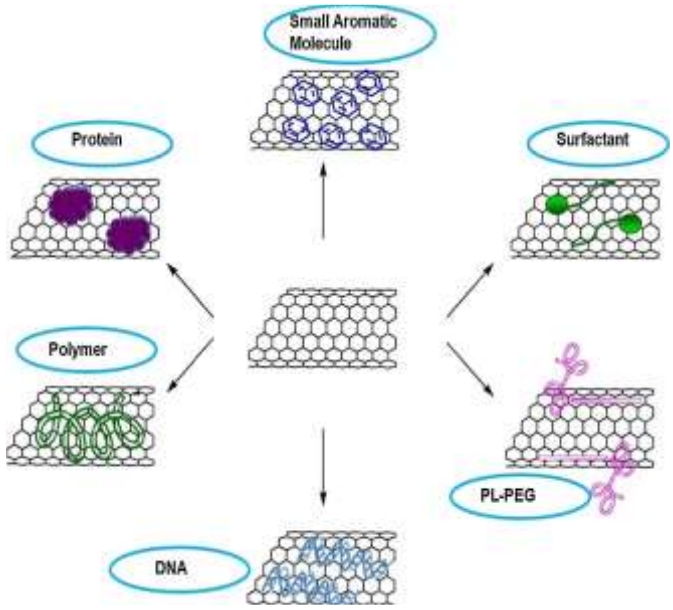

Figure 3: Functionalization of CNTs with various nanomaterials (Yang *et al*., 2015)

between CNTs and the modifier is required. comparing with adsorption enzymes, covalently immobilized enzymes are combined closely with carrier, thus have high stability and repetition of usability.

Working principles of CNT-based biosensors

Biosensors are integrated receptor-transducer devices capable of providing selective quantitative or semi quantitative analytical information using a biological recognition element. Majority of the biosensors developed till dates are based on electrochemical sensors that contain reference electrode, working electrode and a counter electrode. CNTs have been recognised a very prominent material for enhancing electron transfer which make them suitable for integration into electrochemical biosensors (Jain *et al*., 2015). An electrochemical biosensor is an analytical device in which a recognition element is integrated within or intimately associated with a signal transducer (an electrode) that converts the recognition event to a measurable electrical signal for the purpose of detecting a target analyte. Namely, electrochemical biosensors are based on the detection of electroactive species involved in chemical recognition processes and make use of charge transfer from a solid or liquid sample to an electrode or vice versa (Lawal, 2016).

The composition of CNTs biosensor includes two parts: biological sensitive element and the transducer. The CNT are sometimes functionalised with cell receptors, enzymes, antibodies, oligo or polynucleotides, microorganisms, or even whole biological tissues, and thereby working as the biological sensitive element (Fig. 4). The sol-gel derived materials are sometimes being used extensively to encapsulate enzymes, antibodies, microorganisms, and even whole cells (Xu *et al*., 2014; Hossain *et al*., 2015; Wu *et al*., 2015; Shoja *et al*., 2017). The role of transducer is to convert the concentration of analytes to other detectable physical signals, such as currents absorbance, mass or acoustic variables for testing and detecting. Biosensor has been defined as a device that consists of a highly selective and sensitive biological receptor element (e.g. tissue, micro-organisms, organelles, cell receptors, enzymes, antibodies, nucleic acids, etc.) intimately associated with a transducer element that translates the biological

recognition process between the receptor and the analyte into a measurable signal (Fig. 4).

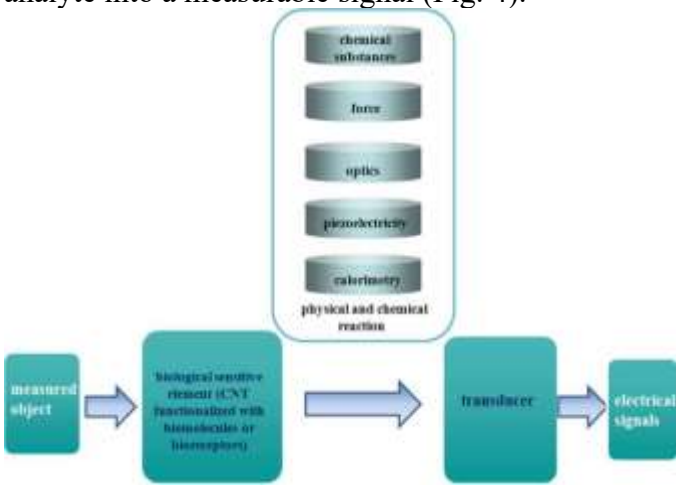

Figure 4: Schematic depiction of different CNTs-based biosensors. The physicalorchemical reaction is transformed into electrical signals after the target molecule was detected by detection device (Yang *et al*. 2015)

Electrochemical biosensors mainly have three types: amperometric-based, potentiometric-based and impedimetric-based, the amperometric-based mode is the most widely used. The sensing mechanism of amperometric CNTs-based biosensors is using the analytes, different enzymes are selected, such as NADH (Zhu, *et al*., 2014; Ertek & Dilgin, 2016; Hamidi & Haghighi, 2016; Lin *et al*., 2016; Mutyala & Mathiyarasu, 2016; Atta *et al*., 2017), glucose oxidase (GOx) (Mansouri *et al*., 2017; Termehyousefi *et al*., 2017; Uwimbabazi *et al*., 2017; Zhou *et al*., 2017), aflatoxin-oxidase (Zhang *et al*., 2016; Costa *et al*., 2017), E. Coli (Yamada *et al*., 2014; Abdalhai *et al*., 2015; Guo *et al*., 2015; Ozkan-Ariksoysal *et al*., 2017), cholesterol oxidase (Gholivand & Khodadadian, 2014; Ashby & Ramasamy 2015; Shukla *et al*., 2015; Ahmadraji & Killard, 2016; Pandey *et al*., 2016), urease (Emami & Haghjoo 2014; Dagar & Pundir, 2017; Dervisevic *et al*., 2018), lactic acid oxidase (Paga´n, *et al*., 2014; Meshram, *et al*., 2015), acetylcholinestterase (Chen *et al*., 2017) and horseradish peroxidase (Moyo *et al*., 2014b; Xu *et al*., 2015; Magyar *et al*., 2016). Oxidisable H_2O_2 or NADH is easily generated as a result of these enzymes, as described in equations (1) and (2):

$$\text{Substrate}+O_2\text{oxidase}\rightarrow\text{Product}+H_2O_2 \quad (1)$$

$$\text{Substrate} + \text{NADdehydeogenase} \rightarrow \text{Product} + \text{NADH} \quad (2)$$

Enzymatic Biosensor

Enzymatic sensors play an important role in human daily life. Extensive studies of enzymatic sensors are focused on improving the activity, stability, and direct electrochemistry of enzymes. Enzymatic biosensors have been valuable bioanalytical devices for analysis of diverse targets in disease diagnosis (Singh *et al*., 2014), biological and biomedical research (Alshehri *et al*., 2016; Chandra, 2016).

Electrochemical biosensors based on the use of enzymes have received considerable attention since the first enzymatic electrode proposed by Clark and Lyons more than 40 years ago, due to the advantages of the association of the biocatalytic activity of enzymes with the high sensitivity and versatility of the electrochemical transduction. The enzyme immobilisation step is critical, since the biocatalyst has to remain active to perform an efficient biorecognition of the substrate and several methods have been used to immobilise these enzymes on CNTs and its composites (Fig.5). The other aspect to consider is that the transducer where the enzyme is immobilised has to allow a fast charge transfer to ensure a rapid and sensitive response. Several strategies for immobilising proteins on CNTs modified electrodes have been proposed, the ones involving noncovalent functionalisation of the sidewalls of SWCNTs being the best to preserve the sp^2 CNT structure and their electronic characteristics.

Electrochemistry of enzymes involves direct electron transfer (DET) between the electrode and the active centre of the enzymes without the participation of mediators or other reagents (Vilian & Chen 2014; Yu *et al*., 2014; Sanzó *et al*., 2015; Luong *et al*., 2017; Muguruma *et al*., 2017, Xia *et al*., 2017) (Fig. 6). New mediator-free (or reagentless) biosensors, enzymatic bioreactors, and biomedical devices employ DET by immobilising enzymes on conducting substrates. But, the redox centres of the biomolecules are usually embedded deep in their large three dimensional structures. CNTs and metal nanoparticles have exhibited excellent performance in enhancing the DET between enzymes

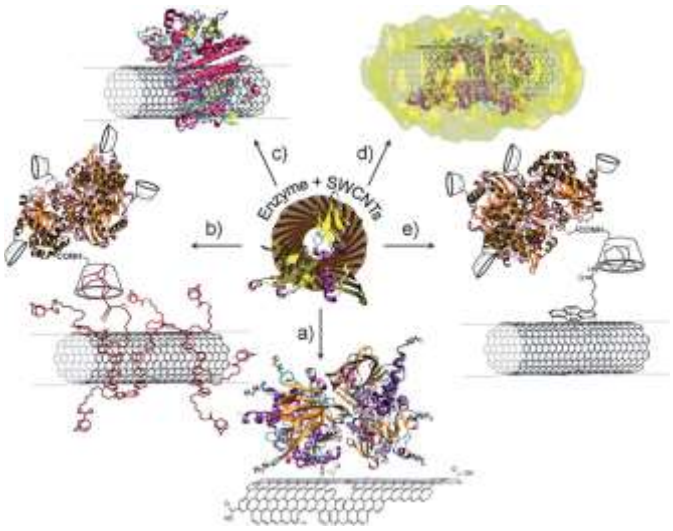

Figure 5: Immobilization strategies of enzymes on SWCNTs: (a) covalent binding via amide coupling with the carboxylic acid groups of oxidized nanotubes; (b) electrochemical coating of nanotubes with affinity partners and subsequent immobilization of affinity counterpart modified enzymes; (c) adsorption of enzymes on SWCNTs via hydrophobic or electrostatic interactions; (d) entrapment of enzymes in a polymer matrix formed around SWCNTs; and (e) immobilization via affinity interactions onto functionalized nanotubes (Yang *et al*. 2015).

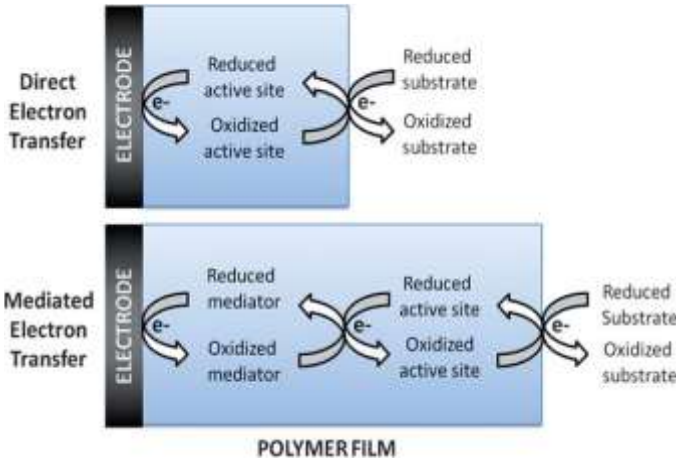

Figure 6: Anodic direct electron transfer and mediated electron transfer (Lawal, 2018).

Non enzymatic biosensor

and electrodes, and are now widely used. Recent research has shown that CNTs can enhance DET between enzymes and electrodes. DET was also evidenced at SWCNT electrodes for many redox proteins such as glucose, haemoglobin, Cytochrome C, microperoxidases and catalases (Figure 4).

Although several researchers have reported low detection limits and high accuracies in enzymatic biosensor, but there are several disadvantages of enzyme-modified electrodes, such as their instability, the high cost of enzymes and the complexity of immobilisation. Since, the activity of enzymes can be affected by temperature, pH, and toxic chemicals; several researchers now pay considerable attention to nonenzymatic electrodes in attempts to eliminate above enzyme problems.

Carbon Nanotube Nano Composites

Hybrid composites based on CNTs with inorganic (Tak *et al.*, 2016; Guzsvány *et al*., 2017; Kaçar *et al*., 2017; Narang *et al*., 2017; Paul *et al*., 2017; Sağlam & Dilgin, 2017; Shiravand & Azadbakht, 2017; Shoja *et al*., 2017; Song *et al*., 2017), conducting polymer (Li & Lee 2015; Meiyazhagan *et al*., 2015; Meshram, 2015; Shrivastava *et al*., 2016; Ates *et al*., 2017; Jasim *et al.*, 2017; Satyanarayana *et al*., 2017; Su *et al*., 2017; Vinay *et al*., 2017; Gui *et al*., 2018) and organic materials (Pereira *et al*., 2015; Rather *et al*., 2015; Thirumalraj *et al*., 2015; Vilian *et al*., 2015; Hien *et al*., 2017; Poo-Arporn, Pakapongpan et al. 2017; Savalia & Chatterjee 2017; Thapa *et al*., 2017) have been reported in the recent times. Hybridisation of nanometals to carbon nanomaterials such as CNTs produces a synergistic effect on the electrocatalytic activity when compared to either material alone. These hybrid materials formed have shown great potential application in catalysis (Baghayeri & Veisi 2015), electronics (Cavallini *et al*., 2015), optics and sensors (Barsan *et al*., 2015; Cernat *et al*., 2015, Zhao *et al*., 2015; Adhikari *et al*., 2017; Correa *et al*., 2017). CNT-inorganic nanocomposites (Braga *et al*., 2015; Cui *et al*., 2015; Narang *et al*., 2017; Sağlam & Dilgin 2017) have opened up an exciting new field in the science and technology of CNT. CNT-metal nanoparticles have excellent conductivity and catalytic properties, which make them suitable for acting as ‘electronic wires’ to enhance the electron transfer between the redox centres in proteins and electrode surfaces, and as catalysts to increase electrochemical reaction rates

(Li *et al.,* 2015; Zhao *et al*., 2015; Dagar & Pundir 2017; Dalkıran *et al*., 2017). Several biosensors have been developed using CNT-metal nanocomposite. The conductivity of nanocomposites enhances electron transfer between the active centres of enzymes and electrodes so that the particles act as electron transfer conduits or mediators (Luong *et al*., 2017; Muguruma *et al*., 2017, Termehyousefi *et al*., 2017; Eguílaz *et al*., 2016). Conductive polymer–CNT nanocomposites have improved the operational characteristics such as selectivity, stability, or sensitivity of the resulting biosensors (Shrivastava *et al*., 2016; Punetha *et al*., 2017).

Carbon Nanotube-Based Enzymatic Electrodes

Electrochemistry of enzymes involves direct DET between the electrode and the active centre of the enzymes without the participation of mediators or reagent (reagentless). Reagentless biosensors, enzymatic bioreactors, and biomedical devices are such that employ DET by immobilising enzymes on conducting substrates. However, the redox centres of the biomolecules are usually embedded deep in their large three dimensional structures. Recent research has shown that CNT can enhance DET between enzymes and electrodes. The use of metal nanoparticles with CNT has been reported to form exceptionally stable and cost-effective biosensors.

Glucose Biosensor

Glucose concentration in blood is most frequently performed routine analyses in medicine. In recent years over 5% of the populations of industrialised nations have diabetes, resulting in a high demand for the detection of glucose in blood. Glucose concentration higher or lower than the normal range of 80–120 mg dL^{-1} (4.4–6.6 mM) leads to metabolic disorder of diabetes mellitus which results in the deficiency of insulin and hyperglycaemia. This disorder is a leading cause of death and disability. The diagnosis and management of the diseases requires close monitoring of blood glucose. The application of CNT in highly sensitive and cost-effective biosensors and can aid the diagnosis of the disorder diabetes mellitus.

Enzymatic glucose biosensor

Diabetes is a major health problem causing deaths worldwide. Thus, monitoring of glucose in blood has become a very important need leading to fabrication of accurate and sensitive advanced blood sugar detection devices for clinical diagnosis and personal care (Lee *et al*., 2016; Zaidi & Shin 2016).

Direct electrochemistry of GOx involves DET between the electrode and the active centre of the GOx (Yu *et al*., 2014; Lee *et al*., 2016, Luong *et al.*, 2017, Muguruma *et al*., 2017; Termehyousefi *et al*., 2017; Xia *et al*., 2017) (Fig.6). The direct electrochemistry of GOx based on redox-active centres was confirmed by CV experiments in the potential range of 0.8–1 V to follow previously proposed reaction mechanisms:

$GOx(FAD)+2H^+ +2e^- \leftrightarrow GOx(FADH2)$ (In the absence of oxygen)…….....(3)

In the presence of oxygen, the reaction mechanism follows different pathways:

$GOx(FADH2) + O2 \rightarrow GOx(FAD) + H_2O_2$…… . ... (4)

GOx(FAD) +Glucose → GOx(FADH2) + Gluconolactone ……. (5)

Several researchers have used GOx for fabrication of carbon nanotube based glucose biosensor.

Buber *et al.* (2017) constructed a novel GOx based amperometric biosensor utilising a conducting polymer (CP), MWCNTs and a novel water soluble zinc phthalocyanine (ZnPc). The constructed biosensor showed a linear response for glucose between 0.025–1.0 mM with a detection limit of 0.018 mM. KM app and sensitivity values were calculated as 0.53 mM and 82.18 μAmm^{-1} cm^{-2}, respectively. SEM) and CV techniques were used to investigate the surface modifications.

Liu *et al*. (2017) co-immobilised Glucoamylase-displayed bacteria (GA-bacteria) and glucose dehydrogenase-displayed bacteria (GDH-bacteria) on MWNTs modified glassy carbon electrode (GCE) to construct GA-bacteria/GDH-bacteria/MWNTs/GCE biosensor. The biosensor was developed by optimizing the loading amount and the ratio of GA-bacteria to GDH-bacteria. The as-prepared biosensor exhibited a wide dynamic

range of 0.2–10 mM and a low detection limit of 0.1 mM maltose (S/N=3). The biosensor also had a linear response to glucose in the range of 0.1–2.0 mM and a low detection limit of 0.04 mM glucose (S/N=3). Interestingly, at the same concentration, glucose was 3.75-fold sensitive than that of maltose at the proposed biosensor.

Gokoglan *et al.* (2017) fabricated a novel flexible glucose biosensor using vertically aligned carbon nanotubes (VACNT). The biosensor response at a potential of −0.7 V versus Ag wire was followed by the decrease in oxygen level as a result of enzymatic reaction. The biosensor exhibited a linear range between 0.02 mM and 0.5 mM glucose and kinetic parameters (K_M^{app}, I_{max}, limit of detection (LOD) and sensitivity) were estimated as 0.193 mM, 8.170 μA, 7.035×10^{-3} mM and 65.816 μA/mM cm^2, respectively. SEM was used for surface characterisation. The constructed biosensor was applied to determine the glucose content in several beverages.

Zhou *et al*. (2017) covalently linked Ferrocene-grafted dendrimer to the surface of CNTs (CNTs)-chitosan (CS) nanocomposite modified electrode for immobilising high-content GOx, which resulted in the successful development a novel reagentless glucose biosensor. EIS, CV, and amperometry were used to characterise the preparation process and the enzymatically catalytic response of this biosensor. The biosensor showed excellent analytical performance such as fast response time less than 10 s, wide linear range from 0.02 to 2.91 mM and low detection limit down to 7.5 μM as well as satisfactory stability and reproducibility toward the amperometric glucose determination. In addition, satisfactory result was obtained when it was used for the glucose measurements in human blood samples.

Uwimbabazi *et al*. (2017) recently, also developed glucose biosensor for the determination of the beef meat freshness based on a glassy carbon electrode (GCE) modified with MWCNTs and chitosan (Chi). They obtained a linear relationship between the current and the glucose concentrations in the range of 0.2 to 1.2 moll L−1, at a signal-to-noise ratio of 3 a detection limit of 0.05 mM was obtained with good linearity (R2 = 0.9902), while the biosensor showed a rapid response to glucose. In addition, they applied the developed biosensor to determine the glucose in beef to indicate the freshness of the beef as compared to the total volatile basic nitrogen (TVB-N) method. They observed an increasing beef storage time.

With decreasing glucose level Amathatogachi *et al.* (2017) also reported a novel amperometric glucose biosensor based on GOx immobilised on a carbon nanotube (CNTs)–poly(diallyldimethyl-ammonium chloride) (PDDA)–platinum nanoparticle (PtNPs) modified carbon-paste electrode (CNTs–PDDA–PtNPs/CPE). The CNTs–PDDA–PtNPs composite materials were characterised by TEM and electrochemical techniques. CV results reveal direct electron transfer of the immobilised GOx, indicated by two quasi-reversible redox peaks at a potential of 0.37 V (vs. Ag/AgCl) in phosphate buffered solution (PBS) (0.10 M, pH 7). Glucose was quantified using amperometric measurements at 0.5 V vs. Ag/AgCl and PBS carrier (0.10 M, pH 7.0) at a flow rate of 1.0 mL min^{-1}. The linear working ranges for glucose measurements were 0.1–3 mM (r^2=0.995) and 5–100 mM (r^2=0.997), with corresponding sensitivities of 0.127 and 0.060 (μA s) mM^{-1}, respectively.

Nenkova *et al.* (2017) prepared four enzyme electrodes (Pt/PAN/ GOx, Pt/PAN/NZ/ GOx, Pt/PAN/NZ/MNP/ GOx, Pt/PAN/NZ/MWNT/ GOx) by cross-linking of GOx on nanocomposite material. Amperometric measurement of the two glucose oxidase electrodes (Pt/PAN/NZ/ GOx and Pt/PAN/NZ/MWNT/ GOx) with best results was carried out. The linear concentration interval of the Pt/PAN/NZ/MWNT/ GOx biosensor was up to 3 mM, the detection limit - 0.02 mM glucose and the storage stability - 81% of its initial current response after 30 days.

Kulkarni & Slaughter (2017) described the characterisation of a self-powered glucose biosensor comprising of a MWCNTs modified with pyroquinoline quinone glucose dehydrogenase (PQQ-GDH) bioanode and bilirubin oxidase biocathode at physiological conditions. The assembly shows an enhancement in peak power and current densities as compared to the self-powered glucose biosensor comprising of PQQ-GDH

bioanode and laccase biocathode. The assembly produced a maximum open circuit voltage of 480.1 mV and short circuit current density of 640 μA/cm^2 with a peak power density of 89.27 μW/cm^2. The self-powered glucose biosensor exhibited an extended linear dynamic range of 0.1 mM to 35 mM with a sensitivity of 12.221 Hz/mM cm^2. The use of bilirubin oxidase as the cathodic enzyme in addition to the design of biofuel cell assembly makes it a viable candidate as a potential power source for bioelectronics devices.

Lopes *et al*. (2017) used TiO_2, glucose oxidase and carbon nanotube microparticles to provide a large surface area for enzyme immobilisation and a favourable microenvironment for direct electron transfer. This simple architecture nanostructure was used to construct a glucose oxidase biosensor, which demonstrated good analytical performance with high reproducibility, and good detection for pathological glucose level.

Non Enzymatic Glucose Biosensor

The number of people requiring glucose sensors has significantly increased over the last decade; there is an overwhelming demand for the development and improvement of glucose sensors. The demand to make sensors which are both biocompatible and have increased sensing capabilities as compared to current technologies is thus on the increase. In order to meet these needs, a move towards nonenzymatic glucose sensors has begun. Various researchers have begun fabrications of different nonenzymatic glucose biosensors:

He *et al*. (2017) reported that $La_{0.6}Sr_{0.4}CoO_{3-\delta}$ (LSC) perovskite oxide can provide comparable performance to these noble metal nanomaterials. The best electrode, i.e., LSC + RGO/GCE provides sensitivity of 500 and 330 μA mM^{-1} cm^{-2} for H_2O_2 and glucose, respectively, and limit of detection of 0.05 and 0.063 μM for H_2O_2 and glucose, respectively (at S/N = 3). Its respective linear ranges are 0.2–3350 μM and 2–3350 μM for H_2O_2 and glucose, respectively.

Qiu *et al*. (2016) reported a one-step synthesis for the incorporation of nickel nanoparticles on CNTs is reported using thermal annealing with $NiCl_2$ and melamine. The morphology and structure of the nickel nanoparticle modified CNTs were characterised by transmission electron microscopy, scanning electron microscopy, and powder X-ray diffraction. X-ray photoelectron spectroscopy demonstrated that the nickel nanoparticles were on the surface of CNTs forming a robust structure. The nickel nanoparticle modified CNTs rapidly oxidised glucose in alkaline solution with an excellent stability. Consequently, the modified CNTs were shown to be a suitable enzyme-free glucose electrochemical sensor when attached to a glassy carbon electrode, with excellent long term stability, a short response time, a low limit of detection, a long linear dynamic range, high sensitivity, and good precision.

Lee & Kim (2016) demonstrated a simple and inexpensive method of carbohydrate detection using a field effect transistor (FET) with Au nanoparticles (AuNPs) attached to MWCNT, which does not require any enzymes or catalysts. The high sensitivity (3.4 mM^{-1} for sucrose and 6.9 mM^{-1} for glucose) of the sensor is adequate to diagnosis diabetes from a patient serum. The sensor is more sensitive to glucose than sucrose. The hypothesised detection mechanism of the FET sensor is a change of the potential barrier of the conductive MWCNT by the adsorption of the carbohydrates to the attached AuNPs

Baghayeri *et al*. (2016), developed a facile strategy to fabricate silver nanoparticles (Ag NPs) through an electrochemical method with the assistance of metformin functionalised MWCNT (Ag@MH/MWCNT nanocomposite). Investigations by field emission scanning electron microscopy (FESEM) confirmed that the prepared nanocomposite have a porous structure that is constructed by interconnecting functionalised MWCNT framework. Electrochemical studies showed that the nanocomposite exhibits high stability and excellent activity for electrocatalytic oxidation of glucose in alkaline solutions, which allows the Ag@MH/MWCNT to be used in enzyme-free amperometric sensors for glucose determination. It was confirmed that the Ag@MH/MWCNT based glucose biosensor presents wide response window for glucose concentrations of 1.0 nM-350 μM, short amperometric response time (4 s), low detection

limit of 0.0003 μM (S/N = 3), high sensitivity as well as good selectivity.

Li *et al*. (2016) prepared self-assembled $NiFe_2O_4$/ CNTs sponge by ice-templating method. The fabricated glucose biosensor exhibited two large linear ranges (0-3.0 and 3.2-12.4 mM) and distinct sensitivities (84.1 and 24.6 μA mM^{-1} cm^{-2}).

Wang *et al*. (2015) fabricated porous Pd nanotubes on a GCE via a one-step galvanic replacement reaction by using cheap, flexible, and ultralong copper nanowires as the sacrificial template. The electrode exhibits excellent electrocatalytic performance for non-enzymatic glucose biosensors, thanks to massive pores and high specific surface area. This non-enzymatic glucose biosensor shows a wide linear response range from 5 μM to 10 mM, with a sensitivity of 6.58 μA mM^{-1} cm^{-2}, and a detection limit of 1 μM (signal-to-noise ratio of 3).

Hydrogen Peroxide Biosensor

H_2O_2 is a simple molecule in nature but a most widely used oxidizing agent. The rapid and accurate analysis of H_2O_2 is of great importance in many fields including food industry, clinical control and environmental protection. Besides adoption in chemistry and food, H_2O_2 was also an important product present in several biological processes. H_2O_2 is a general enzymatic product of oxidases and a substrate of peroxidases, which is important in biological processes and biosensor development. H_2O_2 is also an essential mediator in food, pharmaceutical, clinical, industrial, and environmental analyses. H_2O_2 is present in higher concentrations around cancer cells as compared with normal analogues. It is because that H_2O_2 is not only a by-product of several highly selective oxidases, but also an essential mediator in food, pharmaceutical, clinical, industrial and environmental analyses.

Enzymatic Hydrogen Peroxide Sensing

Various research groups have used various enzymes for the fabrication of CNT based H_2O_2 sensors: Han *et al.* (2016) described a novel approach to construct an amperometric biosensor for determination of H_2O_2. HRP as a base enzyme was immobilised into the mixture of MWNTs and polyvinyl butyral (PVB). The results showed that the fabricated biosensor demonstrated significant electrocatalytic activity for the reduction of $H_2O_2$with wide linear range from 0.000832 to 0.6 mM, and low detection limit 0.000167 mM (S/N = 3) with fast response time less than 8 s. The apparent Michaelis–Menten constant was determined to be 0.049 mM. Additionally, the biosensor exhibited high sensitivity, rapid response and good long-term stability.

Deb *et al*. (2016) fabricated a composite capable of detecting multiple anolytes is important for advancing rapid medical diagnosis technology to assist in treating illnesses. A dendrimer-encapsulated Pt nanoparticle carbon nanotube (Pt–DEN–PANI–CNT) composite-based electrochemical biosensor was fabricated for the detection of H_2O_2, ascorbic acid (AA), and acetaminophen (AP), important for monitoring AP overdose-induced poisoning. Polyaniline (PANI) was used to coat single-walled CNTs, which were then decorated with Pt-encapsulated, fourth-generation NH2-terminated poly(amidoamine) (G4-PAMAM) dendrimers. XPS and attenuated total reflectance infrared (ATR-IR) spectroscopies, and TEM were used to characterise the nanocomposite material. Electrocatalytic activity of the Pt–DEN–PANI–CNT composite was studied using CV and chronoamperometric (CA) techniques. Point-of-zero charge (PZC) measurements showed that the isoelectric point of the composite was at pH 6.8, an important parameter to consider in explaining differences in selectivity of the composite to these various analytes. Measured chronoamperometric signals for AA, H_2O_2, and AP were found in the concentration ranges of 10 μM–10 mM, 50 μM–8 mM, and 20 μM mM, respectively. Within this series of analytes, the Pt–DEN–PANI–CNT composite can selectively detect both H_2O_2 and AP, separately, in the presence of the other analytes with rapid current response (5 s) and good reproducibility.

Anajocic *et al.* (2016) also compared traditional paraffin oil and graphite powder based carbon paste electrode (CPE) surface modified with MWCNTs with composites of MnO_2-MWCNT or Pt-MWCNT by drop coating method to prepare simply, sensitive and reliable voltammetric sensors either for the determination of H_2O_2 or after

additional modification of the appropriate sensor surfaces with GOx for the determination of glucose via H_2O_2 in selected samples. The SEM characterisation in combination with energy dispersive X-ray spectrometry of the composite materials confirmed that the mediators, MnO_2 and Pt particles, are randomly distributed on the surface of the MWCNTs, and represent nearly 5% (m: m) of the composites expressed as Pt and Mn. CV investigations were performed in acetate (pH 4.50), phosphate (pH 7.50) and borate (pH 9.18) buffers to characterise the basic electrochemical behaviors and to select the working potentials suitable for hydrodynamic chronoamperometric (HA) determination of H_2O_2 under different circumstances.

Vilian *et al.* (2015) also designed a novel composite film for use as a highly selective mediator-free amperometric biosensor, and a method was created for accomplishing direct electrochemistry of myoglobin on a MWCNT and tyramine-modified composite decorated with Au nanoparticles on a glassy carbon electrode. The ultraviolet-visible and electrochemical impedance spectroscopy results showed that myoglobin retained its native conformation in the interaction with Au-PTy-f-MWCNT. The surface coverage of Mb-heme-Fe (II)/(III) immobilised on Au-PTy-f-MWCNT and the heterogeneous electron-transfer rate constant were 2.12 × 10 â '9 mol cm â '2 and 4.86 s â '1, respectively, indicating a higher loading capacity of the nanocomposite for direct electron transfer of Mb onto the electrode surface. The proposed Mb/Au-PTy-f-MWCNT biofilm exhibited excellent electrocatalytic behavior toward the reduction of H_2O_2 and the oxidation of nitrite with linear ranges of 2 to 5000 Î 1/4M and 1 to 8000 Î 1/4M and lower detection limits of 0.01 Î 1/4M and 0.002 Î 1/4M, respectively. An apparent Michaelis-Menten constant of 0.12 mM indicated that the Mb immobilised on the Au-PTy-f-MWCNT film retained its native activity. This biosensor can be successfully applied to detect H_2O_2 and nitrite in disinfectant cream, eye drops, pickle juice, and milk samples.

Zhang *et al*. (2015) achieved a large-scale synthesis of a three-dimensional (3D) nitrogen-doped carbon nanotube (NCNT) film via electrospinning assisted by a chemical vapour deposition procedure. The resulting nanostructure with dense and uniform NCNTs was tightly bonded onto the electrospun carbon nanofiber matrix. The novel biomimetic H_2O_2 biosensor has a low detection limit (0.03 mM S/N = 3) and a wide linear range (0.08-137.2 mM). In addition, the biosensor exhibited high reproducibility, good storage stability, and satisfactory anti-interference ability. The facile preparation method and attractive analytical performances make this robust electrode material promising for the development of effective electrochemical sensors.

Thandavan *et al.* (2015) developed a hybrid interface using nano iron oxide and CNTs and this architecture offered an improved performance for the detection of H_2O_2. The morphology of the prepared nanocomposite was observed using FE-TEM and the electrochemical studies were carried out using cyclic voltammetry and amperometry. The linear range of the prepared amperometric sensor was found to be between 1.2 and 21.6 μM with a quick response time of less than 1 s. The interference, reproducibility and stability studies were carried out with satisfactory results. The limit of detection and limit of quantification were found to be 3.7 nM and 12.2 nM respectively. With the convincing results obtained in terms of the performance of the biosensor, this platform was successfully upgraded for the determination of H_2O_{2as} in the presence of milk samples.

Non-Enzymatic Hydrogen Peroxide Sensing

Enzymeless detection of H_2O_2 and glucose offers a more reliable and accurate detection route given the absence of enzyme that is sensitive to temperature, pH, poisoning chemicals, and humidity.

Various research groups have used CNT for fabrication of non –enzymatic H_2O_2 biosensor:

Lorencova *et al.* (2017) reported the use of Ti3C2Tx for ultrasensitive detection of H_2O_2 down to NM level with a response time of ∼10 s, while

Wang *et al***.** (2016) successfully anchored Ni(II)-Based metal-organic framework (Ni(II)-MOFs) on CNTs by in situ solvothermal method. In the as-prepared composites, 2∼3 nm MOFs nanoparticles homogeneously dispersed on

conducting. As the electrode materials of a non-enzymatic H_2O_2 biosensor, the Ni(II)-MOFs/CNTs exhibited excellent electrocatalytic performance including a wide linear detection range from 0.01 to 51.6 mmol L^{-1}, low detection limit of 2.1 μmol L^{-1} and very fast response of 2.5 s for H_2O_2 sensing..

Bai *et al*. (2016) prepared a novel enzyme-free H_2O_2 sensor composed of carbon dots (CDs) and MWCNTs. It was found that the carbon dots-decorated multi-walled carbon nanotubes nanocomposites (CDs/MWCNTs) modified glassy carbon (GC) electrode (CDs/MWCNTs/GCE) exhibited a significant synergistic electrocatalytic activity towards H_2O_2 reduction as compared to carbon dots MWCNTs alone, and the CDs/MWCNTs/GCE has shown a low detection limit as well as excellent stability, selectivity, and reproducibility.

Baghayeri *et al.* (2015) constructed a sensitive amperometric biosensor for H_2O_2 based on synergetic catalysis of haemoglobin and porous $PdFe_3O_4$-MWCNT nanocomposite. With attention to the utilities of large surface area and outstanding catalytic performance, $PdFe_3O_4$-MWCNT nanocomposite was employed as the nano-stabiliser for the immobilisation of Hb. The immobilised Hb on the surface of nanocomposite as an electrochemical biosensor efficiently catalysed the reduction of H_2O_2, amplified the electrochemical signal and enhanced the sensitivity. A linear response from 0.2-500 μM with detection limit of 0.063μM for H_2O_2 was achieved. The apparent Michaelis-Menten constant KappM value was 21μM.

Cholesterol Biosensing

Cholesterol and its ester are essential constituents of all animal cells. They are precursors of bioanalytes such as bile acid and steroid hormones. Increase in cholesterol levels can cause life-threatening coronary heart diseases, cerebral thromboses, and artherosclerosis. Consecuently accurate detection of cholesterol level is medically useful. Cholesterol that is responsible for cardiovascular disease can be effectively managed by a combination of medication and monitoring and there continues to be a need for new point-of-care diagnostics to measure lipid panels, including total cholesterol (Ahmadraji & Killard 2016). .Enzyme assays based on the generation of H_2O_2 have been very effective in this regard. ChOx is an enzyme promoting the oxidation of cholesterol, generating H_2O_2 in the presence of oxygen. Cholesterol enzyme sensors use ChOx to produce hydrogen peroxide for electrochemical detection, with carbon nanotube lowering the over-potential. Several researchers have fabricated CNT based cholesterol biosensor:

Luo *et al.* (2017) synthesised nonstoichiometric CeO_2CNT core/shell nanowire arrays (NWAs) by hydrothermal method in combination with chemical vapour deposition. Morphology and microstructure of the core/shell NWAs were characterised by SEM, XRD, TEM and Raman spectrum techniques. They showed high sensitivity of 336.6 μA cm^{-2} mM^{-1} and low detection limit of 7.4 μm towards cholesterol detection at working potential of −0.4 V due to synergistic effect of nonstoich iometric CeO_2 and CNT, and they also demonstrated excellent selectivity towards interferents co-existing with cholesterol in blood serum.

Xu *et al*. (2016) constructed a simple and high sensitive cholesterol amperometric biosensor, which is based on in situ electropolymerisation of multi-walled carbon nanotube-polyaniline (MWCNT-PANI) nanocomposite and electrodeposition of platinum nanoparticle (nano-Pt) films onto the glassy carbon electrode surface for cholesterol oxidase immobilisation. The preparation process of the modified electrode was characterised by CV, EIS, SEM, and chronoamperometry. Because of the synergistic electrocatalytic activity between MWCNT-PANI nanocomposites and nano-Pt, the cholesterol biosensor exhibited an excellent performance with a linear range of 2.0–510.0 μM, a detection limit of 0.8 μM (signal-to-noise ratio = 3), a high sensitivity of 109.9 μA mM^{-1}, and a short response time within 5 Sec.

Pandy *et al*. (2016) who designed a novel and improved membranous support for electrochemical sensing of cholesterol by the application of CNT. ChOx was immobilised on the CNTs mixed cellulose acetate membrane (CA-CNT). SEM

images have shown that ChOx is uniformly immobilised over the CA-CNT membrane. The electrocatalytic responses of ChOx/CA-CNT were investigated with various concentration of cholesterol ranging from 10^{-3} M to 10^{-8} M. Compared with ChOx/CA, the ChOx/CA-CNT has better electrocatalytic response to cholesterol. This sensor shows excellent performance with high sensitivity, with a linear range of 10^{-3} M to 10^{-8} M, and a detection limit of 10^{-8} M.

Qian *et al.* (2015) synthesised multiwalled carbon nanotube@reduced graphene oxide nanoribbon (MWCNT@rGONR) core-shell heterostructures by the facile unzipping of MWCNTs and subsequent chemical reduction with hydrazine. MWCNTs with diameter <10 nm were selected as the starting material to maintain narrow ribbons <30 nm wide with a few-layer structure..

Nicotinamide Adenine Dinucleotide (NADH) Biosensor

NADH is an important coenzyme that takes part in more than 300 dehydrogenase enzymatic reactions. NADH is involved as a cofactor in over 300 enzymatic reactions of NAD+/NADH dependent dehydrogenases. The application of amperometric NADH sensors provide a promising measurement technique for detection of substrate or enzymatic activity. But, the direct oxidation of NADH at ordinary electrodes often requires high overpotential and suffers from low sensitivity and the fouling of the electrode surface by its oxidation products. CNTs are recently attracting growing attention in decreasing the high overpotential for NADH oxidation and minimising the surface fouling. The NADH generated can be detected by electrochemical oxidation at appropriate electrodes. Electrocatalytic oxidation of NADH has been investigated as part of the development of dehydrogenase-based biodevices. However, its electrochemical oxidation at bare GC electrodes in neutral solutions occurs at a high overpotential (0.5 V) because of slow ET kinetics and electrode fouling. Therefore, the effective oxidation of NADH at low potentials would aid the development of NADH-based bio devices. Various researchers have fabricated CNT based NADH biosensor:

Atta *et al*. (2017) used Glassy carbon (GC) electrode modified by stepwise manual casting of successive layers of ionic liquid crystals (ILC)/CNTs and magnetite nanoparticles. The composite [GC/ (ILC-CNTs)/Fe_3O_4)] as a successful NADH biosensor. The proposed NADH sensor has th following properties: linear dynamic range of 5–700 μmol L^{-1}, a sensitivity of 0.0102 μA μmol^{-1} L, a detection limit of 34.6 nmol L^{-1} and a limit of quantification of 0.115 μmol L^{-1}. The sensor showed a stable amperometric response and anti-interfering ability in presence of ascorbic acid, tryptophan, ibuprofen and morphine.

Hamidi & Haghig (2016) synthesised palladium nanoparticles decorated multiwalled carbon nanotubes (PdNPs-MWCNTs) and simply cast on the surface of a GCE to prepare an amperometric sensor. The fabricated sensor (PdNPs-MWCNTs/GCE) showed excellent electrocatalytic activity towards NADH and H_2O_2 oxidation and H_2O_2 reduction. It has a fast, linear and highly sensitive response for NADH in the concentration range between 0.1 and 200 μM with a detection limit (S/N = 3) of 32 nM and exhibited fast and sensitive responses (< 2 s) towards H_2O_2. The sensitivity and detection limit for H_2O_2 at the operating potential of + 0.35 V were 167 nA μM^{-1} cm^{-2} and 1.2 μM, respectively and better than those obtained at the operating potential of - 0.25 V (68 nA μM^{-1} cm^{-2} and 14 μM). Moreover, further modification of the proposed sensor by glucose oxidase led to the fabrication of a glucose biosensor with satisfactory performance.

Eguílaz *et al*. (2016) reported the use of SWCNT covalently functionalised with polytyrosine (Polytyr) (SWCNT-Polytyr) as a new electrode material for the development of NADH-based biosensors. The oxidation of GCE modified with SWCNT-Polytyr at potentials high enough to oxidise the tyrosine residues have allowed the electrooxidation of NADH at low potentials due to the catalytic activity of the quinones generated from the primary oxidation of tyrosine without any additional redox mediator. The amperometric detection of NADH at 0.200 V showed a sensitivity of (217±3) μA mM^{-1} cm^{-2} and detection limit of 7.9 nM.

Immunosensor

In developed and developing countries where cancer and cardiovascular diseases are rampant, there is a growing demand for a range of portable, rapid and low cost biosensing devices for the detection of these diseases. Analytical immunosensor have been used to diagonise early detections of these diseases. Immunosensors are based on the high affinity reactions antigen/antibody. As a result of the specific binding of antibody to its corresponding antigen, immunosensors based on antibody-antigen interaction are one of the most widely used analytical techniques in the quantitative detection of biomolecules, metal ions, and diseases in blood. Electrochemical immunosensors have sensitive detection limits to monitor both levels of the biomarkers in normal and patient serum. They are simple, rapid, reliable and inexpensive devices.

Electrochemical immunosensors based on antibody specific recognition of its antigen and subsequently transfer the recognition to amperometric, potentiometric, impedimetric conductometric signals to quantify antigen concentrations. Advanced carbon materials were frequently employed in immunosensors due to their adsorption characteristics and excellent electrocatalytical performance. Several strategies can be used to immobilise the recognition element, either the antibody or the antigen, depending on the selected scheme. The detection of the recognition event uses the same principle as the enzymatic immunoassay. In general, an enzyme is coupled to the recognition layer (the antigen or antibody) and the enzymatic reaction is developed once the antigen/antibody interaction occurred and after the addition of the substrate and electrochemically detection of the product. Immunosensor has the benefits of portability, fast response, simple operation, and low cost and has the potential for the development of rapid disease screening devices. Various research groups have fabricated CNT based immunosensor.

Han *et al*. (2017) constructed a novel sensitive, synthetic silver nanoparticles-carbon nanotube/manganese dioxide (Ag NPs-MWCNTs/MnO_2) which was used as labels of secondary antibodies (Ab_2) which improved the surface of electrode and enhanced the electrochemical signal. MnO_2 and Ag NPs achieve dual signal amplification to improve the sensitivity effectively. Under the optimal conditions, the electrochemical immunosensor exhibited a wide linear range of 0.0001–0.5 $ng \cdot mL^{-1}$ and 0.5–10 $ng \cdot mL^{-1}$ respectively with a low detection limit of 0.03 $pg \cdot mL^{-1}$ for CEA.

Sánchez-Tirado *et al.* (2017) used dual screen-printed carbon electrodes modified with 4-carboxyphenyl-functionalised double-walled carbon nanotubes (HOOC-Phe-DWCNTs/SPCEs) as scaffolds for the preparation of electrochemical immunosensors for the simultaneous determination of the cytokines Interleukin-1β (IL-1β) and factor necrosis tumor α (TNF-α). The achieved limits of detection were 0.38 pg/mL (IL-1β) and 0.85 pg/mL (TNF-α).

Sharma *et al.* (2017) immobilised Antigen over the surface of gold nanoparticle/multi-walled carbon nanotube (Nano-Au/C-MWCNT) screen printed electrodes using 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/N-hydroxysuccinimide (NHS) cross linking chemistry followed by interaction with groundnut bud necrosis virus (GBNV)/CaCV specific polyclonal antibody. The electrochemical response was measured by CV, differential pulse voltammetry (DPV) using the redox indicator. Electrode surface characterisation was done by performing SEM. Electrochemical studies showed positive results at different antigenic dilutions ranging from $10^{-2} – 8x10^{-5}$.

Guner *et al.* (2017) developed an electrochemical immunosensor for the common food pathogen Escherichia coli O157:H7. This novel immunosensor based on the PPy/AuNP/MWCNT/Chi hybrid bionanocomposite modified pencil graphite electrode (PGE). The prepared bionanocomposite platform and immunosensor was characterised by using CV. Concentrations of E. coli O157:H7 from 3×10^1 to 3×10^7 cfu/mL could be detected. The detection limit was ∼30 cfu/mL in PBS buffer. Furthermore, Liu *et al*. (2017) described a label-free amperometric immunosensor for the direct determination of ZENs. A glassy carbon electrode (GCE) was first modified with polyethyleneimine-

functionalised MWCNTs. Next, gold and platinum nanoparticles (AuPt-NPs) were electro-deposited. This process strongly increased the surface area for capturing a large amount of antibodies and enhanced the electrochemical performance. In a final step, monoclonal antibody against zearalenone was orientedly immobilised on the electrode, this followed by surface blocking with BSA. The resulting biosensor was applied to the voltammetry determination of ZENs, best at a working voltage of 0.18 V (vs SCE). Under optimised conditions, the method displays a wide linear range that extends from 0.005 to 50 ng mL^{-1}, with a limit of detection of 1.5 pg mL^{-1} (at an S/N ratio of 3).

Hien *et al*. (2017) also successfully developed an effective electrochemical method to produce polyaniline/multiwalled CNTs nanocomposite on interdigitated platinum microelectrodes for the enhancement of biosensing performance. Morphology and structure of nanocomposite were investigated by field emission scanning electron microscopy and UV–visible spectroscopy. FTIR technique was used to identify the presence of polyaniline/MWCNTs on the surface of microelectrodes. IgG polyclonal antibodies against Japanese encephalitis virus (JEV) were immobilised onto nanocomposite-modified microelectrodes, acting as an electrochemical immunosensor for label-free detection of JEV antigens. Results showed that the linear detection range of the immunosensor for JEV antigens was 2–250 ng/mL. The EIS analysis also indicated that a negligible response was found when the immunosensor exposed to non-specific molecules. This work showed the potential use of polyaniline/MWCNTs nanocomposite in the platform of electrochemical immunosensors for label-free detection of pathogens and small biomolecules.

Li *et al.* (2017) designed and fabricated a sensitive sandwich-type non-enzymatic electrochemical immunosensor for quantitative detection of squamous cell carcinoma antigen (SCCA). They used silver nanoflower-molybdenum disulfide/multiwalled carbon nanotubes (SNFs-NH2-MoS2/MWCNTs) as labels of secondary antibodies (Ab2) and exhibit remarkable multiple-signal amplification effects. The immunosensor shows a wide linear range between 0.1 pg mL^{-1} and 20 ng mL^{-1} with a limit of detection 0.03 pg mL^{-1}.

DNA Sensors

DNA a carrier of genetic information is considered to play a significant role in genetics and medical diagnosis. It is one of the most important intracellular targets that undergo modification and damage upon interaction with endogenous and exogenous factors. It is an excellent biomaterial for the construction of new devices, in nanotechnology and biosensor technology, for evaluation of DNA interaction with a broad range of chemical compounds and biomolecules, essential from a biological and a medical point of view. The electrochemical detection of DNA has also attracted extensive attention because of high sensitivity, high selectivity and low cost for the detection of selected DNA sequences or mutated genes associated with human diseases.

In DNA biosensors the biorecognition layer is a DNA molecule. There are, basically, two types of DNA biosensors, for the detection of the hybridisation event and for the detection of the DNA–drugs interaction or DNA damage. There are two fundamental aspects in the development of hybridisation biosensors, sensitivity and selectivity. Traditional methods for detecting the hybridisation event are too slow and require special preparation. Therefore, there is a great interest for developing new hybridisation biosensors, and the electrochemical ones represent a very interesting alternative.

An electrochemical DNA hybridisation biosensor basically consists of an electrode modified with a single stranded DNA. The first and most critical step is the immobilisation of DNA probe on the electrode in the preparation of DNA biosensor (Fig. 7). Hybrid formation under selected conditions of pH, temperature and ionic strength is the second step while the last one, involves the detection of the double helix formation by a given methodology that allows obtaining an electrical signal that clearly demonstrates that the sequence-specific biorecognition event has taken place. Biosensors containing DNA as

biorecognition layer also allow the detection of chemical and physical damage in DNA. In this case, it is necessary to immobilise preferentially double stranded DNA at the electrode surface to build the biosensor. The next step consists of the interaction of the DNA layer confined to the electrode with the given damage agent under controlled conditions, while the last step is the transduction of the signal, either from the oxidation/reduction of the nucleobases, damage agent, and/or the corresponding adducts. Various research groups have fabricated CNT based DNA biosensor:

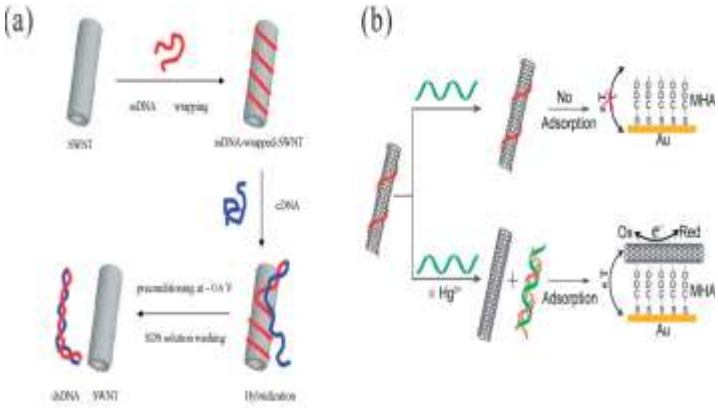

Figure 7: Schematic diagrams illustrating the interaction between SWCNTs and DNA. (b) Schematic representation of the electrochemical sensing strategy for the detection of Hg2+ ions based on DNA-functionalized SWCNTs. (Sengiz *et al*., 2015)

Ozkan *et al.* (2017) introduced DNA-wrapped multi-walled MWCNT-modified genosensor for the detection of Escherichia coli (E.coli) from polymerase chain reaction (PCR)-amplified real samples while Staphylococcus aureus (S.aureus) was used to investigate the selectivity of the biosensor. The capture probe specifically recognizing E. coli DNA and it was firstly interacted with MWCNTs for wrapping of single-stranded DNA (ssDNA) onto the nanomaterial. DNA-wrapped MWCNTs were then immobilised on the surface of disposable pencil graphite electrode (PGE) for the detection of DNA hybridisation. Electrochemical behaviours of the modified PGEs were investigated using Raman spectroscopy and differential pulse voltammetry (DPV). The sequence selective DNA hybridisation was determined and evaluated by changes in the intrinsic guanine oxidation signal at about 1.0 V by DPV. Numerous factors affecting the hybridisation were optimized such as target concentration, hybridisation time, etc. The designed DNA sensor can well detect E. coli DNA in 20 min detection time with 0.5pmole of detection limit in 30 µL of sample volume.

Sadrabadi *et a*l. (2016) designed a biosensor as a new, rapid, and sensitive tool for investigation of binding of zearalenone with double-stranded DNA (dsDNA). Polydiallyldimethylammonium chloride (PDDA) as a polycation and MWCNTs provide a positively charged surface with a high surface area for the immobilisation of dsDNA as a polyanion on the surface of pencil graphite electrode (PGE). Using the dsDNA/MWCNT–PDDA-modified PGE, it was possible to detect the interaction of zearalenone with dsDNA, which allowed application of the dsDNA-modified electrode for trace determination of zearalenone. By using dsDNA/PDDA–MWCNT/PGE, zearalenone could be detected as low as 0.005 ng mL^{-1}. The relative standard deviation of five measurements of 0.5 ng mL−1 zearalenone was found to be 4.2 %.

Mainwhile *et al*. (2016) presented a microfluidic-multiplexed platform that integrates electrochemical sensors based on CNTs associated with ferrocene as redox marker (carbon nanotube (CNT)/ferrocene) for direct detection of pathogenic viral DNA from Hepatitis C and genomic. DNA from Mycobacterium tuberculosis in clinical isolates. By operating the fluidic device under high flow (150 µl/min), the formation of a very thin depletion layer at the sensor surface (δS = 230 nm) enhances the capture rate up to one DNA strand per second. This microfluidic device working under high flow allows selective direct detection of a Mycobacterium tuberculosis (H37Rv) rpoB allele from clinical isolate extracted DNA.

Zhang (2016) developed a novel sensing platform based on Fe_3O_4 nanoparticles functionalised CNTs for highly sensitive label-free detection of BCR/ABL fusion gene from chronic myelogenous leukemia. Under optimal conditions, the dynamic range for detecting the sequence-specific DNA of the BCR/ABL fusion gene was

from 1.0×10^{-15} to 1.0×10^{-9} mol L^{-1} and the detection limit was 2.1×10^{-16} mol L^{-1}.

Taei *et al*. (2016) also prepared Fe_2O_3/SnO_2 nanocomposite by a solid-phase method in an alkaline medium. The Fe_2O_3/SnO_2 composite was characterised by X-ray diffraction, field emission scanning electron microscopy, and Fourier transform infrared spectroscopy. A sensitive electrochemical biosensor is also presented for the determination of doxorubicin (DOX) based on a ds-DNA-decorated multiwalled carbon nanotubes-Fe2O3/SnO2-chitosan (ds-DNA-MWNTs-Fe_2O_3/SnO_2 CHIT) modified pencil electrode. DOX has shown an oxidation peak at 0.34 V on the surface of the bare pencil graphite electrode (PGE) in pH 7.0. The presence of DNA results in a decrease in the current; moreover, a positive shift in the DOX oxidation peak indicates an intercalative interaction. Finally, a PGE modified with ds-DNA-MWNTs-Fe2O3/SnO2 CHIT was tested in order to determine the DOX content in the solution. The dynamic range was from 20.0 to 5552.0 nmol L^{-1} with a detection limit of 0.004 nmol L^{-1}. This sensing platform showed other advantages such as simplicity, good stability, and high sensitivity.

Abdel-Hamid & Newair (2016) used MWCNTs-modified glassy carbon electrode biosensor for electrochemical studies of caffeic acid-dsDNA interaction in phosphate buffer solution at pH 2.12. Caffeic acid, CAF, shows a well-defined cyclic voltammetric wave. The oxidative damage caused to DNA was detected using the biosensor. The damage caused by the reactive oxygen species, hydroxyl radical (OH) generated by the Fenton system on the DNA-biosensor was detected. It was found that CAF has the capability of scavenging the hydroxide radical and protecting the DNA immobilised on the GCE surface.

Wang *et al*. (2016) fabricated an electrochemical biosensor based on MWCNTs and Hb in order to explore the DNA damage mechanism induced by endogenous factors and the activities of the antioxidants. When the glassy carbon electrode (GCE) modified with chitosan (CS), double stranded DNA (ds-DNA), MWCNTs and Hb was subjected to a negative potential of - 1.4 V in PBS of pH 5.8, the dissolved oxygen was reduced to H_2O_2 on the surface of the MWCNTs. Then the H_2O_2 reacted with Hb and formed a Compound I (Hb-C-HOOH) and H2O. The Compound I, highly oxidising specie, can be used as reactive oxygen species (ROS) and to damage DNA in situ in the membrane. The ascorbic acid (AA) can protect the DNA from damage by scavenging the H_2O_2 to inhibit the formation of the Compound I. The ds-DNA oxidative damage degree and the protective effect of AA from DNA damage were monitored by CV, EIS and ultraviolet-visible spectroscopy (UV-vis).

Ascorbic Acid (AA), Uric Acid (UA), Dopamine (DA)

Dopamine (3,4-dihydroxylphenyl ethylamine) (DA) is the most significant neurotransmitter in the human nervous system. Abnormal dopamine levels cause fatal neurological disorders, and thus measuring dopamine level in actual samples is important. DA is one of catecholamine neurotransmitters which have impact on cognitive and behavioural functions in animals, including humans. Lack of DA is one of the reasons of Parkinson's disease. A deficiency of dopamine in the brain is believed to cause schizophrenia and Parkinson's disease. This makes the sensing of dopamine in brain tissue so vital in clinical diagnoses. DA also plays a significant role in the central nervous, renal, hormonal, and cardiovascular systems. Ascorbic acid, Vitamin C, is an anion at physiological pH that can undergo a two-electron transfer oxidation while Uric acid is the final product of purine metabolism and related to disorders such as hyperuricemia and Lesche Nyhan syndrome (Pisoschi *et al*. 2014).

UA and AA are significant health biomarkers and will cause overlapping voltametric response and result in unexpected interferences under simultaneous detections with DA. Although electrochemical methods have been developed for detecting dopamine with high accuracy, certain substances (e.g., ascorbic acid) in actual samples often interfere with electrochemical dopamine detection. Because dopamine, ascorbic acid, and uric acid have similar oxidation potentials and often coexist in biological samples, many researchers have simultaneously determined DA, AA and UA using various methods:

Ghodsi *et al.* (2015) developed a multifunctional biosensor for the simultaneous determination of DA, UA and Try using 2-amino-thiazole (AT)/gold nanoparticles (AuNPs) functionalised multiwalled carbon nanotubes (f-MWCNT) modified electrode. The f-MWCNT/AuNPs-AT composite modified glassy carbon electrode (GCE) was prepared by electrodeposition of AT and followed by electrodeposition of AuNPs and drop casting of f-MWCNT on GCE. The formation of the composite was confirmed by atomic force microscopy, scanning electron microscopy and electrochemical studies. The f-MWCNT/AuNPs-AT modified GCE exhibits good electrocatalytic ability for the simultaneous determination of DA, UA and Try. CV and linear sweep voltammetry were used for simultaneous and selective determination of DA, UA and Try. Moreover, the modified electrode also provides good sensitivity and selectivity for the determination of DA, UA and Try.

Erkal *et al*. (2016) described the development of a novel biosensor for simultaneous determination of dopamine, uric acid, and folic acid by carbon paste electrode modified by hemoglobin which is electrostatically immobilised on silica-coated magnetic nanoparticles and MWCNTs. The modified carbon paste electrode provided a sensitive and stable biosensor for simultaneous determination of dopamine, uric acid, and folic acid whose performance is much better than those of many previously reported sensors. The detection limits were calculated to be about 12 nM, 14 nM and 18 nM and the linear range for determination of DA, UA and FA are 1-30.6 μM, 1-286 μM and 1-369 μM, for dopamine, uric acid, and folic acid, respectively. Finally, the applicability of the proposed biosensor was verified by DA evaluation in serum samples.

Metal ions Biosensing

The presence of metal ions in food chains due to the rapid industrialisation poses serious threat to the environment. They have severe environmental and medical effects and so require careful monitoring, fast, accurate and reliable analytical techniques for their detection in environment and food. The heavy metal ions, especially Cd^{2+}, Pb^{2+} and Hg^{2+}, show extremely hazard to the environment and human being. Electrochemical technique featured with short analytical time, low power cost, high sensitivity and easy adaptability for in-situ measurement is one of the most developed analytical methods used in detection of metal ions in environment and food.

Heavy metal ions are non-biodegradable and contaminate most of the natural resources occurring in the environment including water. Some of the heavy metals including Lead (Pb), Mercury (Hg), Arsenic (As), Chromium (Cr) and Cadmium (Cd) are considered to be highly toxic and hazardous to human health even at trace levels. The development of a sensitive and selective detection method is important to both the environmental and food chemists. Detection and monitoring of metals ions contamination are gaining more attention nowadays but the current analytical methods for the detection of metal ions contamination are very expensive, tedious and can only be handled by trained personnel (Saidur *et al.*, 2017). Various research groups have fabricated CNT based metal ion biosensor:

Ebrahimi *et al.* (2017) reported an electrochemical DNA biosensor based on a G-quadruplex (G4) for the sensitive determination of Pb^{2+} using a carbon paste electrode (CPE) or a multi-walled carbon nanotube paste electrode (MWCNTPE) as working electrodes, ethyl green (EG) as a new G4 intercalator, and a single-stranded nucleic acid sequence rich in guanine (G) as DNA probe. Electrochemical determination of Pb^{2+} relied on probe structural changes from single - stranded to the stabilized intramolecular G4 in the presence of Pb^{2+}, which caused a change in the current of the EG reduction peak due to the intercalation of EG into the G4 structure. The change in the reduction peak of EG before and after its intercalation into the stabilized G4 (ΔI) had a linear correlation to the concentration of Pb^{2+} ions. The linear ranges of 4.0×10^{-10}–5.0×10^{-9} M and 2×10^{-7}–1×1^{-5} M with a detection limit (LOD) of 1.04×10^{-10} M were obtained using CPE, while improved linear ranges of 4.0×10^{-11}–1.0×10^{-9} M and 2×10^{-7}–1×10^{-5} M with a lower LOD of 2.64×10^{-11} M were achieved using the MWCNTPE biosensor. The biosensors exhibited

satisfactory results in terms of selectivity and practical applicability in the analysis of real samples.

Tian *et al*. (2016) described a simple one-step electrodeposition method to fabricate three dimensional ordered macroporous chitosan−prussian blue−single walled carbon nanotubes (3DOM CS−PB−SWCNTs) film onto the gold electrode surface to fabricate a copper ion (Cu^{2+})-specific DNAzyme biosensor. The new sensing strategy for sensitive and selective detection of Cu^{2+} was based on Au nanorods (AuNRs) as signal amplification labels. The electrochemical signal of glucose increased with the concentration of Cu^{2+} increasing. The morphologies and electrochemistry of the composites were investigated by using SEM, TEM and electrochemical techniques including CV and EIS and so on. Linear correlations of copper ion concentration were obtained in the range from 10^{-18} M to 10^{-5} M, achieving with a limit of detection of 10^{-19} M (S/N=3). Parameters affecting the biosensor response such as temperature, the cleavage time and the time of hybridisation were optimized. This biosensor showed a wide range, low detection limit, good reproducibility and high stability. Additionally, these striking properties endow the biosensor with a great promise for analytical applications.

Camara *et al*. (2016) reported the tuning of a fast, disposable, and label-free biosensor for quantification of iron (III) in food liquid samples such as wine. The biosensor is based on a field effect transistor (FET) where a network of SWCNTs acts as the conductor channel, constituting carbonnanotubes field effect transistors (CNTFETs). An antibody such as transferrin with two specific high-affinity iron (III) binding sites, directly adsorbed to SWCNTs, was used as immunoreaction. Several individual CNTFETs were tested showing a linear range between 0.05 and 2 ng mL^{-1} and a limit of quantification below 0.05 ng mL^{-1}, much lower than previously reported analytical techniques. The mean coefficient of variation was 0.13% showing a low variability of the analytical response. On the other hand, it was not observed interference effect of zinc (II) ion at least until 1:4 iron-zinc ratio. Finally, recovery percentages of spiked wine samples were around 100%, showing the high accuracy of method.

Pesticides Biosensing

Organophosphate compounds (OP) are heavily used in agriculture and military activities, while non-organophosphate pesticides are mostly used in agriculture and home defence.

Organophosphorus (OP) compounds are used as pesticides and chemical warfare agents. Hence the detection of OP neurotoxins is essential for the protection of water resources and food supplies, as well as for monitoring detoxification processes. Several researchers have fabricated CNT based pesticides biosensors:

Bagheri *et al.* (2016) synthesised a biocompatible nanocomposite including bovine serum albumin (BSA) template Cu nanoclusters (CuNCs@BSA) and SWCNTmetal to fabricate a highly sensitive electrochemical biosensor for paraoxon as a model of organophosphates. The UV–vis, fluorescence and Fourier transform infrared (FTIR) demonstrated that BSA entrapped in the nanocomposite film have been changed in its secondary structure so that it provided an enzyme like activity attributing to the high electrical conductivity of the entrapped copper nanoclusters. Also, the morphology and structure of prepared nanocomposites were investigated by TEM and SEM. In the prepared nanocomposite, the CuNCs@BSA found to play as a conductive holder as well as an accumulator of redox active centres on the surface of the electrode, and SWCNT improves the electrocatalytic activity along with conductivity of glassy carbon electrode (GCE) surface. The fabricated biosensor exhibited excellent sensitivity, acceptable stability, fast response, and high electrocatalytic activity toward the reduction of Paraoxon. The reduction peak current vs paraoxon concentration was linear over the range 50 nM to 0.5 μM and 0.5–35 μM, with a limit of detection of 12.8 nM. Notable electrocatalytic properties of the developed electrode toward Paraoxon indicated that the nanocomposite possesses a promising potential to fabricate the third generation enzyme-free

electrochemical biosensors, bioelectronics and state-of-the-art biomedical devices in the future

Zheng *et al*. (2016) fabricated a new type of organophosphate pesticide (OP) biosensor based on the immobilization of AChE by cross-linking on a glassy GCE modified with ionic liquid functionalized graphene (IL-GR), Co_3O_4 nanoparticles and chitosan (CHI). The introduction of IL-GR and Co_3O_4 nanoparticles not only enhanced the surface area of the modified electrode for enzyme immobilisation but also facilitated the electron transfer, resulting in a high sensitivity of the biosensor. The fabrication process of the sensing surface was characterized by cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS). For the oxidation of thiocholine, a hydrolysis product of acetylthiocholine, the peak current at the AChE/IL-GR/Co_3O_4/CHI/GCE electrode is larger than those at AChE/IL-GR/CHI/GCE and AChE/Co_3O_4/CHI/GCE electrodes. A linear relationship between the inhibition percentage (I%) and logarithm of the concentration of dimethoate was found in the range from 5.0×10^{-12} to 1.0×10^{-7} M, with a detection limit of 1.0×10^{-13} M (S/N = 3). The proposed biosensor provided an efficient and promising platform for the immobilization of AChE and exhibited higher sensitivity and acceptable stability for the detection of organophosphate pesticides.

Similarly, Bao *et al*. (2016) developed a novel biosensor for rapid, sensitive and selective monitoring of p-nitrophenyl substituted organophosphate pesticides (OPs) in aqueous system using a functional nanocomposite which consists of elastin-like-polypeptide-organophosphate hydrolase (ELP-OPH), bovine serum albumin (BSA), titanium dioxide nanofibers (TiO_2NFs) and carboxylic acid functionalized multi-walled carbon nanotubes (c-MWCNTs). ELP-OPH was simply purified from genetically engineered Escherichia coli based on the unique phase transition of ELP and thus served as biocatalyst for OPs, while BSA was used to stabilize OPH activity in the nanocomposite. TiO_2NFs was employed to enrich organophosphates in the nanocomposite due to its strong affinity with phosphoric group in OPs, while c-MWCNTs was used to enhance the electron transfer in the amperometric detection as well as for covalent immobilization of ELP-OPH. ELP-OPH/BSA/TiO_2NFs/c-MWCNTs nanocomposites were systematically characterized using field emission scanning electron microscopy (SEM), Raman spectra, Fourier Transform infrared spectroscopy (FTIR) and X-ray Diffraction (XRD). Under the optimized operating conditions, the ELP-OPH/BSA/TiO_2NFs/c-MWCNTs based biosensor for OPs shows a wide linear range, a fast response (less than 5 s) and limits of detection (S/N=3) as low as 12 nM and 10 nM for methyl parathion and parathion, respectively. Such excellent sensing performance can be attributed to the synergistic effects of the individual components in the nanocomposite. Its further application for selectively monitoring OPs compounds spiked in lake water samples was also demonstrated with good accuracy. These features indicate that the developed nanocomposite offers an excellent biosensing platform for rapid, sensitive and selective detection of organophosphates compounds.

Bolat *et al.* (2017) fabricated a novel amperometric bienzymatic biosensor based on iron (II, III) oxide nanoparticles (Fe_3O_4NPs), MWCNTs and chitosan (CS) modified glassy carbon electrode (GCE) for the determination of acetylcholine (ACh). The CS was used to immobilize AChE and choline oxidase (ChOx). The nanocomposites of Fe3O4NPs and MWCNTs were characterised by SEM, EIS and CV. The electrochemical measurements were based on the detection of enzymatically produced H_2O_2. The experimental parameters such as working potential, enzyme unit, pH and temperature were optimised. The linear ranges of the biosensor were 0.02 μmol L^{-1}–0.111 μmol L^{-1} and 0.111 μmol L^{-1}–1.87 μmol L^{-1}. The detection limit was calculated as 0.61 nmol L^{-1}. In addition, the amperometric biosensor showed high sensitivity, good selectivity, repeatability, reproducibility and long-term stability. The fabricated biosensor was used to determine ACh levels in serum samples.

Miao *et al*. (2016) designed and developed a novel and highly sensitive electrochemiluminescence (ECL) biosensing

system for individual detection of different OPs in food samples. Bimetallic Pt-Au nanoparticles were electrodeposited on MWNTs-modified GCE to increase the surface area of electrode and ECL signals of luminol. Biocomposites of enzymes from AChE and ChOx were immobilised onto the electrode surface to produce massive H_2O_2, thus amplifying ECL signals. Under optimised experimental conditions, the ECL intensity decreased accordingly with the increase in concentration of OPs, and the inhibition rates of OPs were proportional to their concentrations in the range of 0.1–50 nmol L^{-1} for malathion, methyl parathion and chlorpyrifos, with detection limit of 0.16 nmol L^{-1}, 0.09 nmol L^{-1} and 0.08 nmol L^{-1}, respectively. The linearity range of the biosensor for pesticide dufulin varied from 50 to 500 nmol L^{-1}, with the detection limit of 29.7 nmol L^{-1}. The resulting biosensor was further validated by assessment of OPs residues in cabbage, which showed a fine applicability for the detection of OPs in the realistic sample.

Conclusions and Perspective

This review addresses the progress that have been made using CNTs for electrochemical biosensing. CNTs have the ability to strongly interact with biomolecules. Advantages of CNTs lie in their flexible processability to immobilise biomolecules and create multi-functional materials. The excellent electrochemical properties of CNTs enable direct electrochemistry of biomolecules, especially in case of deeply embedded redox active sites. Hence, CNT-based biosensors can work at low operational potential. The high electroactive area of the CNTs, the surface concentration of biomolecules is increased and the amperometric response often exhibits high current density. But metallic impurities are a major obstacle in electrochemical sensing research with CNTs.

The recent advances reveal that applications of CNTs electrodes will face many challenges in the future, in particular in the engineering of bioelectronics interfaces for the fabrication of nano-bioelectrode arrays or biofuel cells. The future challenge will be a multi-faceted challenging work that needs mutual cooperation between material scientist, chemist and engineers who are committed to the fabrication of future micro/nano biosensor

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