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Synthesis and utilisation of graphene for fabrication of electrochemical sensors

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Abstract

This review summarises the most recent contributions in the fabrication of graphene based electrochemical biosensors in recent years. It discusses the synthesis and application of graphene to the fabrication of graphene-based electrochemical sensors, its analytical performance and future prospects. An increasing number of reviews and publications involving graphene sensors have been reported ever since the first design of graphene electrochemical biosensor. The large surface area and good electrical conductivity of graphene allow it to act as an "electron wire" between the redox centers of an enzyme or protein and an electrode's surface, which make it a very excellent material for the design of electrochemical biosensors. Graphene promotes the different rapid electron transfers that facilitate accurate and selective detection of cytochrome-c, β-nicotinamide adenine dinucleotide, haemoglobin, biomolecules such as glucose, cholesterol, ascorbic acid, uric acid, dopamine and hydrogen peroxide.

Keywords Enzymes; DNA biosensor; Immunosensor; Enzyme biosensor; Graphene electrode; Glucose; Ascorbic acid.

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Content

1. Introduction

Recently, great attention has been focused on graphene and its derivatives and they are being studied in nearly every field of science [1], medicine [2,3] and engineering [4]. Graphene-based materials can have a profound impact on electronic and optoelectronic devices [5], chemical sensors [6, 7], nanocomposites [8-14], optical biosensor [15] and energy storage [16, 17]. New applications of grapheme nanomaterials in electrochemical sensors and biosensors are now on the increase with the advent of nanotechnology [4, 18-21]. Various graphene nanomaterials [20-28], including graphene metal nanoparticle (NP) [29-36], nanocomposite [14, 37-41], metal alloy NP, magnetic NP [42], nanowires [22, 43-45], nanofibers [46], nanorod [47], CNT [21, 48-57], and CNF [58] have been used as electrical connectors between the electrodes and the redox centers of the biomolecules [57-62]. The use of graphene as a nano material can avoid the problems associated with metal alloy NP and CNT. The properties of graphene, such as fast electron transportation, high thermal conductivity, excellent mechanical flexibility and good

biocompatibility, make it a potential in the fabrication of sensitive electrochemical biosensor [63-67]. Graphenes was discovered in 2004 by scientists [68], and since the 2010 Nobel Prize in Physics "for groundbreaking experiments regarding the two-dimensional material grapheme.'' graphenes have been the goal of numerous researchers due to their unique structural, electronic and mechanical properties that make them a very attractive material for a wide range of applications [4, 54, 69-71] Fig. 1. Table1.

Graphene is the basic structure of all graphitic materials and is a one-atom-thick planar sheet of sp2 bonded carbon atoms in a honeycomb crystal lattice [66]. Its remarkable electronic, optical, mechanical, thermal, and electrochemical properties have made it a suitable electronic material for electrochemical sensing, as graphene has a very good electronically low-noise [72, 73]. Many groups all over the world are doing exciting work using graphene and its hybrids in applications such as super capacitors [74-78], fuel cells [79-83], batteries [63, 84-87],photocatalysis [17, 63, 88, 89], photovoltaics [25, 90], chemical and biosensors [7, 91-95],gas sensors [74, 96-99], photonics [100, 101], solar cell [17, 75, 102], light-emitting diodes (LEDs) [103, 104], laser [105] , optoelectronics [100, 106], photocatalyst [107, 108], thin-film transistors [103, 109] and field effect transistor (FET) [110-113] Table 1.

2. Synthesis of graphene

A number of different routes to synthesise graphene have been demonstrated over recent years. There are two ways to synthesise grapheme: mechanical method and chemical method. The chemical method is through oxidation, usually Standenmaier method [114], Brodie method [115] and Hummers method [116]. The mechanical method, 'Scotch tape technique', was used in 2005, to fabricate graphene where multiple layers of graphene are peeled from a slab of highly

ordered pyrolytic graphite using adhesive tape and transferred onto an appropriate substrate [117]. Majority of other fabrication methods of graphene are produced and supplied in solution, such that graphene has to be immobilised onto the desired surface [118, 119]. Graphene and related materials, such as graphene oxide (GO) [120] and reduced graphene oxide (rGO) [121, 122], have come to the forefront of research in electrochemical sensors during recent years. Ratinac et al. [123] synthesised GO following a modified Hummer's method, which has been subsequently reduced by electrochemical procedures. This reduction strategy precludes the employment of toxic solvents, leading to a product electrochemically reduced graphene (ERG), free of contaminants. There are other several reported methods for the synthesis of graphene [85, 90, 124, 125], including exfoliation, cleavage of natural graphite, micromechanical exfoliation of graphite, epitaxial growth on electrically insulating surfaces, such as SiC, opening CNT and the solution-based reduction of GO [90,126-128].

2.1. Chemical vapour deposition (CVD) method

CVD, a fabrication process where graphene is grown upon a substrate, has emerged as an important method for the preparation and production of graphene for various applications since the method was first reported in 2008/2009 [103, 129-131] Fig. 2. Recently, Zhang et al. [132] reviewed graphene CVD on various metal substrates with emphasis on Ni and Cu. In addition, they discussed important and representative applications of graphene formed by CVD, which includes flexible transparent conductors for organic photovoltaic cells as well as field effect transistors. Growth on polycrystalline Ni films leads to both monolayer and few-layer graphene with multiple layers because of the grain boundaries on Ni films. They were able to increase the percentage of monolayer graphene by using single-crystalline Ni (111) substrates, which have a

smooth surface and no grain boundaries. Due to the extremely low solubility of carbon in Cu, Cu has emerged as an even better catalyst for the growth of monolayer graphene with a high percentage of single layers. Zhang et al. [132] also described a method for transferring graphene sheets from the metal using polymethyl methacrylate (PMMA). Paniagua et al. [133] produced heavily n- and p-doped CVD graphene with solution-processed redox-active metal-organic species.

CVD can produce large areas of single layer grapheme [134]. Ambrosi et al. [65] investigated the electrochemical properties of a multilayer graphene film grown by CVD and transferred to an insulating flexible poly (ethylene terephthalate) (PET) sheet. They carefully characterised PET with optical microscopy, Raman spectroscopy, and X-ray photoelectron spectroscopy of the transferred graphene film. They tested its heterogeneous electron transfer properties with $Fe(CN)_6^{3+/4+}$ And $Ru(NH3)_6^{2+/3+}$ redox mediators and its sensing capability toward dopamine (DA), ascorbic acid (AA), and the reduced form of nicotinamide adenine dinucleotide (NADH) as biological relevant molecules. The CVD grown multilayer graphene film transferred to a PET substrate showed an electrochemical behaviour that resembles that of basal plane graphite with a low density of edge-plane defects sites. Li et al. [113] and Reina et al. [134] synthesised graphene by CVD using centimeter-scale copper substrates. Recently, Zhang et al. [135] synthesised graphene by CVD from solid PMMA deposited on a Cu substrate. CVD graphene has electronic properties that are potentially valuable in a number of applications. Zhang et al. [136] found that few-layer graphene grown on Ni can function as flexible transparent conductive electrodes for organic photovoltaic cells. In addition, they synthesised large-grain graphene on Cu foil, such large-grain graphene has electronic properties suitable for use in field effect transistors. CVD of graphene on Cu and Ni substrates are the most promising procedures to

synthesize large-area and good quality graphene films [137]. Ambrose et al. [138] investigated the electrochemical properties of a multilayer graphene film grown by CVD and transferred to an insulating flexible poly(ethylene terephthalate) (PET) sheet Fig. 2. Wu et al. [130] reported wafer-scale synthesis of graphene by CVD and its application in hydrogen sensing. Kim et al. [139-140] synthesised graphene films on Ni substrates for stretchable transparent electrodes .

2.2. Graphene sheet (Gs)

The characterization of the synthesized nanomaterials by combination of techniques confirms that the synthesis methodology affords the production of GO nanosheets, which present a typical lateral dimension of several hundreds of nanometers and a thickness value of 1.3±0.1nm, and the production of graphene nanosheets free of oxygen functionalities with an average lateral dimension of at least 1micrometer and a thickness value of 2.8±0.2nm [141].

Alwarrapan et al. [142-143] chemically synthesised graphene nanosheets as electrode materials and their electrochemical properties were systematically characterised. The surface morphologies of graphene nanosheets were evaluated using Raman spectroscopy and transmission electron microscopy (TEM) as shown in Fig. 3. They also reported electrochemical properties of graphene nanosheets for biosensing applications. Rattana et al., Park, Rauf, Fowler et al. and Wu et al. [144-147] produced GO nanosheets by a chemical exfoliation technique.

Recent studies by Stankovich et al. and other researchers [41, 148-150] have shown that Gs can be prepared in large quantity through chemical conversion from graphite, which can be used in the fabrication of graphene-based electronic devices [137, 151-153] and chemical conversion also made it possible to create new bulk materials comprising graphene sheets for a broader range of applications [154, 155]. It has been recently demonstrated that chemically modified Gs

can be dispersed throughout a polymeric [148, 149] or inorganic matrix [155] to make electrically conducting composites with a percolation threshold as low as 0.1 vol %. Studies by Chen et al. [137] also showed one novel step of the exfoliated accompanying carboxylated graphene sheet from pristine, which is achieved via Friedel-Crafts acylation. By electrophilic aromatic substitution, the succinic anhydride ring is opened and it attaches covalently to the Gs to form exfoliated graphene with grafted 1-one-butyric acid (Gs-BA). The grafting chain converts anions in aqueous solution to maintain Gs-BA in a stable dispersion and noticeably decreases the π-π stacking of the exfoliated Gs during the drying process. Gs-BA retains the Gs electrical properties favourable for developing electrochemical sensors [156].

2.3. Other methods

Dong et al. [157] prepared monolayers of graphene from natural flake graphite using 1, 3, 6, 8-pyrenetetrasulfonic acid and D_2O. Graphene can also be produced via a substrate-free gas-phase synthesis method. This involves sending an aerosol consisting of liquid ethanol droplets and argon gas directly into a microwave-generated argon plasma (at atmospheric-pressure), where over a time scale in the order of 10^{-1} s, ethanol droplets evaporate and dissociate in the plasma forming solid matter. It was confirmed to be true grapheme through characterisation by transmission electron microscopy (TEM) and Raman spectroscopy. Graphene can also be prepared on H_2-etched surfaces of 6H-SiC when heated to 1250–1450 °C for a short time (1–20 min) [145]. Another mass production method involves the chemical or thermal reduction of GO [158] and to date is the most common and economical method. Graphene synthesized by chemical oxidation–reduction has been reported to possess many structural defects, which are advantageous for electrochemical applications [59]. Chakrabati et al. [159] reported on progress

made in the electrochemical modification of graphene-base materials and their applications. Kumar [160] recently reported laser flash synthesis of graphene and its inorganic analogues. This was an innovative breakthrough with immense promise. Jelili et al. [161] worked on graphene oxide dispersion. They showed that GO dispersions exhibit unique viscoelastic properties which show them as a new class of soft materials. The fundamental insights accrued from here provide the basis for the development of fabrication protocols for the two dimensional soft materials produced in a diverse array of processing techniques.

3. Review studies

Because of the excellent properties of graphene, such as large surface-to-volume ratio, high conductivity and electron mobility at room temperature, as well as low energy dynamics of electrons with atomic thickness, robust mechanical and flexibility, it is at the center of an ever-growing research. These unique properties have made many researchers to review synthesis of graphene and its applications in the recent years. Graphene, a single-layered atom, emerging as a true two-dimensional nanomaterial, has tremendous potential for electrochemical catalysis, biosesing and as a novel electrode material.

3.1. Review of graphene synthesis and production

There are many reviews on graphene and its applications to various devices. However, few of the review articles connect the intrinsic properties of graphene with its energy. Wei et al. [62] stated in their review that a lot of scientific results on graphene published to date actually deal with multi-layer groupings' or reduced graphenes from insulating GO, which contains defects and contaminants from the reactions and do not possess any of the intrinsic physical properties of

pristine graphene. Bonaccorso et al. [163] reviewed the state of the art of graphene preparation, production, placement and handling. Geim [164] reviewed graphene's status and prospects and Wee [165] reviewed prospects and applications of graphene. Zhang et al. [132] reviewed graphene CVD on various metal substrates with an emphasis on Ni and Cu. In addition, they discussed important and representative applications of graphene formed by CVD, including as flexible transparent conductors for organic photovoltaic cells and in field effect transistors. Brownson et al. [166] also reviewed recent developments in the fabrication of CVD graphene and explored its utilisation in electrochemistry, considering its fundamental understanding to applications in sensing and energy related devices.

Edwards et al. [167] reviewed and highlighted the different methods available for the synthesis of graphene and discusses the viability and practicalities of using the materials produced via these methods for different graphene-based applications. Allen et al. [66] called graphene a honey comb carbon in their review of graphene. Choi et al. [90], also in their review presented an overview of the advancement of research in graphene in the area of synthesis, properties and applications, such as field emission, sensors, electronics, and energy. They enumerated and highlighted future research directions. Chen et al. [126] in their critical review described recent advances in the development of graphene-based materials from the standpoint of electrochemistry. They discussed electron transfer properties of graphene involving its unusual electronic structure, extraordinary electronic properties and fascinating electron transport. Walcarius et al. [24], in their review, discussed the interest of both nano-objects (metal nanoparticles and quantum dots, carbon nanotubes and graphene) and nano-engineered and or nanostructured materials (template-based materials, advanced organic polymers) for the rational design of bio-functionalized electrodes and related biosensing systems. The attractiveness of

such nanomaterials relies not only on their ability to act as effective immobilization matrices, which are likely to enhance the long-term stability of bioelectrochemical devices, but also on their intrinsic and unique features. Kumar et al. [160] presented an overview of the progress made into laser based synthesis of graphene and its inorganic analogue. Singh et al.'s [168] review provided a comprehensive scientific progress of graphene to date and evaluated its future perspective. Various synthesis processes of single-layer graphene, graphene nanoribbons, chemically derived graphene, and graphene-based polymer and nano particle composites are reviewed. Their structural, thermal, optical and electrical properties were also discussed, along with their potential applications. The article concluded with a brief discussion of the impact of graphene and related materials on the environment, its toxicological effects and its future prospects in this rapidly emerging field. Wang et al. [169] reviewed nitrogen-doped graphene, including various synthesis methods to introduce N-doping and various characterization techniques for the examination of various N-bonding configurations. Potential applications of N-graphene were also reviewed on the basis of experimental and theoretical studies.

3.2. Graphene electrochemical reviews

Fang and Wang [170] provided an overview of electrochemical biosensing with graphene related materials and discussed the role of grapheme in different sensing protocols. Artiles et al. [111] comprehensively reviewed the most recent trends in graphene-based biosensors and attempted to identify the future directions in which the field is likely to thrive. Browson et al. [63, 125] reviewed potential application of graphene and looked into recent understanding of grapheme-modified electrodes, highlighting prominent applications reported in the current literature. Chakrabarti et al. [159] reviewed the electrochemical modification of graphene. They discussed

different composite materials that have been prepared with reduced graphene and enumerated six different methods of electrochemical modification of graphene to prepare composite materials. These include cathodic reduction of GO, electropheric deposition, electro-deposition techniques, electrospinning, electrochemical doping, and electrochemical polymerisation.

Over the past few years, much work has been done in the design and preparation of novel graphene-based materials for a wide range of applications in photoelectron chemistry, ranging from photo electrochemical solar cells, photo catalytic decomposition of organic pollutants, photo catalytic splitting of H_2O, and photo catalytic conversion to fuels. Chen et al. [17, 21, 126] summarised the state of research on graphene-based materials from the standpoint of photoelectron chemistry and electrochemistry. The prospects and further developments in this exciting field of graphene-based materials were also discussed. They also presented the current advances in the field of graphene electroanalytical chemistry, including the modern methods of graphene production and graphene functionalisation. Gan and Hu [171] gave a general view of recent advances in electrochemical sensors based on graphene. They emphasised the important applications of graphene and graphene nanocomposites, and the assayed strategies in electrochemical sensors for DNA, proteins, neurotransmitters, phytohormones, pollutants, metal ions, gases, hydrogen peroxide and in medical, enzymatic and immunosensors. Kuila et al. [124] reviewed and discussed the application of graphene for the detection of glucose, Cyt-c, NADH, Hb, cholesterol, AA, UA, DA, GO and H_2O_2 RGO that had been used for the fabrication of heavy metal ion sensors, gas sensors and DNA sensors. Graphene based FETs were also discussed in details. Putzbach and Ronkainen [20] reviewed immobilisation techniques in the fabrication of graphene nanomaterial-based electrochemical biosensors.

4. Graphene nanocomposites (GN)

Graphene-inorganic nanocomposites have opened up an exciting new field in the science and technology of GN. GN-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 centers in proteins and electrode surfaces, and as catalysts to increase electrochemical reaction rates [36]. The conductivity of nanoparticles enhances electron transfer between the active centers of enzymes and electrodes so that the particles act as electron transfer conduits or mediators [172]. Bai et al. [173] presented an overview of the synthesis and application of GN-inorganic nanocomposites. They also discussed challenges and perspectives of these emerging nanocomposites. Li et al. [174] presented an overview of the latest design of structures, synthetic methods and applications of graphene-based inorganic nanocomposites. The challenges and perspectives of these emerging hybrid heterostructures were also discussed.

Graphene has been incorporated into nanocomposites in order to couple its unique properties with the properties of other nano-materials. Lui et al [175] recently produced graphene nanoplatelet-titanate nanotube composite and its advantages over the two single components as biosensor immobilization materials. Feng et al. [176] synthesised graphene-Au nanocomposites through hydrothermal route. TEM images gave direct evidence of the thin and transparent sheet structure of graphene. X-ray photoelectron spectroscopic (XPS) and X-ray diffraction (XRD) results also showed the presence of Au and the reduction of GO. The graphene-Au nanocomposites provide a novel matrix for protein immobilization and the construction of biosensors via the direct electron transfer of protein. Gao et al. [177] developed a novel electrochemiluminescence (ECL) ethanol biosensor based on Ru $(bpy)_3^{2+}$ and alcohol

dehydrogenase (ADH) immobilized by graphene/bovine serum albumin composite film. The graphene film was directly formed on a glassy carbon electrode surface via an in situ reduction of GO, and $(bpy)_3^{2+}$ was immobilized during its formation. The graphene film acted as both a decorating agent for immobilization of $Ru(bpy)_3^{2+}$ and a matrix to immobilize bovine serum albumin (BSA). Meanwhile, BSA not only acted as reductants to reduce GO, but also provided a friendly environment for ADH immobilization. Furthermore, ADH was separated from $Ru(bpy)_3^{2+}$ by the electron-conductive graphene/BSA composite film to retain its enzymatic activity.

Huang et al. [178] synthesised layered MoS2–graphene composites by a modified l-cysteine-assisted solution-phase method, and they were characterised by XRD, field emission SEM, and high-resolution TEM. The electrochemical properties of the nanocomposite film were investigated by electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV). Acetaminophen as model molecular was employed to study its electrochemical responses at the MoS2–graphene modified electrode, which shows more favourable electron transfer kinetics than graphene modified glassy carbon and bare glassy carbon electrodes. This novel electrochemical sensor exhibits excellent analytical performance for acetaminophen detection, with detection limit of 2.0×10^{-8} mol L^{-1} (S/N = 3) and linear range of 0.1–100 μ mol L^{-1}.

Yue et al. [179] have developed a sensing platform composed of single-layer graphene nanoplatelet and hemeprotein. They found that single-layer graphene nanoplatelet provided a biocompatible microenvironment for protein immobilisation, with suitable electron transfer characteristics. The resulting composite film was characterised and used for the indirect determination of nitrite. Using a polyol process, Zhang et al. [180] prepared a Cu_2O-graphene nanocomposite, which was then deposited on a GC electrode. The modified electrode was then

used to selectively determine the concentration of dopamine with a detection limit of 10 n mol L^{-1}. Fan et al. [181] prepared a TiO_2-graphenenanocomposite, using hydrolysis and *in situ* hydrothermal treatment. The composite was then used to modify a GC electrode, which showed significant improvement in the electro catalytic activity towards adenine and guanine. Du et al. [182] prepared a ZrO_2-graphene nanocomposite, using an electrochemical deposition method. Due to the strong affinity of the composite for phosphoric moieties, it can be used as a capturing agent or as a sensing material for organophosphorous agents. The use of metal NP with graphene has been reported to form exceptionally stable and cost-effective biosensors [183, 184]. Shan et al. [185] reported a graphene/AuNPs/chitosan composites film-based biosensor which exhibited good electrocatalytical activity toward H_2O_2 and O_2. Hong et al. [186] also reported the preparation of gold nanoparticle/graphene composites with controlled weight contents and their application in biosensor. The composite structure is as shown in Fig. 4. Zhang et al. [187] prepared sensitive electrogenerated chemiluminescence (ECL). Cholesterol biosensor was prepared based on cerium oxide-graphene (CeO_2- graphene) composites as an efficient matrix. CeO_2-graphene composites were prepared by depositing CeO_2 onto graphene and were characterized by scanning electron microscopy. The experimental results demonstrated that CeO_2-graphene could catalyze the ECL of a luminol- H_2O_2 system to amplify the luminol ECL signal greatly. In addition, the use of CeO_2-graphene provided a better biocompatible microenvironment for the immobilised enzyme, resulting in excellent stability and a long lifetime of the ECL biosensor. The surface assembly process, ECL behaviours, and electrochemistry of the biosensor were investigated in detail. The quantity of cholesterol was in the linear range from 12 μ mol L^{-1} to 7.2 m mol L^{-1}, with a detection limit of 4.0 μ mol L^{-1} (signal/noise = 3). In addition, the biosensor exhibited outstanding reproducibility, long-term

stability and selectivity. Yang et al. [188] electrodeposited a composite film consisting of GO, chitosan and glucose oxidase directly on a glassy carbon electrode (GCE) through electrochemical reduction of a solution of the 3 components under controlled direct electrical potential. The procedure took only several minutes, and the thickness of the resulting film is uniform and controllable. The GOx has uncompromised bioactivity and exhibits reversible 2-proton and 2-electron transfer in the presence of glucose. It therefore can be used as amperometric sensing of glucose. The biosensor has a fast response (<3 s), a detection limit of 0. 4 μ mol L^{-1} (which is 50-fold lower compared to the biosensor prepared by drop-casting solutions of the same materials onto a GCE), and a linear response in the 0. 4 μ mol L^{-1} to 2 m mol L^{-1} concentration range (which again is much better than that of the biosensor prepared by the drop-casting method). Other features include high reproducibility, long-time storage stability, and satisfactory selectivity. They presumed that the direct single-step electrodeposition of this nanocomposite offers a promising approach towards novel types of highly sensitive and stable electrochemical biosensors. Cao et al. [189] used the TiO_2–graphene–Pt–Pd hybrid nanocomposites (TGPHs) as an enhanced element of the integrated sensing platform for increasing the surface area as well as improving the electronic transmission rate. Subsequently, Au nanoparticles (AuNPS) and cholesterol oxidase (ChOx) were successively self-assembled to TGPHs, with high load amount and superior biological activity. The morphology of TGPHs and stepwise fabrication processes were characterized with CV, AFM, X-ray photoelectron spectroscopy (XPS) and SEM. Based on the efficiently catalytic ability of TGPHs and AuNPS, the fabricated biosensor exhibited wide linear ranges of responses to cholesterol in the concentration ranges of 5.0×10^{-8}–5.9×10^{-4} mol L^{-1}, while the limit of detection was 0.017 μ mol L^{-1} (S/N=3). Cao et al [190] also developed cholesterol biosensor for detection of cholesterol by

using platinum-palladium-chitosan-graphene hybrid nanocomposites (PtPd-CS-GS) functionalized glassy carbon electrode (GCE). An electro-deposition method was applied to form PtPd nanoparticle-doped chitosan-graphene hybrid nanocomposites (PtPd-CS-GS), which were characterised by SEM and electrochemical methods. The presence of the PtPd-CS-GS nanocomposites not only accelerated direct electron transfer from the redox enzyme to the electrode surface, but also enhanced the immobilized amount of cholesterol oxidase (ChOx). Under optimal conditions, the fabricated biosensor exhibited wide linear ranges of responses to cholesterol in the concentration ranges of 2.2×10^{-6} to 5.2×10^{-4} mol L^{-1}. The limit of detection was 0.75 μ mol L^{-1} (S/N=3). Gan and Hu [171] highlightened important applications of grapheme, graphene nanocomposites, and assayed strategies in electrochemical sensors for DNA, proteins, neurotransmitters, phytohormones, pollutants, metal ions, gases, H_2O_2, enzymatic and immunosensors.

5. Electrochemical sensing

5.1. Graphene electrochemical sensing

Electrochemical detection is highly sensitive to electroactive molecules and also offers detection selectivity, as different molecules can be oxidised/reduced at different potentials. Carbon materials (graphene, graphite, fullerene and CNT) are often used for electrochemistry due to their low residual current, readily renewable surface and wide potential window. The large overpotential for O_2 reduction and H_2 density of edge-plane defect sites on it provides multiple active sites for electron transfer to biospecies [7]. Graphene is an excellent conductor of electrical charge and heterogeneous electron transfer occurs at the edges of the graphene or at defects in the basal plane [191]. The high surface area of graphene facilitates large amounts of

defects and a large number of electroactive sites [23]. Electrodes made from graphene have more uniform distribution of electrochemically active sites than do those made from graphite [11]. Its entire volume is exposed to the surroundings due to its 2D structure, making it very good in detecting adsorbed molecules on the electrode [90].

Efficient electrochemistry takes place when metals nanoparticles (NP) decrease the distance between the redox site of a protein and the electrode surface, as the rate of the electron transfer (ET) is inversely proportional to the exponential distance between them [192]. The direct wiring of enzymes to an electrode surface is essential to amplify electrochemical signal of the biochemical reaction [193, 194]. Graphene supports efficient electrical wiring of the redox centers of several metalloproteins containing heme (cytochrome c, myoglobin, and horseradish peroxidase) to the electrode as in Fig. 5. Nanowiring of redox enzyme can also take place by metal NP [194]. Direct electron transfer (DET) between redoxenzymes and the electrode surfaces can be used for the study of enzyme kinetics and thermodynamics of redox transformation of enzymic molecules involving redox transformations. It can also be used to investigate enzyme catalyzed reactions in biological systems [56, 195]. Direct electrochemistry of enzymes involves direct ET between the electrode and the active center of the enzymes without the participation of mediators or other reagents [185, 196, 197]. New mediator-free (or reagentless) biosensors [198-201], enzymatic bioreactor, and biomedical devices employ DET by immobilizing enzymes on conducting substrates. The redox centers of the biomolecules are usually embedded deep in their large three-dimensional structures. Recent research has shown that graphene can enhance DET between enzymes and electrodes. The electron transfer between graphene and redox active species occurs at the edges of the graphene sheet and/or at defects in the basal plane [202]. The high surface area of graphene typically provides a large number of

electroactive sites [156, 203] that enhance ET and promote potential applications in electrochemical sensing.

5.2. Graphene-based electrochemical enzymatic biosensors

Clark and Lyons [204] proposed the first enzymatic electrode and since then, electrochemical biosensors based on the use of enzymes have received great attention, because of the advantages of the association of the biocatalytic activity of enzymes with the high sensitivity and versatility of the electrochemical transduction. The immobilisation of enzyme is critical, since the enzyme has to remain active to perform an efficient biorecognition of the substrate. The transducer where the enzyme is immobilized has to allow a fast charge transfer to ensure a rapid and sensitive response for a good biosensor as shown in Fig. 6. Several strategies for immobilizing redox enzymes and other proteins on graphene modified electrodes have been explored [205, 206]. Proper conjugation between biological molecules such as enzymes, ssDNA, RNA, Ab, receptors and aptamers needs to be developed for graphene-based electrochemical sensing electrodes. Appropriate functionalisation of graphene and the immobilisation of biomaterials on it are important, as functional groups can create defects on graphene surfaces [59]. Table 2. shows different types of enzymatic grapheme-based biosensor with their limit of detection and RSD.

6. Use of electrodes based on graphene for sensing different analytes

6.1. Glucose oxidase biosensor

The metabolic disorder of diabetes mellitus results in the deficiency of insulin and hyperglycemia and is reflected by blood glucose concentration higher or lower than the normal range of 80–120 mg dL^{-1} (4.4–6.6 m mol L^{-1}). The disease is a leading cause of death and

disability [207]. This is reflected by the multibillion USD glucosensing markets [208]. Therefore, the diagnosis and management require close monitoring of blood glucose levels. The application of graphene in highly sensitive and cost-effective biosensors can aid the monitoring diabetic diseases [19]. Graphene has been employed in many schemes for sensing glucose [188, 209-224]. The glucose oxidase oxidises glucose to gluconic acid and shuffles electrons into oxygen, which is dissolved in the solution, and then reduced to hydrogen peroxide. Hydrogen peroxide is detected electrochemically. The direct electrochemistry of GOx based on redox-active centers was confirmed by CV experiments in the potential range of 0.8–0 V [188, 225]. Direct electron transfer from the enzyme is possible, making this an analytically valuable signal [208]. Cui et al. [226] reported direct electrochemistry of glucose oxidase (GOD) on three-dimensional (3D) interpenetrating porous graphene electrodes, which have been fabricated by one-step electrochemical reduction of GO from its aqueous suspension. Hui et al. [227] studied direct electrochemistry of GOD based on Nafion-Graphene-GOD-modified gold disk electrode (GE). Immobilised GOD on graphene protected by nafion film exhibited good bioactivity, stability and apparent electron transfer rate constant (ks) 1.96 s^{-1}. DET from GOD has been reported by several authors. Fu et al. [228] immobilised glucose oxidase enzyme was on a Nafion polymer film with graphene nanoplatelets which demonstrated that such simple non-covalent bonding enhances the redox current of a ferrocyanide solution and leads to a lowering of the overpotential of hydrogen peroxide. Other direct electron transfer was observed in graphene/ionic liquid/glucose oxidase systems [229] and in graphene CdS nanocrystal [230]. Wang et al. [19, 230] and Shan et al. [185, 229] used a polyvinylpyrrolidone-protected graphene/polyethylenimine-functionalised IL/GOx electrochemical biosensor to study the DET of GOx. CV measurements revealed characteristic reversible ET of the redox active center.

Shan et al [185] reported another method for enzymatic detection of glucose, using Au NPs/graphene/chitosan composites. Zhang et al. [231] recently explored and investigated the effect of the structure of enzyme electrodes with glucose oxidase (GOD) that were modified by reduced graphene oxide (rGO) sheets . The rGO sheets, with different defect density, layers, and oxygen concentrations, were chosen to modify the enzyme electrode, and all the modified enzyme electrodes exhibited excellent electrocatalytic activities and performances towards glucose. The abundant defects in rGO induce easy absorption of GOD. Yu et al. [232] also reported direct electron transfer of GOD and biosensing for glucose based on PDDA-capped gold nanoparticle-modified graphene/multi-walled carbon nanotubes electrode. Luo et al. [233] synthesised highly dispersed titanium dioxide nanocluster (TDN) on rGO in a toluene-water system under microwave irradiation. The prepared rGO-TDN hybrids were used to modify glassy carbon electrode for loading GOD. The fabricated glucose biosensor exhibits excellent performance for glucose sensing, including low work potential (-0.7 V), high sensitivity (35.8 μA m mol L^{-1-1} cm^{-2}), low detection limit (4.8 μ mol L^{-1}), wide linear range from 0.032 to 1.67 m mol L^{-1}, small Michaelis-Menten constant (Km) (0.81 m) and short response time (10 s).

Yuan et al. [234] developed a bimetallic PdCu nanoparticle (NP)-decorated three-dimensional graphene hydrogel (PdCu/GE) by a simple one-step hydrothermal method. The PdCu/GE hybrids exhibited an interconnected microporous framework with PdCu NPs dispersed and encapsulated within the GE layers. The PdCu/GE hybrids showed significant electrocatalytic activity toward glucose oxidation. Lu et al. [235] used graphene platelets as a transducing material for the biosensing of glucose.

Various groups have shown that graphene-based glucose biosensors exhibit good sensitivity, selectivity and reproducibility [185, 222, 227, 235, 236, 237-249]. Wang et al. [154] used

electrochemically reduced single layers of graphene to detect glucose. The presence of CdS nanocrystal with graphene showed very low detection limit of 0.7 m mol L^{-1}. Kang et al. [250-252] fabricated CS–GR/GOx modified electrodes for direct electrochemical glucose sensing. The excellent performance of the biosensors was attributed to the large surface area to volume ratio and high conductivity of graphene and the good biocompatibility of chitosan with GOx. CS–GR/PtNPnanocomposite film has also been used for the detection of glucose. Introduction of PtNP increased the sensor's sensitivity, allowing a detection limit of 0.6 μ mol L^{-1} glucose. The biosensor possessed good reproducibility and long-term stability with negligible interference signals from AA and UA. Guets et al. [253] also developed a glucose biosensor that reduced the interference from AA and UA. Shan et al. [185, 229] designed CS–GR/AuNP nano composite films for glucose sensing, which exhibited good amperometric responses to glucose with a linear ranges of 2–10 m mol L^{-1} ($R = 0.999$) at −0.2 V and 2–14 m mol L^{-1} ($R = 0.999$) at 0.5 V. This was attributed to the synergy effect of graphene and the AuNP. Zhouet al. [139, 205] investigated glucose sensitivity of Nafion-GR/AuNP biocomposite films. The linear range of the sensor was 15–5.8 m mol L^{-1}, with a detection limit of 5 m mol L^{-1} (S/N = 3). Andreescu and Luck [254] used studies of the binding and signalling of surface-immobilized periplasmic glucose receptors on gold nanoparticles for glucose biosensor application. Zeng et al. [255, 256] used organically modified graphene for enzyme-based glucose and maltose biosensing. The CV response of the modified electrode increased with increasing concentration of glucose in buffer solution. The detection limit and sensitivity were 0.168 m mol L^{-1} (S/N = 3) and 0.261 μA m mol L^{-1-1} cm^{-2}, respectively. GO has severally been used for the detection of glucose [257-259]. Its biocompatibility with GOx led to a stable glucose biosensor with a sensitivity of 8.045 mA cm^{-2} mol L^{-1-1}. Yang et al. [260] developed a glucose biosensor, using CMG and IL.

Chen et al. [126] prepared Nafion-GR/GOx film-modified electrodes for the detection of glucose. The sensor showed good stability, with a RSD of 4.21% ($n = 5$). Huang et al. [261, 262] used CVD-grown graphene to develop real-time glucose biosensors. Alwarappan et al. [263] employed PPy-GR/GOx-based enzymatic biosensors for invitro electrochemical glucose detection. Nafion-GR/PtNP or AuNP-modified electrodes exhibited best sensing performances, with a linear response up to 30 m mol L^{-1} and an excellent detection limit of 1 μ mol L^{-1}. Alwarappan et al. [264] also used enzyme-doped graphene nanosheets for enhanced glucose biosensing. Wang et al. [169, 265] showed that N-doped graphene provides significantly enhanced oxidation currents for the enzymatic detection of glucose compared to ordinary graphene materials. Baby et al. [266] and Wang et al. [154] also investigated the effect of nitrogen doping on the biosensing performances of graphene electrode. N-doped graphene exhibited excellent electrocatalytic activity for the reduction of H_2O_2, fast ET kinetics, high sensitivity and selectivity for glucose biosensing. Ruan et al. [267] fabricated a glucose biosensor based on polydopamine-graphene hybrid film modified glucose oxidase enzyme electrode. Dopamine, GO and GOD were mixed and casted on Au electrode. After electrochemical processing, polydopamine, glucose oxidase and graphene modified electrode were obtained. The as-synthesized enzyme electrodes were characterized by scanning electron microscopy, transmission electron microscopy, Fourier transform infrared and X-ray diffraction spectra. The biosensor showed excellent amperometric biosensing performances, e.g., a high periods (4 s) and a low Michaelis-Menten constant (6.77 m mol L^{-1}). Vinu Moham et al. [268] developed amperometric detection of glucose using Prussian blue-graphene oxide-modified platinum electrode. Gupta et al [269] developed a novel glucose biosensor platform based on AgAuNPs modified graphene oxide nanocomposite and SERS application. The linearity range of

glucose was obtained as 2-6. m mol L^{-1} with detection limit of 0.33. m mol L^{-1}. The developed biosensor was also applied successfully for the determination of glucose in blood samples. The concentration value of glucose in blood samples was calculated to be 1.97 ± 0.002. m mol L^{-1} from measurements repeated for six times.

Zou et al. [270] fabricated Amperometric glucose biosensor prepared with biocompatible material and carbon nanotube by layer-by-layer self-assembly technique. Lui et al. [30] fabricated a bionanocomposite film of glucose oxidase/Pt nanoparticles/graphene-chitosan (GOD/PtNPs/GR-Chit) for glucose sensing. The hybrid bionanocomposite-modified GCE was characterised by SEM, CV, and amperometric i-t curve. Cai et al. [271] reported the utilisation of graphene-chitosan-ZrO_2 (ER-GO/CS/ZrO_2) composite as an immobilisation matrix for GOD. In comparison with electrodes modified with the component materials individually, the ER-GO/CS/ZrO_2-modified electrode exhibited excellent electron transfer properties for GOD with a rate constant of 3.12 s^{-1}. The obtained glucose biosensor displayed satisfactory performance over an acceptable linear range from 0.2 m mol L^{-1} to 1.6 m mol L^{-1}, with a detection limit of 45.6 μ mol L^{-1} at -0.4 V and a sensitivity of 7.6 μA m mol L^{-1} /cm^2. Chen et al. [272] reported electrochemiluminescence biosensor for glucose, based on Graphene/Nafion/GOD film-modified glassy carbon electrode. Ge et al. [273] fabricated a glucose biosensor based on immobilization of glucose oxidase on polyaniline/graphene composite membrane-modified glassy carbon electrode. CV demonstrated that modified electrodes had good electrochemical activity, superior sensitivity and high stability. The good electrocatalytical activity toward H_2O_2 and O_2 might be attributed to the synergistic effect of graphene and polyaniline. The results showed that the electrochemical biosensor had a wide linear response from 0.1 to 10 m mol L^{-1}. Jang et al. [240] synthesised graphene-based noble metal composites such as Pt-Gaphene and

Au-Graphene for sensitive glucose biosensors. Aerosol spray pyrolysis (ASP) was employed to synthesize the noble metal nanoparticles-Graphene composites, using a colloidal mixture of GO and noble metal precursor ($H_2PtCl\ 6{\cdot}6H_2O$ and $AuCl_4{\cdot}3H_2O$). The amperometric response of the glucose biosensor, based on the Pt-crumpled graphene composite, indicated the highest sensitivity as 62 μA/m mol L^{-1} cm^2. Lee et al. [274] fabricated graphene and Nafion polymer composite not only for enhancing processability, but also maintaining properties. The easily fabricated glucose biosensor shows good performances with fast electron transfer rate, high selectivity, and low concentration range of detection with linear response.

6.2. Haemoglobin (Hb) biosensor

Hb is the most important part of blood and is responsible for transporting O_2 throughout the circulatory system. Change of Hb concentration in blood can cause several diseases such as anemia and even death. Therefore, accurate determination of Hb content in blood is medically very essential.

Xu et al. [15] used a CS–Graphene-modified electrode for the electroanalysis of Hb. The cyclic voltammogram of Hb at the CS–Graphene/GC electrode showed a well-resolved redox peak compared with a CS/GC electrode. The current response of Hb at the CS–Graphene/GC electrode increased linearly with scan rate from 30 to 150 mV s^{-1}, indicating a surface-controlled electrochemical process. He et al. [275] studied the effect of magnetite-graphene NP on Hb detection. The biosensor exhibited fast response time (<3 s), broad linear response to H_2O_2 in the range of 1.50–585 μ mol L^{-1} L^{-1} and a relatively low detection limit of 0.5 μ mol L^{-1} (S/N = 3). Wang et al. [154] designed CS–Graphene/Hb/GR/IL/GC electrode for the detection of

nitromethane. The designed biosensor achieved a detection limit down to 6.0×10^{-10} mol L^{-1} for quantitative nitromethane analysis. He et al. [276] used magnetite-graphene for the direct electrochemistry of hemoglobin and its biosensing application. Sun et al. [277-279] prepared a graphene and Mg_2Al layered double hydroxide (LDH) composite, which was used for the immobilisation of hemoglobin (Hb) on a carbon ionic liquid electrode (CILE) to obtain an electrochemical biosensor. The presence of Graphene-LDH composite could facilitate the electron transfer rate between CILE and the electroactive center of Hb. The immobilized Hb in Graphene-LDH modified electrode exhibited excellent electrocatalytic reduction to trichloroacetic acid in the concentration range from 1.6 to 25.0 m mol L^{-1}, with the detection limit as 0.534 m mol L^{-1}. The CV spectra indicated the successful preparation of a third-generation electrochemical biosensor.

6.3. Hydrogen peroxide biosensor (H_2O_2)

Hydrogen peroxide (H_2O_2) is a general enzymatic product of oxidases and a substrate of peroxidases, which is important in biological processes and biosensor development [280, 281]. H_2O_2 is an important analyte in chemistry, biology, biochemical and food industry, clinical control and environmental protection. Thus the rapid and accurate analysis of H_2O_2 is of great importance [59]. The high level of H_2O_2 is closely associated with cancer and progressive neurodegenerative diseases, such as Parkinson's disease. High level of oxidative stress is involved in the formation of incipient tumour and carcinomatous cells. Recent studies have shown that graphene-based H_2O_2 biosensors exhibit good sensitivity, selectivity and reproducibility [176, 265, 282, 283-288] Chang et al. [289] explored a facile strategy to assess the oxidative stress elicited by H_2O_2 in cells with amperometric current-time technique in vitro.

An electrochemical biosensor exhibiting high sensitivity and selectivity to H_2O_2 is fabricated by integration. Bai et al. [290] developed a novel CuS nanoparticle-decorated reduced graphene oxide-based electrochemical biosensor for the reliable detection of H_2O_2. The new electrocatalyst, CuS/RGO composites were successfully prepared by heating the mixture of $CuCl_2$ and Na_2S aqueous solutions in the presence of PVP-protected graphene oxide at 180 C. The application of CuS/RGO composite-modified electrode as a biosensor to monitor H_2O_2 was investigated. The steady-state current response increases linearly with H_2O_2 concentration from 5 to 1500 μ mol L^{-1}, with a fast response time of less than 2 s. The detection limit (3σ) for determination of H_2O_2 was estimated to be 0.27 μ mol L^{-1}, which was lower than certain enzymes and noble metal nanomaterial-based biosensors. Electrochemical methods are more convenient for this than other conventional methods. Zeng et al. [256] developed an SDBS-Graphene/HRP-modified electrode for the detection of H_2O_2. It displayed high electrocatalytic activity to H_2O_2 with high sensitivity, wide linear range, low detection limit and fast amperometric response. The current signal was proportional to the concentration of H_2O_2 and closely related to the activity of the HRP. The reaction mechanism of the catalytic process can be summarised as follows:

$$HRP(Red) + H_2O_2 \rightarrow HRP(Ox) + H_2O$$

$$HRP(Ox) + Hydroquinone \rightarrow HRP(Red) + Benzoquinone$$

$$Benzoquinone + 2e^- + 2H+ \rightarrow Hydroquinone$$

The HRP/Graphene electrode remained stable after 30 measurements without significant loss of sensitivity (>90%). Lu et al [291-292] developed another biosensor for the detection of H_2O_2, using horseradish peroxidase or haemoglobin. The modified electrode (Graphene/HRP) could reach 95% of the steady state current within 1 s, indicating very fast electrocatalytic response.

Liu et al. [257] developed a sensor for the detection of glucose and hydrogen peroxide on the basis of Cu_2O nanocubes wrapped by graphenenanosheets (Cu_2O/GNs) as electrocatalysts. Cubic Cu_2O nanocrystals/graphene hybrid has been successfully fabricated by a chemical reduction method at low temperature. Qing et al. [281] developed a novel electrochemical sensing system for direct electrochemistry-based hydrogen peroxide biosensor single-layer graphene nanoplatelet (SLGnP). The composite film demonstrated excellent electrochemical responses for the electrocatalytic reduction of, H_2O_2 thus suggesting its great potential applications in direct electrochemistry-based biosensors. Lu et al [293] reported self-assembly of cyclodextrin (CD) functionalized graphene and adamantane-modified horseradish peroxidase (HRP-ADA) by host-guest supramolecular interaction into novel nanostructures in aqueous solution. The proposed biosensor showed good reproducibility and high sensitivity to H_2O_2 with the detection limit of 0.1μ mol L^{-1}. In the range of 0.7-35μ mol L^{-1}, the catalytic reduction current of H_2O_2 was proportional to H_2O_2 concentration.

Another novel H_2O_2 biosensor was designed by Zhou et al. [139] based on CS–GR/AuNP/HRP biocomposites. The linear response range to H_2O_2 was 5×10^{-6} to 5.13×10^{-3} mol L^{-1}, with a detection limit of 1.7×10^{-6} mol L^{-1} (S/N = 3). Zhou et al. [8, 294] prepared CS–GR/Fe_3O_4/HRP composite biosensor for the detection of H_2O_2. The resultant biosensor exhibited high sensitivity, low detection limit, wide linear range, and long term stability. Song et al. [295] researched and developed hemin-graphenenano-sheets (H-GNs)/gold nano-particles (AuNPs) electrochemical biosensor for the detection of H_2O_2. It was constructed by consecutive, selective modification of the GCE electrode. Performance of the H-GNs/AuNPs/GCE was investigated by chronoamperometry and AFM measurements suggested that the graphene flakes thickness was ~1.3nm and that of H-GNs was ~1.8nm, which ultimately indicated that each hemin layer was

~0.25nm. This biosensor exhibited significantly better electrocatalytic activity for the reduction of H_2O_2 in comparison with the simpler AuNPs/GCE and H-GNs/GCE. It also displayed a linear response for the reduction of H_2O_2 in the range of 0.3μ mol L^{-1} to 1.8m mol L^{-1},with a detection limit of 0.11μ mol L^{-1} (SN-1=3), high sensitivity of 2774.8μAm mol $L^{-1-1}cm^{-2}$ and a rapid response, which reached 95% of the steady state condition within 5s. In addition, the biosensor was unaffected by any interfering substances and was stable over time. The biosensor was potentially suitable for H_2O_2 analysis in many types of sample. Dey and Raj [296, 297] developed a highly sensitive amperometric biosensor based on a hybrid material derived from PtNP and graphene for the detection of H_2O_2. You et al. [285] used GO with aminothiophenol (ATP) and covalently bonded to the palladium (Pd) NPs via sulfur atom. The GO-ATP-Pd was electrochemically reduced to graphene oxide (ERGO) at a potential range of 0 to -1.5 V and was used in electrochemical biosensing for H_2O_2. The ERGO-ATP-Pd-modified electrode showed the advantages of excellent electrocatalytic activity toward H_2O_2 in PBS solution. The ERGO-ATP-Pd was characterized by transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), energy dispersive X-ray spectroscopy (EDS) and electrochemical impedance spectroscopy (EIS). CV and chronoamperometry (CA) were used to characterize the performance of the biosensor. The proposed H_2O_2 biosensor exhibited a wide linear range from 0.1 μ mol L^{-1} to 10 m mol L^{-1}, and a low detection limit of 0.016 μ mol L^{-1} (S/N = 3), with a fast response time of less than 10 s. The biosensor, therefore, demonstrated excellent capability for the analysis of H_2O_2. Recently, Kung et al. [282] used 3D Graphene foam (GF), incorporating it with platinum–ruthenium (PtRu) bimetallic nanoparticles as an electrochemical nanocatalyst for the detection of H_2O_2. PtRu/3D GF nanocatalyst exhibited a remarkable performance toward electrochemical oxidation of H_2O_2 without any additional mediator, showing a high sensitivity

(1023.1 μA m mol L^{-1-1} cm^{-2}) and a low detection limit (0.04 μ mol L^{-1}) for H_2O_2. Amperometric results demonstrated that GF provided a promising platform for the development of electrochemical sensors in biosensing and PtRu/3D GF nanocatalyst possessed the excellent catalytic activity toward the H_2O_2 detection. Huang et al. [298] performed electrochemical sensing using conductive carbon composite films containing rGO and single-walled carbon nanotubes (SWCNTs) as electrode modifiers on glassy carbon electrodes (GCEs). Raman spectroscopy, transmission electron microscopy, atomic force microscopy and scanning electron microscopy, all suggested that the rGO acted as a surfactant, covering and smoothing out the surface and that the SWCNTs acted as a conducting bridge to connect the isolated rGO sheets, thereby minimising the barrier for charge transfer between the rGO sheets and increasing the conductivity of the film. They used the rGO/SWCNT-modified GCE as a sensor to analyze H_2O_2 and B-nicotinamide adenine dinucleotide (NADH), obtaining substantial improvements in electrochemical reactivity and detection limits relative to those obtained from rGO- and SWCNT-modified electrodes. The electrocatalysis response was measured by cyclic voltammetry and amperometric current-time (i-t) curve techniques. The linear concentration range of H_2O_2 and NADH detection at rGO/SWCNT-modified electrode is 0.5-5M and 20-400μM. The sensitivity for H_2O_2 and NADH detection is 2732.4 and 204μAmM-1cm-2, and the limit of detection is 1.3 and 0.078μM, respectively.

Bai et al. [290] used copper sulphide-decorated reduced graphene oxide composites for enhanced detecting of H_2O_2 in cancer/tumor growth. The sensor was applied to determine the H_2O_2 levels in human serum and urine samples and H_2O_2 released from human cervical cancer cells, with satisfactory results. Chang et al. [289] used layer-by-layer assembly of graphene, Au and poly(toluidine blue O) films sensor for evaluation of oxidative stress of tumor cells elicited by

H_2O_2. The efflux of H_2O_2 from several representative tumor cells and normal cells on exposure to ascorbic acid could be detected by using the graphene-based nanocomposite films. The results indicated that tumor cells release much more H_2O_2 than do the normal cells. The novel sensor raises the possibility for clinical diagnostic application to evaluate the higher level of intracellular oxidative stress of tumor cells in comparison with normal cells.

Chen et al. [156] used highly conjugated water-dispersible graphene-butyric acid for the enhancement of electron transfer within polyamic acid-benzoxazole for high performances H_2O_2 sensing. Cheng et al. [10] developed a biosensor based on carboxymethyl cellulose functionalised reduced graphene oxide and haemoglobin hybrid nanocomposite film that exhibited excellent catalytic activity toward H_2O_2 over a wide linear range of 0.083-13.94 μ mol L^{-1} with a detection limit of 0.08 μ mol L^{-1} at 3σ. Li et al. [299] synthesised1, 3-Di(4-amino-1-pyridinium) propane tetrafluoroborate (DAPPT) ionic liquid, which was used as a modifier to functionalize grapheme nanosheets through covalent binding of amino groups and epoxy groups in an alkaline solution. The as-prepared graphene-DAPPT nanosheets (Gr-DAPPT) were confirmed with TEM, X-ray diffraction XRD, X-ray photoelectron spectroscopy (XPS), UV/vis and FTIR spectroscopy. This was used for biosensing H_2O_2. Zhong et al. [294] reported a double pulse electrochemical method to controllably prepare silver nanocrystals (AgNCs) on graphene thin film electrode for fabricating a high performance H_2O_2 biosensor. The approach relies on two potential pulses that can independently control the nucleation and subsequent growth processes of AgNCs on graphene substrate. This method also allows the observation of AgNCs growing from a particle shape to a nanoplate form by increasing the growth time with the maximum lateral scale up to micrometer scale range. A proposed mechanism for this silver nanoplates (AgNPLs) formation was the oriented growth of small AgNCs and two-dimensional

graphene template inducing effect. Such obtained graphene–AgNPLs hybrid thin films exhibit remarkable electrocatalytical activity toward H_2O_2 electrochemical reduction. The fabricated nonenzymatic H_2O_2 biosensor displays a fast amperometric response time of less than 2 s and a good linear range from 2×10^{-5} mol L^{-1} to 1×10^{-2} mol L^{-1}, with an estimated detection limit of 3×10^{-6} mol L^{-1}. This biosensor also exhibits good stability (RSD, 1.3%) and high sensitivity of 183.5 μA cm^{-2} m mol L^{-1-1}, as well as high selectivity. Kung et al. [282] produced graphene foam (GF), a three-dimensional (3D) porous architecture, consisting of extremely large surface and high conductive pathways. In their study, 3D GF was used, incorporating platinum–ruthenium (PtRu) bimetallic nanoparticles as an electrochemical nanocatalyst for the detection of H_2O_2. PtRu/3D GF nanocatalyst exhibited a remarkable performance toward electrochemical oxidation of H_2O_2 without any additional mediator, showing a high sensitivity (1023.1 μA m mol L^{-1-1} cm^{-2}) and a low detection limit (0.04 μ mol L^{-1}) for H_2O_2. Amperometric results demonstrated that GF provided a promising platform for the development of electrochemical sensors in biosensing and PtRu/3D GF nanocatalyst possessed the excellent catalytic activity toward the H_2O_2 detection. A small particle-size and a high degree of the dispersion in obtaining a large active surface area were important for the nanocatalyst for the best H_2O_2 detection in biosensing and interference by ascorbic acid and uric acid appeared to be negligible. Deng et al. [300] prepared a nanoscale hybrid of chemically reduced graphene oxide (CRGO) with ferrocene (Fc), through π-π stacking interaction between Fc and CRGO. FT-IR, Raman spectroscopy, SEM and CV were utilised to characterize the nanohybrid of Fc with CRGO (Fc-CRGO). Fc-CRGO exhibited good stability and greatly improved electron-transfer behaviour. Fc-CRGO and HRP were casted on the surfaces of glass carbon electrode (GCE) with the aid of chitosan for determination of H_2O_2.

Ma et al. [301] reported the layer-by-layer assembly of polyelectrolyte functionalized graphene sheets. The electrode exhibited elctrocatalytic activity for the reduction of H_2O_2.

6. 4. β-nicotinamide adenine dinucleotide (NADH)

The electrochemical detection of NADH is one of the most studied areas of bioelectroanalysis because of the importance of NAD(P)H-based enzymatic reactions in nature [302-304]. Radoi et al [302] used pristine graphene platelets and GO as electrode modifiers, aiming the investigation of their electrochemical efficacy towards (NADH). l-lactic dehydrogenase (l-LDH) was successfully immobilised in a 1 % Nafion® membrane. The developed biosensor, working at +250 mV versus Ag/AgCl reference electrode, was used to assess l-lactic acid in four different types of yogurts, revealing l-lactic acid concentration ranging between 0.3 and 0.6 %. Shan et al [305] reported that low-potential NADH detection and biosensing for ethanol are achieved at an ionic liquid-functionalised graphene (IL-graphene) modified electrode. A substantial decrease (440 mV) in the overvoltage of the NADH oxidation was observed using IL-graphene/chitosan coating, with oxidation starting at 0.0 V (vs. Ag|AgCl). The NADH amperometric response at such a modified electrode is more stable (95.4% and 90% of the initial activity remaining after 10 min and 30 min at 1 mM NADH solution) than that at bare electrode (68% and 46%). Furthermore, the IL-graphene/chitosan-modified electrode exhibited a good linearity from 0.25 to 2 m mol L^{-1} and high sensitivity of 37.43 μA m mol L^{-1-1} cm^{-2}. The ability of IL-graphene to promote the electron transfer between NADH and the electrode exhibited a novel and promising biocompatible platform for the development of dehydrogenase-based amperometric biosensors.

Li et al. [306] prepared a nanocomposite film by cyclic voltammetric deposition of electroreduced graphene oxide (ERGO) and polythionine (PTH) on a glassy carbon (GC)

electrode. The electrodeposition of ERGO-PTH film is also investigated via the electrochemical quartz crystal microbalance (EQCM) method for more in-depth understanding of the process. The ERGO-PTH nanocomposite film is applied as a transducer for facilitated electrocatalytic oxidation of NADH and for the construction of dehydrogenase-based amperometric biosensor. Under optimum conditions, the amperometric detection of NADH provides a wide linear detection range (0.01-3.9 m mol L^{-1}), a high sensitivity (143 μA m mol L^{-1-1} cm $^{-2}$) and a low limit of detection (LOD = 0.1 μ mol L^{-1}, S/N = 3). Lin et al. [116] used graphene modified basal and edge plane pyrolytic graphite electrodes for electrocatalytic oxidation of H_2O_2 and NADH.

Ambrose et al. [138] used a multilayer graphene film grown by CVD and transferred to an insulating flexible poly(ethylene terephthalate) (PET) sheet to sense dopamine (DA), ascorbic acid (AA), and the reduced form of NADH as biological relevant molecules. Huang et al. [298] performed electrochemical sensing using conductive carbon composite films containing rGO and single-walled carbon nanotubes (SWCNTs) as electrode modifiers on glassy carbon electrodes (GCEs) for electrochemical sensing. They used the rGO/SWCNT-modified GCE as a sensor to analyze H_2O_2 and NADH. The electrocatalysis response was measured by CV and amperometric current-time (i-t) curve techniques. The linear concentration range of H_2O_2 and NADH detection at rGO/SWCNT-modified electrode were 0.5-5 mol L^{-1} and 20-400 μ mol L^{-1}. The sensitivity for H_2O_2 and NADH detection is 2732.4 and 204 μAm mol $L^{-1-1}cm^{-2}$, and the limit of detection is 1.3 and 0.078μ mol L^{-1}, respectively. Furthermore, interference tests indicated that the carbon composite film exhibited high selectivity toward H_2O_2 and NADH. Li et al. [307] reported the fabrication of a sensitive NADH and ethanol biosensor based on graphene-Au nanorods nanocomposite. The hybrid nanosheets exhibited excellent performance toward NADH oxidation, with a low detection limit of 6 μ mol L^{-1}.

Zang et al. [308] reported electrocatalytic oxidation of NADH on graphene oxide and rGO modified screen-printed electrode.

6.5. Cholesterol biosensor

Increases in cholesterol levels can cause life-threatening coronary heart diseases, cerebral thromboses and artherosclerosis [296]. Therefore, accurate detection of cholesterol level is medically very important. In recent years, most researchers have shown that grapheme-based cholesterol biosensor exhibits good sensitivity, selectivity and reproducibility [187].

Dey et al. [297] developed grapheme-platinum-nanparticle (GR/PtNP) cholesterol biosensor by immobilizing cholesterol oxidase and cholesterol esterase on the surface of the GR/PtNP hybrid material. The sensitivity and detection limit of the electrode towards cholesterol ester were 2.07 ± 0.1 μA μ mol L^{-1-1} cm^{-2} and 0.2 μ mol L^{-1}, respectively. The high sensitivity and low detection limit were due to the synergistic effect ofthe synergy between graphene and PtNP. The sensitivity is as shown in amperometric results in Fig. 7. Cao et al. [190] developed a new electrochemical biosensor with enhanced sensitivity for the detection of cholesterol by using platinum-palladium-chitosan-graphene hybrid nanocomposites (PtPd-CS-GS) functionalized glassy carbon electrode (GCE). An electrodeposition method was applied to form PtPd nanoparticles-doped chitosan-graphene hybrid nanocomposites (PtPd-CS-GS), which were characterized by SEM and electrochemical methods. The presence of the PtPd-CS-GS nanocomposites not only accelerated direct electron transfer from the redox enzyme to the electrode surface, but also enhanced the immobilised amount of cholesterol oxidase (ChOx). Under optimal conditions, the fabricated biosensor exhibited wide linear ranges of responses to cholesterol in the concentration ranges of 2.2×10^{-6} to 5.2×10^{-4} mol L^{-1}. The limit of detection

was 0.75 μ mol L^{-1} (S/N=3). The response time was less than 7 s and the Michaelis-Menten constant (Km app) was found to be 0.11 m mol L^{-1}. In addition, the biosensor also exhibited excellent reproducibility and stability. Along with these attractive features, the biosensor also displayed very high specificity to cholesterol with complete elimination of interference from UA, AA and glucose. Cao et al. [14] also used the TiO_2-graphene-Pt-Pd hybrid nanocomposites (TGPHs) as an enhanced element of the integrated sensing platform for increasing the surface area as well as improving the electronic transmission rate. Au nanoparticles (AuNPS) and cholesterol oxidase (ChOx) were successively self-assembled to TGPHs with high load amount and superior biological activity. The morphology of TGPHs and stepwise fabrication processes were characterized with CV, AFM, X-ray photoelectron spectroscopy (XPS) and scanning electron microscopy (SEM). Based on the efficient catalytic ability of TGPHs and AuNPS, the fabricated biosensor exhibited wide linear ranges of responses to cholesterol in the concentration ranges of 5.0×10^{-8}-5.9×10^{-4} mol L^{-1}. The limit of detection was 0.017μ mol L^{-1} (S/N=3). Manjunathar et al [309] covalently-immobilised Cholesterol oxidase (ChOx) and cholesterol esterase (ChEt) onto functionalised graphene (FG)-modified graphite electrode. Enzymes modified electrodes were characterized using cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS). FG accelerates the electron transfer from electrode surface to the immobilised ChOx, achieving the direct electrochemistry of ChOx. A well-defined redox peak was observed, corresponding to the direct electron transfer of the FAD/FADH 2 of ChOx. The electron transfer coefficient (α) and electron transfer rate constant (Ks) were calculated and their values are found to be 0.31 and 0.78 s^{-1}, respectively. For the free cholesterol determination, ChOx-FG/Gr electrode exhibits a sensitive response from 50 to 350 μ mol L^{-1} (R=-0.9972) with a detection limit of 5 μ mol L^{-1}. For total cholesterol determination, co-immobilisation of ChEt

and ChOx on modified electrode, i.e. (ChEt/ChOx)-FG/Gr electrode, showed linear range from 50 to 300 μ mol L^{-1} (R=-0.9982) with a detection limit of 15 μ mol L^{-1}. Some common interferents like glucose, ascorbic acid and uric acid did not cause any interference, due to the use of a low operating potential. Ruecha et al. [310] recently prepared a nanocomposite of graphene (G), polyvinylpyrrolidone (PVP) and polyaniline (PANI) and used it for the modification of paper-based biosensors via electrospraying. The droplet-like nanostructures of G/PVP/PANI-modified electrodes are obtained with an average size of 160±1.02 nm. Interestingly, the presence of small amounts of PVP (2 mg mL^{-1}) in the nanocomposites can substantially improve the dispersibility of graphene and increase the electrochemical conductivity of electrodes, leading to the enhanced sensitivity of the biosensor. The well-defined cyclic voltammogram of standard ferri/ferrocyanide is achieved on a G/PVP/PANI-modified electrode, with a 3-fold increase in the current signal compared to an unmodified electrode. Cholesterol oxidase (ChOx) is attached to G/PVP/PANI-modified electrode for the amperometric determination of cholesterol. Under optimum conditions, a linear range of 50 μ mol L^{-1} to 10 m mol L^{-1} is achieved and the limit of detection is found to be 1 μ mol L^{-1} for cholesterol. The proposed system can be applied for the determination of cholesterol in a complex biological fluid (i.e. human serum).

Zhang et al. [187] developed a simple and sensitive electrogenerated chemiluminescence (ECL) cholesterol biosensor based on cerium oxide-graphene (CeO_2- graphene) composites as an efficient matrix. CeO_2-graphene composites were prepared by depositing CeO_2 onto graphene and were characterized by SEM. The experimental results demonstrated that CeO_2-graphene could catalyze the ECL of a luminol- H_2O_2 system to amplify the luminol ECL signal greatly. In addition, the use of CeO_2-graphene provided a better biocompatible microenvironment for the

immobilised enzyme, resulting in excellent stability and a long lifetime of the ECL biosensor. The surface assembly process, ECL behaviours, and electrochemistry of the biosensor were investigated in detail. The quantity of cholesterol was in the linear range of from 12 μ mol L^{-1} to 7.2 m mol L^{-1}, with a detection limit of 4.0 μ mol L^{-1} (signal/noise = 3). In addition, the biosensor exhibited outstanding reproducibility, long-term stability and selectivity.

6.6. Electrochemical Immunosensing

Immunosensors are based on the high affinity reactions antigen/antibody. 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 occurs and after the addition of the substrate and electrochemical detection of the product [311].

Graphene has been used for electrochemical immunosensing, the direct electrochemical detection of antibody antigen recognition is usually not possible and electrochemically active labels must typically be used. There are two strategies in which graphene can be used. First, graphene can be used as an electrode surface for sensitive detection of a label [312]. This case was employed for the graphene-enhanced detection of α-fetoprotein, which is a cancer biomarker. Graphene sheets were modified with antibodies, then the α-fetoprotein was added and consequently, secondary antibodies loaded with microspheres bearing horseradish peroxidase enzyme as a sensitive label. The second approach employs graphene as a label-bearing nanocarrier [313]. A gold nanoparticle electrode was modified with a probe antibody, to which phosphorylated protein was entrapped. The secondary antibody was conjugated with GO and

horseradish peroxidase to generate large amounts of electroactive molecules and thus a larger signal [312]. Huang et al. [314] developed a simple label-free amperometric immunosensor for protein detection based on TiO_2-graphene (TiO_2-Gr), chitosan and gold nanoparticles (AuNPs) composite film-modified glassy carbon electrode (GCE). The negatively charged AuNPs can be adsorbed on the positively charged chitosan/TiO_2-graphene composite film by electrostatic adsorption, and then used to immobilise α-fetoprotein antibody for the assay of α-fetoprotein (AFP).

Recently, Lui et al. [315] fabricated an Au–ionic liquid functionalized reduced graphene oxide nanocomposite (IL-rGO–Au) via the self-assembly of ionic liquid functionalized reduced graphene oxide (IL-rGO) and gold nanoparticles (AuNPs) by electrostatic interaction. The IL-rGO can be synthesized and stabilized by introducing the cations of the amine-terminated ionic liquids (IL-NH_2) into the graphene oxide (GO). With the assistance of IL-NH_2, AuNPs were uniformly and densely absorbed on the surfaces of the IL-rGO. The proposed IL-rGO–Au nanocomposite can be used as an immunosensing platform because it can not only facilitate the electrons transfer of the electrode surface, but also provide a large accessible surface area for the immobilisation of abundant antibody.

Feng et al. [201] prepared azearalenone (ZEN) biosensor by immobilising nitrogen-doped graphene sheets (N-GS) captured primary antibody (Ab1) on GCE. The analytes were then bound to Ab1 for further capture of antibodies, labeled by the nanoporous bimetallic alloy, nanoporousPtCo alloy (NP-PtCo). NP-PtCo, with three-dimensional bicontinuous spongy structures and various hollow channels was prepared by corrosion of PtCoAl alloy and it exhibited remarkably improved electrocatalytic activity toward H_2O_2. Within ZEN concentration range (0.005-25 ng mL^{-1}), the biosensor exhibited a highly sensitive response to ZEN with a

detection limit of 2.1 pg mL $^{-1}$. Zhang et al. [316] developed a novel surface plasmon resonance (SPR) biosensors based on Au-graphene (Au-Gra) nanohybrids and Ag-graphene (Ag-Gra) nanohybrids for the detection of mouse IgG. The biosensors proposed are label-free, and have high sensitivity and selectivity for biosensing. Au-Gra and Ag-Gra nanohybrids were synthesised in a simple, effective and rapid way. It further characterized by X-ray photoelectron spectroscopy (XPS), transmission electron microscopy (TEM) and UV–vis absorption spectroscopy. These nanohybrids were assembled on the Au film through 1, 6-hexanedithiol by covalent attachment. The antibody was bounded to the nanohybrids through 3-mercaptopropinic acid. Some experimental conditions were determined and optimised. In the optimal conditions, the biosensors based on Au-Gra nanohybrids and Ag-Gra nanohybrids, showed a good response to mouse IgG in the concentration range of 0.30–40.00 μg mL^{-1} and 0.15–40.00 μg mL^{-1}, respectively. Xu et al. [15] developed a graphene-based signal-amplification nanoprobe by combining anti-immunoglobulin G (anti-IgG) and horseradish peroxidase (HRP) with graphene oxide (GO). The structure and function of HRP in the nano-interface of GO were firstly investigated, which demonstrated that the enzyme retained 78% of its native activity and 77% of its native α-helix content. HRP and anti-IgG were then co-adsorbed onto GO to form bifunctional nanoprobes. The nanoprobes provide both improved binding ability and signal-amplification ability. Comparing with conventional bioconjugates such as enzyme-linked antibody, co-adsorption could avoid chemical conjugation between biomolecules, keeping their bioactivity well. As an example of their application, the nanoprobes were used to obtain amplified signals in a sandwich-type immunoassay for cancer marker, instead of conventional colorimetric conjugates. This approach provided a detection limit of 10. Pg/mL alpha-fetoprotein (AFP), which was much more sensitive than conventional enzyme-linked immunosorbent assay

(ELISA) methods. Jung et al. [317] developed a novel GO-based immuno-biosensor that could quickly detect viruses with high sensitivity and selectivity. The fluorescence quenching efficiency of GO arrays was affected by several factors, such as the concentration of immobilised Ab, their surface area and the number of AuNP quenchers. Su [318] used Graphene modified basal and edge plane pyrolytic graphite electrodes for electrocatalytic oxidation of hydrogen peroxide and β-nicotinamide adenine dinucleotide. Zhu et al. [319] designed a novel immunoassay protocol for simultaneous electrochemical determination of alpha-fetoprotein (AFP), carcinoembryonic (CEA) and streptococcus suis serotype 2 (SS2). As standard sandwich-type immunoassay format, three primary antibodies (Ab1), anti-CEA and anti-AFP and anti-SS2, were immobilised via protein A (PA) adsorbed by Nafion-modified electrodes, and functionalized graphene sheets (GS) containing abundant gold nanoparticles (AuNPs) and carboxyl group were used to immobilise secondary antibody redox-probe so as to act as tracer. Concentration of each analyte was quantitatively related to the reduction peak current of corresponding redox-probe in differential pulse voltammetry (DPV) scan. The resulting immunosensor exhibited high selectivity and sensitivity in simultaneous determination of three analytes. The linear range was from 0.016 to 50. ng/mL for AFP, with a detection limit of 5.4. pg/mL, 0.010 to 50. ng/mL for CEA, with a detection limit of 2.8. pg/mL and 0.012 to 50. ng/mL for SS2, with a detection limit of 4.2. pg/mL (S/. N=3).

Du et al. [312] also described a novel electrochemical immunosensor for sensitive detection of cancer biomarker α-fetoprotein (AFP) that uses a graphene sheet sensor platform and functionalised carbon nanospheres (CNSs) labeled with horseradish peroxidase-secondary antibodies (HRP-Ab2). Greatly enhanced sensitivity for the cancer biomarker is based on a dual

signal amplification strategy: first, the synthesised CNSs yielded a homogeneous and narrow-size distribution, which allowed several binding events of HRP-Ab2 on each nanosphere.

6.7. DNA sensors

Electrochemical DNA sensors offer high sensitivity, high selectivity and low cost for the detection of selected DNA sequences or mutated genes associated with human disease and promise to provide a simple, accurate and inexpensive platform of patient diagnosis. Various research groups have demonstrated that graphene-based DNA biosensors exhibit good sensitivity, selectivity and reproducibility [6, 320-324].

Gupta et al. [325] developed a highly sensitive method for the detection of DNA hybridization. This method was based on the modification of glassy carbon electrode with gold nanoparticles (AuNPs) involving p-aminothiophenol (ATP) functionalised GO. This GO was used as a platform for impedimetric genosensing, using 5′-TA GGG CCA CTT GGA CCT-(CH2)3-SH-3′ single-stranded probe (ss-DNA), 5′-AGG TCC AAG TGG CCC TA-3′ (target DNA), 5′-SH-C6-TAG GGC CA-3′ (non-complementary-1) and 5′-SH-C6-TGC CCG TTA CG 3-′ (non-complementary-2) oligonucleotide sequences. The film exhibited excellent properties for immobilising DNA probes and sensing DNA hybridization. The DNA immobilisation and hybridization on the film were studied by CV, and electrochemical impedance spectroscopy (EIS), and it was found that the charge transfer resistance (Rct) of the electrode increased with the concentration of the target DNA hybridized with the ss-DNA. The linear detection range was from 1.0×10^{-13} mol L^{-1} to 1.0×10^{-7} mol L^{-1} and the detection limit was 1.10×10^{-14} mol L^{-1} (n = 6). Chen et al. [129] used graphene-based field-effect transistors based on large-area monolayer graphene produced by chemical vapour deposition for label-free electrical detection of DNA hybridisation. The gate materials, buffer concentration and surface condition of

graphene have been optimized to achieve the DNA detection sensitivity as low as 1p mol L^{-1} (10^{-12} mol L^{-1}), which is more sensitive than the existing report based on few-layer graphene.

Cho et al. [129] developed chemiluminescence (CL) detection of DNA, using ssDNAaptamer-conjugated 6-FAM fluorescein (DAF), GO bound with magnetic nanoparticle (GMN), and 3, 4.5-trimethoxyphenylglyoxal (TMPG). When thrombin was incubated in TE buffer (pH 7.5) containing 200 n mol L^{-1} DAF for 10 minutes, thrombin binds strongly to DAF.

Fojta et al. [129] detected DNA directly, using the oxidative signals of DNA bases or by using electroactive labels [326]. Direct detection has an advantage because it is label free, but offers poorer sensitivity than label-based DNA assays. Adenine (A) and guanine (G) bases give analytically useful signals while cytosine (C) and thymine (T) do not provide well-resolved signals. Huang et al. fabricated a novel electrochemical sensor based on functionalized graphene for the simultaneous determination of adenine and guanine in DNA.

Shou et al.'s [121] biosensor revealed that chemically reduced graphene oxide provides well-resolved signals of all four A, G, C, and T bases with higher sensitivity than with graphite. This is attributed to the high defect density of the CRGO, and thus has superior electrochemical performance when compared to graphite. Lim et al. [114] compared the electrochemistry of DNA bases on epitaxially grown grapheme. Electrochemical oxidation of pristine epitaxially grown graphene led to the creation of defects on its surface and also leads to a significantly higher response. It was suggested that electrochemically oxidised graphene or graphene with large amounts of defects, could be used for highly sensitive electrochemical sensing. Zhu et al. [328] applied electrochemically oxidized graphene to discriminate between ssDNA and hybridised DNA. Liu et al. [329] used adsorption of a fluorophore-labeled DNA probe by GO to produce a sensor that gives fluorescence enhancement in the presence of its complementary

DNA (cDNA). Ambrose et al. [46] showed that large amounts of defects are beneficial for the electrochemical detection of DNA, using stacked graphene platelet nanofibers. These nanofibers are the direct opposites of carbon nanotubes, because they consist of perpendicularly stacked graphene sheets along the *c*-axis, exhibiting exclusively electrochemically-active edges (with the exception of terminal basal planes). Such nanofibers also provide significantly enhanced signals for all four DNA bases when compared to graphite, glassy carbon or pure carbon nanotubes. Lui et al [330] fabricated a novel electrochemical DNA biosensor based on graphen-three-dimensional nanostructure gold nanocomposite modified glassy carbon electrode (G-3D Au/GCE) for the detection of surviving gene which was correlated with osteosarcoma. The G-3D Au film was prepared with one-step electrochemical coreduction with graphite oxide and $HAuCl_4$ at cathodic potentials. The active surface area of G-3D Au/GCE was 2.629 cm^2, which was about 3.8 times compared to that of an Au-coated GCE under the same experimental conditions, and 8.8 times compared to a planar gold electrode with a similar geometric area.

Recently, Li et al. and Lu et al. [113, 331-333] reported that graphene and ssDNA assemblies can be used for the homogeneous detection of biomolecules. The electrochemical detection of four free bases (G, A, T and C) has been considered in the discussion of DNA sensors. Lu et al. [113] and Lui et al. [258,329] studied fluorescence quenching properties of GO in DNA biosensing. GO sheets were employed as a novel DNA biosensor by applying the GO in an array to recognize specific DNA–DNA hybridization. Lu et al. [334-336] used MB with GO as a "nanoquencher" to construct a highly sensitive, selective and economic sensor of biomolecules. Zhou et al. prepared CR-GO electrodes for label-free electrochemical detection of four DNA bases in ssDNA/dsDNA. DPV of G, A, T and C were studied at GC, graphite/GC and CR-GO/GC electrodes at pH 7. Shou et al [121] characterised and applied a chemically rGO

modified glassy carbon (CR-GO/GC) electrode, a novel electrode system, for the preparation of electrochemical sensing and biosensing platform. Different kinds of important inorganic and organic electroactive compounds (i.e., probe molecule (potassium ferricyanide), free bases of DNA (G, A, T, and C), oxidase/ dehydrogenase-related molecules H_2O_2/β-nicotinamide adenine dinucleotide (NADH)), neurotransmitters DA, and other biological molecules AA, UA, and acetaminophen (APAP)) were employed to study their electrochemical responses at the CR-GO/GC electrode, which shows more favourable electron transfer kinetics than graphite-modified glassy carbon (graphite/GC) and glassy carbon (GC) electrodes. Zhao et al. [67] designed a simple but smart platform in this work to fabricate electrochemical biosensors by using graphene quantum dots-modified pyrolytic graphite electrode, coupled with specific sequence ssDNA molecules, as probes. Due to the excellent conductivity of graphene material, the modified electrode can exhibit very fine electrochemical response. Nevertheless, the probe ssDNA will inhibit the electron transfer between the electrochemical active species [Fe(CN)6]3-/4- and the electrode, after the probe molecules are strongly bound to the surface of the modified electrode via their interaction with graphene. However, when the target molecules, such as target ssDNA and target protein also exist in the test solution, the probe ssDNA will bind with the target instead of graphene if the sequence of the probe ssDNA is designed as complementary to the target DNA or as the aptamer of the target protein. As a result, the obtained peak currents of $[Fe(CN)_6]$3-/4- will increase with the target molecules, thus various electrochemical biosensors can be easily developed with this proposed platform.

Bo et al. [92, 93] reported the fabrication of a DNA biosensor, based on graphene paste electrode modified with Prussian blue and chitosan and a novel electrochemical DNA biosensor, based on graphene and polyaniline nanowires.

Nui et al. [337] constructed a novel and sensitive electrochemical DNA biosensor based on the gold electrode, modified by graphene and gold nanoparticles (AuNPs), whose sensitivity was improved by using 1,10- phenanthroline cobalt ([Co(phen) 2(Cl)(H2O)]+) as an electroactive indicator. The gold electrode was firstly modified with sulfurgraphene (GR-SH) and then covalently grafted with AuNPs via sulfur-gold affinity. The target DNA from Escherichia coli (E. coil), could be detected in a linear range from 2.50×10^{-11} to 1.25×10^{-9} mol L^{-1} (R = 0.9981) with a detection limit of 8.33×10^{-12} mol L^{-1} (3σ, n = 11). Du et al. [338] described the fabrication of a novel electrochemical deoxyribonucleic acid (DNA) biosensor based on electrochemical-reduced graphene oxide (ERGO) and peptide nucleic acid (PNA)-DNA hybridisation. Primarily, the ERGO-modified electrode was achieved by one-step electrodeposition technique on the glassy carbon electrode (GCE) through CV reduction of a graphene oxide colloidal solution. Subsequently, PNA was immobilised onto the surface of the ERGO through a linker (1-pyrenebutanoic acid succinimidyl ester-PASE), and then the PNA-functionalised electrochemical biosensor was used to detect DNA via PNA-DNA hybridisation. Differential pulse voltammetry (DPV) was employed to monitor the hybridisation event by using methylene blue (MB) as the electrochemical indicator. It was found that the peak currents of MB were linear with the logarithm of the complementary target DNA concentrations, and the dynamic detection range for the target DNA was from 1.0×10^{-7} to 1.0×10^{-12} mol L^{-1}, with a detection limit of 5.45×10^{-13} mol L^{-1} (3σ/S). Furthermore, the fabricated biosensor could successfully discriminate the one-base mismatched and non-complementary DNA sequences from the complementary DNA sequence.

Chen et al. [129] used high transconductance and low noise of graphene-based field-effect transistors based on large-area monolayer graphene produced by CVD for label-free electrical

detection of DNA hybridization. The gate materials, buffer concentration and surface condition of graphene have been optimised to achieve the DNA detection sensitivity as low as 1p mol L^{-1} (10^{-12} mol L^{-1}), which is more sensitive than the existing report based on few-layer graphene. The graphene films obtained using conventional PMMA-assisted transfer technique, exhibits PMMA residues, which degrade the sensing performance of graphene. Li et al. [339] used GO as an electrode material on which double-stranded DNA was effectively immobilised. The electrochemical experimental results indicated that the electrochemical response of DNA on the electrode was dramatically increased by GO, which facilitates the electron transfer between DNA and electrode. While hydroquinone, a typical environmental pollutant, was present in the electrolytic solution, the electrochemical response of DNA on the GO electrode was decreased, owing to the interaction of hydroquinone with DNA. Accordingly, the DNA-immobilised GO electrode was developed as the electrochemical biosensor for the monitoring of hydroquinone. Under optimal condition, the as-prepared electrochemical biosensor showed a linear response to hydroquinone in the concentration range from 1.0×10^{-7} to 1.0×10^{-4} mol L^{-1}. Lui et al. [329] observed that adsorption of a fluorophore-labeled DNA probe by GO produces a sensor that gives fluorescence enhancement in the presence of its complementary DNA (cDNA). Lui et al. [341] prepared a new nanocomposite, which was composed of ionic liquid functionalised graphene sheet (IL-GS)- loaded gold nanoparticles (AuNPs). The IL-GS was directly synthesized by the electrochemical exfoliation of graphite in ionic liquid (IL). Due to the modification of the IL, IL-GS cannot only be dispersed easily in aqueous solution to form a homogeneous colloidal suspension of individual sheet, but also exhibits an improved conductivity. Meanwhile, the loaded AuNPs on the nanocomposites can increase the specific surface area to capture a large amount of antibodies as well as improve the capability of electron transfer. The IL-GS-Au

nanocomposites were successfully employed for the fabrication of a facile and sensitive electrochemical immunosensor. Carcinoembryonic antigen (CEA) was used as a model protein. The immunosensor exhibited a wide linear detection range (LDR) from 1fgmL^{-1} to 100ngmL^{-1}, and an ultralow limit of detection (LOD) of 0.1fgmL^{-1} (S/N=3). Lui et al [340] also designed graphene/DNA-based label-free colorimetric biosensors.

6.8. Ascorbic Acid (AA), Uric Acid (UA) and Dopamine (DA)

Determination of AA is a problem in analytical neuro-chemistry and bio-chemistry [121]. Recently, graphene-based electrodes have been used for simultaneous detection of AA, DA and UA. Shang et al. [342] used MGNF for the selective determination of DA, AA and UA in 50 m mol L^{-1} PBS solution containing 1 m mol L^{-1} AA, 0.1 m mol L^{-1} DA, 0.1 m mol L^{-1} UA, and their ternary mixture at a scanrate of 100 mV s−1. The MGNF demonstrated good ET kinetics and allowed well-resolved simultaneous discrimination of AA, DA and UA at a detection limit of 0.17 m mol L^{-1}.

Zhou et al. [121] investigated the biosensing efficiency of CR-GO. The electroanalytical performances towards the detection of AA, DA and UA were much better, compared to bare GC or graphite/GC electrode. Wang et al. [56] employed a graphene-modified electrode for the selective detection of DA. The CV curve of 1 m mol L^{-1} DA on CS–GR/GC, CS/GC, and GC electrodes showed well-defined and resolved voltammetric peaks for the direct oxidation of DA on CS–GR/GC as compared with CS/GC or GC. Tan et al. [343] developed a CD/GR nanocomposite platform for the detection of DA in the presence of AA. Hou et al. [344] modified the surface graphene with NtrimethoxysilylpropylEDTA-silane for the sensitive and selective detection of DA. EDTA-silane linked to the graphene surface and provided a favourable environment for the oxidation of DA with a negative oxidation peak potential. Li et

al. [345] fabricated PtNP/IL/GR nanocomposites for the simultaneous determination of AA and DA. The difference between the two oxidation peak potentials is >200 mV, sufficient for the distinction between AA and DA. Three independent oxidation peaks have been detected at PtNP/IL/GR-modified electrodes in human urine samples containing AA and DA. Such electrodes displayed satisfying life times and reproducibility. Therefore, IL functionalised graphene can play an important role in the clinical analysis of AA and DA.

Alwarappan et al. [142] fabricated a novel biosensor for DA sensing in which chemically synthesized graphene nanosheets were used as electrode materials and their electrochemical properties were systematically characterized. The surface morphologies of grapheme nanosheets were evaluated using Raman spectroscopy and transmission electron microscopy. They found that graphene electrodes exhibited a superior biosensing performance than SWCNTs toward dopamine detection in the presence of common interfering agents such as ascorbic acid and serotonin. Gao et al. [346] prepared a graphene oxide - modified glassy carbon electrode (GCE), namely GO/GCE, by covalent coupling method which was characterised by AFM, CV and electrochemical impedance spectra (EIS). On this modified electrode, it was found that the electrochemistry of DA is greatly enhanced, while that of AA is totally impressed, showing that the modified layer of GO has completely different impacts on the electrochemical response of DA and AA. Pakapongpan et al. [347] successfully fabricated electrochemical sensor based on graphene/ copper phthalocyanine (CuPc)/ polyaniline (PANI) nanocomposite- modified screen printed electrode (SPE) for detection of AA. Copper phthalocyanine was immobilised on graphene by using PANI as a matrix. The nanocomposites were characterized by electrochemical techniques such as CV. The sensor exhibited a linear range from 100 μM to 3.6 m mol L^{-1} (a correlation coefficient of 0.9967). The sensitivity of the sensor was found to be 22.92 mA mol L^{-}

^{1} /cm^{-2} and the limit of detection was 8.3 μ mol L^{-1} (S/N = 3). This sensor exhibited good electrocatalytic properties and lowered the potential for the oxidation of AA, which makes it a suitable sensor for the detection of AA. Lu et al. [348] synthesized graphene-poly (3, 4-ethylenedioxythiophene) (graphene-PEDOT) nanocomposite film based on simultaneous electrodeposition of PEDOT and electrochemical reduction of GO on a GC electrode. Data from SEM, UV-vis spectroscopy (UV-vis) and EIS demonstrated that the graphene/PEDOT nanocomposite film was successfully synthesised. The obtained graphene-PEDOT nanocomposite film showed large specific area, high conductivity, good biocompatibility, fast redox properties and had encapsulated structures, which make it a promising novel material for biological applications. As an enzyme model, ascorbate oxidase (AO) was entrapped onto the film-modified electrode and used to construct an electrochemical AA biosensor. The modified-electrode showed good electrocatalytic performance towards AA with high selectivity, wide linear range and good stability.

Mishra et al. [349] reported a new chemical method for the synthesis of graphene with good yield. Graphene obtained by this chemical route was subjected to electrochemical characterisation, using two different redox materials for their suitability in electrochemical biosensing applications. The synthesised graphene was used for the detection of neurotransmitters like DA and serotonin. The electrodes exhibited 20%±5% (N = 5) decreased in their signal after forty-five days storage in the laboratory atmosphere. Zeng et al. [350] prepared a composite of SiO_2-coated GO and molecularly imprinted polymers (GO/SiO2-MIPs. The GO/SiO_2-MIPs sensor had a wide linear range over DA concentration from 5.0×10^{-8} to 1.6×10^{-4} mol L^{-1}, with a detection limit of 3.0×10^{-8} mol L^{-1} (S/N=3). The sensor based on this novel imprinted composite was applied to the determination of DA in injections and human urine

samples with satisfactory results. Yu et al. [351] fabricated a facile electrochemical sensor based on poly(diallyldimethylammonium chloride) (PDDA)-functionalised graphene (PDDA-G) and graphite. The composite electrode exhibited excellent selectivity and sensitivity towards UA, owing to the electrocatalytic effect of graphene nanosheets and the electrostatic attractions between PDDA-G and UA. The anodic peak current of UA obtained by CV increased over 10-fold, compared with bare carbon paste electrode (CPE). The reversibility of the oxidation process was improved significantly. Differential pulse voltammetry (DPV) was used to determine UA in the presence of AA and DA. It was found that all of oxidation peaks of the three species could be well resolved and the peak current of UA was much stronger than the other two components. More importantly, considerable amount of AA and DA showed negligible interference to UA assay. The calibration curve for UA ranged from 0.5 to 20 μ mol L^{-1}, with a correlation coefficient of 0.9934. The constructed sensor has been employed to quantitatively determine UA in urine samples. Li et al. [352] prepared a biosensor using water-soluble sulfonated graphene with the aim of achieving the selective and sensitive determination of DA in the presence of AA and uric acid UA. The aromatic π–π stacking and electrostatic attraction between positively charged DA and negatively charged sulfonated graphene can accelerate the electron transfer, though weakening AA and UA oxidation on the sulfonated graphene-modified electrode. The proposed method was used to detect DA in real hydrochloride injection sample, human urine and serum samples with satisfactory recovery results.

Kaur et al. [353] reported the synthesis of silver nanoparticle-decorated reduced GO composite (AgNPs/rGO) by heating the mixture of GO and silver nitrate aqueous solution in the presence of sodium hydroxide. The analytical performance of this material as a chemical sensor was demonstrated for the determination of ascorbic acid and dopamine in commercial pharmaceutical

samples, such as vitamin C tablets and dopamine injections, respectively. The applicability of this sensor was also extended in the determination of uric acid in human urine samples.

Sheng et al. [354] prepared nitrogen-doped graphene (NG) by thermally annealing graphite oxide and melamine mixture, the electrochemical sensor based on NG was constructed to simultaneously determine small biomolecules such as AA, DA and UA. The sensor shows a wide linear response for AA, DA and UA in the concentration range of 5.0×10^{-6} to 1.3×10^{-3} mol L^{-1} , 5.0×10^{-7} to 1.7×10^{-4} mol $L^{-1}$and 1.0×10^{-7} to 2.0×10^{-5} mol L^{-1} , with detection limit of 2.2×10^{-6} mol L^{-1}, 2.5×10^{-7} mol $L^{-1}$and 4.5×10^{-8} mol L^{-1} at S/N = 3, respectively.Wang et al. [355] reported the application of graphene-modified electrode for selective detection of DA.

6.9. Cytochrome c (Cyt-c)/cysteine.

Song et al. [356] developed a novel biosensor by entrapping Cyt-c in thin films of room temperature ionic liquid (RTIL) containing nanocomposites of poly(diallyldimethylammonium chloride)-graphenenanosheets-goldnanoparticles (PDDA-Gp-AuNPs) at an 11-mercaptoundecanoic acid-6-mercapto-1-hexanol modified gold electrode. The synthesised PDDA-Gp-AuNPs hybrid nanocomposites were characterized by UV-vis spectroscopy, Raman spectroscopy, SEM and AFM. The PDDA-Gp-AuNPs nanocomposites could increase the effective surface of the electrode, enhance the fixed amount of Cytc on the electrode surface, promote the electron transfer and facilitate the catalytic activity of Cy-tc.

Chen et al. [357] prepared nanocomposite of polymerised ionic liquid (PIL), poly (1-vinyl-3-ethyl imidazolium) bromide, modified graphene nanosheet (PIL-Gr). The PIL-Gr nanosheet composite was evaluated, using scanning electron microscopy, transmission electron microscopy and Fourier transform infrared spectroscopy. Direct electrochemistry and electrocatalysis of

immobilised Cyt-c were investigated in detail. The CV results indicated that the PIL-Gr nanocomposite film showed an obvious promotion for the direct electron transfer between Cyt c and the underlying electrode. The immobilised Cyt-c exhibited an excellent electrocatalytic activity towards the reduction of nitric oxide (NO). Wu et al. [358] prepared graphene nano-flakes were successfully immobilised on glassy carbon electrode to construct a graphene modified electrode. Cytochrome c was adsorbed tightly on the surface of the modified electrode and the direct electron transfer of Cytochrome c was achieved. Cytochrome c on the surface of electrode maintains its bioactivity and shows an enzyme-like activity for the reduction of nitric oxide, displaying a potential application for the fabrication of novel biosensors to sense nitric oxide. Xiang et al. [359] reported direct electron transfer of cytochrome c and its biosensor, based on gold nanoparticles/room temperature ionic liquid/carbon nanotubes composite film.

Recently, Hosseine [360] synthesised Graphene oxide–cobalt phthalocyanine (GO–PcCo) hybrid material as a new electrocatalyst and was used successfully for the fabrication of new biosensor for the electrooxidation of l-cysteine (CSH) in aqueous media. Fourier transform infrared spectroscopy (FT-IR), X-ray photoelectron spectroscopy (XPS), thermogravimetric analysis (TGA) and transmission electron microscopy (TEM) images revealed that cobalt phthalocyanine is covalently attached on graphene oxide sheets as single layers GO–PcCo. CV studies showed that the GO–PcCo/glassy carbon electrode (GO–PcCo/GCE) improves electrochemical behavior of CSH oxidation, as compared to the GO and PcCo. Li et al. [361] demonstrated on the basis of cytochrome c-induced self-assembled graphene quantum dots, a novel fluorescent biosensor for trypsin, with remarkable fluorescence enhancement, as well as high selectivity and sensitivity.

Zhang et al. [9] developed a novel electrochemical biosensor for highly sensitive and selective detection of cysteine. Based on in-situ synthesis of gold nanoparticles (AuNPs)/reduced graphene oxide (RGO), nanocomposites were developed. GO was reduced by DA, and then in situ synthesis of AuNPs by the phenolic hydroxyl groups of DA on the RGO surface. The sulphydryl group of cysteine could bind not only with AuNPs through AuS bond, but also with polydopamine on the RGO surface through Michael addition reaction. Combination of cysteine with the AuNPs/RGO leads to the decrease in the peak currents of electrochemical probe $[Ru(NH_3)_6]3+$, which could be used for indirect electrochemical sensing of cysteine. The change of the peak currents value of $[Ru(NH_3)_6]3+$ was linear with the concentration of cysteine in the range from 1.0×10^{-9} to 3.0×10^{-8} mol L^{-1} ,with a linear co-efficiency of 0.991. The detection limit was 1.0×10^{-10} mol L^{-1} (S/N=3). The proposed electrochemical biosensor is rapid, convenient and low-cost for effective sensing of cysteine.

7. Conclusions

This review presents recent synthesis and applications of graphene for electrochemical biosensing. A rapid growth in the use of graphene-based electrodes for electrochemical sensing and biosensing has been witnessed. These biosensors have exhibited excellent sensitivity and selectivity towards the detection of glucose, cholesterol, Hb, H_2O_2, UA, AA, DA. DNA. Studies of graphene-based materials will enhance research in the field of bio-sensor, because graphenes are excellent materials for the development of electrochemical sensors. Graphene immobilised within composites offers the advantages of an easy preparation and the dispersion of graphene in polyelectrolytes is another excellent platform for further design of different sensors or biosensors once immobilised on an electrode.

Future development of sensors and biosensors will address future sensing and biosensing challenges in clinical diagnostics; environmental monitoring and security control. This will depend on the unique properties of grapheme, with the powerful recognition properties of biomolecules and the known advantages of the electrochemical techniques.

8. Future work

The future of graphene and some of the graphene-like materials produced in the pursuit of graphene in many applications will emerge because of high surface area of graphene prepared by CVD and chemical exofilation. Many different strategies will be explored for the construction of novel biosensors that employ graphene or graphene-like materials as sensing elements, to detect small biomolecules i.e (DNA). Heteroatom-doped graphene can be used to form novel biosensor and more research will be carried out on graphene/conducting polymer /nanocomposites and graphene/carbon paste electrode. Biocompatibility of graphene in different sensing applications will need to be addressed further in future work, while mass production of single layer graphene is a major challenge that needs to be overcome in the future.

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- The review summarises recent contributions in the fabrication of graphene biosensors.
- Its large surface area and good electrical conductivity make it excellent material for sensor.
- Graphene promotes rapid electron transfer that facilitates rapid detection of biomolecules.
- An increasing number of reviews and publications involving graphene sensors have been reported.

Figures Caption

Table 1 Applications of graphene and related materials.

Table 2 Various types of enzymatic electrodes made from graphene and GO [124].

Fig. 1. Applications of grapheme [167].

Fig. 2. CVD processes [166].

Fig. 3. (A) A typical low-magnification TEM image of the graphene sheets; the scale bar is 100 nm. **(B)** A high-resolution TEM image, where the white arrow indicates the edge of the graphene sheet; the scale bar is 4 Å. **(C)** An atomic-resolution image (TEAM 0.5) of a clean and structurally perfect synthesised graphene sheet. Individual carbon atoms appear white in the image. The image was obtained through the reconstruction of the electron exit wave function from 15 lattice images using MacTempas software [363].

Fig. 4. TEM images of gold nanoparticle-pyrolitic functionalised graphene composites with a gold to graphene weight ratio of (A) 10:1 and (B) 300:1. Scale bar: 50 nm [186, 364].

Fig. 5. Wiring of proteins by graphene for electrochemistry. Graphene-oxide (GO)-supported heme proteins at the surface of glassy-carbon electrodes [228].

Fig. 6. Scheme of a biosensor. The biosensor consists of a receptor layer, which consists of a biomolecule (e.g., DNA or protein), and a transducer, which is a graphene-based material [108]. Reproduced from by permission of American Chemical Society, USA.

Fig.7. Amperometric responses of cholesterol (A) and cholesterol ester (B) biosensors. Cholesterol (5 μM) and cholesteryl stearate (5 μM) were injected at regular intervals [297].

Table 1

S/N	Application	Reference
1	Energy storage	16-12
2	Batteries	63, 84-87
3	Gas sensor	74, 96-99
4	Capacitors	75-78
5	Chemical and biosensors	7, 91-95
6	Fuel cell	79-83
7	Photocatalysis	17,63,
8	Phtovoltaics	25,90
9	Solar cell	17,75,102
10	Light emitting diode	103,104
11	Laser	105
12	Optoelectronics	100,106
13	Phtocatalyst	107,108
14	Thin film transistor	103,109
15	FET	110-113

Table 2

Type of biosensor	Sensor materials	RSD (%)	Detection limit	References
Glucose	Graphene-PPy	–	3 ± 0.5 μ mol L^{-1}	[263]
	Metal decorated graphene	–	1 μ mol L^{-1}	[266]
	Graphene/Nafion	4.21	1.0×10^{-6} mol L^{-1}	[126]
	CVD grown graphene	–	0.1 m mol L^{-1}	[58]
	CS–GR	5.3	0.02 n mol L^{-1}	[250]
	GO	5.8	–	[257]
	PVDF-protected graphene	3.2	2–14 m mol L^{-1}	[229]
	CS–GR-AuNP	4.7	180 μ mol L^{-1}	[59]
	GO	–	–	[19]
	Graphene-CdS	5.3	0.7 m mol L^{-1}	[230]
	CS–GR-AuNP	6.0	0.6 mol L^{-1}	[145]
	Graphene	2.5	10 ± 2 μ mol L^{-1}	[252]
	CMG	–	0.376 m mol L^{-1}	[260]
	Graphene	–	0.168 m mol L^{-1}	[256]
	CR-GO	4.3	2.0 μ mol L^{-1}	[121]
	Graphene	3.2	5 μ mol L^{-1}	[139]
NADH	IL functionalized graphene	4.2	5 μ mol L^{-1}	[185]
	Graphene	3.5	–	[362]

Type of biosensor	Sensor materials	RSD (%)	Detection limit	References
Hb	Fe_3O_4–graphene	1.6	0.5 μ mol L^{-1}	[275]
	Graphene	–	5.1×10^{-7} mol L^{-1}	[15]
	Graphene	4.48	1.05×10^{-7} mol L^{-1}	[334]
HRP	SDBS–graphene	–	1.0×10^{-7} mol L^{-1}	[256]
	AuNP–graphene	3.6	1.0×10^{-6} mol L^{-1}	[139]
	CS–GR/Fe_3O_4/HRP	–	6.0×10^{-7} mol L^{-1}	[67]
Cholesterol	PtNP–graphene	–	0.5 n mol L^{-1}	[296-297]

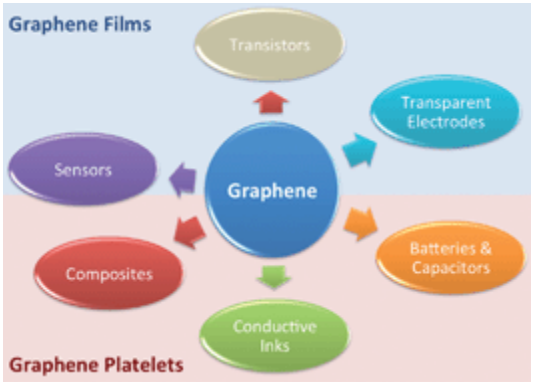


Fig. 1.

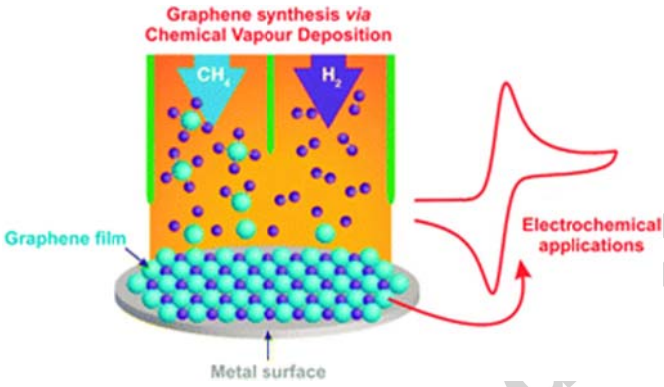


Fig. 2.

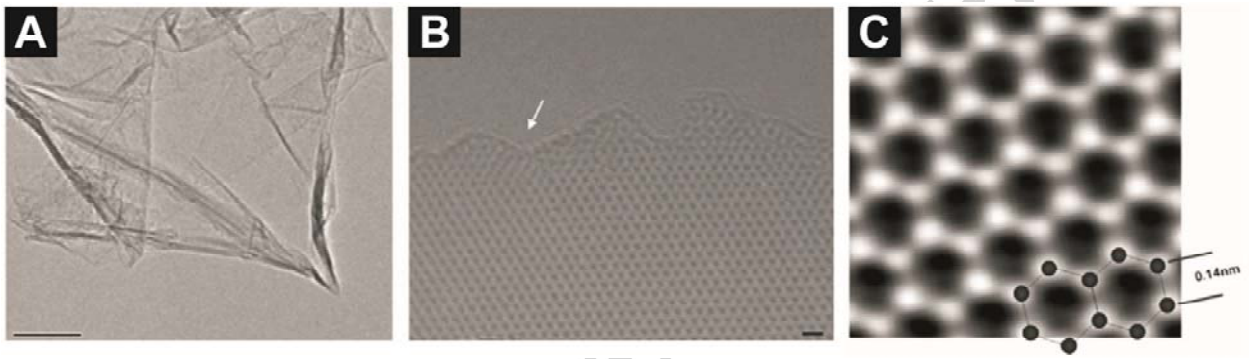


Fig. 3.

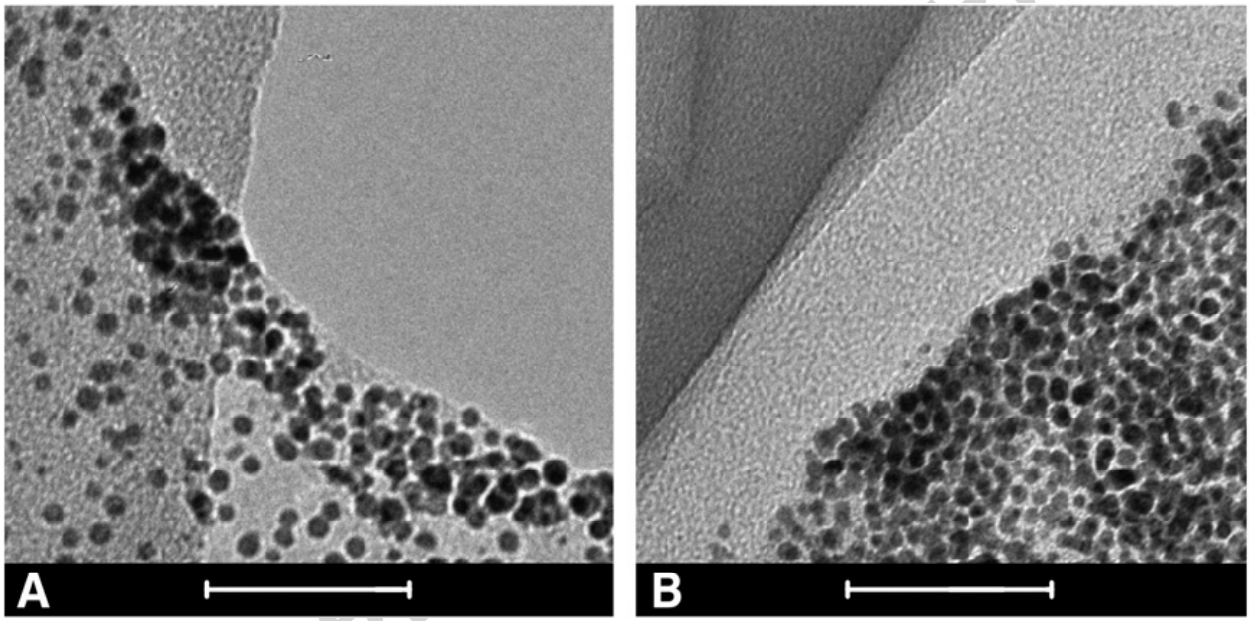


Fig. 4.

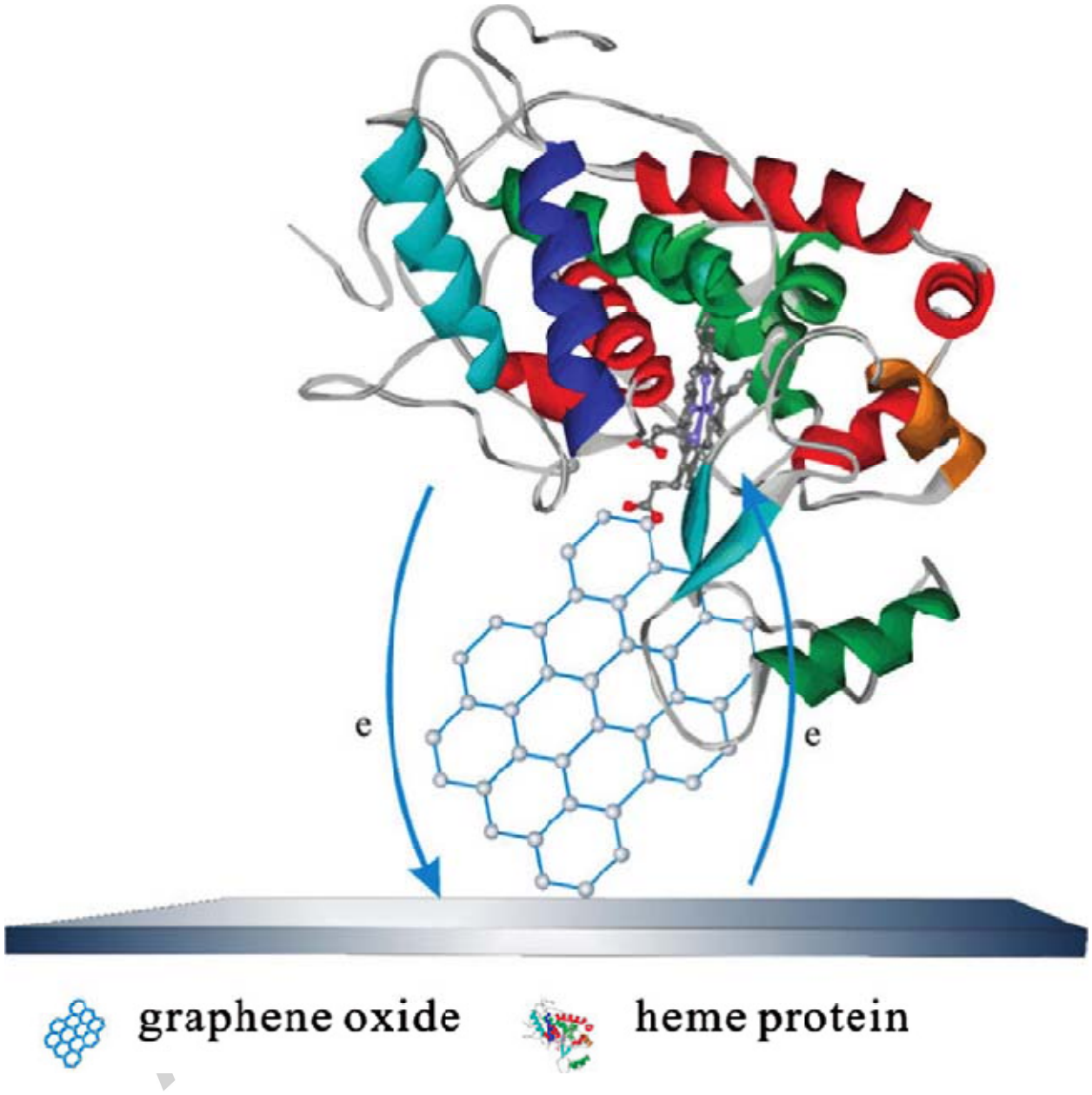


Fig. 5.

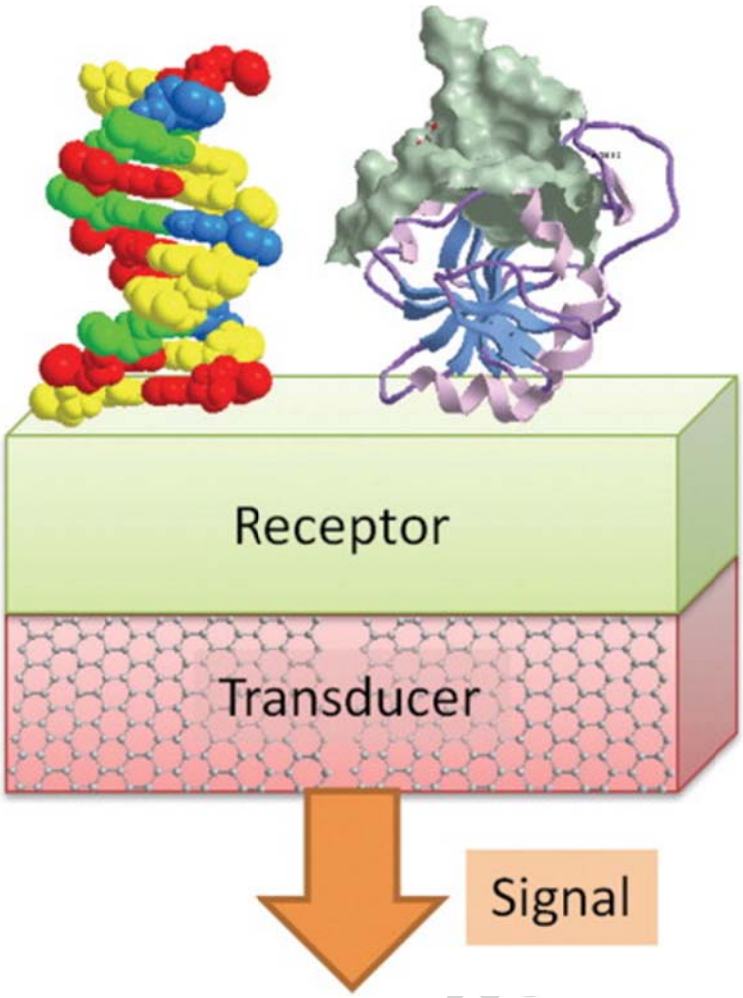


Fig. 6.

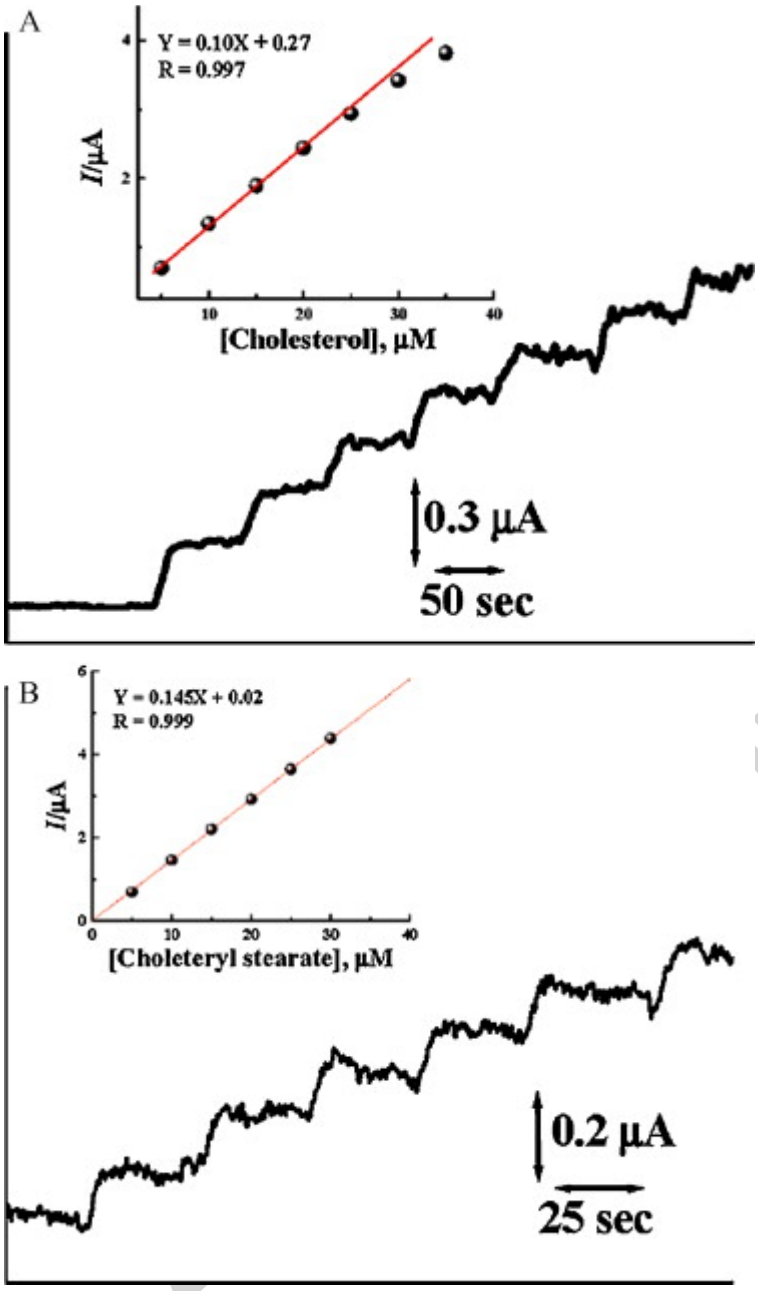
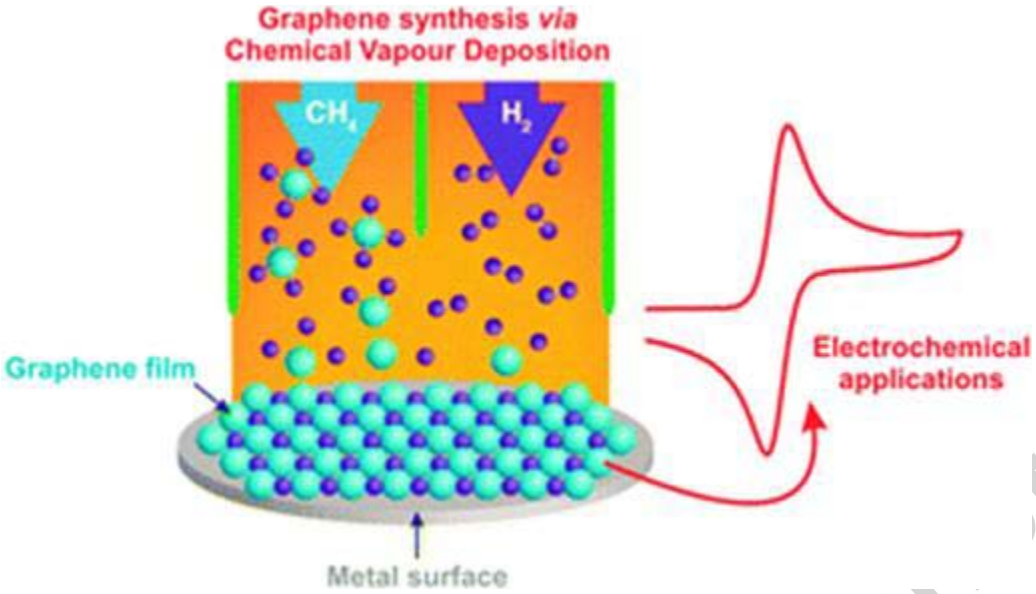

A
Y = 0.10X + 0.27
R = 0.997
I/μA
[Cholesterol], μM
0.3 μA
50 sec
B
Y = 0.145X + 0.02
R = 0.999
I/μA
[Choleteryl stearate], μM
0.2 μA
25 sec

Fig. 7.



Graphical abstract