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Graphene — A Platform for Sensor and Biosensor Applications

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Abstract

Graphene, mother of all carbon materials, has opened up new era of exploration due to its unique properties. Graphene, one-atom thick, exhibits a unique chemical structure and outstanding electronic, optical, thermal, and mechanical properties that made it compelling for various engineering applications. Graphene and graphene-based materials are promising candidates for fabricating state-of-the-art nano-scale sensors and biosensors. They featured with good conductivity and large specific surface area thereby; graphene-based sensors/biosensors performed well with good accuracy, rapidness, high sensitivity and selectivity, low detection limits, and long-term stability. They are ideally used as gas sensors, electrochemical sensors for heavy metal ions, immunosensors and dihydronicotinamide dinucleotide NADH, DNA, catecholamine neurotransmitters, paracetamol, glucose, H_2O_2 , hemoglobin, and myoglobin biosensors. This chapter reviews the applications of graphene in nano-technology since it came to the field particularly in sensing and biosensing applications. It updates the reader with the scientific progress of the current use of graphene as sensors and biosensors. There is still much room for the scientific research and application development of graphene-based theory, materials, and devices. Despite the vast amount of research already conducted on graphene for various applications, the field is still growing and many questions remain to be answered.

Keywords: Graphene, Graphene-based materials, Nano-composites, Sensors, Biosensors

1. Introduction

Carbon is an abundant element playing a major role in the chemistry of life [1]. Some of the advantageous properties of carbon-based electrodes include wide potential windows, fairly inert electrochemistry, and good electrocatalytic activity for many redox reactions [2]. Various carbon allotropes including diamond (the carbon atoms are bonded together in a tetrahedral lattice arrangement, 3D), graphite (the carbon atoms are bonded together in sheets of a hexagonal lattice, 3D), graphene (2D), carbon nanotubes (single-walled carbon nanotubes (SWCNT), multi-walled carbon nanotubes (MWCNT), 1D), and fullerenes (the carbon atoms are bonded together in spherical, tubular, or ellipsoidal formations, 0D) have very different physical and electrochemical properties from each other (see Table 1 and Figure 1) [2-4]. The advents of sp^2 and/or sp^3 hybridized structures, such as fullerenes, carbon nanotubes, and conducting diamond, provide a route for surface modification and are very beneficial to electrochemical research, especially electrocatalysis [2]. The former 3D allotropes have been known and widely used for centuries whereas fullerenes and nanotubes have been only discovered and studied in the last two decades. With the exception of diamond, it is possible to think of fullerenes, nanotubes, and graphite as different structures built from the same hexagonal array of sp^2 carbon atoms, namely, graphene [3].

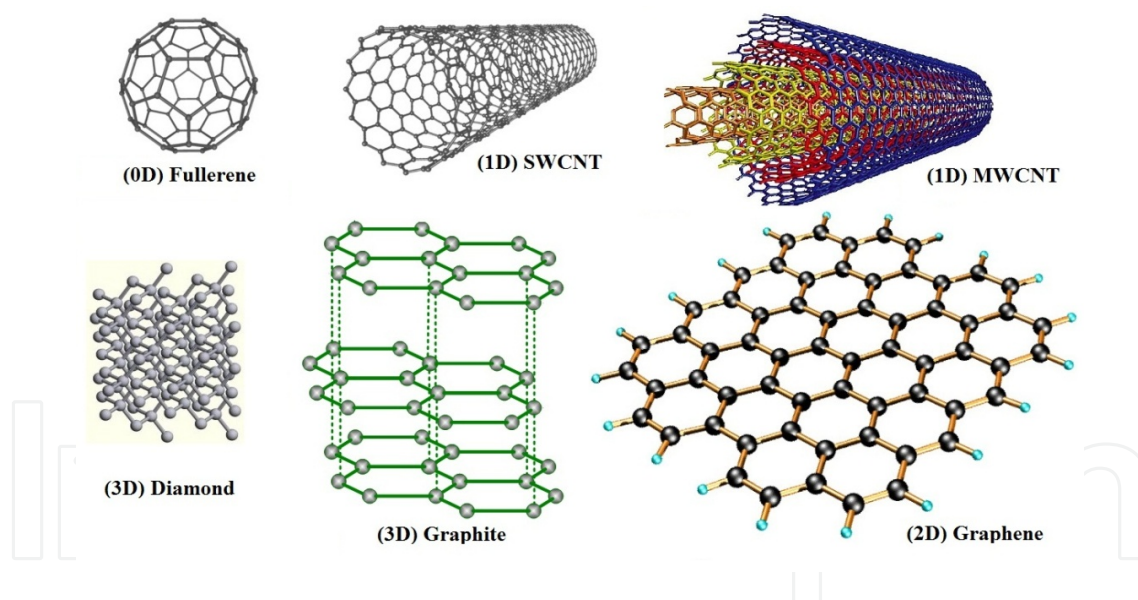


Figure 1. Different allotropes of carbon.

Graphene consists of a single sheet of carbon atoms that bind with each other in a honeycomb lattice. Graphene sheets are one-atom thick and 2D layers of sp^2 -bonded carbon [4]. It is the basic building block for graphitic materials of all other dimensionalities. Graphene can be wrapped up into spherical shape to form 0D fullerenes (buckyballs), rolled into a cylindrical shape to form 1D nanotubes or stacked in layers to form 3D graphite as illustrated in Figure 2 [1, 3, 5-8]. The electronic structure of graphene sheets, individual layers of graphite, was first discussed by Wallace in 1947 [2]. Boehm and co-workers separated thin lamellae of carbon by

heating and chemical reduction of graphite oxide in 1962 [6]. Until 2004, single layers of graphite were believed to be thermodynamically unstable under ambient conditions [2, 6]. Since the historical observation of single layer graphene in 2004 by two Nobel Laureates in physics, Prof. Andre Geim and Prof. Konstantin Novoselov, this atomically thin carbon film has received ever increasing attention and become the hottest topics and a rapidly “rising star” on the horizon of materials science and condensed-matter physics attracting enormous interests [8-10]. This revolutionary discovery has added a new dimension of research in the fields of physics, chemistry, biotechnology, and materials science [6]. Technologists and materials scientists have rapidly grabbed some of the assets of graphene and are already exploring the ways of incorporating graphene into applied devices and materials [3].

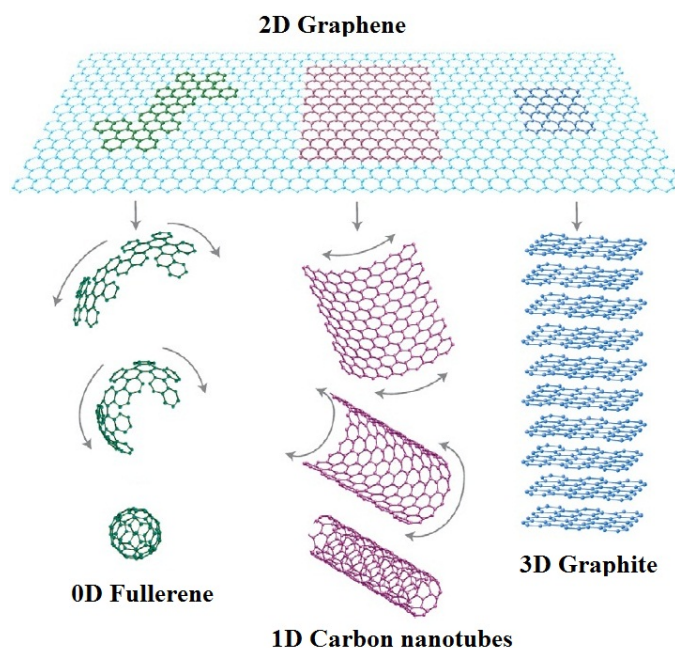


Figure 2. Basis of all graphitic forms. Graphene is a 2D building material for carbon materials of all other dimensionalities. It can be wrapped up into 0D buckyballs, rolled into 1D nanotubes or stacked into 3D graphite [6].

Dimension	0D	1D	2D	3D
Isomer	Fullerene	Nanotube	Graphene	Diamond
Hybridization	sp^2	sp^2	sp^2	sp^3
Density (g/cm^3)	1.72	1.2-2.0	2.26	3.515
Bond length (Å)	1.40 (C=C) 1.46 (C-C)	1.44 (C=C)	1.42 (C=C)	1.54 (C-C)
Electronic properties	Semiconductor $E_g = 1.9$ eV	Meta/semiconductor $E_g \approx 0.3-1.1$ eV	Zero-gap semiconductor	Insulator

Table 1. Important parameters of carbon materials of different dimensionalities [6].

2. Graphene: Promising material for different applications

Graphene, a monolayer of sp^2 -bonded carbon atoms arranged in a honeycomb lattice, has attracted tremendous attention from both the theoretical and experimental scientific communities in recent years because of its unique nanostructure and extraordinary properties [11, 12]. It has become a novel and very promising material for nanoelectronics, nanocomposites, optoelectronic devices, electrochemical supercapacitor devices, fabricated field-effect transistors, drug delivery systems, solar cells, memory devices, and constructed ultrasensitive chemical sensors such as pH sensors, gas sensors, biosensors, etc. [6, 11, 12]. The rapid adoption of graphene as a material of interest lies in its actual availability by a range of techniques and methods and may also be principally because monolayer and few-layer graphene possess a diverse set of unusual properties. These properties happen to be matching the short-comings of other materials, such as carbon nanotubes, graphite, or indium tin oxide (ITO) that have been studied and used for some time [3]. In the following points, we will give an exhaustive account of the unique physical and chemical properties of graphene.

- Graphene implies large theoretical specific surface area ($\sim 2630 \text{ m}^2 \text{ g}^{-1}$, for single-layer graphene), exhibiting high electrocatalytic activities and ultrahigh loading capacity for biomolecules and drugs [6, 8, 13].
- Graphene is a unique bendable material with excellent mechanical flexibility and high crystallographic quality. It is strictly 2D and stable under ambient conditions [6, 11, 14].
- Graphene exhibits high optical transparency [6, 11] with an absorption of $\sim 2.3\%$ toward visible light [15]. Indeed, in the visible range, thin graphene films have a transparency that decreases linearly with the film thickness. For 2-nm thick films, the transmittance is higher than 95% and remains above 70% for 10-nm thick films. This optical characteristic combined with the excellent conductivity of graphene-based materials holds promises as a replacement to the cost-raising standard ITO [3].
- The breaking strength of graphene is 200 times higher than steel making it the strongest material ever tested. Graphene exhibits high values of Young's modulus ($\sim 1.1 \text{ Tpa}$) [6, 11].
- It is one of the thinnest known materials. The carbon atoms are densely packed in a honeycomb crystal lattice with a bond length of 0.141 nm. Different research groups have measured the thickness of graphene from 0.35 nm to 1.00 nm. Novoselov et al. have determined platelet thicknesses of 1.00–1.60 nm [6].
- It is well established that the superior properties of graphene are associated with its single layer [6]. Figure 3 (a) shows the honeycomb lattice of graphene that is formed by a triangular lattice with a basis of 2 atoms per unit cell. Each atom has four valence electrons: one s and three p orbitals. The s and two p orbitals hybridize to form strong covalent bonds in the plane. The out of plane p orbital contributes to the conductivity [1, 3]. The hexagonal structure of graphene possesses an alternate double bond arrangement that makes it perfectly conjugated in sp^2 hybridization. In this case, its p_x and p_y orbitals contain one electron each and the remaining p_z has only one electron. This p_z orbital overlaps with the

p_z orbital of a neighbor carbon atom to form a π -bond while the remaining orbitals form σ -bonds with other neighboring carbons. The π -electrons in graphene are delocalized and are largely responsible for its conduction properties while π -orbitals are the most important for determining the solid state properties of graphene [4]. Thus, graphene has extraordinary electronic transport properties and high electrocatalytic activities owing to its subtle electronic characteristics and attractive π - π interaction [12].

- It exhibits excellent room temperature electrical conductivity ($\sim 7200 \text{ S.m}^{-1}$) [6, 11] with amazing intrinsic mobilities of $\sim 200,000 \text{ cm}^2\text{V}^{-1}\text{s}^{-1}$. The room temperature thermal conductivity values have been determined to be $\sim (4.84 \pm 0.44) \times 10^3$ to $(5.30 \pm 0.48) \times 10^3 \text{ WmK}^{-1}$ for single-layer graphene [5, 6, 16].
- One of the factors that made graphene so attractive in the research field is its low energy dynamics of electrons. The 2D crystal of sp^2 hybridized carbon is a zero band gap semiconductor in which the π and π^* bands touch in a single point at the Fermi energy at the corner of the Brillouin zone and close to this so-called Dirac point, the bands display a linear dispersion (see Figure 3(b)) [1]. This topology of the bands gives rise to exotic electronic transport properties – the charge carriers behave like relativistic particles – which manifest themselves in unusual phenomena such as room-temperature anomalous quantum Hall effect and electrons behaving like massless (zero effective mass) Dirac fermions [2, 10, 16]. The ballistic charge carrier transport at 300 K and at high charge carrier concentrations makes graphene also interesting for applications in electronic devices [14].
- Graphene exhibits strong adsorptive capability [12] since every atom in a graphene sheet is a surface atom thus molecular interaction and electron transport through graphene can be highly sensitive to adsorbed molecules [17]. The unique electrochemical responses of graphene to target molecules are from the planar geometric structure and special electronic character of graphene [10].
- Easy synthesis, low cost, and non-toxicity of graphene make this material a promising candidate for many technological applications [5, 16].
- Graphene is an ideal material for various applications because of its very large 2D electrical conductivity, large surface area, and low cost. In comparison with carbon nanotubes (CNTs), two advantages of graphene are obvious as follows:
 1. Graphene does not contain metallic impurities as CNTs do. In many cases, such impurities dominate the electrochemistry of CNTs and lead to misleading conclusions.
 2. The production of graphene can be achieved using graphite that is cheap and accessible [18].

3. Methods of graphene preparation

The rapid adoption of graphene as a material of interest lies in its actual availability by a range of techniques and methods [3, 5]. In 2004, Geim and coworkers first reported graphene sheets

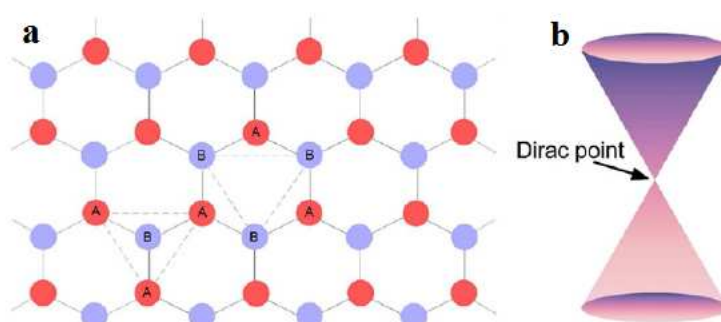


Figure 3. (a) Honeycomb lattice of graphene showing two triangular sublattices A and B. (b) Linear energy bands in the honeycomb lattice close to the Dirac point [1].

prepared by mechanical exfoliation (repeated peeling) of highly oriented pyrolytic graphite. This method, which is called the “scotch-tape” method, is still widely used in many laboratories to obtain pristine perfect structured graphene layer(s) for basic scientific research and for making proof-of-concept devices [18, 19]. However, this method is not suitable for the large-scale production of graphene necessary to fulfill the requirements in different areas. A large amount of recent effort has been devoted to develop methods to synthesize graphene at large scale for practical electronic applications. These methods include mechanical exfoliation and cleavage of natural graphite, chemical vapor deposition on metals, electric arc discharge, epitaxial growth on electrically insulating surfaces, unzipping of carbon nanotubes, solution-based chemical approaches (chemical or thermal reduction of graphite oxide), and thermal decomposition of SiC wafer under ultrahigh vacuum conditions [2, 5, 6, 19].

3.1. Chemical vapor deposition

Chemical vapor deposition (CVD) is a simple, scalable, and cost-efficient method to prepare single and few-layer of graphene on various substrates. It opens a new route to large-area production of high-quality graphene films for practical applications [20-23]. In general, CVD techniques involve the decomposition of fluid (gas and liquid sprays) at high temperature to form either thin films on substrates or powders through filters. There are many forms of CVD like hot wire CVD, thermal CVD [24], plasma-enhanced CVD [25], radio-frequency CVD, and ultrasonic spray pyrolysis. Evaporated Ni film on SiO₂/Si wafers or copper foils are ideal substrates for graphene synthesis. Synthesis of graphene on Ni supported on Si/SiO₂ wafers facilitated the breakthrough approach for large-scale graphene. This is attributed to the excellent geometrical fit of the ordered graphene/graphite phase of carbon to the crystalline metal surface that is provided by Ni films. Another reason is the convenient interactions that favor bond formation between carbon atoms at specific conditions. Carbon atoms dissolve into the Ni crystalline surface and they arrange epitaxially on the Ni (111) surface to form graphene at certain temperatures (Figure 4). CVD synthesis of graphene can be carried out at ambient pressure or vacuum by systematically varying parameters such as gas composition and flow rate, temperature, and deposition time [4, 19]. The carbon precursor in CVD is methane [26-29]. By using diluted methane, single and few-layers of graphene (less than 5 layers) were grown, while using concentrated methane results in multilayer growth [4]. Other carbon precursors can be used in CVD such as ethanol [30], isopropanol [27], ethylene, acetylene, and others [4].

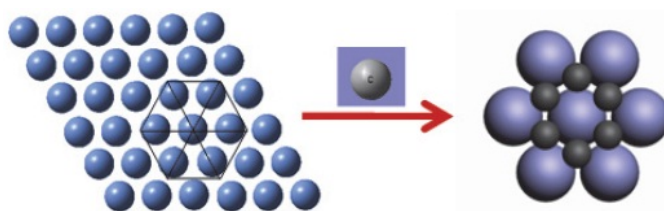


Figure 4. Schematic representation of the atomic arrangement of the hexagonal lattice of the (111) face of nickel (blue spheres) and how carbon atoms (gray spheres) would arrange on the Ni (111) surface to form graphene [4].

3.2. Unzipping of CNTs into monolayer graphene

The method of unzipping single-walled carbon nanotubes to form monolayer graphene has been reported recently accomplishing by harsh acids and the right thermodynamic conditions (Figure 5) [31]. Recently, Dai and coworker have taken a unique approach to fabricate graphene nanoribbons (GNRs) with well-controlled dimensions. Based on the concept that CNTs are considered to be GNRs rolled up into seamless tubes and the fact that the size of CNTs has been well controlled, Dai's group developed a method to produce GNRs through controlled unzipping of CNTs using the Ar plasma etching method. Shimizu and coworkers produced GNRs through the oxidation and longitudinal unzipping of MWCNTs in concentrated sulfuric acid followed by treatment with KMnO_4 [32]. Another approach involved the preparation of longitudinal unzipped MWCNTs by controlled oxidation and intercalation through reaction with concentrated H_2SO_4 and HNO_3 at room temperature in order to control the reaction rate. The unzipped MWCNTs are thermally treated up to 1000°C and 2500°C in an inert atmosphere to exfoliate and reduce the edge defects. The sonication process is responsible for chemo-mechanical breaking and the separation of multi-layer nanoribbons [33]. Furthermore, graphene nanoribbons were synthesized by the oxidative unzipping of SWCNTs using a mixture of concentrated $\text{HNO}_3/\text{H}_2\text{SO}_4$ in a 1:3 volume ratio followed by 8 hours of ultrasonic treatment performed at 50 W at 45°C [34]. In addition, catalytic unzipping of single-, double-, and multi-walled carbon nanotubes (SWCNTs, DWCNTs, and MWCNTs) in the presence of Pd nanoparticles and an oxygen-containing liquid medium yielding few layer graphene sheets was performed under microwave irradiation [35].

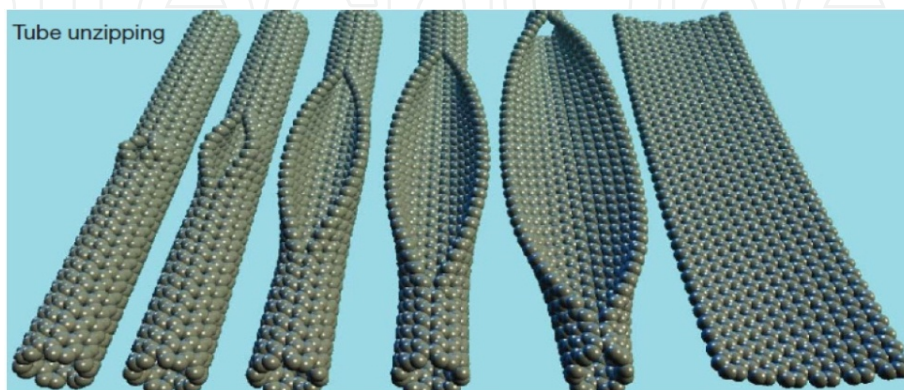


Figure 5. Modelling illustration of the SWCNT unzipped into monolayer graphene [31].

3.3. Arc discharge

Arc discharge is a versatile and low-cost method for producing various kinds of carbon nanomaterials. Compared to other methods, the graphene sheets synthesized by arc discharge method have merits of good dispersibility in organic solvent, few defects, and high thermal stability [36]. In the arc discharge technique, graphite rods (purity: 99.99 %) are used as electrodes for high voltage arcing. At extremely high voltages between the electrodes that are separated by very small distances, very high electric fields can be produced leading to instantaneous sparks like in a welding process. The fall-out during the discharge process is the end product that contains the carbon nano-structures [31]. To prepare pure few-layered graphene, a direct current arc discharge of graphite evaporation was carried out in a water-cooled stainless steel chamber filled with different buffer gases after evacuating the chamber by a mechanical pump [31, 36]. When the arc discharge process ended, the generated soot was collected under ambient conditions. The soot deposited on the inner and top wall of the reaction chamber was only collected in order to exclude relatively heavy products (amorphous carbon nanoparticles or multi-layered graphene sheets) dropped to the bottom of the chamber during the arc discharge process [36]. Different discharge atmospheres may induce different chemical bonds that cause the prepared graphene sheets to have different properties. Direct current hydrogen arc discharge evaporation of pure graphite electrodes in various gas mixtures can be used to mass-produce high-crystalline few-layer graphene sheets [40]. Various gas mixtures were reported such as H_2 , He, mixture of H_2 and He, mixture of NH_3 and He, and mixture of CO_2 and He to synthesize few-layered graphene sheets with high electrical conductivity [36-38]. On the other hand, a novel method for the large-scale production of graphene flakes in an arc discharge enhanced with a specially shaped magnetic field and a custom-designed catalyst was reported [39].

3.4. Reduction of graphene oxide into graphene

Graphene oxide (GO) was synthesized by the strong oxidation of flake graphite using acid via Hummers' method [40, 41] or modified Hummers' method [42-44]. GO, an oxidized form of graphene, is decorated by hydroxyl and epoxy functional groups on the hexagonal network of carbon atoms with carbonyl and carboxyl groups at the edges. GO is highly hydrophilic and forms stable aqueous colloids due to the large number of oxygen-containing functional groups as well as the repulsive electrostatic interactions at the edges of the platelets [41, 45]. It was reported that GO can be reduced via thermal, chemical, electrochemical, and laser-scribing methods.

3.4.1. Thermal reduction

The thermal method is believed to be a green method in which no hazardous reductants are used. This process requires heating up to $1050^\circ C$ in an oven under argon gas, up to $800^\circ C$ under hydrogen gas, or up to $700^\circ C$ in a quartz tube. The thermal reduction of GO was accompanied by the elimination of epoxy and carboxyl groups in the forms of O_2 , CO, CO_2 , and H_2O as predicted from thermogravimetry data [46-48]. Recently, graphene sheets were prepared by a solvothermal reduction of GO suspension in water, octadecylamine, butanol,

or N,N-dimethylacetamide [46]. Wei Huang synthesized high-performance graphene nanosheets by thermal reduction of GO under ethanol atmosphere at 900°C. This method can effectively remove the oxygen-containing functional groups and restore its graphic structure compared to the ones obtained using hydrazine or hydrogen. It can provide a simple, low-cost, and high yield approach for the preparation of high performance graphene nanosheets [49]. Furthermore, graphene sheets with different reduction levels were produced through thermal reduction of GO in the temperature range of 200–900°C under N₂ atmosphere for supercapacitor applications [50, 51]. Thermal reduction can produce few layer graphene with less agglomeration, higher specific surface area, and higher electrical conductivity compared to other reduction routes [51].

3.4.2. Chemical reduction

GO formation was followed by subsequent chemical reduction with a reducing agent such as hydroquinone, sodium borohydride, hydrazine, and hydrazine with NH₃ [42, 47, 52]. Hydrazine hydrate was proved to be the best reducing agent for the chemical reduction of GO into graphene and very thin graphene-like sheets were obtained. Moreover, the hydrazine treatment resulted in the formation of unsaturated and conjugated carbon atoms, which in turn imparts electrical conductivity of the graphene sheets [41]. These reducing agents, particularly hydrazine, are highly toxic, explosive, and their use should be with extreme care and minimized [42, 52]. The chemical reduction may also leave some residual epoxide groups on the reduced GO sheets leading to some loss in electron mobility [52]. On the basis of these observations, a new approach was employed to develop a “green” synthesis method for the production of graphene by using environmentally friendly reducing agents such as vitamin C [44], reducing, sugars and l-glutathione under mild conditions [42].

On the other hand, the chemical reduction methods of exfoliated GO with reducing agents such as hydrazine hydrate provide a promising approach for the efficient large-scale production of chemically converted graphene (CCG) sheets. However, in most cases heating to nearly 100°C over several hours is required. A novel, facile, convenient, and scalable method for the synthesis of CCG sheets as well as metallic and bimetallic nanoparticles supported on the CCG sheets using a simple household microwave oven was utilized [53–56]. It was reported that graphene is a good microwave-absorbing material and can reach a high temperature in minutes [57]. Microwave irradiation (MWI) has been demonstrated for the synthesis of a variety of nanomaterials with controlled size and shape without the need for high temperature or high pressure. The main advantages of MWI over other conventional heating methods are (i) rapid reaction velocity, (ii) clean and energy efficient, and (iii) uniform heating of the reaction mixture [47, 58–60]. Due to the difference in the solvent and reactant dielectric constants, selective dielectric heating can provide significant enhancement in the transfer of energy directly to the reactants causing an instantaneous internal temperature rise. Dried GO was sonicated in deionized water until homogenous dispersion was obtained. After that it was placed inside a conventional microwave after adding 100 µl of a reducing agent [hydrazine hydrate, ethylenediamine, or ammonium hydroxide] in 30 s cycles for a total reaction time of 60 s. A black color was obtained indicating the complete chemical reduction to graphene. The

graphene sheets were separated by using centrifuge operated at 5000 rpm for 15 min and dried overnight under vacuum [53]. Microwave-assisted methods allowed the rapid chemical reduction of GO using a variety of reducing agents in either aqueous or organic media. By using this method, many types of metallic and bimetallic nanoparticles can be dispersed on the graphene sheets via simultaneous reduction of GO and a variety of metal salts to create novel nanocatalysts supported on the large surface area of the thermally stable 2D graphene [61]. Moreover, this method provides a low-cost approach to the facile production of nanoparticles/graphene composites on a large scale for applications [57, 61, 62].

3.4.3. *Electrochemical reduction*

As pointed out by Kaner and co-workers, both chemical and thermal reduction techniques have some obvious drawbacks, namely, the highly toxic reductant hydrazine, lack control of the film thickness, and the incompatibility of the thermal reduction process under some conditions. Thus, the electrochemical method was adopted as an effective and controllable alternative technique for the modification of electronic states [63]. It has drawn great attention due to its fast and green nature [17, 52]. This is done by adjusting the external power source to change the Fermi energy level of the electrode surface that reduces GO in the presence of direct current bias [63]. Typically, the electrochemical synthesis of graphene was carried out via two steps, namely, GO being first assembled on the electrodes by solution deposition methods then being subjected to electrochemical reduction by scanning the potential (cyclic voltammetry) [45, 47, 52, 64, 65] or by applying constant potential (bulk electrolysis) [66, 67]. Another approach was achieved via a one-step technique in which graphene films can be prepared on electrodes directly from GO dispersions by simultaneous electrodeposition and electroreduction [17]. The reduction of GO can be confirmed from the color of GO electrodes that changes from yellow (before reduction) to black (after reduction) [64], involving the reduction of the high number of functional groups present in the GO sheets such as OH, COOH, and epoxides [52].

The properties of electrochemically converted graphene (ECG) are quite different from other nanostructured carbons (CNTs) and even different from CCG. The morphology of CCG and ECG on glassy carbon sheet was characterized by high field emission-scanning electron microscopy (FE-SEM) (Figure 6 (A, B)), respectively. The micrographs show that CCG sheets are rippled and crumpled with a dimension of several nm to few μm while ECG sheets are more homogeneous and more compact on the surface than CCG [66]. ECG exhibits greatly enhanced activity for the electrocatalytic reduction of O_2 and H_2O_2 and much higher electrochemical capacitance for potential application in ultracapacitors [64]. Moreover, the ECG coating is very stable as a result of its poor insolubility in common solvents [17].

3.4.4. *Laser-scribing technology*

Compared to chemical and thermal methods, pulsed laser irradiation reduction is simple, rapid (shorten the reaction time from several hours to few minutes), energy efficient, and free from poisonous material and high temperature. Also, the pulsed laser reduction of GO in solution makes it particularly attractive for producing graphene composites by pre-mixing

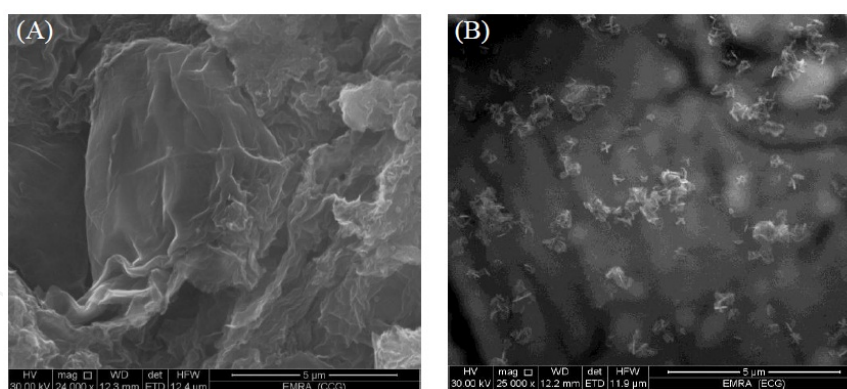


Figure 6. SEM images using FE-SEM for a) CCG, b) ECG [66].

with other materials [68]. Moreover, Feng-Shou Xiao fabricated graphene microcircuits by direct reduction and patterning of GO films using femtosecond laser representing well-conductivity for electrical applications [69]. Recently, Kaner and co-workers prepared graphene using standard laser-scribing technology more typically used to etch labels and images onto DVDs. Initially, a thin film of GO dispersed in water was drop-cast onto a flexible substrate (a DVD covered with a layer of plastic). Irradiation of the film with an infrared laser inside an inexpensive commercially available light scribe CD/DVD optical drive reduces the GO to laser-scribed graphene (LSG), as indicated by the change in film color from golden brown to black. Analysis of cross sections of the film with scanning electron microscopy showed that the initially stacked GO sheets were converted into well-exfoliated LSG sheets without any sticking together through laser irradiation [70].

4. Functionalization of graphene

GO contains oxygen functional groups such as epoxides, OH, and COOH that make it hydrophilic and well dispersed in water. However, GO is incompatible with most organic polymers [52]. It is well established that the superior properties of graphene are associated with its single layer. However, the fabrication of single-layer graphene is difficult at ambient temperature. Graphene sheets with a high specific surface area tend to form irreversible agglomerates or even restack to form graphite through π - π stacking and van der Waals interactions if the sheets are not well separated from each other. Aggregation can be reduced by the attachment of other small molecules or polymers to the graphene sheets. The presence of hydrophilic or hydrophobic groups prevents aggregation of graphene sheets by strong polar-polar interactions or by their bulky size. The attachment of functional groups to graphene also aids in dispersion in a hydrophilic or hydrophobic media as well as in the organic polymer [6, 52]. Furthermore, the oxidized rings of functionalized and defective graphene sheets contain abundant C-O-C (epoxide) and C-OH groups while the sheets are terminated with C-OH and -COOH groups. Defects of graphene may change its electronic and chemical properties. The functionalized and defective graphene sheets are more hydrophilic and can be easily dispersed in solvents with long-term stability [12]. Moreover, they are

more easily produced in mass quantities as compared with the carbon nanotubes [12, 16, 52]. They may be used to prepare some novel graphene-based nanocomposite films that could facilitate the further manipulation and processing of these materials for developing novel electronic devices such as chemical sensors, biosensors [12], cellular imaging, and drug delivery [52]. On the other hand, various polymer and nanoparticle (metal, metal oxide, semiconductor) composites have been developed based on the unique properties of graphene. The bulk production of GO and graphene has given opportunities to explore this flat structure of carbon with polymer and nanoparticles in composites [32]. Pristine graphene is a hydrophobic material and has no appreciable solubility in most solvents. Nevertheless, the processing of graphene composites concerns itself foremost with the solubilization of graphene. To improve the solubility of graphene, different functional groups have been attached to the carbon backbone by chemical modification, covalent or non-covalent functionalization [15].

- **Covalent modification:** The structural alteration can take place at the end of the sheets and/or on the surface. Surface functionalization is associated with rehybridization of one or more sp^2 carbon atoms of the carbon network into the sp^3 configuration accompanied by simultaneous loss of electronic conjugation. Covalent functional groups can attach to the surface through the reaction between the functional groups (-OH, -COOH, -CO) present on the GO and reduced graphene oxide (rGO) surfaces and edges [15, 32]. The covalent modification of graphene can be achieved in four different ways: nucleophilic substitution, electrophilic addition, condensation, and addition [6].
- **Non-covalent modification:** It is based on the van der Waals force or the π - π interaction between reduced graphene oxide (rGO) and stabilizers that not only gives less negative impact on the structure of graphene and its derivatives, but also provides the feasibility to tune their solubility and electronic properties [15, 32].

5. Applications of graphene to sensors and biosensors

Graphene has recently attracted tremendous interest because of its unique thermal, mechanical, and electrical properties. One of the promising applications of graphene is electrochemical sensing. Since every atom in a graphene sheet is a surface atom, molecular interaction and thus electron transport through graphene can be highly sensitive to adsorbed molecules [17, 71]. Graphene is a strictly 2D material and as such enables devices based on graphene to have an identical performance on a large scale. In addition, with the 2D structure, the monolayer graphene has its whole volume exposed to the environment that can maximize the sensing effect. The principle of graphene devices is based on changes in device conductance due to chemical or biological species adsorbed on the surface of graphene acting as electron donors or acceptors [19]. On the other hand, graphene-based nanomaterials have recently shown fascinating applications in electrochemical sensors and biosensors. Owing to the extraordinary electronic transport property and high electrocatalytic activity of graphene, the electrochemical reactions of analyte are greatly promoted on graphene film resulting in enhanced voltammetric response. Moreover, the electrochemical properties of graphene can be effectively

modified by integration with other functional nanomaterials such as catalyst nanoparticles to produce versatile electrochemical sensing performance. Comparing with CNTs, graphene has shown the advantages of high conductivity, ease of production and function, good biocompatibility, and abundance of inexpensive source material [71, 72]. Thus, graphene was a good candidate of advanced electrode materials and could be combined with other functional materials to fabricate the sensing interface for electroanalysis [8, 10].

5.1. Gas sensors

Graphene has potential use in gas sensors owing to its 2D structure with extremely high surface area. Gas sensing by graphene generally involves the adsorption and desorption of gaseous molecules (which act as electron donors or acceptors) on the graphene surface leading to change in the conductance of graphene. The high sensitivity of graphene toward different gaseous molecules has led to its use as gas sensor for hydrogen, H_2O , CO , NH_3 , NO_2 , Cl_2 , ethanol, I_2 , and O_2 [73]. Graphene/ZnO hybrid [74] and reduced graphene oxide (rGO) [75] were utilized as highly efficient gas sensors. Qingkai Yu et al. synthesized Pd-decorated graphene films to be used as hydrogen sensor. This gas sensor was fabricated on graphene film with a 1 nm Pd film deposited for hydrogen detection in the concentration range of 25–10,000 ppm. H_2 sensor based on Pd-decorated graphene films showed high sensitivity, fast response, and good recovery and can be used with multiple cycles [19]. Besides, Gupta et al. prepared a nanocomposite film based on poly(methyl methacrylate) (PMMA), rGO, and PMMA/rGO to be used as NH_3 gas sensor. The sensor performance in terms of selectivity and sensitivity was much better in the case of PMMA/rGO nanocomposite compared to the individual layers of rGO or PMMA [76]. On the other hand, an acetylene gas sensor was fabricated by synthesizing Ag-loaded ZnO-rGO hybrid via a facile chemical route (Figure 7). A well-structured crystalline nature and mixed phases of Ag, graphene (Gr), and ZnO was obtained. The morphological characterization revealed that particle-like nanostructures of ZnO and Ag were well distributed and closely distributed onto the surface of thin-layer RGO sheets. A low detection limit of 1 ppm, fast response of 25 s, recovery of 80 s, and good repeatability were obtained [77].

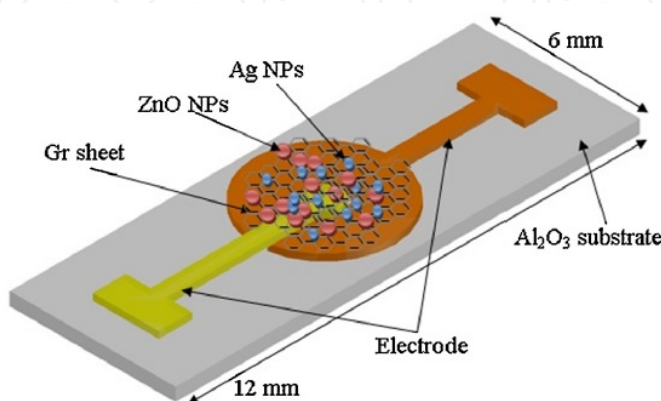


Figure 7. Schematic diagram of the fabricated sensor device [77].

5.2. Graphene-based electrochemical sensors for heavy metal ions

Metal ions such as lead, cadmium, silver, mercury, and arsenic have severe environmental and medical effects so that they require careful monitoring. Therefore, the development of a sensitive and selective detection method would benefit both the environmental and food chemists [5, 73]. A novel stannum film/poly(p-aminobenzene sulfonic acid, p-ABSA)/graphene composite modified glassy carbon electrode (GCE) was used for sensitive determination of trace Cd^{2+} ions by square wave anodic stripping voltammetry. Graphene layer presents enhanced electron transfer and enlarged specific surface area. The resulting matrix offers a good stripping performance for the analysis of Cd^{2+} in the linear range from 1.0 to 70.0 $\mu\text{g L}^{-1}$ with a detection limit of 0.05 $\mu\text{g L}^{-1}$ [78]. Furthermore, Erkang Wang used graphene nanosheets dispersed in Nafion (Nafion-G) solution in combination with in situ plated bismuth film electrode for fabricating the enhanced electrochemical sensing platform for Pb^{2+} and Cd^{2+} by differential pulse anodic stripping voltammetry. The prepared Nafion-G composite film exhibited improved sensitivity for the metal ion detections and alleviated the interferences as a result of the synergistic effect of Nafion-G. The stripping current signal is greatly enhanced and well distinguished on graphene electrodes with a wide linear range and 0.02 $\mu\text{g L}^{-1}$ detection limit for both ions (Figure 8) [5, 79]. Moreover, various modified surfaces were constructed for the sensitive and simultaneous determination of Pb^{2+} and Cd^{2+} such as graphene/polyaniline/polystyrene nanoporous fiber [80] and graphene/ionic liquid/bismuth film composite modified screen-printed electrodes [81], functionalized graphene (GNS^{PF_6}) with potassium hexafluorophosphate [82], and a hybrid nanocomposite of one-dimensional MWCNTs and graphene sheets [83]. Large surface area, good ionic and electronic conductivity, wide electrochemical window, as well as high stability, sensitivity, low detection limit, and applicability in real samples are the obvious characteristics of the proposed sensors. On the other hand, functionalized graphene sheets were fabricated and used for simultaneous removal of high concentration of inorganic species of arsenic (both trivalent and pentavalent) and sodium from aqueous solution using a supercapacitor-based water filter. Also, they were utilized for the desalination of sea water. High adsorption capacity for both inorganic species of arsenic and sodium along with the desalination ability of a graphene based supercapacitor provides a solution for a commercially feasible water filter. Additionally, the cost effective production of graphene sheets and better performance compared to other adsorbents like CNTs provides a platform for the development of commercially feasible supercapacitor-based water filter [84]. Furthermore, rGO-lead dioxide composite was presented as an excellent material for the detection of a low level of arsenic with a low detection limit of 10 nM. This study opens up the possibility of using the composite for simultaneous detection of arsenic and lead [85]. Furthermore, Zhuangjun Fan synthesized a type of graphene nanosheet/ δ - MnO_2 (GNS/MnO_2) composite by a microwave-assisted method to be used as an adsorbent for the removal of nickel ions from waste water [86].

5.3. Biosensor for some biological compounds

5.3.1. Paracetamol

Paracetamol or acetaminophen (ACOP) is a long-established and one of the most extensively employed “over the counter” drugs in the world. It is non-carcinogenic and an effective

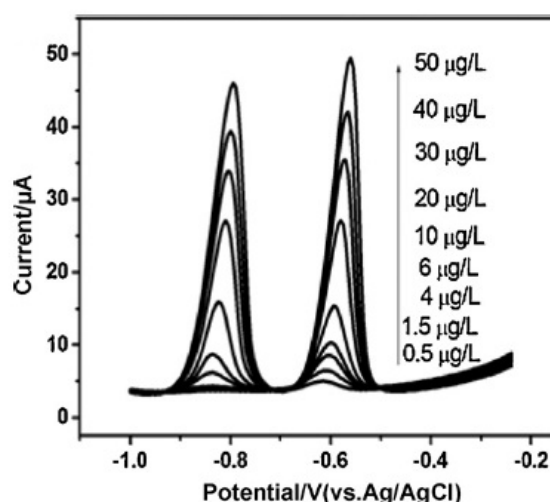


Figure 8. Stripping voltammograms for the different concentrations of Cd^{2+} and Pb^{2+} on an in situ plated Nafion-G-BFE (bismuth film electrode) in solution containing $0.4 \text{ mg L}^{-1} \text{ Bi}^{3+}$ [79].

Electrode	Linear range	Detection limit	Reference
Nafion/ TiO_2 -graphene nanocomposite	1-100 μM	210 nM	[7]
Electrochemically reduced and deposited graphene onto GCE	5.0 nM-800 μM	2.13 nM	[91]
Electrochemically reduced graphene loaded nickel oxides (Ni_2O_3 -NiO) nanoparticles coated onto GCE	0.04-100 μM	0.02 μM	[92]
Poly(4-aminobenzoic acid)/electrochemically reduced graphene oxide composite film modified GCE	0.1-65 μM	0.01 μM	[93]

Table 2. Examples of modified electrodes for ACOP detection.

substitute for aspirin for patients with sensitivity to aspirin. It is used to reduce fever, cough, and cold and reduce mild to moderate pain. It is also useful in osteoarthritis therapy, protects hardening of arteries, relieves asthma patients, and protects against ovarian cancer. So it is very important to establish a simple, fast, sensitive, and accurate detection method for ACOP [87, 88]. Yuehe Lin et al. presented an electrochemical sensor for ACOP based on the electrocatalytic activity of functionalized graphene. Graphene-modified GCE obviously promotes the sensitivity of the determination of paracetamol with a low detection limit of 32 nM and a satisfied recovery from 96.4% to 103.3% [12]. Moreover, SWCNTs [89] or MWCNTs [90] graphene nanosheet nanocomposite modified GCE (SWCNTs-GNS/GCE or MWCNTs-GNS/GCE) was utilized as a novel, simple, and highly selective electrochemical sensor for tyrosine and paracetamol. The proposed sensor exhibited perfect characteristics like high effective

surface area, high porosity, more reactive sites, excellent electrochemical catalytic activity, and applicability in human blood serum and pharmaceutical samples. Very low detection limits of 0.19 μM and 0.10 μM were obtained for tyrosine and paracetamol, respectively [90]. Table 2 contains examples of various modified electrodes for ACOP detection [7, 91-93].

5.3.2. Catecholamine neurotransmitters

Catecholamines are a class of neurotransmitters and their detection in the human body has been of great interest to neuroscientists. They include dopamine (DA), epinephrine (EP), and norepinephrine (NE) playing important roles in various biological, pharmacological, and physical processes. They are widely distributed in the mammalian central nervous system for message transfer [94, 95].

EP, a hormone secreted by the medulla of adrenal glands, is an important catecholamine inhibitory neurotransmitter. The presence of EP in the body affects the regulation of blood pressure and the heart rate, lipolysis, immune system, and glycogen metabolism. Low levels of EP have been found in patients with Parkinson's disease. Therefore, the quantitative determination of EP in different human fluids such as plasma and urine is important for developing nerve physiology, pharmacological research, and life science [96]. Xiaoli Zhang fabricated graphene/Au nanocomposites modified GCE (GR/Au/GCE) for the detection of EP with high sensitivity. The oxidation of EP at this modified electrode occurred at less positive potentials than on bare GCE. In addition, the oxidation peaks of EP and ascorbic acid (AA) were separated from each other by approximately 180 mV. At the same time, this electrode also showed favorable electrocatalytic activity toward some other small biomolecules (such as DA, b-nicotinamide adenine dinucleotide, and uric acid) suggesting the potential applications of GR/Au nanocomposites for constructing biosensors [97]. Moreover, GR modified Pd was prepared to be used as a voltammetric sensor for NE, an important neurotransmitter. GR as well as Pd nanoparticles presented perfect characteristics for the proposed sensor-like excellent electrocatalytic activity for the oxidation of NE in terms of remarkable enhancement in the peak current and lowering of peak potential. Also, low detection and quantification limits were obtained that were 67.44 nM and 224.8 nM, respectively. The application of the proposed sensor in pharmaceutical dosage forms and human urine samples in the presence of high concentration of uric acid was achieved with excellent recovery results [98].

On the other hand, DA, ascorbic acid (AA), and uric acid (UA) are compounds of great biomedical interests playing determining roles in human metabolism. DA is one of the crucial catecholamine neurotransmitters playing an important role in the function of central nervous, renal, hormonal, and cardiovascular systems. Thus, a loss of DA-containing neurons may lead to neurological disorders such as Parkinsonism and schizophrenia [94, 95, 99]. AA (vitamin C), an antioxidant, is a vital vitamin in human diet existing in both animal and plant kingdoms. It has been used for the prevention and treatment of the common cold, mental illness, infertility, and cancer and in some clinical manifestations of human immunodeficiency virus infections. UA is the primary end product of purine metabolism. The extreme abnormalities of UA levels in the body are symptoms of several diseases including gout, hyperuricemia, and Lesch-Nyhan. Therefore, simultaneous detection of DA, AA, and UA is a challenge of critical

importance not only in the field of biomedical chemistry and neurochemistry but also for diagnostic and pathological research [94, 95]. Feng Li et al. prepared a graphene doped carbon paste electrode (CPE) by the addition of graphene into the carbon paste mixture for the successful determination of AA. This sensor showed an excellent electrocatalytic oxidation activity toward AA with a lower overvoltage, pronounced current response, and good sensitivity. The proposed sensor exhibited a rapid response to AA within 5 s and a good linear calibration plot from 0.1 to 106 μM with low detection limit of 70 nM [8]. On the other hand, Jinghong Li et al. synthesized graphene chemically by the Hummers and Offeman method and the graphene-modified electrode was applied for the selective determination of DA in the linear range of 5–200 μM in a large excess of AA. Selective detection was realized in completely eliminating AA based on the unique planar structure of graphene. The interesting performance of graphene to DA and AA may be correlated with the following reasons:

1. The high quality of the sp^2 conjugated bond in the carbon lattice, graphene is highly conductive and shows metallic conductance even in the limit of zero carrier density. The unusual density of electronic states of graphene affects its electrochemical reactivity.
2. Molecular structures of DA and AA are distinct from each other. The π – π interaction between the phenyl structure of DA and 2D planar hexagonal carbon structure of graphene makes the electron transfer feasible. AA oxidation is inactive most likely because of its weak π – π interaction with graphene [10].

Several sensors were utilized for the simultaneous determination of DA and AA such as graphene modified electrode [100], graphene sheets/Congo red-molecular imprinted polymers [101], and Pt nanoparticles/polyelectrolyte-functionalized ionic liquid/graphene sheets [102]. On the other hand, TiO_2 -graphene nanocomposite modified GCE exhibited remarkable electron transfer kinetics, electrocatalytic activity, and selective determination of DA in the presence of UA and AA. Differential pulse voltammetry (DPV) peaks of DA, AA, and UA are well resolved with peak potentials at 108 mV, 272 mV, and 403 mV for AA, DA, and UA, respectively. The separation of DPV peak potentials for AA–DA and DA–UA are calculated to be 164 mV and 131 mV, respectively, which are large enough to determine DA selectively [103]. Several electrochemical sensors based on graphene-modified surfaces were employed for the simultaneous determination of DA, AA, and UA like polystyrene-grafted-graphene hybrid [104] and nafion covered core-shell structured Fe_3O_4 @graphene nanospheres (GNs) [105] modified GCE, graphene-AuAg (Au/Gr-AuAg) composite modified gold electrode [106], Au nanoplates and rGO modified GCE (Au/rGO/GCE) [107], three-dimensional reduced graphene oxide (3D-rGO) material [108], water-soluble sulfonated graphene [109], ferulic acid functionalized electrochemically reduced graphene [110], graphene/nickel hydroxide composite [111], and well-defined flower-like graphene-nanosheet clusters (f-RGO) modified GCE [112]. In addition, Pd–Pt bimetallic nanoparticles anchored on functionalized rGO nanomaterials [113], electrochemically reduced graphene oxide (ERGO) [114], nitrogen-doped graphene (NG) [115], and tryptophan-functionalized graphene nanocomposite (Trp-GR) [116] were fabricated for the simultaneous detection of DA, AA, and UA and multi-walled carbon nanotubes (MWNTs) bridged mesocellular graphene foam (MGF) nanocomposite (MWNTs/MGF) modified GCE for the simultaneous determination of DA, AA, UA, and tryptophan

[117]. As well, graphene (Gr)/copper(II) phthalocyanine-tetrasulfonic acid tetrasodium salt/polyaniline nanocomposites [118] and NiO nanoparticles-graphene composite film were employed as electrochemical sensors for the selective determination of AA in the presence of DA and UA [118] and in the presence of folic acid [119], respectively.

On the other hand, serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter and it is important to sensitively determine its concentration. A double-layered membrane of rGO/polyaniline nanocomposites and molecularly imprinted polymers embedded with Au nanoparticles was employed as an electrochemical sensor for 5-HT. The prepared sensor displayed obvious selectivity to 5-HT and a low detection limit of 11.7 nM in the linear range of 0.2–10.0 μ M [120]. Moreover, graphene nanosheets [121] and graphene grafted poly(lactic acid) with Pd nanoparticles [122] were applied as 5-HT sensor showing high sensitivity, good selectivity, low detection limit, fast response time, and stability. In addition, electrochemically reduced GO-P (graphene oxide and 5,15-pentafluorophenyl-10,20-p-aminophenyl porphyrin) was employed as an electrochemical sensor for the simultaneous and selective determination of DA and 5-HT in the presence of AA. The detection limits of DA and 5-HT were 35 nM and 4.9 nM, respectively [123].

Levodopa (LD), an important neurotransmitter, was determined at modified CPE modified with graphene (GR), 1-(6,7-dihydroxy-2,4-dimethylbenzofuran-3-yl) ethanone (DE), and ionic liquid (IL) (GR–DE–IL/CPE). GR–DE–IL/CPE showed enhanced electrocatalytic activity toward LD with a lower oxidation potential and good electrochemical performance with higher conductivity and lower electron transfer resistance. Very low detection limit of 5.0 nM in the linear range of 0.015 to 1000 μ M was obtained [124]. An assembly of rGO, Au nanoparticles, and 2-(3,4-dihydroxy phenyl) benzothiazole [125] and graphene nanosheets modified GCE [126] and reduced graphene nanoribbons modified carbon screen-printed electrode [127] were employed for the simultaneous determination of LD, UA and folic acid, LD and carbidopa and AA, LD and UA, respectively.

5.3.3. Hydroquinone and catechol

Graphene has the great potential for distinguishing a diverse range of aromatic isomers. Chengbin Liu et al. had utilized graphene modified electrode (EG/GCE) for the simultaneous detection of hydroquinone HQ (1,4-dihydroxybenzene) and catechol CC (1,2-dihydroxybenzene). It showed enhanced electron transfer properties, good potential separation of oxidation peaks between HQ and CC (about 110 mV), wide linear concentration ranges, low detection limits, excellent reproducibility and stability, and high resolution capacity to the HQ and CC isomers [17]. On the other hand, a highly stable (pyridine-NG) was used as an electrochemical sensor for simultaneous determination of HQ and CC. Excellent electrocatalysis of pyridine-NG for simultaneous determination of HQ and CC was achieved due to the π - π interactions between the benzene ring of CC and graphene layer and the hydrogen bonds formed between hydroxyl in HQ molecule and pyridinic nitrogen atoms within graphene layers, especially the less density distribution of π electron cloud in pyridinic-NG in acidic condition [128]. Several novel sensors like poly(3,4-ethylenedioxythiophene)/nitrogen-doped graphene composite [129], MWCNTs-poly(diallyldimethylam-

monium chloride)-graphene [130], and laser reduced graphene [131] modified GCE were fabricated for the simultaneous detection of CC and HQ with low detection limit, high sensitivity, excellent potential peak separation, and anti-interference ability. Table 3 contains examples of modified electrodes for HQ and CC detection [132-135].

Electrode	Linear range of HQ	Detection limit of HQ	Linear range of CC	Detection limit of CC	Reference
Graphene and TiO ₂ nanocomposite	0.5–100 μ M	0.082 μ M	0.5–100 μ M	0.087 μ M	[132]
Electrochemically reduced graphene oxide- MWCNTs and terthiophene	---	35 nM	---	4.9 nM	[133]
1D MWCNTs and 2D graphene modified GCE using 1-butyl-3-methyl-imidazolium hexafluorophosphate ionic liquid	---	0.1 μ M	---	0.06 μ M	[134]
Au nanoparticle and graphene composite film modified carbon ionic liquid electrode	0.06-800 μ M	0.018 μ M	---	---	[135]

Table 3. Examples of modified electrodes for HQ and CC detection.

5.4. Drug biosensor

Morphine, noscapine, and heroin are three major alkaloids in heroin samples. Morphine and noscapine that are directly extracted from poppy are the most abundant constituents in opium. The widespread use of illicit drugs has led to an increased effort toward developing and improving methods for their determination in biological samples, which is still a very challenging task. Graphene nanosheets (GNSs) modified GCE was employed for the simultaneous determination of morphine, noscapine, and heroin exhibiting excellent electrocatalytic activity at reduced overpotentials in wide pH range. Fast response time, high sensitivity and stability, low cost, low detection limit, and ease of preparation method without using any specific electron-transfer mediator or specific reagent are the advantages of the proposed sensor [136]. In addition, electrochemically reduced MWNTs-doped GO (ER-MWNTs-doped-GO) composite film modified GCE was employed as morphine sensor combining the excellent conductivity of MWNTs and ER-GO with the film forming properties of GO [137]. Also, rGO-Pd (rGO-Pd) hybrid had higher current response toward morphine oxidation compared to the unmodified rGO with a low detection limit of 12.95 nM [138].

On the other hand, graphene and Nafion film modified GCE was fabricated for the detection of codeine displaying an excellent analytical performance and enhanced applicability for codeine detection in urine samples and cough syrup. The high electrocatalytic activity of the

proposed sensor toward codeine was attributed to the outstanding electric conductivity of graphene and the high codeine loading capacity on the electrode surface [139]. Furthermore, a nanocomposite of Gr and CoFe_2O_4 nanoparticles modified CPE was proved to be an ultra-sensitive electrochemical sensor for codeine and ACOP with low detection limits of 0.011 and 0.025 μM , respectively. The proposed method was free from interference effects of glucose, ascorbic acid, caffeine, naproxen, alanine, phenylalanine, glycine, and others [140]. On the other hand, rapid and simultaneous determination of tramadol and ACOP was achieved based on NiFe_2O_4 /graphene nanoparticles modified CPE with a low detection limit of 0.0036 and 0.0030 μM , respectively [141]. Table 4 contained a summary of some modified electrodes for drug sensing.

Electrode	Drug	Linear range	Detection limit	Reference
Graphene nanosheets modified GCE	morphine, noscapine and heroin	up to 65, 40 and 100 μM , respectively	0.4, 0.2 and 0.5 μM , respectively	[136]
electrochemically reduced MWNTs-doped GO modified GCE	morphine	---	---	[137]
rGO-Pd modified GCE	morphine	0.34-12 μM	12.95 nM	[138]
graphene and Nafion film modified GCE	codeine	5×10^{-8} to 3×10^{-5} M	15 nM	[139]
a nanocomposite of Gr and CoFe_2O_4 nanoparticles modified CPE	codeine and ACOP	0.03 to 12.0 μM for both	0.011 μM and 0.025 μM , respectively	[140]
NiFe_2O_4 /graphene nanoparticles modified CPE	tramadol and ACOP	0.01-9 μM	0.0036 and 0.0030 μM , respectively	[141]

Table 4. Examples of modified electrodes for drug detection.

5.5. NADH biosensor

B-nicotinamide adenine dinucleotide (NAD) and its reduced form (NADH) are a cofactor of many dehydrogenases, which have received considerable interest in developing amperometric biosensors, biofuel cells, and bioelectronic devices [2, 5, 18, 73]. The oxidation of NADH serves as the anodic signal and regenerates the NAD cofactor, which is of great significance in biosensing important substrates such as lactate, alcohol, or glucose. Problems inherent to such anodic detection are the large overvoltage for NADH oxidation and surface fouling associated with the accumulation of reaction products. Graphene shows promise in addressing these problems [73, 142]. Jinghong Li studied the oxidation of NADH at GCE and reduced graphene sheet films (rGSF)/GC. The oxidation of NADH occurs at bare GC electrode at 0.75 V vs. Ag/AgCl , which decreased to 0.42 V at rGSF/GC [2]. Table 5 contained examples of several sensors for the sensitive and selective determination of NADH with low detection limit.

Electrode	Linear range	Detection limit	Reference
methylene green functionalized graphene modified GCE	---	---	[5]
ionic liquid functionalized graphene modified GCE	---	---	[73]
chemically reduced graphene oxides modified GCE	---	---	[18]
graphene assembled electrode modified GCE	---	---	[142]
electroreduced graphene oxide and polythionine modified GCE	0.01–3.9 mM	0.1 μ M	[144]
nitrogen-doped graphene modified GCE	---	---	[145]
graphene–Au nanorods hybrid nanosheets modified GCE	5 to 377 μ M	1.5 μ M	[146]
Au nanoparticles /reduced graphene oxide nanocomposites modified GCE	50 nM to 500 μ M	1.13 nM	[147]
graphene paste electrode modified GCE	---	---	[148]
GCE modified with deoxyribonucleic acid, graphene methylene blue	10 μ M to 1.50 mM	1.0 μ M	[143]

Table 5. Examples of modified electrodes for NADH detection.

5.6. DNA biosensors

Electrochemical DNA sensors offer high sensitivity, good 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. Electrochemical DNA sensors also allow device miniaturization for samples with a very small volume. Among all kinds of electrochemical DNA sensors, the one based on the direct oxidation of DNA is the simplest [5, 13]. Zhou et al. reported an electrochemical DNA sensor based on CR-GO. The current signals of the four free bases of DNA (i.e., guanine (G), adenine (A), thymine (T) and cytosine (C)) on the CR-GO/GC electrode are all separated efficiently indicating that CR-GO/GC can simultaneously detect four free bases but neither graphite nor

GCE can. This is attributed to the antifouling properties and the high electron transfer kinetics for bases oxidation on CR-GO/GC electrode resulting from a high density of edge-plane-like defective sites and oxygen containing functional groups on CR-GO. These functional groups are beneficial for accelerating electron transfer between the electrode and species in solution providing many active sites. CR-GO/GC is also able to efficiently separate all four DNA bases in both single-stranded DNA (ssDNA) and double-stranded DNA (ds-DNA), which are more difficult to oxidize than free bases at physiological pH without the need of a prehydrolysis step. This is attributed to the unique physicochemical properties of CR-GO (the single sheet nature, high conductivity, large surface area, antifouling properties, high electron transfer kinetics, etc.) [5, 73]. Furthermore, a zinc sulfur-coated poly (3,4-ethylenedioxythiophene)-reduced graphene oxide hybrid film was developed for the simultaneous determination of three deoxyribonucleic acid (DNA) bases: G, A, and T. This electrochemical sensor displayed a good photoelectronic effect and the peak currents of G, A, and T increased obviously. The proposed sensor was successfully applied to the analysis of G, A, and T contents in real-life samples such as herring sperm DNA samples, milk powder, and urine sample from human beings with satisfactory results [149]. As well, an electrochemical DNA biosensor for the detection of ssDNA sequence related to transgenic maize MON810 was fabricated based on electrochemical reduced graphene (ERG) modified carbon ionic liquid electrode (CILE) and methylene blue (MB). The presence of ERG increased the adsorption amounts of probe ssDNA sequence on the electrode resulting in the enhancement of the reduction peak current of MB that used as the hybridization indicator. Under optimal conditions, the linear range of ssDNA sequences was 1.0×10^{-11} to 1.0×10^{-6} M with the detection limit of 4.52×10^{-12} mol/L [150]. In addition, the simultaneous determination of adenine and guanine was achieved at the ionic liquid-functionalized graphene-modified carbon paste electrode (IL-graphene/CPE) with very low detection limits of 65 nM for guanine and 32 nM for adenine [13]. Moreover, TiO₂-graphene nanocomposite modified GCE exhibited high electrocatalytic activity, wide linear range, and low detection limit for the simultaneous determination of adenine and guanine. The excellent performance of this electrochemical sensor was attributed to the high adsorptivity and conductivity of TiO₂-graphene nanocomposite providing an efficient microenvironment for the electrochemical reaction of these purine bases [151]. On the other hand, a graphene-based electrochemical DNA sensor was developed for the detection of low concentrations of breast cancer-related BRCA1 gene. The sensor was stable, reproducible, and sensitive and it could detect up to 1 femtomolar BRCA1 gene (5.896 femtogram/ml) [152]. Moreover, a graphene sheets/polyaniline/gold nanoparticle based DNA sensor was employed for the electrochemical determination of BCR/ABL fusion gene in chronic myelogenous leukemia. Under optimum conditions, the DNA sensor exhibited a detection limit as low as 2.11 pM (S/N=3) with an excellent differentiation ability. It has been applied for assay of BCR/ABL fusion gene from real samples with satisfactory results [153]. Also, a riboflavin electrochemical sensor based on homoadenine single-stranded DNA/molybdenum disulfide-graphene nanocomposite modified gold electrode was fabricated. This sensor possessed a wide linear range from 0.025 to 2.25 μ M with a low detection limit of 20 nM [154]. A brief summary of DNA biosensors is given in Table 6.

Electrode	DNA sequences and mutated genes	Linear range	Detection limit	Reference
zinc sulfur-coated poly (3,4-ethylenedioxythiophene)-reduced graphene oxide hybrids film	guanine, adenine and thymine	---	---	[149]
Chemically reduced graphene oxide modified GCE	guanine, adenine, thymine and cytosine	---	---	[5, 73]
electrochemical reduced graphene modified carbon ionic liquid electrode and methylene blue	ssDNA sequence related to transgenic maize MON810	1.0×10^{-11} to 1.0×10^{-6} M	4.52×10^{-12} mol/L	[150]
ionic liquid-functionalized graphene modified carbon paste electrode	adenine and guanine	---	65 nM and 32 nM for guanine and adenine, respectively	[13]
TiO ₂ -graphene nanocomposite modified GCE	adenine and guanine	0.5–200 μ M	0.10 and 0.15 μ M for adenine and guanine, respectively	[151]
graphene-based electrochemical DNA sensor	breast cancer-related BRCA1 gene	---	---	[152]
graphene sheets/polyaniline/gold nanoparticles based DNA sensor	BCR/ABL fusion gene in chronic myelogenous leukemia	---	2.11 pM	[153]
homoadenine single-stranded DNA/molybdenum disulfide-graphene nanocomposite modified gold electrode	riboflavin	0.025 to 2.25 μ M	20 nM	[154]

Table 6. Examples of modified electrodes for DNA detection.

5.7. Graphene-based immunosensor

Increasing attention has been focused on the development of immunoassay because it has become a major analytical tool in clinical diagnosis. In immunoassay, the determination of cancer markers associated with certain tumors in patients plays an important role in diagnosing cancer diseases. Carcinoembryonic antigen (CEA) is one of the most extensively used tumor markers. An elevated CEA level in serum may be an early indication of lung cancer, ovarian carcinoma, colon cancer, breast cancer, and cystadenocarcinoma. Hence, Sheng Yu used gold nanoparticles (AuNPs), reduced graphene oxide (R-GO) and poly(L-Arginine) composite material modified CILE as the platform for the construction of a new electrochem-

ical CEA immunosensor. The poly(L-Arginine)/R-GO composite film was used to modify CILE to fabricate Arg/R-GO/CILE through electropolymerization of L-Arginine on R-GO/CILE. AuNPs were adsorbed on the modified electrode to immobilize the CEA antibody and to construct the immunosensor. By combining the specific properties such as the biocompatibility and big surface area of AuNPs, the excellent electron transfer ability of R-GO and the high conductivity of CILE, the synergistic effects of composite increased the amounts of CEA antibody adsorbed on the electrode surface resulting in the greatly increase of the electrochemical responses. The proposed immunosensor showed good reproducibility, selectivity, low detection limit, and acceptable stability [155]. As well, ultrathin Au-Pt nanowire-decorated thionine/reduced graphene oxide (AuPtNWs/THI/rGO) [156] and Au nanoparticles-graphene-chitosan nanocomposite cryogel electrode [157] were developed for CEA detection showing high sensitivity, reproducibility, stability, and applicability in real samples (Table 7). Moreover, Jiadong Huang developed an ultrasensitive electrochemical immunosensor based on nanogold particles (nano-Au), Prussian Blue (PB), polyaniline/poly(acrylic acid) (PANI (PAA)), and Au-hybrid graphene nanocomposite (AuGN) for the detection of salbutamol (SAL). SAL is the most widely used β_2 -adrenergic receptor agonist that induces bronchodilation making it highly useful for curing bronchial asthma, chronic obstructive pulmonary disease, and other allergic diseases associated with respiratory pathway. Nano-Au, PB, and PANI (PAA)-incorporated film was used to enhance the electroactivity, stability, and catalytic activity for hydrogen reduction of the electrode. AuGN was used to immobilize chitosan, nano-Au, and horseradish peroxidase-anti-SAL antibody (HRP-AAb). The resulting nanostructure (AuGN-HRP-AAb) was used as the label for the immunosensor. This is attributed to the high surface-to-volume ratio of graphene that allows the immobilization of a high level of chitosan, nano-Au, and HRP-AAb and its good electrical conductivity that can improve the electron transfer among HRP, H_2O_2 , and electrode. The proposed immunosensor showed low detection limit, excellent selectivity, good reproducibility, long-term stability, and high accuracy [158]. Furthermore, the synergistic effect between graphene sheet (GS) and cobalt hexacyanoferrate nanoparticle (CoNP) was investigated showing that the electroactivity of CoNP was greatly enhanced in the presence of GS due to the great electron-transfer ability of GS. A label-free electrochemical immunosensor for the sensitive detection of prostate specific antigen (PSA), it was widely used in prostate cancer diagnosis and screening, was fabricated. Molecule 1-pyrenebutanoic acid, succinimidyl ester (PBSE) was adsorbed onto GS and the colloidal solution containing GS-CoNP-PBSE was added onto the GCE surface to form a stable thin film with high electroactivity. After anti-PSA antibody was conjugated onto PBSE, the modified electrode could be used as an amperometric immunosensor for the detection of PSA. This immunosensor has the advantages of high sensitivity with a low detection limit of 0.01 ng/mL, good selectivity, and stability and could become a promising technique for cancer marker detection [159]. In addition, highly conductive graphene (GR)-gold (Au) composite modified electrode [160] and amino-functionalized graphene sheet-ferrocenecarboxaldehyde composite materials (NH_2 -GS@FCA) and silver hybridized mesoporous silica nanoparticles ($Ag@NH_2$ -MCM48) [161] were utilized as PSA immunosensor displaying an enhanced electron transfer and high sensitivity toward PSA (Table 7). On the other hand, ultrasensitive electrochemical immunosensor for carbohydrate antigen 19-9 was developed using Au nanoparticles functionalized porous graphene (Au-PGO) as sensing platform and Au@Pd core shell bimetallic functionalized graphene nanocomposites (Au@Pd-Gra) as signal enhancers [162].

Moreover, an electrochemical immunosensor for the sensitive detection of carbohydrate antigen 15-3 (CA15-3) was fabricated based on ionic liquid functionalized graphene and Cd²⁺-functionalized nanoporous TiO₂. The good performance of the immunosensor was attributed to (i) high surface-to-volume ratio of graphene, (ii) excellent biocompatibility and electron transfer rate originating from ionic liquid functionalized graphene, and (iii) the highly specific surface area of nanoporous TiO₂ facilitating the adsorption of a high amount of Cd²⁺ for signal amplification [163].

Electrode	Immunosensor	Linear range	Detection limit	Reference
gold nanoparticles, reduced graphene oxide and poly(L-Arginine) composite material modified CILE	Carcinoembryonic antigen (CEA)	0.5 to 200 ng mL ⁻¹	0.03 ng mL ⁻¹	[155]
ultrathin Au-Pt nanowire-decorated thionine/reduced graphene oxide	CEA	50 fg/mL to 100 ng/mL	6 fg/mL	[156]
Au nanoparticles–graphene–chitosan nanocomposite cryogel electrode	CEA	1.0 × 10 ⁻⁶ to 1.0 ng/mL	2.0 × 10 ⁻⁷ ng/mL	[157]
nanogold particles, Prussian Blue, polyaniline/poly(acrylic acid) and Au-hybrid graphene nanocomposite	salbutamol	0.08 ng/mL and 1000 ng/mL	0.04 ng/mL	[158]
graphene sheet and cobalt hexacyanoferrate nanoparticle	prostate specific antigen (PSA)	---	0.01 ng/mL	[159]
graphene-gold composite modified electrode	PSA	0–10 ng/mL	0.59 ng/mL	[160]
amino-functionalized graphene sheet–ferrocenecarboxaldehyde composite materials and silver hybridized mesoporous silica nanoparticles	PSA	0.01–10.0 ng/mL	2 pg/mL	[161]
Au nanoparticles functionalized porous graphene and Au@Pd core shell bimetallic functionalized graphene nanocomposites	carbohydrate antigen 19-9	0.015 to 150 U/mL	0.006 U/mL	[162]
ionic liquid functionalized graphene and Cd ²⁺ -functionalized nanoporous TiO ₂	carbohydrate antigen 15-3	0.02–60 U/mL	0.008 U/mL	[163]

Table 7. Examples of modified electrodes used as immunosensors.

5.8. Hemoglobin and myoglobin biosensors

Hemoglobin (Hb) is the most important part of blood responsible for transporting O_2 throughout the circulatory system. Change of Hb concentration in blood can cause several diseases and even death. Therefore, accurate determination of Hb content in blood is medically very essential [73]. Chunming Wang and Jun-Jie Zhu synthesized functionalized graphene nanosheets (PDDA-G) with poly(diallyldimethylammonium chloride) (PDDA) and used to combine with room temperature ionic liquid (RTIL). The resulting RTIL/PDDA-G composite displayed an enhanced capability for the immobilization of Hb to realize its direct electrochemistry. The proposed biosensor showed a fast direct electron transfer of Hb. Moreover, the RTIL/PDDA-G based biosensor exhibited excellent electrocatalytic activity for the detection of nitrite with wide linear range and low detection limit. The present strategy definitely paves a way for the functionalization of graphene sheets with good biocompatibility and solubility, thus provides a novel and promising platform for the study of the biological application of graphene [164]. Moreover, Ke-Jing Huang fabricated a promising biosensor, hemoglobin (Hb)/chitosan (Chit)-ionic liquid (IL)-ferrocene (Fc)/graphene (Gr)/GCE, that exploited the synergistic beneficial characteristics of Fc, Gr, and IL for Hb detection. The proposed biosensor showed a strong electrocatalytic activity toward the reduction of H_2O_2 , which could be attributed to the favored orientation of Hb in the well-confined surface as well as the high electrical conductivity of the resulting Chit-IL-Fc/Gr inorganic hybrid composite. The developed biosensor exhibited a fast amperometric response, a good linear response toward H_2O_2 over a wide range of concentration, and a low detection limit of $3.8 \mu M$. High sensitivity and stability, technically simple, and the possibility of preparation at short period of time are of great advantage of the developed biosensors [165]. Moreover, GR and Mg_2Al layered double hydroxide composite was prepared and used for the immobilization of Hb on a CILE to obtain an electrochemical biosensor exhibiting electrocatalytic reduction to trichloroacetic acid [166]. As well, a biocompatible biosensor based on immobilized Hb on carboxymethyl cellulose functionalized reduced graphene oxide (rGO) nanocomposite was developed. The proposed Hb biosensor exhibited excellent bioelectrocatalytic activity toward the reduction of NO and H_2O_2 . This biosensor opened up a promising platform for protein immobilization and biosensor preparation [167]. Also, a mediator-free biosensor was fabricated by the immobilization of Hb on TiO_2 NPs-rGO with a double-layered structure. TiO_2 NPs-rGO nanocomposite was an excellent matrix for immobilization and biocompatibility for redox protein presenting good protein bioactivity and stability. The direct electron transfer of Hb is facilitated due to the special double-layered structure of TiO_2 NPs-rGO. The prepared biosensor showed good performance for H_2O_2 detection with a low detection limit of 10 nM in the linear range of 0.1–140 μM [168]. On the other hand, a novel biocompatible sensing strategy based on a graphene (GR), ionic liquid (IL) 1-ethyl-3-methylimidazolium tetrafluoroborate ($EMIMBF_4$) and chitosan (CTS) composite film for the immobilization of myoglobin (Mb) was adopted. The CTS-Mb-GR-IL modified electrode exhibited an excellent enzyme-like catalytic activity for the reduction of trichloroacetic acid [169]. Another nanocomposite based on Pt nanoparticle decorated GR nanosheet was developed for the direct electrochemistry and electrocatalysis of Mb. GR-Pt nanocomposite was integrated with Mb on the surface of CILE. Nafion/Mb-GR-Pt/CILE electrochemical biosensor had potential applications for the electrocatalytic reduction of

trichloroacetic acid in the linear range of 0.9 to 9.0 mM with the detection limit of 0.32 mM [170]. Moreover, 1-hexylpyridinium hexafluorophosphate based CILE was used as a substrate for the in situ electrodeposition of GR and nickel oxide (NiO) to get NiO/GR/CILE. Nafion/Mb/NiO/GR/CILE electrochemical sensor was constructed by the immobilization of Mb on the surface of NiO/GR/CILE with a Nafion film. The presence of the NiO/GR nanocomposite on the electrode promoted the direct electron transfer of Mb. A third-generation electrochemical Mb biosensor based on NiO/GR/CILE was constructed for the electrocatalytic reduction of trichloroacetic acid and H₂O₂ [171]. Table 8 contained a brief summary of some hemoglobin and myoglobin biosensors.

Electrode	Hb and Mb biosensor	Linear range	Detection limit	Reference
poly(diallyldimethylammonium chloride) functionalized graphene nanosheets combined with room temperature ionic liquid and modified with Hb	nitrite	0.2 to 32.6 μM	0.04 μM	[164]
Hb/chitosan–ionic liquid–ferrocene/graphene/GCE	H ₂ O ₂	50 μM to 1200 μM	3.8 μM	[165]
Hb/ GR and Mg ₂ Al layered double hydroxide composite	trichloroacetic acid	1.6 to 25.0 mM	0.534 mM	[166]
immobilized Hb on carboxymethyl cellulose functionalized reduced graphene oxide (rGO) nanocomposite	NO and H ₂ O ₂	0.864 μM–19.8 μM and 0.083–13.94 μM for NO and H ₂ O ₂ , respectively	0.37 μM and 0.08 μM for NO and H ₂ O ₂ , respectively	[167]
Hb/ TiO ₂ NPs–rGO	H ₂ O ₂	0.1–140 μM	10 nM	[168]
myoglobin (Mb)/graphene , 1-ethyl-3-methyl-imidazolium tetrafluoroborate and chitosan composite film	trichloroacetic acid	---	---	[169]
Mb/ Pt nanoparticle decorated GR nanosheet	trichloroacetic acid	0.9 to 9.0 mM	0.32 mM	[170]
Nafion/Mb/NiO/GR/1-hexylpyridinium hexafluorophosphate CILE	trichloroacetic acid and H ₂ O ₂	---	---	[171]

Table 8. Examples of modified electrodes used as Hemoglobin and Myoglobin Biosensors.

5.9. Glucose and H₂O₂ biosensors

Glucose biosensors are becoming increasingly important due to their applications in biological and chemical analyses, clinical detection, and environmental monitoring. The immobiliza-

tion of enzymes on electrodes is generally the first step in fabrication attracting significant efforts because enzymes are highly selective and quickly responsive to specific substrates. Glucose oxidase (GOD) is employed as the enzyme in most of the glucose biosensors. It catalyzes the electron transfer from glucose to oxygen accompanied by the production of gluconolactone and hydrogen peroxide. The quantification of glucose can be achieved via electrochemical detection of the enzymatically liberated H_2O_2 [172]. Hua Zhang proposed a direct electrochemical method to reduce single-layer GO adsorbed on the 3-aminopropyltriethoxysilane (APTES) modified GCE. The reduced GO was modified with GOD and the obtained GCE-APTES-rGO-GOD was successfully used to detect glucose opening up a potential application in biosensing [52]. In addition, a bionanocomposite film consisting of GOD/Pt/functional graphene sheets/chitosan (GOD/Pt/FGS/chitosan) was employed for glucose sensing. With the electrocatalytic synergy of FGS and Pt nanoparticles to H_2O_2 , a sensitive biosensor with a detection limit of 0.6 μM for glucose was achieved displaying good reproducibility, long-term stability, and anti-interfering ability from AA and UA. The large surface area and good electrical conductivity of graphene suggests that graphene is a potential candidate as a sensor material [173]. Also, AuNPs-graphene nanocomposite was prepared and its electrocatalytic activity toward glucose oxidation was investigated. The results indicated that AuNPs-graphene nanocomposite had a higher catalytic activity than AuNPs or graphene alone indicating the synergistic effect of graphene and AuNPs [174]. Furthermore, Li Niu developed a novel glucose biosensor based on graphene/AuNPs/chitosan at gold electrode exhibiting good electrocatalytic activity toward H_2O_2 and O_2 . With GOD as a model, the graphene/AuNPs/GOD/chitosan composite-modified electrode was constructed through a simple casting method. The resulting biosensor exhibited good amperometric response to glucose with linear range, good reproducibility, and low detection limit of 180 μM [175]. Also, amperometric glucose biosensors were fabricated by using Pt-Au and Au nanoparticle spacers decorated functionalized graphene (f-G) nanosheets. The immobilization of GOD over nafion-solubilized metal nanoparticles dispersed graphene f-G-(Pt-Au) and f-G-(Au) electrodes has been achieved by physical adsorption. The resultant bioelectrode retains its biocatalytic activity offering fast and sensitive glucose quantification. The fabricated f-G-(Au) based glucose biosensor exhibited best sensing performance with a linear response up to 30 mM with an excellent detection limit of 1 μM [172]. Moreover, a dual biosensor platform based on hemin-functionalized graphene nanosheets (H-GNs) was presented. The nanomaterial combines the features of both graphene (high conductivity and surface area) and hemin (excellent catalysis and intrinsic peroxidase-like activity). Based on these features, the simple, economical, and highly sensitive amperometric and colorimetric biosensors for H_2O_2 and glucose have been developed. The detection limits for H_2O_2 and glucose reached 0.2 μM and 0.3 μM by the amperometric method, respectively. By the colorimetric methods, the detection limits for H_2O_2 and glucose were as low as 20 nM and 30 nM, respectively. The rapid, simple, and sensitive sensing platform showed great promising applications in the pharmaceutical, clinical, and industrial detection of H_2O_2 and glucose [176]. Also, GCE modified with electrochemically reduced graphene oxide/sodium dodecyl sulfate (GCE/ERGO/SDS) was further modified with GOD to be used as an enzymatic glucose biosensor with a low detection limit of 40.8 μM [177]. On the other hand, graphene functionalized with poly(diallyldimethylammonium chloride) (PDDA) can be used as non-enzymatic H_2O_2 biosensor showing enhanced electrocatalytic activity toward H_2O_2 reduction. As well, this modified surface can be used as an enzymatic glucose sensor by the immobiliza-

tion of the negatively charged GOD onto the positively charged PDDA-G matrix through electrostatic interaction. GOD/PDDA-G bionanocomposite can detect glucose with a low detection limit of 8 μM in the linear range of 0.02 to 1.8 mM [178]. In addition, a graphene and cobalt oxide nanoparticle composite was employed as non-enzymatic H_2O_2 and enzymatic glucose biosensor [179]. Several modified surfaces were utilized as non-enzymatic H_2O_2 biosensors, which were summarized in Table 9. On the other hand, a stable and sensitive non-enzymatic glucose biosensor based on CuO and rGO nanocomposite was developed. The proposed biosensor presented a high sensitivity of 2221 $\mu\text{A}/\text{mM}\cdot\text{cm}^2$ and a wide linear range from 0.4 μM to 12 mM toward glucose with good selectivity and stability. The TEM of rGO sheets showed a typical wrinkled and crumpled shape with thin layers. Upon CuO modification, there is a uniform distribution of rod-like nanoparticles with an average length of 20–30 nm on the surface of rGO indicating the successful synthesis of CuO-rGO nanocomposite [186]. Also, $\text{Ni}(\text{OH})_2$ /electroreduced graphene oxide-MWCNTs film was employed as non-enzymatic H_2O_2 and glucose biosensors [187].

Electrode	H_2O_2 and glucose biosensor	Linear range	Detection limit	Reference
GOD modified reduced GO adsorbed on the 3-aminopropyltriethoxysilane (APTES) modified GCE	enzymatic glucose	---	---	[52]
GOD/Pt/functional graphene sheets/chitosan	enzymatic glucose	---	0.6 μM	[173]
AuNPs–graphene nanocomposite	enzymatic glucose	---	---	[174]
graphene/AuNPs/GOD/chitosan composite-modified electrode	enzymatic glucose	2 to 10 mM	180 μM	[175]
GOD modified Pt–Au and Au nanoparticle spacers decorated functionalized graphene (f-G) nanosheets	enzymatic glucose	up to 30 mM	1 μM	[172]
hemin-functionalized graphene nanosheets (H-GNs)	H_2O_2 and glucose	---	0.2 μM for H_2O_2 and 0.3 μM for glucose	[176]
GCE modified with electrochemically reduced graphene oxide/sodium dodecyl sulfate and GOD	enzymatic glucose	---	40.8 μM	[177]
graphene functionalized with poly(diallyldimethylammonium chloride)	Non-enzymatic H_2O_2 and enzymatic glucose	0.02 to 1.8 mM	8 μM	[178]

Electrode	H ₂ O ₂ and glucose biosensor	Linear range	Detection limit	Reference
graphene and cobalt oxide nanoparticle composite	non-enzymatic H ₂ O ₂ and enzymatic glucose	0.5 mM to 16.5 mM for glucose. 0.2 to 211.5 μM for H ₂ O ₂	0.06 μM for H ₂ O ₂	[179]
prussian blue nanocubes on nitrobenzene-functionalized reduced graphene oxide	non-enzymatic H ₂ O ₂	1.2 μM to 15.25 mM	0.4 μM	[180]
layer-by-layer deposited low dimensional building blocks of graphene-prussian blue onto graphite screen-printed electrodes	non-enzymatic H ₂ O ₂	---	---	[181]
Ag nanoparticles/graphene nanosheet	non-enzymatic H ₂ O ₂	0.1 to 100 mM	0.5 μM	[61]
prussian blue-graphene modified GCE	non-enzymatic H ₂ O ₂	10–1440 μM	3 μM	[182]
graphene/Nafion/azure I/Au nanoparticles composites modified GCE	non-enzymatic H ₂ O ₂	30 μM to 5 mM	10 μM	[183]
rGO and Fe ₃ O ₄ nanocomposites	non-enzymatic H ₂ O ₂	0.1 mM to 6 mM	3.2 μM	[184]
cationic polyelectrolyte-functionalized ionic liquid decorated graphene sheets nanocomposite	non-enzymatic H ₂ O ₂	---	---	[185]
CuO and rGO nanocomposite	non-enzymatic glucose	0.4 μM to 12 mM	---	[186]
Ni(OH) ₂ /electroreduced graphene oxide-MWCNTs film	non-enzymatic H ₂ O ₂ and non-enzymatic glucose	10-1500 μM and 10 μM-9050 μM for glucose and H ₂ O ₂ , respectively	2.7 μM and 4.0 μM for glucose and H ₂ O ₂ , respectively	[187]

Table 9. Examples of modified electrodes used as Glucose and H₂O₂ Biosensors.

6. Conclusions

Graphene exhibits a unique chemical structure and outstanding properties making it very attractive for various engineering applications. Graphene and graphene-based materials have a profound impact on electroanalysis, electrocatalysis, sensors, and biosensors. In sensing applications, graphene-based materials featured with good conductivity and large specific surface area have demonstrated accurate, rapid, selective, sensitive, and even single-molecular

sensing abilities. Graphene-based materials are ideally used as gas sensors, electrochemical sensors for heavy metal ions, immunosensors and NADH, DNA, catecholamine neurotransmitters, paracetamol, glucose, H₂O₂, hemoglobin, and myoglobin biosensors. Future investigations on graphene-based sensing platforms, combined with versatile sensing strategies, are expected to continually lower the detection threshold.

7. Permissions

Figure number (in chapter)	Figure Source (reference number)	Permission number
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7	[77]	3556441025155
8	[79]	3556441165370
Table 1	[6]	3556460926032

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