Front. Mater. Sci. 2018, 12(1): 1–20
https://doi.org/10.1007/s11706-018-0409-0

REVIEW ARTICLE

Graphene: from synthesis to engineering to biosensor applications

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ABSTRACT: Graphene is a fascinating material of recent origin whose first isolation was being made possible through micromechanical cleavage of a graphite crystal. Owing to its fascinating properties, graphene has garnered significant attention in the research community for multiple applications. A number of methods have been employed for the synthesis of single-layer and multi-layer graphene. The extraordinary properties of graphene such as its Hall effect at room temperature, high surface area, tunable bandgap, high charge mobility and excellent electrical, conducting and thermal properties allow for the development of sensors of various types and also opened the doors for its use in nanoelectronics, supercapacitors and batteries. Biological aspects of graphene have also been investigated with particular emphasis on its toxicity and drug delivery. In this review, many of the salient aspects of graphene, such as from synthesis to its applications, primarily focusing on sensor applications which are of current interest, are covered.

KEYWORDS: graphene; nanoelectronics; Hall effect; tunable bandgap; supercapacitors; sensors; catalysis

Contents

Received October 23, 2017; accepted December 4, 2017

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1 Introduction

Graphene and carbon nanotubes (CNTs) are two of the most studied materials in recent years. There is an increasing interest in two-dimensional (2D) graphene due to its unique electrical properties like very high carrier mobility, the quantum Hall effect (QHE) at room temperature and ambipolar electric field effect along with ballistic conduction of charge carriers [1–5]. Other attractive properties of graphene include unexpected high absorption of white light [6], high elasticity [7], unusual magnetic properties [8–9], high surface area [10], gas adsorption [11], and charge-transfer interactions with molecules [12–13]. Generally, graphene is defined as a single layer of sp^2 hybridized carbon atoms arranged in hexagonal format. Over the years new and more efficient methods are evolved to prepare high-quality single-layer graphene (SLG) and functionalized graphene (FG). Direct visualization of defects in the graphene lattice, such as the Stone–Wales defect, has been possible by aberration-corrected transmission electron microscopy (TEM) with amonochromator. In many studies, it has been shown that graphene can enfold into a zero-dimensional (0D) fullerene, rolled to resemble one-dimensional (1D) carbon nanotubes, or stacked to three-dimensional (3D) graphite (Fig. 1) [14].

Due to many important structures properties, researchers focused their attention to develop various carbon nanostructures for multifunctional applications [15–28].

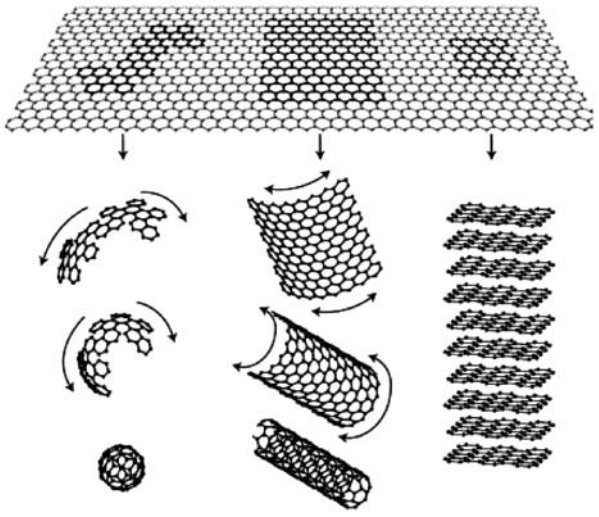

Fig. 1 Schematic diagram showing that graphene can be wrapped to form 0D fullerenes, 1D CNTs, or stacked to form 3D graphite. Reproduced from Ref. [14].

2 Properties of graphene

The pristine graphene has numerous attractive properties like high charge (electrons and holes) mobility (230,000 $cm^2 \cdot V^{-1} \cdot s^{-1}$) with the absorption of visible light up to 2.3%, thermal conductivity (3000 $W \cdot K^{-1} \cdot m^{-1}$), high strength (130 GPa), and high theoretical specific surface area (2600 $m^2 \cdot g^{-1}$) [29–31]. Also, graphene shows QHE even at ambient temperature (minimum Hall conductivity 4 e^2/h, even at zero carrier concentration).

2.1 Electrical properties

Pristine graphene is zero-gap semiconductor [31]. In graphene, atoms of carbon are linked in hexagonal fashion with sp^2 hybridization. A remarkable fact about graphene is the abnormal behaviour of its charge carriers, acting as massless relativistic particles (Dirac fermions) which are considered electrons without their rest mass. These particles can be better described with a (2 + 1)-dimensional Dirac equation. In general, the behaviour of Dirac fermions is anomalous in comparison with electrons under a magnetic field. For example, the strange integer quantum Hall effect (IQHE) was noticed even at room temperature [31–35]. Summary of unique capabilities of graphene includes:

i) Electrons scattering is negligible up to micrometer distance even at room temperature.

ii) Electrons travel ballistically.

iii) Electrons pass through the graphene sheet as if they hold no mass, as fast as just one hundredth that of the speed of light.

2.1.1 Band structure

Graphene exhibit zero bandgap and symmetrical structure. Electrons in insulator or semiconductor are bound to an atom and needs energy to jump the bandgap. But, due to infinitesimal bandgap of graphene, electrons can move easily and very fast. Also, by applying electric field perpendicularly to the graphene, the bandgap symmetry can be removed. Therefore, we can say that the graphene exhibits tunable bandgap. It means bandgap of graphene can be changed with variations of electric field (Fig. 2) [36]. The capability to change a device's energy gap could lead to detectors that respond only to a particular wavelength of light or light emitters whose colour is controlled [36].

2.1.2 Graphene efficiently filters electrons according to the direction of their spin

The movement of electrons can be controlled by applying astrong magnetic field, in which electrons can travel only along the edges, and are stopped from moving in the interior. In addition, only electrons with one direction of spin can travel in only one direction by the side of the edges while electrons with the opposite spin are blocked.

2.2 Optical properties

It is clear from numerous reports that single layer graphene absorbs 2.3% of incident light over a broad wavelength range. The transmittance of graphene can be well described in terms of fine-structure constants [6,31,37]. The absorption of light was found to increase linearly with the addition of a number of layers (each layer absorption $A = 1 - T = \pi\alpha = 2.3\%$, where $\alpha = 1/37$ is the fine-structure constant). Also, the study established that the zero bandgap, large-area monolayer, and few-layer graphene field-effect transistors (FETs) can be used as ultrafast photodetectors. The electron–hole pairs are generated in graphene by absorption of light which recombine quickly (picoseconds), depending upon the temperature as well as the density of holes and electrons. However, both the holes and electrons are separated by applying an external field, which ultimately leads to the generation of photocurrent.

The unique properties of graphene are its ability to provide high-bandwidth ($>$ 500 GHz) light detection, wide wavelength detection range, zero current operation, and excellent quantum efficiency. By combining optical and electrical properties of graphene many new phenomena arise which are necessary for various photonics and optoelectronics applications. Other interesting and possible applications of graphene include its use as photodetectors, touch screens, light-emitting devices, photovoltaics, transparent conductors, terahertz devices, and optical limiters [38].

The monolayer graphene can absorb light from 200 to 2500 nm; the peak at about 250 nm in the ultraviolet (UV) region is ascribed to the interband electronic transition

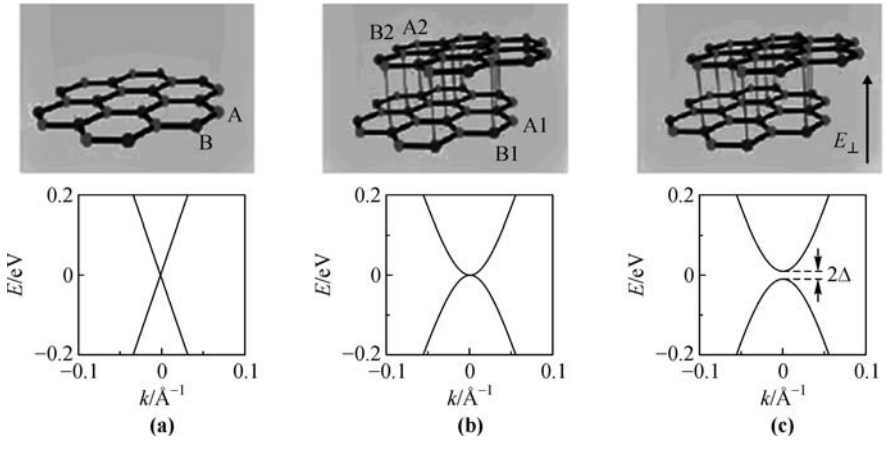

Fig. 2 Schematic diagram showing the band structure of graphene in absence and presence of electric field: **(a)** monolayer and **(b)** bilayer graphene. **(c)** When an electric field E is applied perpendicular to the bilayer, a bandgap is opened in bilayer graphene, whose size (2Δ) is tunable by the electric field. Reproduced from Ref. [36].

from the unoccupied p-states (Fig. 3) [39]. By the application of electrical gating, their optical transition can be altered, because due to electrical gating Fermi energy is changed [31,40–41]. Therefore, by using electrical gating the charge injection in graphene-based optoelectronics can be controlled and help to develop tunable infrared (IR) detectors, modulators, and emitters [40–41].

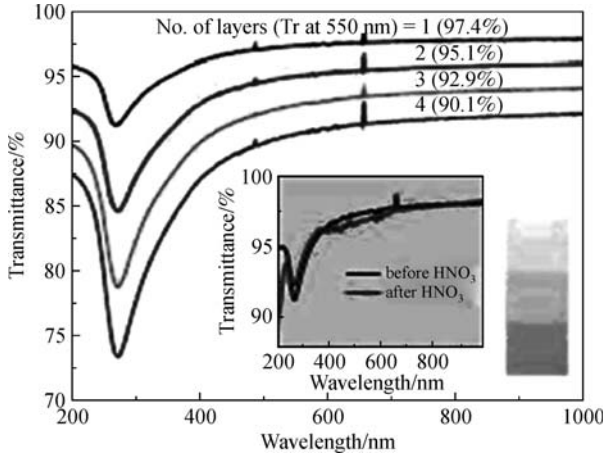

Fig. 3 Schematic diagram showing the representative transmittance of different graphene layers. UV-vis spectra roll-to-roll, layer-by-layer transferred graphene films on quartz substrates. The inset shows the UV spectra of graphene films with and without HNO_3 doping. Reproduced from Ref. [39].

Photoluminescence (PL) is another important property of graphene [31]. To make a luminescent graphene, the suitable bandgap is induced in it by using two methods. In the first method, graphene is cut into nanoribbons and quantum dots. In the second method, the physical or chemical treatment of graphene with different gases to diminish the connectivity of the π-electron network is involved.

2.3 Mechanical properties

Graphene exhibits high elastic modulus (0.5 TPa) and tensile strength (130 GPa). The intrinsic superior mechanical properties of graphene are determined by phonon frequency variation on the application of tensile and compressive loading [41–46]. To monitor the phonon frequency under uniaxial tensile and hydrostatic stress, Raman spectroscopy is commonly used [31,42–46]. Phonon softening is induced by tensile stress, due to adecrease in vibrational frequency. However, phonon hardening is caused by compressive stress (hydrostatic) due to increase in vibrational frequency mode [31]. As a consequence, in graphene, the information regarding stress transfer to individual bonds is provided by the vibrational frequency of phonon as a function of strain. Raman spectroscopy is used to measure the tensile and compressive strain in a graphene layer by calculating the variation in the 2D and G peaks with the applied stress. A red shift occurs due to increase in the strain and it also results in the splitting of "G" peak [31]. For a minute strain of 0.8%, a 2D split was observed without any shoulder [42–46].

2.4 Thermal properties

Graphene has a vital role in electronic devices due to its unique thermal properties [31]. This assists in thermal management to enhance performance and reliability of electronic components. In a recent work, it was found that defect-free graphene exhibited the highest room temperature thermal conductivity (5000 $W \cdot K^{-1} \cdot m^{-1}$) [47]. In the case of supported graphene, the conductivity was about 600 $W \cdot K^{-1} \cdot m^{-1}$. In various reports in the past, the conductivity of graphene was not studied in depth. However, the effect on conductivity using graphene as a channel was first predicted by Klemens [48]. A novel strategy followed to check the thermal conductivity of a thin atomic layer of graphene is shown in Fig. 4 [49].

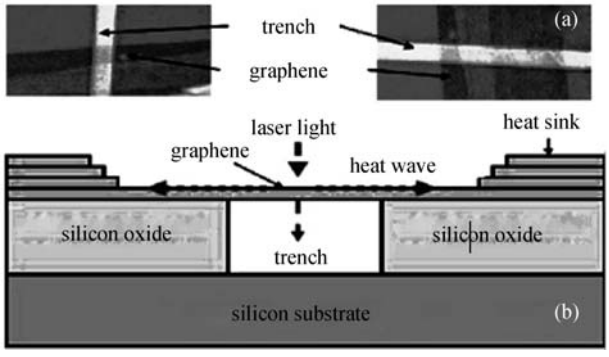

Fig. 4 Schematic diagrams: **(a)** High-resolution scanning electron microscopy image of the suspended graphene flakes; **(b)** Schematic of the experimental setup for measuring the thermal conductivity of graphene. Reproduced from Ref. [49].

3 Synthesis methods of graphene

3.1 Exfoliation methods

Graphene is a unique nanostructured material that has strong potential in applications such as in polymer composites, conductive coatings and inks, fuel cells batteries, catalysts and ultracapacitors. A large quantity of graphene is thus required for fulfilling these goals.

Exfoliation techniques provide the solution for bulk production of nano-graphene at a low cost. Moreover, the exfoliation produced graphene has the lowest number of defects and highest electron mobility. Various exfoliation techniques have been discussed in the following subsections.

3.1.1 Mechanical exfoliation

In this process, a scotch tape is used to produce graphene in bulk but the quality of graphene is not that high. A few inches long (about 6 inches long**)** scotch tape is taken (Fig. 5) [50]. The adhesive side of the tape is pressed onto the highly ordered pyrolytic graphite (HOPG) for about 10 s. Then the tape is gently peeled away taking away a thick layer of graphite sticking on it. The newly made surface of tape with layers from HOPG is again pressed along the pristine adhesive part of the remaining tape. This process continues until the glassy surface of tape turn into dark and gray. Si/SiO_2 substrate softly pressed against the taped to get the graphite layers transferred on its surface from the tape surface. Graphene sheets of various thicknesses can be produced by mechanical exfoliation method or by peeling off layers from graphitic materials such as highly ordered pyrolytic graphite, single-crystal graphite, or natural graphite. Peeling and manipulation of graphene sheets have been achieved through atomic force microscopy (AFM) and scanning tunneling microscopy (STM) tips [51–56].

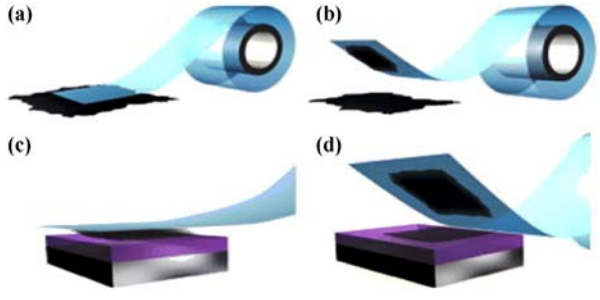

Fig. 5 Schematic diagram showing steps of the mechanical exfoliation of graphene from graphite using scotch tape: **(a)** adhesive side of the tape is pressed onto the HOPG; **(b)** tape is peeled away with graphite layer sticking on it; **(c)** newly made surface is again pressed along the pristine adhesive; **(d)** Si/SiO_2 substrate softly pressed against the taped to get the graphite layers. Reproduced from Ref. [50].

3.1.2 Chemical exfoliation

This method constitute of two steps. In order to mitigate the effect of interlayer vander Waal forces the interlayer distance is to be increased. This is done by graphite intercalation compounds (GICs) [57]. The GICs are then exfoliated into graphene with single to a few layers by rapid heating or sonication. GICs can be prepared by the intercalation of alkali metal ions. Viculis et al. [58] prepared potassium, cesium and NaK_2 intercalated graphite by reacting alkali metals with acid-intercalated exfoliated graphite in Pyrex sealed tubes. GICs are then rinsed with ethanol causing a vigorous reaction to yield exfoliated FG (Fig. 6(a)) [58]. Direct exfoliation and noncovalent functionalization and solubilization of graphene in water are done by using the potassium salt of coronene tetracarboxylic acid to yield monolayer graphene–coronene tetracarboxylic acid composites (Fig. 6(b)) [58]. Stable high-concentration suspension of FG is then obtained by direct sonication in ionic liquids.

3.1.3 Electrochemical exfoliation

The electrochemical exfoliation is an eco-friendly technique for producing high-quality graphene. The electrochemical exfoliation of graphite because of ions present in the solution produces the few-layer graphene (FLG) or graphene oxide (GO) depending upon the nature of electrolyte. The electrolyte is subjected to the requirement of the oxidizing environment and more importantly on the size of the intercalating ion. The framework consists of two electrodes one of them being graphite or HOPG the other can be Cu, Pt or even HOPG/graphite. Generally, ± 10 V is applied for an unequal period of time. Due to the effect of applied voltage, intercalating ions present in the solution exfoliates the graphite into anodic few-layer graphene (AFLG) by penetrating in between the sheets (Fig. 7) [59]. The need for negative voltage is to bring the intercalated ions back into the solution along with the sheets, hence the need of unequal application time for the voltages [59].

3.2 Epitaxial growth of graphene on SiC

The fundamentals of this methodology are based on the differences between the vapor pressures. The vapor pressure of silicon is higher, as a result on heating the SiC wafer, Si evaporates leaving behind the graphene layers on the substrate. The silicon carbide substrate is heated at a temperature around 1200°C and the conditions of the chamber are set accordingly. The Si atoms evaporate due to thermionic emission leaving behind the carbon atoms on the remaining substrate (Fig. 8) [60]. The final

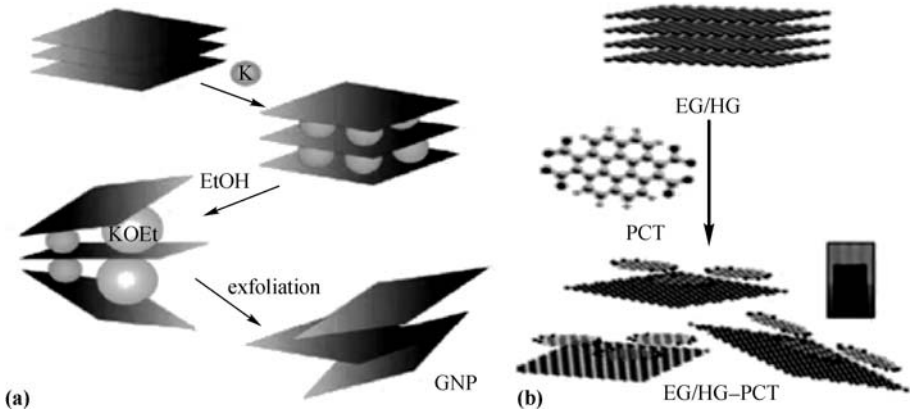

Fig. 6 Schematic diagrams: **(a)** GICs prepared by the intercalation of alkali metal ions; **(b)** direct exfoliation and noncovalent functionalization and solubilization of graphene by using the potassium salt of coronene tetracarboxylic acid (PCT). Reproduced from Ref. [58].

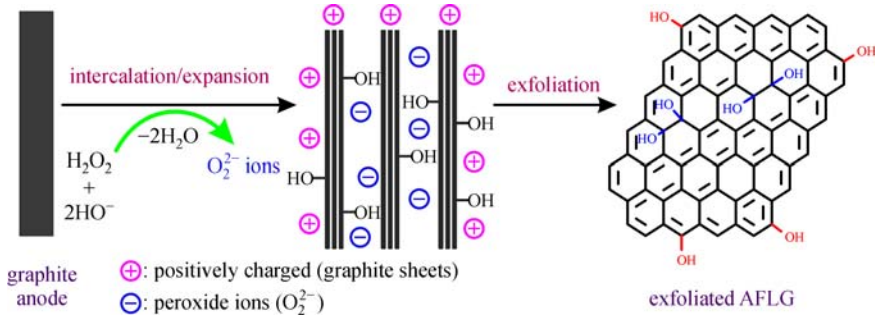

Fig. 7 Schematics of the exfoliation mechanism for the peroxide electrolyte. Reproduced from Ref. [59].

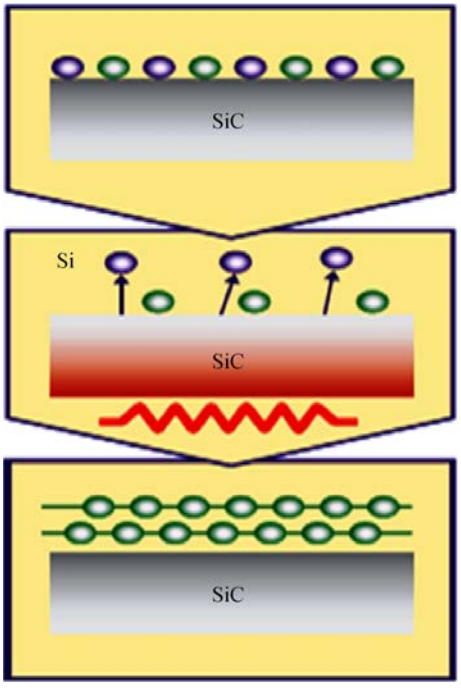

Fig. 8 Schematic illustration of the thermal decomposition method. Reproduced from Ref. [60].

SiC substrate is covered with the carbon layers which can be either monolayer, bilayer or multilayer graphene [60].

3.3 Hummers method

This method produces graphene by oxidizing graphite to graphite oxide by using suitable oxidizing agents such as $KMnO_4$. The GO so produced is chemically reduced to get graphene. The Hummers method introduces a way to get a more stable GO colloidal solution. Ultra-sonication is used for stabilizing the GO solution and enhancing the exfoliation in the GO solution (Fig. 9) [61].

3.4 Reduction of graphite oxide

Chemical reduction of graphite oxide is one of the established procedures to prepare graphene in large quantities [62]. Graphite oxide, when ultrasonicated in water, forms a homogeneous colloidal dispersion of predominantly sufonated graphene oxide (SGO) in water. Reduced graphene oxide (RGO) with properties similar to that of graphene is prepared through chemical, thermal, or

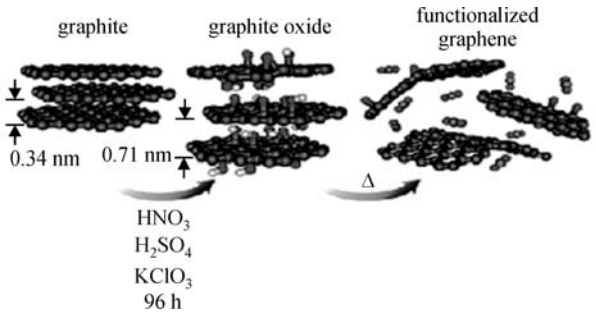

Fig. 9 Schematic showing the steps in Hummers method. Reproduced from Ref. [61].

electrochemical reduction pathways [63]. Hydrazine monohydrate is one of the preferred options for reducing aqueous dispersions of graphene oxide [64]. Other reducing agents include $NaBH_4$ [65], phenyl hydrazine [66], hydroxylamine [67], glucose [68], ascorbic acid [69], hydroquinone [70], alkaline solutions [71], and pyrrole [72]. Electrochemical reduction is another means to synthesize graphene in large scale [73–75]. The reduction initiates at -0.8 V and is completed by -1.5 V, with the formation of black precipitate onto the bare graphite electrode.

3.5 Chemical vapour deposition (CVD)

CVD is one of the most efficient, inexpensive, and pragmatic approaches for the bulk scale deposition of reasonably high-quality graphene onto transition-metal substrates such as Ni [76], Pd [77], Ru [78], Ir [79], and Cu [80]. The working principle of process is that metal absorption increases with increase in temperature and vice versa. Exposure of transient metal substrate to hydrocarbon at high temperature results in the absorption of carbon on it and this is continued until carbon saturation is reached. On cooling the substrate, the solubility of carbon in the transition metal decreases and a thin film of carbon precipitates from the surface. Different hydrocarbons like ethylene, methane, benzene, and acetylene were decomposed on different transition-metal substrates for e.g. Co, Au, Ni, Cu, and Ru [81]. A plasma-enhanced chemical vapor deposition (PECVD) technique that makes use of radio frequency is also used to synthesize graphene on a variety of metal substrates such as Mo, Si, W, Zr, Cr, Ti, Ta, Hf, Nb, stainless steel, SiO_2, and Al_2O_3. The advantages of this method are that energy consumption is decreased and the formation of amorphous carbon or another type of unwanted product are averted [82–84].

3.6 Unzipping multi-walled carbon nanotubes (MWCNTs)

Unzipping of MWCNTs can be performed by the intercalation of lithium and ammonia followed by exfoliation in acid and abrupt heating [85]. The product that results will consist of a mixture of partially open MWCNTs and graphene flakes. Unzipping of MWCNTs can also be performed by the plasma etching of MWCNTs partially embedded in a polymer film [86]. The etching procedure basically opens the MWCNTs to form graphene. In a different approach, MWCNTs were unzipped by a multi-step chemical treatment, including exfoliation by concentrated H_2SO_4, $KMnO_4$, and H_2O_2, stepwise oxidation using $KMnO_4$, followed by a reduction in NH_4OH and hydrazine monohydrate ($N_2H_4 \cdot H_2O$) solution [87]. This new route of unzipping MWCNTs to produce graphene opens the possibilities of synthesizing graphene in a substrate-free manner.

Advantages and disadvantages of techniques currently used to produce graphene source are compared in Table 1 [88].

4 Applications of graphene composites

Graphene composite have various intended applications to create unique and innovative materials. The possible applications of graphene composite involve medical implants, engineering materials for aerospace and renewable and many more. Graphene composites are of three types namely polymer, metal and ceramic. But the most

Table 1 Advantages and disadvantages of techniques currently used to produce graphene [88]

Method	Advantages	Disadvantages
Mechanical exfoliation	• low cost and easy • no expensive equipment needed	• uneven films • labour intensive • not suitable for large-scale production
Epitaxial growth	• most even films (of any method) • large-scale area	• difficult control of morphology and adsorption energy • high-temperature process
Graphene oxide	• easy to upscale • versatile handling of the suspension • rapid process	• fragile stability of the colloidal dispersion • reduction to graphene is only partial

interesting composite is the polymer graphene composite as they generally do not involve high pressure and temperature. The applications appear to be countless as graphene polymers manifest to be flexible, light and outstanding electrical conductor. These composites are discussed in the following section.

4.1 Polymer–graphene nanocomposites

Graphene exhibits superior mechanical, gas barrier, thermal, flame retardant and electrical properties which can assist in enhancing the performance of polymers for wider engineering applications. Various applications of polymer–graphene nanocomposites in biomedical field are investigated. Some of them are mentioned in Table 2 [89–101]. Some examples of polymer-based graphene containing composites are listed below:

i) PVA/graphene nanocomposites

This type of nanocomposites are used as biocide nanocomposites in food and drink package applications, and they show antibacterial activity both gram positive and gram negative bacteria [102].

ii) Polyaniline/graphene nanocomposites

In many studies, PANI/GN are synthesized by *in situ* polymerizations for high-performance supercapacitors [103–104].

iii) Epoxy/graphene nanocomposites

For heat dissipation, epoxy/graphene nanocomposites are used as interface material. These films show high transmittance, which is very useful in potential applications like power-producing windows or metal-foil-supported dye-sensitized solar cells. Also, these nanocomposites are used for cryo-tank composite application [105].

4.2 Metal–graphene nanocomposites

Graphene is used as a reinforcement in metallic matrices owing to its high tensile strength ≈ 130 GPa and Young modulus Y ≈ 1 TPa [7]. Some of the examples of metal–graphene composites are listed below:

i) Mg–graphene nanocomposites

Graphene nanoplatelets addition into Mg alloys like Mg–1Al–1Sn alloy matrix leads to considerable improvement in tensile strength of the resulting composite; however, ductility was adversely affected [106]. The targeted applications of these materials are in weight critical sectors such as transportation sector.

ii) Al–graphene nanocomposites

Al–graphene nanocomposite shows tensile strength of 256 MPa and 13% elongation which are ~62% higher and around 2 times lower than the strength of unreinforced Al matrix (154 MPa) and elongation (27%), respectively. Results of this study revealed that addition of graphene into aluminum increases the strength appreciably and maintain ductility exceeding 5% which is an acceptable norm for engineering applications [107].

iii) Ni–graphene nanocomposites

Ni–graphene nanocomposites are used for hydrogen storage with nickel (10 nm in size) uniformly dispersed over a graphene substrate. This system exhibits attractive features like high gravimetric density, ambient conditions, and low activation temperature for hydrogen release [108].

4.3 Ceramic–graphene nanocomposites

The fascinating properties of graphene make it a suitable candidate as advanced fillers in composite material.

Table 2 Applications of polymer–graphene nanocomposites in biomedical field [89–101]

Application	Purposes	Graphene/polymer composites used	Refs.
Drug delivery	• CPT delivery	• GO–PVA–CPT • CNT–PVA–CPT • PNI–PAM–GS	[89–90]
Gene delivery	• anticancer drug delivery • DNA transfection • CPT drug and report • DNA delivery • Si RNA and DOX delivery	• NGO–PEG • PEI–GO • GO–chitosan • GO–PEI	[91–96]
Cancer therapy	• tumor ablation • multifunctional cancer therapy • hepatocarcinoma diagonosis	• PEG–NGS • Ce6 loaded PEG–GO • GO–PEG–FA/Gd/DOX	[97–99]
Bio-imaging	• cell imaging	• NGO–PEG • GO–PEI	[100]
Actuators	• artificial muscles	• graphene/PDMS	[101]

Integrating graphene into ceramic has considerable possibilities in producing tough, strong and electrically conductive ceramic composites which could further solve extensive material related challenges in processing aerospace, transportation, industries and military applications [109–112].

The exceptional electrical and mechanical properties of graphene deliver an enormous prospective for functional and structural applications of graphene–ceramic composites such as low-temperature fuel cells [113], electronic devices [114], surface renewable electrodes [115], hip-joint prosthetics [116], energy storage materials [117].

5 Biocompatibility and toxicity of graphene

Due to the advantageous physiochemical properties, ascendable production and extensive applications of graphene, there has been an increasing interest to develop nanoscale biocompatible graphene structure.

Zhang et al. compare the cytotoxicity of graphene and single-walled carbon nanotubes (SWCNTs), where both the materials were tested on pheochromocytoma (PC12) cells at dosages from 0.1 to 100 $g \cdot mL^{-1}$. Lactase dehydrogenase (LDH) and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) release assays were used to estimate cell membrane disruption and the mitochondrial toxicity respectively. Both graphene as well as SWCNT presented a dose-dependent toxic response after a 24 h exposure, and graphene induced greater toxicity than SWCNT at lower concentrations, although the opposite was observed at the higher concentration [118].

Also Wang et al. has synthesized graphene/chitosan composite and this composite was found to be biocompatible to L929 cells as shown by MTT chlorimetric assays. Moreover, the absence of metallic impurities on graphene sheets makes them potential applicant as frameworks for tissue engineering [119].

Graphene and its other forms can pierce through the physiological barriers or cellular structures by various exposure methods or administration routes and enter the body or cells which ultimately results in toxicity *in vivo* and *in vitro*. The wavering administration routes and entry paths, different tissue distribution and excretion, even several cell uptake configurations and locations, possibly can determine the degree of the toxicity of graphene-family nanomaterials (GFNs) [120–122]. So to make them clear may be helpful to better understand the laws of the occurrence and development of graphene toxicity.

6 Graphene-based sensors

Graphene's distinctive optical properties, exceptional electrical conductivity, high thermal conductivity, appreciative carrier mobility and density, large surface to volume ratio and many other attributes makes graphene greatly beneficial for sensor application. Due to these anticipated properties of graphene, it will facilitate sensors to be smaller and lighter, thus imparting countless design opportunities. Also, they will be additionally sensitive to identify smaller changes in matter making them more sensitive; work more swiftly and eventually will be less expensive than traditional sensors. Also, many nanocarbon materials are used in sensor applications as described in Table 3 [123–131].

Some of the graphene-based sensors are explained below.

Table 3 Different nanocarbon materials used in sensor applications [123–131]

Nanocarbon material	Analytes	Method	Sensor	Sensing parameter	Refs.
Carbon black	ethanol vapors	electrical resistance	gas sensor	sensitivity, 27.7%	[123]
Carbon nanofibers	ethanol vapors	electrical resistance	gas sensor	sensitivity, 40%	[123]
MWCNTs	ethanol vapors	electrical resistance	gas sensor	sensitivity, 47.4%	[123]
SWCNTs	DNAs	DPV [b)]	biosensor	detection limit, 1.43 μmol/L	[124]
Graphene	uric acid	amperometry	biosensor	detection limit, 0.132 μmol/L	[125]
Buckypaper–SWCNTs	glucose	amperometry	biosensor	detection limit, 0.022 mmol/L	[126]
Nitrogen-doped graphene	uric acid	DPV [b)]	biosensor	detection limit, 0.045 μmol/L	[127]
Graphene–Pt	ascorbic acid	DPV [b)]	biosensor	detection limit, 0.03 μmol/L	[128]
MWCNTs	cholesterol	amperometry	biosensor	detection limit, 0.2 mmol/L	[129]
Graphene–Au nanorod	NADH [a)]	amperometry	biosensor	detection limit, 1.5 μmol/L	[130]
SWCNTs	dopamine	DPV [b)]	biosensor	detection limit, 48 nmol/L	[131]

a) NADH, nicotinamide adenine dinucleotide. b) DPV, differential pulse voltammetry.

6.1 Graphene-based biosensors

The graphene-based materials have been implemented to construct different types of biosensors based on various sensing mechanisms including optical (fluorescence) and electrochemical sensors [132]. Figure 10 illustrates different representations of graphene-based electrochemical sensors in biomedical applications [133]. Depending on the specific working principle, graphene-based biosensors either use their electrical properties (i.e. high charge-carrier mobility), electrochemical properties (i.e. high electron-transfer rates), or unique structure (i.e. atomic layer thickness and high surface-to-volume ratio) for biomolecule detection [134]. Due to these advantages, graphene is selected for synthesis of biological sensors with high sensitivity, selectivity, and low detection limit. Using fast electron transportation criteria of graphene, the tiny biological information can be converted into an electronic format, thus making the sensors with high sensitivity. In general, biosensors are composed of two parts: a receptor and a transducer. The receptor can be any material that can interact with a target analyte. The highly sensitive biological element acting as a receptor is connected to a transducer, which acts on its part converting biological data to electrical data. The transducer, in turn, connects to a measuring device translating the electrical signal to a measurable quantity. In graphene-based biosensors, graphene is used as a transducer element.

6.2 Graphene-based gas sensors

Because of the absence of dangling bonds on the graphene surface, the gaseous molecules cannot be easily adsorbed onto its surface. The sensitivity of chemical sensor responds according to the thin layer of receptor molecules. Presence of certain polymer on graphene enriches its sensitivity. The ability to detect any local small change in electrical resistance depicts the power and efficiency of sensor acting on a gas molecule adsorption. Graphene has high electrical conductivity due to its unique structure and low noise, making even small change catchable thus proving its superiority over other material to be used in a sensor. Chen et al. [135] demonstrated the possibility of sensitive gas sensing with graphene materials. Chen et al. designed their sensing device with the help of gold interdigitated electrodes and aqueous GO suspension

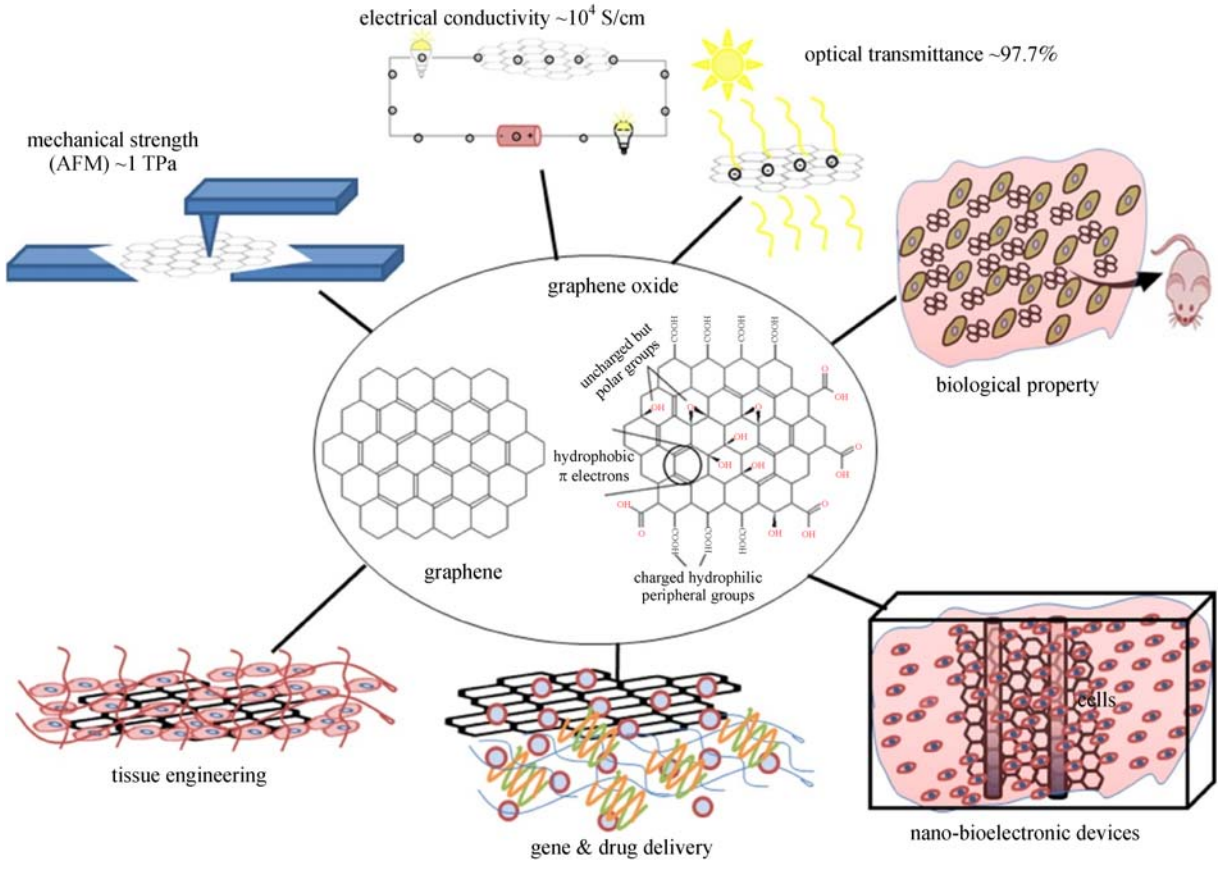

Fig. 10 Graphene-based electrochemical sensors for DNA, protein and cancer cell detection. Reproduced from Ref. [133].

[136] with both finger-width and interfinger spacing (source–drain separation) of about 1 μm. A few drops of the GO suspension were cast onto gold interdigitated electrodes, and a discrete network of GO sheets was left behind on the wafer after water evaporation. The working principle of the sensing device is that the drain–source channel becomes closed after GO is partially reduced by low-temperature thermal treatments thus the conductance of the device varies with exposure to various gases. Both two-terminal direct current (DC) and three-terminal field-effect transistor (FET) measurements were performed on GO devices using a Keithley 2602 source meter (Fig. 11) [135]. Electrical conductance of the GO device was measured by ramping the drain-source voltage V_{ds} and simultaneously recording the drain-source current I_{ds} to evaluate the influence of thermal treatment on the device characteristics.

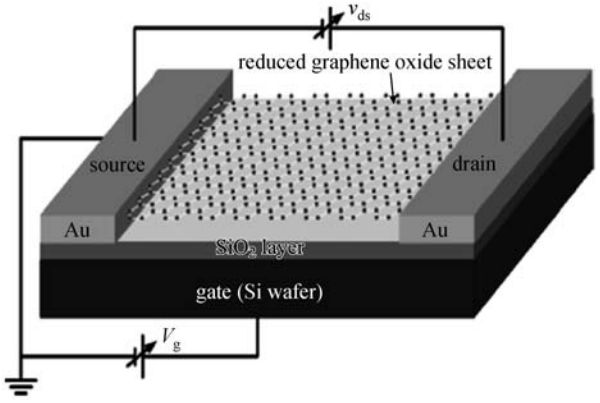

Fig. 11 Schematic diagram of the RGO device. An RGO sheet bridges the source and drains electrodes, which closes the circuit. Reproduced from Ref. [135].

6.3 Graphene chemiresistors as pH sensors

These were fabricated by Lei and co-workers using graphene sheets produced by mechanical exfoliation and platinum electrodes fabricated using focused ion beam technique. Annealing was used to improve the electrical contact. Results revealed that resistance of graphene device increased with decreasing pH value (in the range of 4–10) of the surrounding liquid environment [137].

6.4 Photodetectors based on graphene

Graphene and various other 2D materials, such as transition metal dichalcogenides, are quite intriguing building blocks for optoelectronic applications with a strong focus on various photodetection platforms [138–140]. The different characteristics and adaptability of this material system make them suitable for application in fields like ultrafast and ultrasensitive detection of light in the ultraviolet, visible, terahertz and infrared frequency. This detector system can be upgraded by attaching to other photonic components on the same material as well as with silicon photonic and electronic technologies [141].

7 Graphene-based biosensor for health and environmental monitoring

Due to the unique properties of graphene, it is expected soon to become extensive in diagnostics and biosensors. Considering the large surface area of graphene, it can augment the surface loading of desired biomolecules. Also the small bandgap and excellent conductivity, it is said to be beneficial for conducting electrons between electrode surface and biomolecules. Biosensors can be further used for the detection of various analytes like hemoglobin, glucose, cholesterol, glutamate and many more. Also to detect toxic gases or organic pollutants in the environment graphene-based sensors can be utilized. Some of the graphene-based biosensors for monitoring health and environmental condition are explained in the next subsection.

7.1 Graphene-based DNA biosensors

In recent years, graphene and GO have emerged as a distinctive platform for developing DNA-based biosensors, given the DNA adsorption by detection of DNA hybridization techniques [142–143] and fluorescence-quenching properties of GO. Lin et al. [144] reported an electrochemical DNA biosensor in which the captured DNA was immobilized on the surface of a graphene-modified glassy carbon electrode (GCE) through p–p stacking. Gold nanoparticles (AuNPs) modified with single nucleotide probes were then cohybridized on the surface of GCE for the detection of the targeted DNA sequence. Then, the target DNA sequence and oligonucleotide probes-labeled AuNPs were able to hybridize in a sandwich assay format following the AuNPs-catalysed silver deposition. Owing to the high DNA loading capability of graphene and the different signal amplification by AuNPs-catalysed silver staining, the resulting biosensor exhibited a good analytical performance with a wide detection linear range from

200 pmol·L^{-1} to 500 nmol·L^{-1} and a low detection limit of 72 pmol·L^{-1}.

7.2 Graphene-based haemoglobin (Hb) biosensor

Hb is the most important component in the blood for transporting O_2 and CO_2 throughout the circulatory system. Change of Hb concentration in the blood can cause various disorders such asanemia, leukemia, heart diseases, while its normal level displays the well-functioning of the organism. Xu et al. [145] fabricated a chitosan–graphene (CS–GN) modified electrode for the electroanalysis of Hb. The cyclic voltammogram (CV) of Hb at the CS–GN/GCE exhibited well-defined redox peak when compared to CS–GCE. Sun et al. [146] prepared a new electrochemical biosensor using three-dimensional graphene (3D-GN) as the substrate electrode by immobilization of Hb on the electrode surface with a chitosan film. This electrochemical process shows that a pair of well-resolved redox peaks appeared on CV, illustrating the realization of direct electron transfer of Hb.

7.3 Graphene-based glucose biosensors

Diabetes is critical diseases in the world and it is important to make a quantitative determination of glucose levels in the blood for the diagnosis of this disorder. Shan et al. applied the first graphene-based glucose biosensor with graphene/polyethyleneimine-functionalized ionic liquid nanocomposites modified electrode that exhibited wide linear glucose response (2–14 mmol·L^{-1}, R = 0.994), effective reproducibility (normal standard deviation of the current response to 6 mmol·L^{-1} glucose at 0.5 V was 3.2% for ten measurements), strong stability (response current + 4.9% after one week) [147]. Zhou et al. [148] produced a glucose biosensor based on chemically reduced graphene oxide (CRGO). This biosensor showed enhanced amperometric signals for sensing glucose in the blood, wide linear range (0.01–10 mmol·L^{-1}), high sensitivity (20.21 μA·$mmol^{-1}$·L·cm^{-2}) and low detection limit of 2.00 μmol·L^{-1} (S/N = 3). Kang et al. explored the efficiency of chitosan in dispersing graphene and constructed glucose biosensors with the desired sensitivity. Chitosan helped to form a well-dispersed graphene suspension and immobilized the biomolecules, and the graphene-based biosensor showed high sensitivity (37.93 μA·$mmol^{-1}$·L·cm^{-2}) and long-term stability for measuring glucose. These investigations show great promise for graphene-based glucose biosensors.

7.4 Graphene-based cholesterol biosensor

High cholesterol level in arteries leads to well-defined health problems such as coronary heart diseases, cerebral thrombosis and atherosclerosis [149]. Therefore, the quantitative determination of cholesterol levels in the arteries is clinically important. Cao et al. [150] explored an electrochemical biosensor for detection of cholesterol by using platinum-palladium–CS–GN hybrid (PtPd–CS–GN) nanocomposites functionalized GCE with enhanced sensitivity. The PtPd–CS–GN nanocomposite not only facilitated direct electron transfer from the redox enzyme to the surface of the electrode but also improved the immobilized amount of cholesterol oxidase (ChOx). Li et al. [151] developed a novel cholesterol biosensor by immobilizing ChOx on GCE functionalized by CS–GN nanocomposites. The results of TEM and Fourier transform infrared spectroscopy (FTIR) showed that the GO was successfully prepared and deoxygenated.

7.5 Graphene in bio-FETs

FET-based biosensors rely on biorecognition events between the probe and target biomolecules at the gate of the FET [152–153]. In these devices, upon target–receptor interaction, the electric charge distribution changes the charge carrier density at the biorecognition layer and modulates the channel conductance making them especially appropriate for sensing charged molecules like DNA [154]. A FET immunosensor for the detection of immunoglobulin G (IgG) was implemented using thermally-reduced graphene oxide (TRGO) sheets decorated with AuNPs-antibody conjugates using a simple method that combines electrospray through electrostatic force directed assembly [155]. This novel biosensor allowed the specific detection of the target protein with a limit of detection (LOD) of 2 ng·mL^{-1}. The same authors have recently developed other sensitive and selective FET immunosensors using vertically-oriented graphene (VG) sheets directly grown on the sensor electrode using a PECVD method and labeled with AuNPs-antibody conjugates (Fig. 12) [156].

7.6 Graphene impedimetric biosensors

Electrochemical impedance spectroscopy (EIS) is a highly sensitive technique suitable for integration with graphene platforms. Recent advances in graphene-based platforms for impedimetric genosensors and immunosensors were

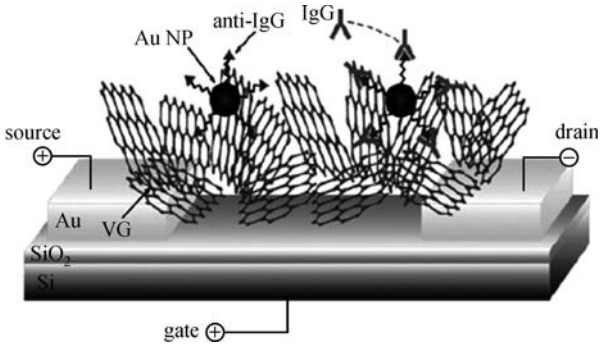

Fig. 12 Schematic of the VG-based FET immunosensor. Reproduced from Ref. [156].

reviewed by Bonanni et al. [157]. They also provided an overview on EIS and the preparation of graphene by different methods. These graphene-based impedimetric platforms have been developed mainly for detection of DNA hybridization events. Bonanni et al. [158] combined the advantages of using graphene-based platforms and the EIS technique with the high selectivity of hairpin DNA probes to develop impedimetric genosensors for the rapid detection of single nucleotide polymorphism (SNP) correlated to the development of Alzheimer's disease (Fig. 13) [158].

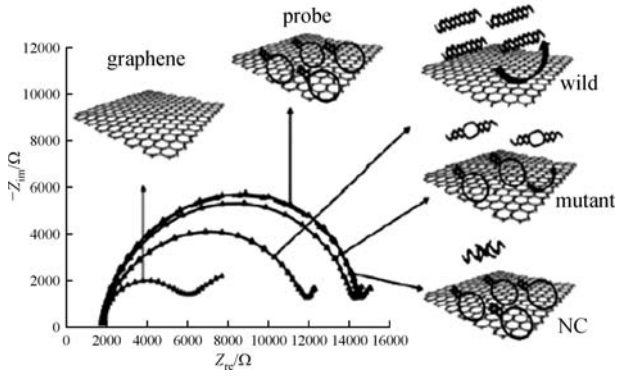

Fig. 13 Schematic of the protocol and Nyquist plots of the graphene surface implemented in the presence of the probe, complementary target, 1-mismatched sequence and a non-complementary sequence. Reproduced from Ref. [158].

7.7 Detection of toxic gases in air

The detection of gas molecules is required in many fields especially environmental monitoring due to their toxicity and risk. Wang et al. [159] used partially RGO thin films prepared by thermal treatment (at 500°C in a vacuum) as an active sensing element to develop a hydrogen gas sensor. The sensor exhibited good sensitivity (~4.5%), fast response and recovery times (~20 and 10 s), respectively to 160 ppm of hydrogen gas at room temperature. Mao et al. [160] came up with a new gas sensor in which RGO surface is covered with tin oxide nanocrystals (RGO–SnO_2 NCs) showing enhanced NO_2 but weakened NH_3 sensing compared with bare RGO (Fig. 14) [160].

7.8 Detection of heavy metal ions

Rapid and accurate captivity of metal-based contaminants has utmost importance as these hazardous materials pose risk for human health and environment. Sudibya and co-workers [161] introduced a nanoscale FET sensor using micropatterned, protein-functionalized RGO films as the conducting or sensing channel. These RGO-FETs were able to detect various metal ions (Ca^{2+}, Mg^{2+}, Hg^{2+}, and Cd^{2+}) in real-time with high sensitivity via the change of conductance caused by these metal ions addition. A more sensitive voltammetric method for detecting Hg^{2+} was presented by Zhou et al. [162] based on rational covalent functionalization of GO with cysteamine through a nucleophilic ring-opening reaction between the epoxy of GO and the amino group of cysteamine in KOH solution (Fig. 15) [161].

This sensor provided a LOD of 3×10^{-9} mol·L^{-1} and demonstrated excellent selectivity towards Hg^{2+} in the presence of a 200 fold higher concentration of Fe^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+} and Mn^{2+}.

7.9 Detection of organic pollutants

The phenolic compounds, among the organic pollutants, are widely used as raw materials for pesticides, dyes and cosmetics in chemical and pharmaceutical industries and the maximum level permitted are defined strictly by the wastewater discharge standard. For the detection of phenolic compounds, Li et al. [163] constructed an electrochemical sensor using TRGO as an electrocatalyst for simultaneous detection of dihydroxybenzene isomers, including resorcinol (RC), hydroquinone (HQ) and catechol (CC). Regarding pesticides detection, the efforts are focused mainly on organophosphate pesticides. Wang et al. [164] self-assembled acetyl cholinesterase (AChE) on nanohybrids of AuNPs/CRGO using as linker poly-(diallyldimethylammonium chloride) (PDDA) which apart from improving the dispersion of AuNPs stabilized also the enzyme with high activity and loading efficiency. The resulting biocomposites were utilized for the ultrasensitive detection of paraoxon (LOD of 1.0×10^{-13} mol·L^{-1}). Zhang and co-workers prepared another AChE

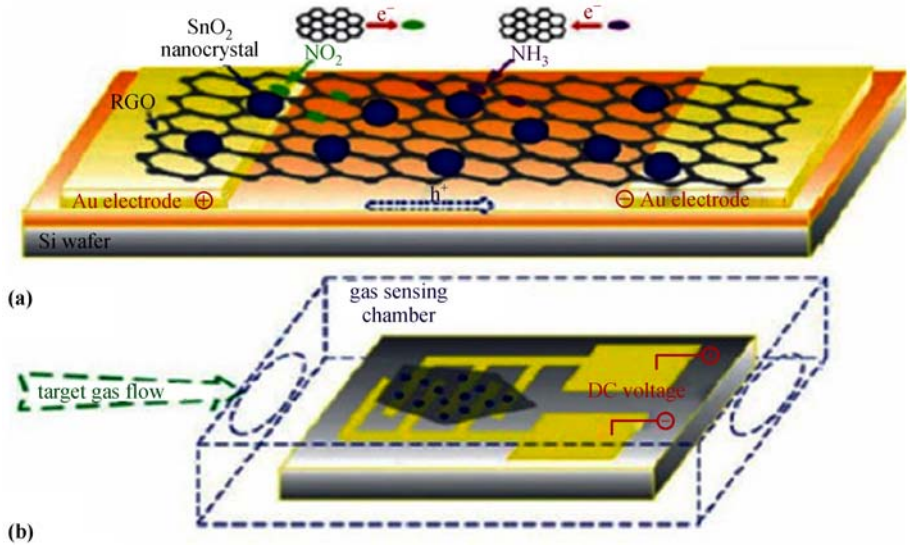

Fig. 14 Schematic of **(a)** the novel gas-sensing platform of an RGO sheet decorated with SnO_2 NCs and **(b)** of the sensor testing system. Reproduced from Ref. [160].

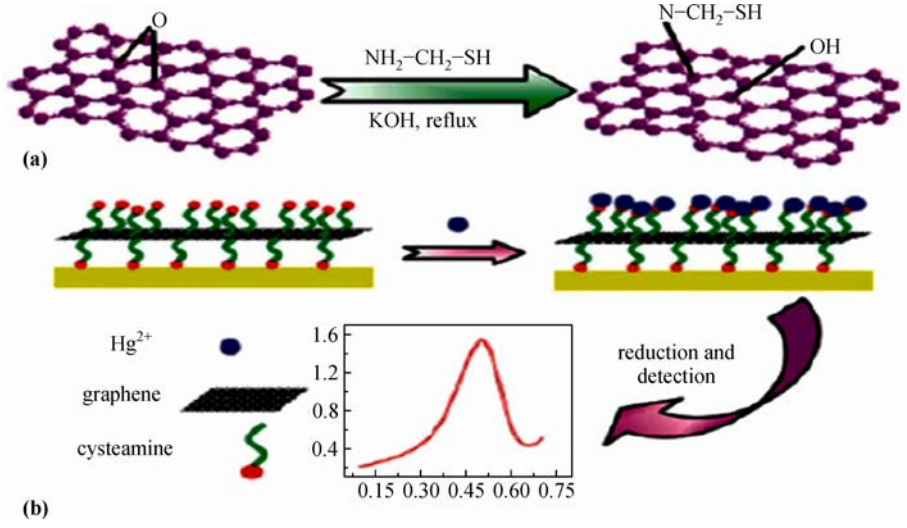

Fig. 15 Schematic illustration of **(a)** protocols employed for functionalization of GO with cysteamine and **(b)** for Hg^{2+} determination. Reproduced from Ref. [161].

biosensor synthesizing a reduced graphene oxide/Prussian blue nanocubes (rGO/PBNCs) nanocomposite (Fig. 16) [165]. The resulting rGO/PBNCs-based AChE biosensor demonstrated a high electrocatalytic activity towards the oxidation of acetylthiocholine and rapid response and high sensitivity for detection of monocrotophos with a LOD of 0.1 $ng \cdot mL^{-1}$.

8 Summary

In this review an attempt is made to address the sustained development and challenges with a wide scope of interest, highlighting a fundamental understanding of the synthesis, characterization, reduction of graphene and its potential applications in various applications. Graphene exhibits exceptional electrical, optoelectric, mechanical and thermal properties and thus, has excellent potential to the scientific community for its widespread applications in emerging research areas of interest like transparent electrode, FET, biosensors and energy applications. Simple and cost effective methods have evolved recently enabling the use of graphene and graphene-based materials in the applications that require a large amount of graphene. Readily available functional groups set up to bind with various

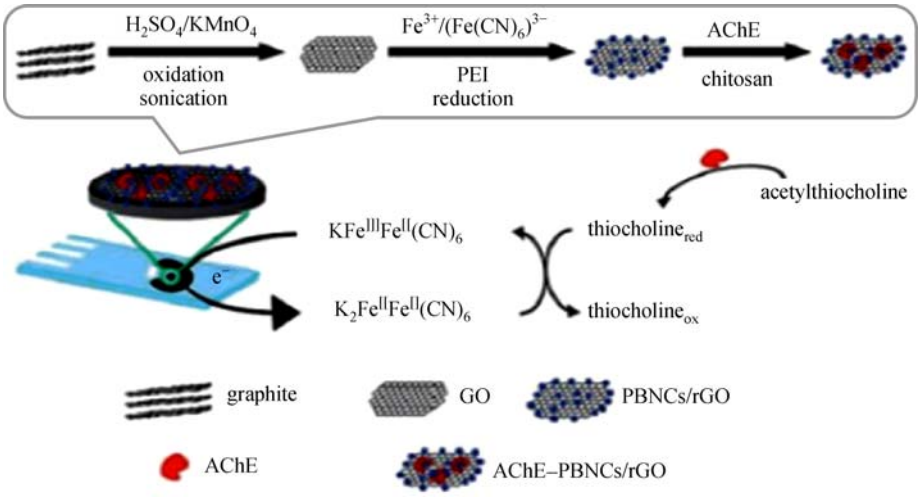

Fig. 16 Schematic showing preparation of PBNCs/rGO nanocomposite-based AChE biosensor and the electrocatalytic mechanism for acetylthiocholine oxidation. Reproduced from Ref. [165].

other nanostructures, drugs and biological molecules like DNA, peptide, proteins, lipids etc. make GO as one of the most suitable candidate for energy storage, electrochemical devices, biosensors, catalysis, imaging/mapping of the cancer cells, photo-thermal therapy, targeted drug delivery, contamination purification and extraction devices for chemical, biological, and environmental samples. Graphene research and its applications are expected to expand rapidly in the coming decade with a strong potential to make a positive impact on our lives.

Conflict of interest The authors declare that they have no conflict of interest.

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