Chapter

Nanocomposite-Based Graphene for Nanosensor Applications

Rumei Cheng and Shengju Ou

Abstract

Nanocomposites based on carbon nanomaterial particularly in graphene oxide, graphene quantum dots, and doped graphene quantum dots with improved biocompatibility have been increasing interests in the field of drug delivery, biosensor, energy, imaging and electronic. These nanomaterials as new kinds of fluorescent probes and electrochemical sensors all display ultrasmall size, good photostability, and excellent biocompatibility. In this chapter, we summarize an updated advance in the development of graphene and its related derivatives of synthesis methods and biomedical applications as nanosensors for detection of metal ions, inorganic ions, amino acids, proteins, saccharides and small molecules, drug molecules, and so on.

Keywords: nanocomposite, graphene oxide, graphene quantum dots, sensor, detection, application

1. Introduction

Graphene, as an atom-thick sp^2-hybridized carbon nanosheet, has been extensively studied since it was first separated and characterized by Andre Geim and Konstantin Novoselov in 2004 [1]. The graphene presents a unique property including large specific surface area, easy functionalization, unique optical properties, chemical stability, high electronic conductivity, and photonic and mechanical properties and provides a promising platform for the design and construction of useful nanomaterials. Recently, the field involving graphene nanomaterials is a rapidly developing area due to their potential applications in biomedical and clinical medicine field. One of the most valuable virtues of graphene is their applications in sensors, particularly in fluorescence sensors and electrochemical sensors [2].

Mainly graphene-based nanomaterials are graphene oxide (GO, 2-D), graphene quantum dots (GQDs, 0-D), and heteroatom (N, P, S atom)-doped graphene quantum dots (doped GQDs, 0-D). The structures of different materials are shown in **Figure 1**. GO is a layered stack of nanosheets, while GQDs are regarded as GO nanosheets cutting into nanodots in oxidation process showing excellent performance of graphene. Recently, the GQDs have greatly attracted attention of scientific workers due to the good biocompatibility, excellent water solubility, and stable photoluminescence (PL) and chemical inertness [3, 4]. The GQDs contain carboxyl group, hydroxyl group, and epoxy groups at the edge and show similar structure to graphene and can be easily functionalized by various biological and non-biological species. Meantime, heteroatom-doped GQDs showed enhanced chemical activity, higher fluorescence quantum yields, and effectively modulated performance of bandgap.

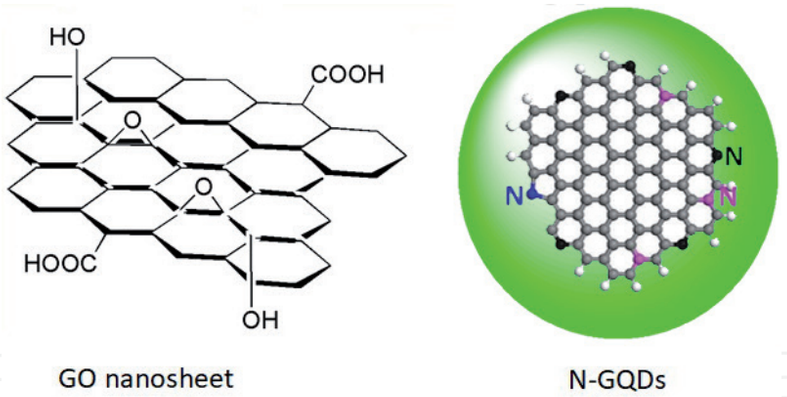

Figure 1.
Structure of graphene oxide (GO) and nitrogen-doped graphene quantum dots (N-GQDs).

In this chapter, efforts have been made on summarizing the design, synthesis, and applications of nanocomposite-based graphene. We mainly focused on the recent development of graphene-based nanocomposites as fluorescence sensors and electrochemical sensors for the detection of biological species and non-biological species in human serum, respectively.

2. Applications of nanocomposite-based graphene as nanosensors

2.1 Nanocomposite-based graphene oxide as fluorescence sensors

2.1.1 Detection of amino acids

People are very interested in the detection of amino acids due to their multiple biological functions. Cheng and co-workers designed and synthesized a turn-on fluorescent nanosensor based on the alizarin red aluminum (III) complex covalently binding to graphene oxide (GO) for the detection of lysine with high sensitivity and high selectivity [5]. The nanosensor was prepared by GO, Al(III) ions, and alizarin red (GO-Al-AR) by coordination mode. The as-prepared GO-Al-AR nanosensor was depicted in **Figure 2**. It showed weak fluorescence due to photo-induced electron transfer (PET). However, the fluorescence intensity of GO-Al-AR obviously enhanced upon addition of lysine. The fluorescence response of GO-Al-AR nanosensor exhibited good linear relationship with the concentrations of lysine within 25 mg/L to 250 mg/L. The detection limit was 2.0 mg/L. The premium pH value was between 6.5 and 7.2, suggesting the as-synthesized sensor is suitable for detection of lysine in living cells.

Another novel fluorescence sensing method was developed for the detection of tyramine based on CdSe/ZnS quantum dots-GO using imprinting technique [6]. The fluorescent sensor was synthesized by using CdSe/ZnS quantum dots, GO, 3-mercaptopropyltriethoxysilane (MPTES) (monomer), and tetraethyl orthosilicate (TEOS) (cross-linking agent) and targeted molecule tyramine for synthesizing molecularly imprinted polymers (MIPs), namely, Gra-QDs@MIPs. The as-synthesized sensor showed a high selectivity for the detection of tyramine. The fluorescence intensity of Gra-QDs@MIPs showed a good linear relationship with concentrations of tyramine between 0.07 and 12 mg/L. The Gra-QDs@MIPs can be used to detect tyramine in rice wine samples. A biosensor was constructed and reported based on reduced GO field-effect transistor (rGO-FET) modified by the cascading enzymes arginase and urease for the monitoring of L-arginine [7]. The rGO-FET was employed to immobilize arginase and urease through electrostatic

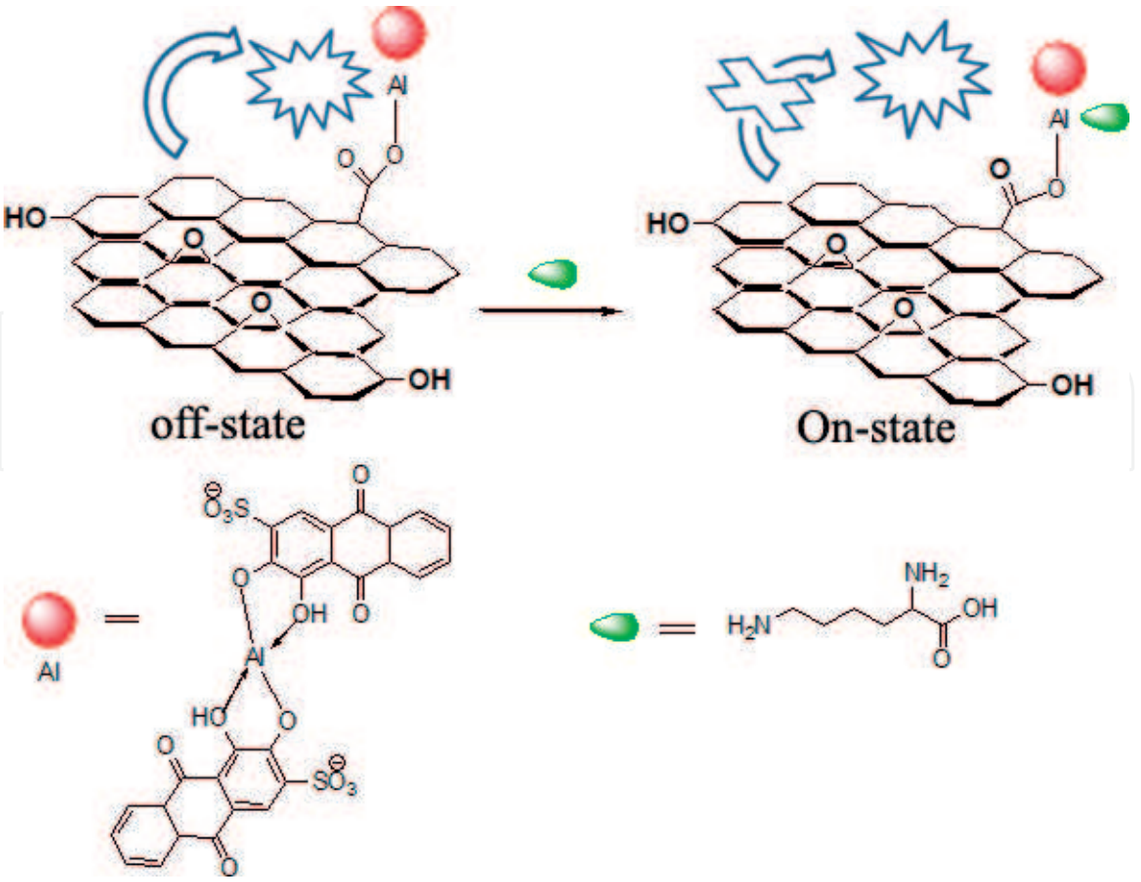

Figure 2.
A schematic illustration of a turn-off/turn-on fluorescence response of GO-Al-AR to lysine.

interaction based on cationic polyethylenimine (PEI) building block. The functionalized transistors showed high sensitivity and high selectivity for the detection of L-arginine within 10–1000 μM. The detection limit was 10 μM. The sensor showed fast response and good stability.

2.1.2 Detection of drug molecules

Bao and co-workers designed RhBPy-graphene oxide (GO) complex as a fluorescent probe for the sensitive and selective detection of doxorubicin (DOX) in MeOH/H_2O solution [8]. The fluorescence of RhBPy[2] rotaxane can be efficiently quenched by addition of graphene oxide (GO) due to fluorescence resonance energy transfer (FRET), while the fluorescence of RhBPy[2] rotaxane can be recovered due to different interaction forces between DOX and RhBPy[2] rotaxane toward GO. Li et al. developed a fluorescent probe for the monitoring and detection of antibiotic virginiamycin based on GO-supported carbon quantum dots (GO/C-dots) as the signal element and molecularly imprinted polymer (MIP) as the recognition template [9]. MIP with virginiamycin as the template molecule was constructed and designed using o-aminophenol as monomer on the surface of ITO electrode deposited by GO/C-dots. The specific sensor can be obtained by removing the virginiamycin from the MIP. The GO/C-dot complex displayed strong fluorescence signal, while its fluorescence intensity declined obviously upon adsorption of virginiamycin. The specific probe showed high selectivity and high sensitivity toward virginiamycin, and detection limit is 1.56×10^{-11} mol/L.

The novel doxorubicin (DOX) functionalized GO nanosensor was designed and synthesized for the detection of dopamine based on mechanism of fluorescence resonance energy transfer (FRET) [10]. The DOX showed strong property, but the

fluorescence was quenched upon addition of GO (**Figure 3**). The GO-DOX complex as sensing platform showed a high selectivity toward dopamine based on different adsorption interactions between dopamine and DOX and GO. The fluorescence intensity of DOX-GO complex was partly recovered upon addition of dopamine based on competitive adsorption of DOX and dopamine on the surface of GO. The fluorescence response of DOX-GO exhibited a linear relationship with concentrations of dopamine between 8.3×10^{-7} M and 3.3×10^{-5} M in aqueous solution and 1.44 and 11.48 μmol/L in human serum, respectively. The DOX-GO can be an efficient nanosensor for sensing dopamine in human serum and living cells.

2.1.3 Detection of the other small molecules

The hexylenediamine-functionalized high fluorescent GO was constructed and prepared for the detection of hypochlorous acid (HOCl) in aqueous solution [11]. The fluorescence of functionalized GO was quenched upon addition of HOCl based on the mechanism of intramolecular charge transfer (ICT) between GO and chloramines forming by the oxidation of amino groups of functionalized GO using HOCl. The functionalized GO showed high selectivity and sensitivity for the determination of HOCl. The detection limit was 3.5 μM. The obtained sensor can be used to detect HOCl in tap water. The water-soluble and good biocompatible nanocomposite sensor was designed and prepared based on GO, Cu^{2+}, and histidine-functionalized perylenediimide (PDI-HIS) for the determination of pyrophosphate (PPi) in biological conditions [12]. The as-synthesized sensor can be used as an efficient sensing platform in physiological conditions by fluorescence turn-on switch. The obtained sensor PDI-HIS-Cu-GO (PCG) displayed high selectivity and high sensitivity for the PPi detection with affinity constant 1.0×10^{6} M^{-1}. The detection limit was 0.6×10^{-7} M. Compared to the PDI-HIS+Cu^{2+} complex, the PDI-HIS-Cu-GO nanocomposites showed higher selectivity for PPi in intracellular detection.

Cheng et al. designed a dual-output nanosensor based on GO for the detection of Ag^{+} in aqueous solution with high sensitivity and high selectivity [13]. The nanosensor (**Figure 4**) was prepared by conjugation of GO with well-known fluorophore 1,8-diaminonaphthalene (DAN). The addition of Ag^{+} ions significantly

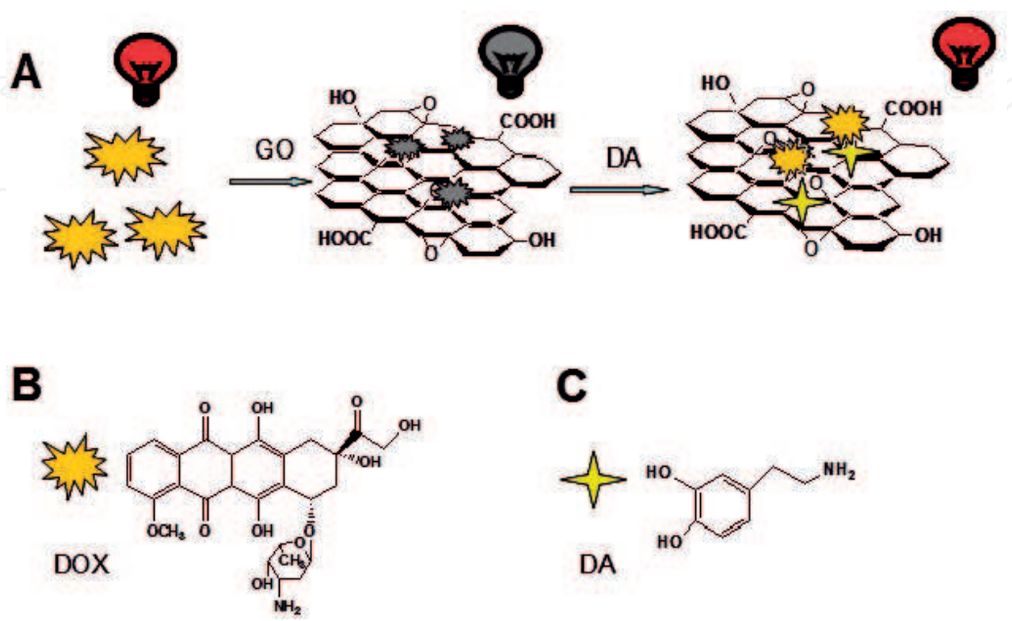

Figure 3.
A schematic illustration of the fluorescence response of a DOX-GO complex to dopamine (a); Molecular structures of DOX (b) and dopamine (c).

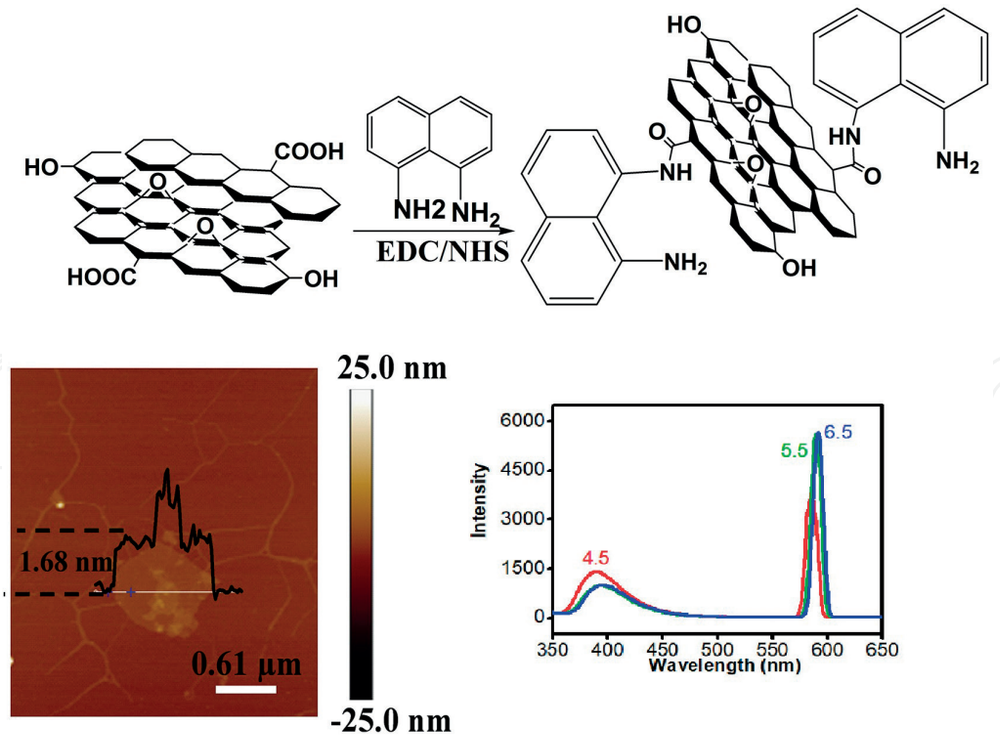

Figure 4.
Synthetic pathway and AFM images of GAP and its fluorescence response to fivefold Ag^+ in aqueous solutions with various pHs.

quenched the fluorescence of resultant sensor based on the mechanism of PET, while the intensity of second-order scattering obviously enhanced. Furthermore, the intensity of as-prepared sensor showed a good linear relationship with the concentrations of Ag^+ ranging from 6 to 12 mg/L. The fluorescent sensor showed no or weakly response to Na(I), K(I), Ca(II), Mg(II), Cr(III), Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), and Fe(III).

2.2 Nanocomposite-based graphene oxide as electrochemical sensors

2.2.1 Detection of proteins

Gevaerd et al. designed and synthesized imidazole-functionalized graphene oxide (GO-IMZ) as non-enzymatic electrochemical sensor for the detection of progesterone [14]. Progesterone (P4) plays an important role in the stabilization and maintenance of gestation as most important progestogen of mammals. The GO-IMZ complex as an artificial enzymatic active site was reported using voltammetric determination of progesterone. The as-synthesized sensor displayed a synergistic effect of GO nanosheets and imidazole showing the obvious enhancement on the electrochemical response of P4. The electrochemical response signal showed a linear relationship with concentrations of P4 between 0.22 and 14.0 μmol/L. The detection limit was 68 nmol/L. The limit of quantification was 210 nmol/L. The higher sensitivity was presented compared to the unmodified electrode.

Tomita and co-workers designed and reported the construction of high accessible and high tunable multi-fluorescent sensing system, and this sensing system presented protein fluorescent signals from a single microplate well [15]. The principal mechanism of approach was based on three single-stranded DNAs (ssDNAs) functionalized-nano-graphene oxide (nGO). The single-stranded DNAs showed different sequences and functions, and fluorophores exhibited different optical

properties. The fluorescence of three fluorophore-modified ssDNAs was quenched upon conjugation with nGO. The partial recovery of fluorescence intensity of individual ssDNAs was observed upon addition of analyte proteins.

2.2.2 Detection of drug molecules

Abdallah and Ibrahim designed and developed an imprinted potentiometric sensor for the detection of gabapentin that is an anticonvulsant agent [16]. The sensor was constructed using carbon paste electrode following three steps: (i) the GO was decorated by silver nanoparticles; (ii) silver nanoparticles modified with GO mixed physically with molecularly imprinted polymers nanoparticles with gabapentin as a template molecule and then leached the template molecule; and (iii) the abovementioned mixture deposited on carbon paste electrode. The sensor showed good selectivity and high sensitivity, and the detection limit is 4.8×10^{-11} mol/L. Yang and co-workers designed and prepared CdTe quantum dot (QD)-decorated poly(diallyldimethylammonium chloride) (PDDA)-functionalized graphene (CdTe-PDDA-Gr) nanocomposite based on the presence of PDDA and CdTe QDs using chemical reduction of exfoliated graphite oxides [17]. The CdTe-PDDA-Gr nanocomposite showed very fast electron transfer behavior and obvious absorption effect for puerarin due to high surface area and good conductivity. They exhibited very good electrocatalytic behavior toward the oxidation of puerarin. The oxidation peak current showed a good linear relationship with the concentrations of puerarin within 0.001–1.0 μM by differential pulse voltammetry (DPV). The limitation of detection was 0.6 nM (SNR of 3).

The nickel tetra-amined phthalocyanine-graphene oxide covalent compound was developed as a photoelectrochemical sensor for the detection of erythromycin with high sensitivity [18]. The graphene oxide was modified by tetra-amined phthalocyanine (NiTAPc) by covalent bonding getting the final product NiTAPc-Gr. The as-synthesized sensor exhibited a higher photoelectrochemical efficiency and showed a peak wavelength of 456 nm by irritation of visible light. Compared to that of GO/ITO, the photocurrent of NiTAPc-Gr/ITO was 50-fold at the same conditions. The photocurrent showed a good linear relationship with the concentrations of erythromycin between 0.40 and 120.00 μmol/L. The detection limit was 0.08 μmol/L. The constructed photoelectrochemical sensors have been successfully applied to detect erythromycin in human blood plasma.

2.2.3 Detection of the other small molecules

A bimetallic electrochemical sensor was designed and constructed for the sensitive detection of uric acid (UA) with high selectivity [19] as shown in **Figure 5**. The bimetallic nanoparticles (NPs) were synthesized by electrodeposition on the glassy carbon electrode (GCE) using the $HAuCl_4$ and $AgNO_3$ as precursors by co-reduction through cyclic voltammetry scanning. Firstly, the GO-TH complex was formed by electrostatic interactions between GO and thionine (TH); then, the GO-TH complex was drop-coated on Au-Ag NPs to construct Au-Ag NPs/GO/TH@GCE. The redox current peak intensity showed regular increase with the increase of concentration of UA. The good linear relationship was exhibited between I_{UA}/I_{TH} and [UA] within 1–100 μM with linearly plotted (R^2 = 0.9929). The detection limit was 0 .3 μM.

A non-enzymatic sialic acid (SA) electrochemical sensor was designed and constructed based on indicator displacement assay (IDA) of dopamine with high sensitivity and high selectivity [20]. The mechanism of SA detection was based on reversible covalence with boronic acid-diol complex. In other words, the SA and DA all can covalently interact with 2-fluorophenylboronic acid (FPBA) by replacing of 1,2-diols. The electrode was constructed and synthesized based on

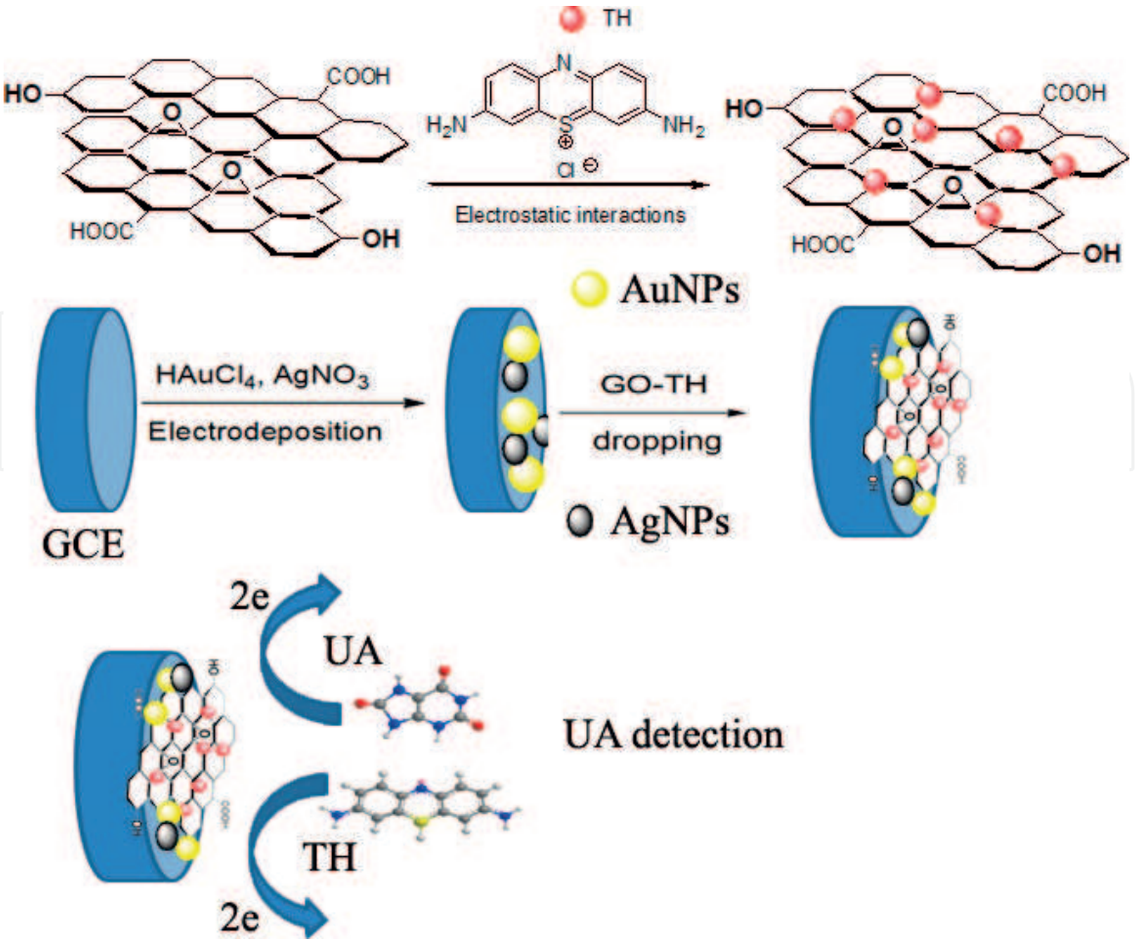

Figure 5.
Illustration of the preparation and applications of the Au-Ag NPs/GO/TH@GCE sensing platform.

tetra(4-carboxyphenyl) porphine-graphene oxide (TCPP-GO), DA, and FPBA on the surface of glassy carbon electrode (GCE), respectively. The TCPP-GO complex obviously enhanced the sensitivity of the electrochemical sensor. The recovered anodic current intensity of DA showed a good linear relationship with the concentration of SA within 0.1–7.5 mM. The detection limit was 28.5 μM. The sensor has been successfully applied to detect SA in human blood and urine samples.

The gold/silver/gold/chitosan-graphene oxide (Au/Ag/Au/CS-GO) sensor was designed and constructed for the detection of Pb^{2+} and Hg^{2+} ions with high sensitivity [21]. The higher affinity constant of Pb^{2+} binding with the CS-GO showed higher affinity than that of Hg^{2+} binding with the CS-GO. The maximum S/N was 1.53. The Au/Ag/Au/CS-GO surface plasmon resonance (SPR) sensor displayed good repeatability toward Pb^{2+} ions due to the coordination interaction. The adsorption behaviors of Pb^{2+} and Hg^{2+} ions onto the surface of CS-GO sensor fit to the Langmuir isotherm model. The affinity constant of $Pb^{2+}$and Hg^{2+} to bind Au/Ag/Au/CS-GO sensor was $7 \times 10^5\ M^{-1}$ and $4 \times 10^5\ M^{-1}$, respectively. Priya et al. resigned and prepared a voltammetric sensor based on graphene oxide/κ-carrageenan/L-cysteine nanocomposite (GO/κ-Car/L-Cys) for the detection of Cd^{2+} and Pb^{2+} ions [22]. The GO/κ-Car/L-Cys composite modified with glassy carbon electrode (GCE) was successfully synthesized. The electrochemical response of GO/κ-Car/L-Cys composite showed a good linear relationship with the concentrations of Cd^{2+} and Pb^{2+} ions within 5–50 nM, and the detection limit was 0.58 and 1.08 nM for Cd^{2+} and Pb^{2+} ions, respectively. The sensitivity for Cd^{2+} and Pb^{2+} ions was 1.39 μA/nM and 1.32 μA/nM, respectively. The interference experiment results showed no affect even on the presence of other species.

2.3 Nanocomposite-based graphene quantum dots (GQDs) as fluorescence sensors

2.3.1 Detection of amino acids

The fluorescent graphene quantum dots-gold nanoparticles as nanosensor showed a high selectivity and high sensitivity for the detection of cysteine [23]. The AuNPs@r-GQDs nanocomposite was prepared by the following processes. First, nitrogen-doped graphene quantum dots (N-GQDs) were reduced to r-GQDs by $NaBH_4$ as reductant and subsequently the r-GQDs converted $HAuCl_4$ to Au nanoparticles (AuNPs) by reduction reaction and coated onto AuNPs forming core-shell-structured AuNPs@r-GQDs. The AuNPs@r-GQDs showed good dispersion behavior with an intensive surface plasma band at 525 nm. The AuNPs@r-GQDs exhibited aggregation behavior and led to their color change by using cysteine as cross-linking agent through adsorption of Ag ions onto their surface. The detection limit was 5.6 nM. Furthermore, the AuNPs@r-GQDs showed higher selectivity for cysteine than that of glutathione (GSH) even at the interfere condition of 1000-fold concentrations of GSH.

The GQD-MnO_2 complex as a convenient fluorescence nanosensor has been constructed and prepared for the detection of glutathione (GSH) with high selectivity and high sensitivity [24]. The fluorescence intensity of GQDs was quenched upon addition of MnO_2 nanosheet based on the mechanism of fluorescence resonance energy transfer (FRET). The fluorescent signal recovered upon GSH reducing MnO_2 nanosheets into Mn^{2+} ions and releasing GQDs. The GQD-MnO_2 complex as nanoprobe showed a sensitive response to GSH between 0.5 and 10 μmol/L. The fluorescence intensity showed a good linear relationship with the concentrations of GSH. The detection limit was 150 nmol/L. The GQD-MnO_2 complex exhibited higher selectivity for the GSH than that of other metal ions and biomolecules and successfully applied to detect GSH in living cells.

2.3.2 Detection of drug molecules

Zhou et al. designed and developed a convenient fluorescent sensor based on the molecularly imprinted polymers (MIPs)-functionalized GQDs for the detection of tetracycline (TC) with high sensitivity and high selectivity [25]. The GQDs were prepared by one-pot method, and the amino-functionalized GQDs and carboxyl-functionalized GQDs were fabricated, respectively. The GQD-MIPs were synthesized by sol-gel method. The GQD-MIPs exhibited strong fluorescence property, and the fluorescence was quenched upon addition of TC. The fluorescence quench efficiency showed a linear relationship with concentrations of TC between 1.0 and 10^4 μg/L. The detection limit was 1 μg/L.

2.3.3 Detection of inorganic ions

The sulfanilic acid and glutathione-functionalized GQDs was constructed and synthesized as fluorescent sensor for the detection of sulfide anions and ascorbic acid [26]. The sulfanilic acid and glutathione-functionalized GQDs were prepared through amide linkage using 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC) as catalyst, namely, SSGQDs. The SSGQDs showed strong fluorescence property. The fluorescence of SSGQDs was quenched upon addition of Cu^{2+} ions, forming SSGQD-Cu(II) complex. The S^{2-} ions showed high coordination interaction with Cu^{2+} ions from SSGQD-Cu(II) complex and induced the fluorescence recovery of SSGQDs. The ascorbic acid (AA) as a reduction can reduce Cu^{2+} into Cu^{+} and induced the disaggregation of the SSGQDs, and fluorescence of

SSGQDs was recovered again. The GQDs as a green sensor were synthesized for the detection of free chlorine with high selectivity and high sensitivity [27]. The GQDs showed strong fluorescence property, and fluorescence of GQDs was quenched upon addition of chlorine-based fluorescence resonance energy transfer. The fluorescence quenching efficiency exhibited a good linear relationship with concentrations of chlorine with a wide range from 0.05 to 10 μM. The sensing system has been applied to detect chlorine in drinking water.

The europium-functionalized GQDs (Eu-GQDs) were synthesized by treatment of Eu-decorated graphene (3D Eu-graphene) through a strong acid oxidation [28]. The amount of Eu was 2.54%. The Eu-GQDs complex showed higher electron density and surface chemical activities compared to that of GQDs. The as-synthesized Eu-GQDs exhibited a sensitive response for the detection of Cu^{2+} and L-cysteine with high selectivity and high sensitivity. The fluorescence of Eu-GQDs was quenched upon addition of Cu^{2+} due to the coordination interaction between Cu^{2+} and carboxyl groups of Eu-GQDs. The fluorescence of Eu-GQDs was recovered in the presence of L-cysteine due to strong affinity of Cu^{2+} and S of L-cysteine. The good linear relationship was shown within the range of 0.1–10 μM for Cu^{2+} and 0.5–50 μM for L-cysteine, respectively. The detection limit was 0.056 μM for Cu^{2+} and 0.31 μM for L-cysteine, respectively. The proposed nanosensor can be used to detect Cu^{2+} and L-cysteine in serum samples.

A fluorescence sensor based on gold nanoparticles-functionalized GQDs has been designed and synthesized for the detection of Pb^{2+} with high sensitivity and high selectivity [29]. The GQDs showed strong fluorescence property. The fluorescence of GQDs was quenched in the presence of Au nanoparticles due to the aggregation of GQDs. The fluorescence of GQDs was recovered upon addition of Pb^{2+} ions inducing de-aggregation of gold nanoparticles-GQD complex. The fluorescence intensity exhibited a good linear relationship with the concentrations of Pb^{2+} ions within 50 nM–4 μM. The detection limit was 16.7 nM. The dopamine-functionalized GQDs (DA-GQDs) was constructed and prepared for the detection of Fe^{3+} ions with high sensitivity and high selectivity [30]. The DA-GQDs showed bright blue fluorescence, and the fluorescence of DA-GQDs was quenched in the presence of Fe^{3+} ions. The fluorescence quenching efficiency exhibited a good linear relationship with the concentrations of Fe^{3+} ions between 20 nM and 2 μM. The detection limit was 7.6 nM. The DA-GQD sensing probe displayed excellent selectivity for the detection of Fe^{3+} ions in the presence of other biomolecules. The reaction mechanism of Fe^{3+} was based on coordination interaction and oxidation of dopamine. The as-synthesized nanosensor as sensing platform can be widely used for environmental monitoring and biomedical applications.

The folic acid-functionalized GQDs (FA-GQDs) were designed and synthesized by thermal pyrolysis of maleic acid (MA) and folic acid (FA) [31]. The FA-GQDs showed obvious fluorescence behavior, and fluorescence property depends on the different ratio of FA/MA used in thermal pyrolysis. The FA-GQDs as a turn-on fluorescent sensor showed a high sensitivity for the detection of folate receptor-positive cancer cells. The resulting FA-GQDs also exhibited a fluorescence response to Hg^{2+} ions. The fluorescence quenching efficiency showed a good linear relationship to the concentrations of Hg^{2+} ions within 2.0×10^{-6} to 5.0×10^{-12} M. The detection limit was 1.7×10^{-12} M (S/N = 3). The FA-GQD nanosensor displayed excellent selectivity for the detection of Hg^{2+} ions in the presence of other metals and biomolecules.

2.3.4 Detection of proteins

The fluorescence sensor lecithin/β-CD@NR@ GQD complex was constructed and synthesized by covalence Nile red (NR) onto GQDs using

lecithin/β-cyclodextrin (lecithin/β-CD) complex as linker [32]. The GQDs connect with NR through lecithin/β-CD complex based on electrostatic interaction and hydrophobic interaction. The fluorescence of GQDs was quenched upon addition of lecithin/β-CD@NR based on Förster resonance energy transfer. Meantime, the fluorescence intensity of NR obviously enhanced. The lecithin/β-CD@NR@ GQD complex as nanosensor exhibited high sensitivity for the detection of acid phosphatase (ACP). The detection limit was 28 μU/mL. The proposed sensor has been successfully applied to monitor ACP in PC-3 M cells.

The graphene oxide quantum dots@silver (GQDs@Ag) nanocrystals with core-shell structure was designed and prepared as fluorescence sensing platform for the detection of prostate-specific antigen (PSA) [33]. The quantities of GQDs on GQDs@Ag decided the intensities of fluorescence signal. The incorporated GQDs can be released by removing of silver shell based on oxidative reaction without affecting their fluorescence performance. The anti-PSA antibody (Ab_1) and antibody (Ab_2) was immobilized onto magnetic beads (MBs) and GQDs@Ag, respectively. The GQDs@Ag showed a high sensitivity and high selectivity for the detection of PSA. The fluorescence intensity exhibited an excellent linear relationship with concentrations of PSA within 1 pg/mL to 20 ng/mL. The detection limit was 0.3 pg/mL. The as-synthesized immunosensor has been successfully applied to detect PSA in human serum. The antibody anti-cardiac troponin I (anti-cTnI) modified with amine-functionalized GQDs (afGQDs) was constructed and prepared by carbodiimide coupling reaction, namely, anti-cTnI/afGQDs [34]. The complex anti-cTnI/afGQDs exhibited sensitive response for detection of target antigen (cTnI) with high sensitivity and high selectivity. The as-synthesized complex as nanosensor showed strong fluorescence behavior, and the fluorescence of anti-cTnI/afGQDs was quenched in the presence of graphene (Gr). The fluorescence of anti-cTnI/afGQDs was recovered upon the addition of target antigen (cTnI) on anti-cTnI/afGQDs/Gr-inducing Gr apart from GQDs. The fluorescence intensity showed a good linear relationship with the concentrations of cTnI between 1.0 pg/mL and 1.0 ng/mL. The detection limit was 0.192 pg/mL.

2.4 Nanocomposites based on graphene quantum dots (GQDs) as electrochemical sensors

The functionalized glassy carbon electrode (GCE) based on composites of GQDs and β-cyclodextrins (β-CDs) was designed and synthesized as an electrochemical sensor for the detection of tyrosine (Tyr) enantiomers [35]. The as-synthesized β-CDs-GQDs/GCE exhibited an ultrasensitive response signal for the monitoring of Tyr enantiomers using GQDs as substrate and β-CDs as recognition molecule. The β-CDs-GQDs/GCE showed obvious difference in the oxidation peak current between L-Tyr and D-Tyr. The quantities of L-Tyr of healthy people showed higher than that of depression patients. The detection limit was 6.07×10^{-9} M and 1.03×10^{-7} M for L-Tyr and D-Tyr, respectively.

The gold nanoparticles/proline-functionalized GQDs (GNs/Pro-GQDs) were constructed and prepared as ultrasensitive electrochemical sensor for the monitoring of p-acetamidophenol [36]. The proline-GQDs were synthesized using pyrolysis of citric acid and proline. The GNs/Pro-GQDs were formed by directly reacting $HAuCl_4$ with proline-GQDs. The peak current (I_p) showed a good linear relationship with the concentration of p-acetamidophenol within 0.08–100 mM. The detection limit was 0.02 μM (S/N = 3).

The GQDs/riboflavin (RF) functionalized glassy carbon elec-trode (GC/GQDs/RF) was developed as a sensitive electrochemical sensor to detect persulfate ($S_2O_8^{2-}$) [37]. The modified electrode exhibited a stable redox peak between pH 1

and pH 10. The obtained GC/GQDs/RF showed a good electrochemical activity for the detection of $S_2O_8^{2-}$. The linear calibration range was from 1.0 μM to 1 mM. The detection limit and sensitivity were 0.2 μM and 4.7 nA/μM, respectively. One electrochemiluminescent (ECL) sensor was developed and synthesized to monitor Cr(VI) ions in water samples based on fluorescence signal changes of graphene quantum dots/peroxodisulfate (GQD/$S_2O_8^{2-}$) complex [38]. The fluorescence of GQD/$S_2O_8^{2-}$ complex was quenched in the presence of Cr(VI) ions based on mechanism of fluorescence resonance energy transfer (FRET). The linear response range was 50 nM–60 μM. The detection limit was 20 nM (S/N = 3). The obtained sensor has been successfully applied to detect Cr(VI) in river water.

The hybrid GQDs/TiO_2 NTs were constructed based on titanium dioxide nanotube arrays (TiO_2 NTs) infilled with GQDs as an efficient ECL sensor for detection of PSA [39]. The fabricated GQDs/TiO_2 NP composite electrode presented good stability and showed higher fluorescence intensity compared to that of pure TiO_2 NT electrode. The TiO_2 functionalized Fe_3O_4 magnetic nanoparticles (CdTe/MNPs) acted as quencher for the sensor. The GQDs/TiO_2 NT sensing platform showed high sensitivity and high selectivity for the detection of PSA. The ECL quenching efficiency exhibited a good linear relationship with log of the concentration of the PSA within 1.0 fg/mL to 10 pg/mL. The detection limit was 1 fg/mL (S/N = 3). The obtained nanosensor has been successfully applied to detect PSA in clinical human serum samples. The label-free ECL immunosensor was designed and synthesized based on GQDs [40]. The Au/Ag-rGO complex was prepared and employed to immobilize GQDs. The aminated-GQDs and carboxyl-GQDs were loaded onto electrode. The antibody of PSA was conjugated with modified electrode by absorbing Au/Ag to target proteins. The ECL quenching efficiency showed a linear relationship with log of concentrations between 1 pg/mL to 10 ng/mL. The detection limit was 0.29 pg/mL.

The chitosan-functionalized GQDs (GQD-CS) were constructed and employed to mobilize methylene blue (MB) using glass carbon electrode (GCE) based on aminohydroxy reaction [41]. The non-enzymatic sensor showed high sensitivity and high selectivity for the detection of H_2O_2. The obtained GQD-CS/MB/GCE displayed an obviously catalytic behavior toward H_2O_2 reduction. Compared with bare GCE, GQDs/GCE, and GQD-CS/GCE, the hybrid GQD-CS/MB/GCE showed higher electrochemical activities based on synergistic effect between GQD-CS and MB. The sensitivity was 10.115 μA/mM and detection limit was 0.7 μM.

The GQDs coated on hollow nickel nanospheres (hNiNS) modified with glass carbon electrode (GCE) were designed and synthesized as a molecularly imprinted electrochemical sensor (MIECS) for the monitoring of bisphenol S (BPS) with high sensitivity and high selectivity [42]. The pyrrole serves as monomer and BPS as template to polymerized molecularly imprinted polymer (MIP) film. The response signal showed linear relationship with the concentration of BPS between 0.1 and 50 μM. The detection limit was 0.03 μM. The ultrasensitive electrochemical sensor based on modified glass carbon electrode (GCE) was constructed and prepared for the determination of metronidazole (MNZ) [43]. The GQDs coated with molecularly imprinted polymers (MIPs) were synthesized. The complex of graphene nanoplatelets (GNPs) and MIPs exhibited obviously enhanced electrocatalytic property for MNZ based on good synergistic effect of GNPs and MIPs. The proposed electrochemical sensor displayed two linear ranges within 0.005–0.75 μmol/L and 0.75–10.0 μmol/L. The detection limit was 0.52 nmol/L. The electrochemical sensor has been applied to inspection of human serum samples. The GQD self-assembled monolayer-modified electrode was constructed as highly selective electrochemical sensor for the detection of dopamine (DA) [44]. The GQD-$NHCH_2CH_2NH_2$ functionalized GCE was prepared. The functionalized

electrode showed excellent electrical conductivity and displayed sensitive response to DA. The modified GCE showed a good linear relationship with the concentrations within 1–150 μM. The detection limit was 0.115 μM (S/N = 3). The obtained GQD-$NHCH_2CH_2NH_2$ functionalized GCE displayed good stability and excellent anti-interference capability.

2.5 Nanocomposite-based doped graphene quantum dots as nanosensors

The chemical doping is a common strategy and used for tailoring the properties of GQDs. The heteroatom-doped GQDs showed exceptional properties such as tunable emission, changeable spin density, and charge distribution of carbon atoms [45]. Dopants include N, sulfur (S), phosphorus (P), boron (B), fluorine (F), and chlorine (Cl).

2.5.1 Nitrogen-doped graphene quantum dots (N-GQDs) as nanosensors

The first successful synthesis of nitrogen-doped GQDs was reported by Li and co-workers in 2012 [46]. Liu et al. synthesized N-GQDs by hydrothermal method using citric acid as carbon sources and ammonia as nitrogen sources with N/C atomic ratio of ca. 4.3% emitting an obviously blue luminescence [47]. The fluorescence quantum yield of N-GQDs was 2.46% by calculation. The as-prepared N-GQDs can strongly adsorb 18 mer ssDNA (5′-ATACCAGCTTATTCAATT-3′) via π-π interaction force. The fluorescence of N-GQDs was quenched by photo-induced electron transfer mechanism between N-GQDs and ssDNA. The fluorescence of N-GQDs can be recovered upon addition of mixture of bleomycin and Fe(II) due to the noncovalent binding between bleomycin and ssDNA.

Fan and co-worker constructed N-GQD-Hg(II) complex system as a highly sensitive fluorescence sensor for cysteine detection [48]. The N-GQDs was prepared by one-pot method using citric acid as carbon source and urea as nitrogen sources. The N-GQD-Hg(II) complex as fluorescence sensor showed weak fluorescence. The fluorescence was recovered upon addition of cysteine to the complex system of N-GQD-Hg(II) due to the coordinate interaction between cysteine and Hg(II). The fluorescence intensity showed good linear relationship with the concentration of cysteine within a range of 0.05–30 μmol/L. The detection limit was 1 .3 nmol/L.

Zhao et al. prepared oxygen-rich nitrogen-doped GQDs by using one-pot synthesis strategy as pH-sensitive sensor for the detection of Hg(II) ion [49]. The oxygen-rich N-GQDs were synthesized by using citric acid (CA) and 3,4-dihydroxy-L-phenylalanine (L-DOPA) as the carbon source and the N source, respectively. The N-GQDs showed excitation-wavelength-independent fluorescent behavior, and the quantum yield was 18%. The N-GQDs as an efficient fluorescent sensor displayed the highly sensitivity and highly selectivity for the detection of Hg(II) based on the mechanism of nonradiative electron transfer. The detection limit was 8.6 nM. The fluorescence quenching efficiency showed good linear relationship with the concentration of Hg(II) within concentration from 0.04 to 6 μM. The competitive experiments showed that the N-GQDs showed high selectivity and sensitivity for the detection of Hg(II) even in the interference of other metal ions.

The strip-based fluorescence molecularly imprinted sensor was designed and constructed for monitoring thiacloprid [50]. The fluorescence molecularly imprinted sensor was synthesized based on polydopamine (PDA) polymer, thiacloprid, and N-GQDs. Firstly, the filter paper is dipped into N-GQD aqueous solution; secondly, the dopamine with thiacloprid self-polymerized on the surface of strip. The polydopamine molecularly imprinted polymer acted as an high efficient

sensor for the detection of thiacloprid. The as-prepared fluorescence molecularly imprinted sensor showed a linear relationship between 0.1 and 10 mg/L, and detection limit was 0.03 mg/L.

The hydrogen peroxide (H_2O_2) holds an important role in the biological system and is closely related with many diseases such as cancer, Parkinson disease, and so on [51]. The Pd nanoparticles decorated with N-GQDs @N-carbon hollow nanospheres was designed and synthesized as a high electrochemical sensor for the hydrogen peroxide detection [52]. The proposed NGQD@NC@Pd HNSs sensor showed highly efficient electrocatalytic activity as non-enzymatic catalyst for the reduction of H_2O_2. The NGQD@NC@Pd/GCE exhibited excellent repeatability and reproducibility by detecting eight different NGQD@NC@Pd/GCE in fixed concentration H_2O_2 with relative standard deviation (RSD) 2.7 and 3.6%, respectively. The cytotoxicity of NGQD@NC@Pd/GCE was evaluated by using Cell Counting Kit-8 (CCK8) assay. The results of CCK-8 assay displayed over 95% viability incubating NGQD@NC@Pd/GCE using MDA-MB-231 and HBL-100 cells for 4 h, indicating good biocompatibility of the NGQD@NC@Pd/GCE.

Peng and co-workers designed and reported a strategy method to detect Hg(II) ions by accelerating reaction rate between porphyrin and Mn(II) based on synergistic effect of N-GQDs and Hg(II) [53]. The reaction mechanism is based on larger Hg(II) of porphyrin-Hg(II) complex, which was replaced by smaller Mn(II) ions forming porphyrin-Mn(II) complex in a relatively faster speed. Such course was accompanied by the absorption red-shift and fluorescence quenching of porphyrins; meantime, the fluorescence intensity of N-GQDs enhanced. The CCK-8 assay showed over 90% viability by incubating 5.0 μM TMPyP, 40 μM Mn(II), or 20 μg/L N-GQDs for 24 h using A549 cells, indicative of good biocompatibility.

2.5.2 Nitrogen and phosphorus co-doped graphene quantum dots (N,P-GQDs) as nanosensors

Liu and co-workers prepared N,P-GQDs as fluorescence sensor for the detection of nitrite with high sensitivity and high selectivity [54]. The N,P-GQDs were synthesized by hydrothermal method using tetrakis(hydroxymethyl)phosphonium chloride and ethylenediamine endcapped polyethylenimine as phosphorus, carbon, and nitrogen source, respectively. The N,P-GQDs were prepared by using different temperatures (230° and 250°) and showed higher oxygen, nitrogen, and phosphorus levels at 230° compared to the those at 250°. The absolute quantum yield of N,P-GQDs was 9.4%. The N,P-GQDs showed a fast response to NO_2^- with high sensitivity and high selectivity. The fluorescence quenching efficiency exhibited a good linear relationship with concentration of NO_2^- within 5–30 nM. The detection limit was 2.5 nM. The results of MTT assays displayed over 90% cell viability by incubating N,P-GQDs with T24 cells for 24 h, suggesting good biocompatibility and imaging nitrite in live cell.

Ananthanarayanan et al. used carbonization strategy for the preparation of N,P-GQDs from biomolecule adenosine triphosphate (ATP) as nitrogen and phosphorus source [55]. Firstly, adenosine triphosphate (ATP) was carbonized for 1 h at 90° and got carbonized ATP; then the carbonized ATP was exfoliated in HNO_3 for 24 h and got final product N,P-GQDs. The results of Raman spectrum characterization of carbonized ATP exhibited prominent D and G bands, indicative of the presence of sp^3 carbon with graphitic nature. The N,P-GQDs have many advantages, such as excellent biocompatibility, good photostability, high fluorescence quantum yield (QY ~ 27.5% by calculation and ~53.0% after chemical reduction using $NaBH_4$), and low molecular weight (~1.4 kDa). The doping proportions of N and P are

6.2 (C/N = 7.0) and 6.9 (C/P = 6.3), respectively. The N,P-GQDs exhibited good two-photon upconversion properties. The strong upconverted photoluminescence phenomenon was showed with maximum emission at ~560 nm upon excitation at 800 nm. The lifetime measurements of N,P-GQDs exhibited τ_1 (A_1) and τ_2 (A_2) to be 320 ps (0.44) and 1.62 ns (0.56), respectively, where τ_1 and τ_2 are time constants and A_1 and A_2 are the corresponding amplitudes. The imaging and real-time tracking of transferrin receptors in human cervical cancer cells came true upon conjugating N,P-GQDs with a transferrin.

Mahyari and Gavgani designed and constructed cobalt porphyrin-supported N,P-GQDs/graphene (CoPP@N,P-GQDs/G) complex as noble metal-free photocatalysts [56]. Firstly, the N,P-GQDs were synthesized by carbonization of adenosine triphosphate as nitrogen source and phosphorous source; secondly, the N,P-GQDs were embedded on graphene oxide; and thirdly, the cobalt porphyrins with photoactive property were loaded through ionic interaction. The resultant product CoPP@N,P-GQDs/G showed good dispersion in the reaction medium (water). The CoPP@N,P-GQDs/G complex as recyclable photocatalysts showed high efficiency with the aerobic oxidation reaction of alcohols by using visible-light irradiation. Furthermore, CoPP@N,P-GQDs/G complex displayed the good selectivity for various alcohols by mild and green ways.

2.5.3 Nitrogen and sulfur co-doped graphene quantum dots (N,S-GQDs) as nanosensors

Mondal et al. designed and synthesized N,S-GQDs from the mixture of graphene oxide solution and thiourea by hydrothermal method [57]. The N,S-GQDs exhibited strong emission peak at 405 nm upon excitation at 320 nm. The N,S-GQDs showed a sensitive response to 2,4,6-trinitrophenol with highly selectivity, and the detection limit was 19.05 ppb. The fluorescence of N,S-GQDs significantly decreased upon addition of 2,4,6-trinitrophenol based on photo-induced electron transfer (PET) mechanism. The fluorescence quenching efficiency showed good linear relationship with concentration of 2,4,6-trinitrophenol. The N,S-GQDs showed higher quenching efficiency compared to these of N-GQDs, S-GQDs, and GQDs. Gavgani and co-workers constructed an ammonia (NH_3) sensor based on N,S-GQDs/polyaniline (PANI) hybrid with high sensitivity and high selectivity [58]. The N,S-GQDs were synthesized by hydrothermal process using citric acid as carbon source and using thiourea as sulfur source, respectively. The N,S-GQDs/PANI hybrid was prepared by using in situ chemical oxidative polymerization. The increased proportion of N,S-GQDs in N,S-GQDs/PANI hybrid showed considerable improvement of NH_3 response, such as around 42% at 100 ppm and 385% at 1000 ppm, respectively. The N,S-GQDs/PANI hybrid showed fivefold higher response compared to that of free PANI. The enhancement of sensing properties for the N,S-GQDs/PANI hybrid attributed to the synergistic effect between the N,S-GQDs and PANI.

Chen et al. synthesized N,S-GQDs by one-pot pyrolysis method with quantum yield of 67% using citric acid and cysteine as carbon source and nitrogen and sulfur source, respectively [59]. The N,S-GQDs showed an excitation-independent emission property. The fluorescence of N,S-GQDs was quenched upon addition of AgNPs, and the fluorescence of N,S-GQD-AgNPs was recovered in the presence of CN^-. The N,S-GQDs have no effect on the adsorption spectrum of AgNPs; however, addition of CN^- obviously decreased the absorbance of AgNPs. The detection limit was 0.52 μM for fluorescent sensors and 0.78 μM for colorimetric sensors. The as-synthesized N,S-GQD-AgNPs as nanosensor has been successfully applied to detect CN^- in realized water samples.

2.5.4 Sulfur-doped graphene quantum dots (S-GQDs) as nanosensors

The S-GQDs were prepared and reported by Bian and co-workers through one-pot hydrothermal method using compound 1,3,6-trinitropyrene as carbon source and 3-mercaptopropionic acid (MPA) as sulfur source [60]. The S-GQDs as fluorescent sensing probes showed highly sensitive response to the Ag^+ ions with high selectivity within a wide linear range of 0.1–130.0 μM. The detection limit was 30 nM. The fluorescence intensity of S-GQDs was obviously decreased upon addition of Ag^+ ions. The fluorescence quenching efficiency showed a good linear relationship with concentration of Ag^+ ions based on photo-induced electron transfer (PET) mechanism. The feasibility of as-synthesized S-GQDs as fluorescent sensing probe in practical application was assessed by Ag^+ detection in local lake. The detection results obtained from S-GQDs and ICP-MS were close.

Li et al. synthesized the S-GQDs by electrochemical approach using graphite electrode in sodium p-toluenesulfonate aqueous solution [61]. The S-GQDs obviously improved surface chemistry and electronic properties. The S-GQDs as fluorescent sensor showed a sensitive response to the Fe^{3+} ions with high selectivity and high sensitivity. The fluorescence intensity of S-GQDs obviously decreased upon addition of Fe^{3+} ions concentration between 0.01 and 0.70 μM. The fluorescence quenching efficiency showed good linear relationship with the concentration of Fe^{3+} ions. The detection limit was 4.2 nM. The S-GQDs as a fluorescent sensor can be reused over five times without signal lost. This fluorescence sensing probe can be successfully applied to detect Fe^{3+} ions in human serum. Dong et al. prepared S-GQDs by hydrothermal process using the mixture of 1,3,6-trinitropyrene, Na_2S, and NaOH in aqueous solution [62]. The reported S-GQDs exhibited a stable yellow-green emission. It was found that fluorescence quenching was pH-dependent and showed best quenching efficiency at pH 7.0. The as-synthesized S-GQDs showed excitation-independent photoluminescence property. The S-GQDs as a newly fluorescent probe showed high selectivity and high sensitivity for the detection of Pb(II) ions. Compared to Pb(II) ions, ions such as Na(I), K(I), Cu(II), Ca(II), Mg(II), Fe(III), Ni(II), Co(II), and Cd(II) have no obvious effect on the fluorescence intensity of S-GQDs. The fluorescence intensity of S-GQDs significantly decreased upon addition of Pb(II) ions from 0.1 to 220.0 mM in aqueous solution. The fluorescence quenching efficiency showed good linear relationship with concentrations of Pb(II) from 0.1 to 140.0 μM. The detection limit was 0.03 μM.

3. Conclusion

In this chapter, we concluded recent development of modified graphene-based nanocomposites (including of GO, GQDs, doped GQDs) as novel and convenient fluorescence nanosensors and electrochemical sensors for the detection of amino acids, proteins, metal ions, inorganic anions, drug molecules, and small molecules, pH, respectively. The obtained functionalized fluorescence sensors and electrochemical sensors as sensing platforms displayed high sensitivity and high selectivity for the detection of biomolecules, respectively.

The graphene-based composites attracted the interest of scientific workers due to its nanosize, quantum confinement, edge effects, low toxicity, and good conductivity. We comprehensively summarized the preparation, dopant element, interaction mechanism, and practical applications. The relationship between response signals and analyte concentrations was discussed in detail. The functionalized graphene-based nanocomposites showed good biocompatibility and low toxicity.

The as-synthesized fluorescence sensors and electrochemical sensors have been successfully applied for the monitoring of biomolecules in the human serum samples. The graphene-based nanocomposites showed great potential as sensing platforms for the biomedical applications and clinic research.

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Conflict of interest

The author(s) declare that they have no competing interests.

Author details

Rumei Cheng[1*] and Shengju Ou[2]

1 Institute of Advanced Materials for Nano-Bio Applications, School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, Zhejiang, China

2 Hangzhou Zhe Da Femtosecond Test Technology Co., Ltd., Zhejiang University National Science Park, Hangzhou, Zhejiang, China

*Address all correspondence to: rumeicheng@yahoo.com

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