

Electrochemical sensor and biosensor platforms based on advanced nanomaterials for biological and biomedical applications

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ABSTRACT

Introduction of novel functional nanomaterials and analytical technologies signify a foremost possibility for the advance of electrochemical sensor and biosensor platforms/devices for a broad series of applications including biological, biomedical, biotechnological, clinical and medical diagnostics, environmental and health monitoring, and food industries. The design of sensitive and selective electrochemical biological sensor platforms are accomplished conceivably by offering new surface modifications, microfabrication techniques, and diverse nanomaterials with unique properties for *in vivo* and *in vitro* medical analysis via relating a sensibly planned electrode/solution interface. The advantageous attributes such as low-cost, miniaturization, energy efficient, easy fabrication, online monitoring, and the simultaneous sensing capability are the driving force towards continued growth of electrochemical biosensing platforms, which have fascinated the interdisciplinary research arenas spanning chemistry, material science, biological science, and medical industries. The electrochemical biosensor platforms have potential applications in the early-stage detection and diagnosis of disease as stout and tunable diagnostic and therapeutic systems. The key aim of this review is to emphasize the newest development in the design of sensing and biosensing platforms based on functional nanomaterials for biological and biomedical applications. High sensitivity and selectivity, fast response, and excellent durability in biological media are all critical aspects which will also be wisely addressed. Potential applications of electrochemical sensor and biosensor platforms based on advanced functional nanomaterials for neuroscience diagnostics, clinical, point-of-care diagnostics and medical industries are also concisely presented.

1. Introduction

Design of nanomaterials has an immense brunt on catalysis, sensors and biosensors, energy conversion and energy storage devices over the last decade. A diversity of nanomaterials with well-controlled physicochemical features, surface charge, shape and dimension are produced by significant advances in synthetic methodologies. Owing to the high reactive surface area and small particle size, nanomaterials based nanosensors offer significant advantages, including upgraded physical, chemical, and biological properties (Farka et al., 2017). Superior surface area to volume ratio allows higher catalysis and sensing response as well as better optical, magnetic and electrical properties, representing significant benefits over macroscale materials for biological and biomedical applications (Piscitelli et al., 2017). Fig. 1 shows the schematic representation of the most important nanomaterials employed for the biological and biomedical applications.

The chemical composition, surface texture, crystal structure perfection, crystallographic axis orientation, etc. control electron transport

mechanism on the nanomaterials derived electrodes for the *in vivo* and *in vitro* measurements to diagnose diseases and to monitor the clinical status of patients at various level (X. Huang et al., 2017a; Y. Huang et al., 2017b). The design of nanomaterials that are capable of interacting with specific organic/biological compounds and polymers are currently facing significant challenges. On the other hand, nano entity-support matrix interactions and critical structural parameters also affect the catalytic and biosensing properties of the nanomaterials (Rong et al., 2017). In medical diagnostics and clinical analysis, the use of nanobiosensors in the detection of scrupulous cell-type or precise anatomical sites in a human body is potentially expanding. The nanobiosensors offer high sensitivity and ease of miniaturization, which may assist in developing a new pattern for clinical and field-deployable analytical instruments (Kneipp, 2017; B. Bali Prasad, 2017; P. Bali Prasad, 2017, B.B. Prasad et al., 2017).

Electrochemical sensors and biosensors are powerful analytical tools due to their portability, self-contained and low-cost. Advanced functionalized nanomaterials based electroanalytical strategies are highly

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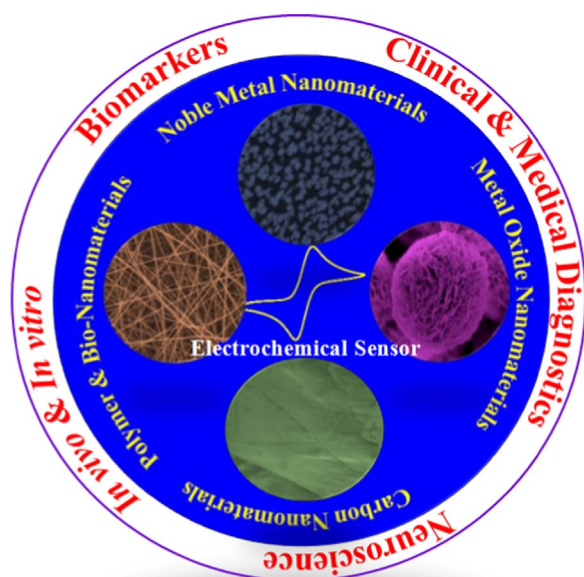


Fig. 1. Schematic illustration of nanomaterials employed as sensing materials for electrochemical biological and biomedical applications.

sensitive and selective with rapid response tools, which are highly essential in the field of biomedical and certainly in many areas of analytical sciences (Bo et al., 2017). It has been shown that numeral electrochemical sensing and biosensing approaches have been established based on numerous nanostructures for various biological and biomedical applications. An immediate requirement for the design of advanced electrochemical sensing platforms to enable biological and health monitoring has been intensively pursued, and it has potential to enlarge vastly. The convergence of functional nanomaterials, micro-fabrication of electrodes, and sensor engineering technology is an efficient approach for the detection of level of blood, metabolites, etc. (Xiao et al., 2016; Sassolas et al., 2012; Vashist et al., 2011; Chan et al., 2017). Several electrochemical sensors and biosensors have been established with the detection limits of nano-, femto-molar or even lower concentrations that are suitable for many practical applications (Jiang et al., 2017; X. Huang et al., 2017; Y. Huang et al., 2017).

The present review mainly focuses on the modern advances in the growth of nanomaterials based electrochemical sensor and biosensor platforms for the detection of potent biologically and bio-medically important analytes, which are presented in the clinical, pharmaceutical, biomedical, and biological fluids. In addition, it endeavours to explain how advanced nanomaterials could be employed in the fabrication of high-efficient electrochemical sensor and biosensor platforms for the sensitive detection of countless diseases and to expedite appropriate medical therapies. We believe that the perceptions discussed in the current review will impetus on the advanced nanomaterials, construction and the integration of the sensors platforms for prolonging the human life. We will also highlight the latest developments on the improved electrochemical sensors/biosensors and the perspectives related to biological and biomedical applications which may inspire readers with broader interests in diverse areas.

2. Noble metal nanomaterials

Noble metal nanoparticles such as gold (Au), silver (Ag), platinum (Pt), palladium (Pd), corresponding bi- or tri-metallic alloys and core-shell nanoparticles have primarily engaged in the progress of electrochemical sensor and biosensor platforms for *in vivo* and *in vitro* biomedical analyses owing to their exceptional size and shape dependent physical, chemical, and electrochemical properties (Smith and Gambhir, 2017). Noble metal nanoparticles based electrochemical

sensors have a great potential to improve both sensitivity and selectivity through tuned signal amplifications. For practical real world biomedical applications, the design of nanomaterials with minimal toxicity and environmental impact via nanoengineering has a huge impact over selective targeting of specific cells and tissues of interest, as well as to clearly identifying the affected tissues. Noble metal based nanomaterials have been directed toward the development of several analytical approaches for clinical, pharmaceutical and medical diagnostics, cancer therapeutics, etc. (Chen et al., 2016). The synthesis of metal nanoparticles, bio-functionalized nanoparticles and nanocomposites or nanohybrids have fascinated in the design of sensor and biosensors. In this section, we highlight exclusive characteristics of noble metal nanoparticles and their nanocomposites for the development of highly selective and sensitive sensing platforms for biological and biomedical applications.

2.1. Gold nanoparticles

Owing to the unique properties, including delicately adjustable physiochemical properties, towering surface area, greater stability, and complete recovery in biochemical redox reactions, significant efforts have been made in the expansion of the gold nanoparticles based electrochemical sensor and biosensor platforms for numerous biomedical applications (Masitas et al., 2016; Qi et al., 2016; Su et al., 2016). Gold nanoparticles and their nanocomposites have been recognized as potential candidate in the area of biomedical research because of the following merits: (i) simple preparation methods; (ii) easy fabrication process; (iii) high chemical stability; (iv) great biocompatibility; (v) wide electrochemical potential range; and (vi) high catalytic activity, which open the opportunity for the miniaturization of sensing platforms, offering excellent sensing and biosensing prospects in near future (Masitas et al., 2016; Gupta et al., 2016; Chang et al., 2017; Li et al., 2017).

Gold nanoparticles have been widely employed in the field of nanomedicine because of their high biocompatibility with wide range of drugs or biomarkers (Rao et al., 2017; Baldim et al., 2016). It has been shown that the comparative concentration of plasma S-nitrosothiol derivatives (RSNOs) might be connected with inflammatory conditions and various diseases (Baldim et al., 2016; Taladriz-Blanco et al., 2013). The accurate sensing of RSNOs in biological medium using gold nanoparticles based sensor platform has recently been developed with a detection limit of ~ 100 nM by Baldim et al. (Baldim et al., 2016). The gold nanoparticles based electrochemical sensor for the detection of RSNOs was performed in the presence of free thiols through RSNOs decomposition by gold nanoparticles with an ultra-microelectrode (Taladriz-Blanco et al., 2013).

Wang et al. have established hydroxylamine sensor using of gold nanoparticles immobilization on metal–metalloporphyrin networks (Au NPs/MMPF-6(Fe)) via electrostatic adsorption (Wang et al., 2016a). The developed sensor showed a couple of linear dynamic ranges, $0.01 - 1.0$ and $1.0 - 20.0 \mu\text{M L}^{-1}$ with a low detection limit of 4.0 nM ($S/N = 3$). The integration of gold nanoparticles and MMPF-6(Fe) offered a potential hydroxylamine sensor because of its strong catalytic sites, enhanced electrochemical active sites, and their soaring electronic conductivity. Electrogenerated chemiluminescence (ECL) biosensor platform based on gold nanomaterials for clinical application has displayed several advantages and numerous commercial ECL systems in clinical analyses. For instance, Dong et al. recently have demonstrated ECL aptasensor based on gold nanoparticles/graphene oxide (Au NPs/GO) nanocomposites (Dong et al., 2016). The ECL aptasensor exhibited responsive and discriminatory detection of adenosine triphosphate (ATP) in the range of $0.02 - 200$ pM with a low detection limit of 6.7 fM ($S/N = 3$). Fig. 2 shows the proposed ECL aptasensor involving ATP binding aptamer and Au NPs/GO nanocomposite for the accurate detection and determination of ATP. Chauhan and co-worker have developed an electrochemical biosensor using of nanocomposite of gold

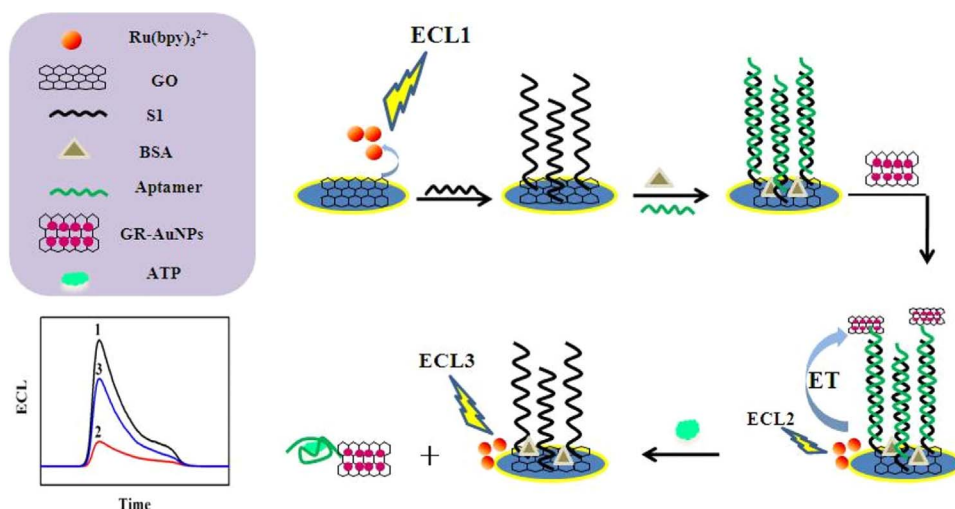


Fig. 2. Proposed scheme for the modification of the glassy carbon electrode and sensing of ATP (Dong et al., 2016).

nanoparticles embedded N-doped graphene nanosheets for the detection of glycated hemoglobin (HbA1c) (Jain and Chauhan, 2017). The fabricated biosensor showed an extensive linear collection from 0.3 to 2000.0 μM with a low detection limit of 0.2 μM . The electrochemical HbA1c biosensor exhibited an excellent selectivity towards the intrusive varieties including ascorbic acid, uric acid, triglycerides, bilirubin, glucose, and urea.

2.2. Silver nanoparticles

Silver nanoparticles based electrochemical sensor and biosensor platforms have made significant impact for biomedical applications due to their high conductivity, amplified electrochemical signal, and excellent biocompatibility. Over the last two decades, enormous efforts have been made towards the design of novel analytical methods for various analytes such as disease markers, biological and infectious agents in the early-stage detection of disease and other physiological threats based on silver nanoparticles and their nanocomposites (Fekry, 2017; Godfrey et al., 2017; Kumar-Krishnan et al., 2016). The construction of nanocomposite based on silver nanoparticles with matrices such as metal oxides, silicate networks, polymers, graphene, fibers, dendrimers, etc. led to enhanced biosensing performance because of the versatile nature of the materials (Liu et al., 2017a; Martin-Yerga et al., 2016; Sheng et al., 2017; Yusoff et al., 2017). The sensitivity and stability of the biosensor platform depend on the dispersion and the prevention of the aggregation of silver nanoparticles in the network or matrices.

Sheng et al. have recently constructed a hydrogen peroxide (H_2O_2) sensor using of Ni doped Ag@C (Ni/Ag@C) nanocomposites (Sheng et al., 2017) which exhibited a linear range of 0.03 – 17.0 mM with a detection limit of 0.01 mM ($S/N=3$). Another electrochemical detection method for moxifloxacin hydrochloride (MOXI) was developed by Fekry using carbon paste (CP) modified with silver nanoparticles (Fekry, 2017). The sensor showed a sensing limit of 2.9 nM and it successfully tested in Delmoxa tablet and human urine. The homogeneous dispersion of silver nanoparticles on reduced graphene oxide (rGO) as a nanocomposite was used for the electrochemical oxidation of NO (Ikhsan et al., 2016). Amperometric i-t curve technique was used to detect NO based on the optimized rGO-Ag nanocomposite-modified electrode and showed a detection limit of 2.8 μM . Thus Ag-based biosensor platform could serve as an ideal alternate to other sensors based on other noble metals and polymeric nanomaterials for detection of NO. The same research group also developed another non-enzymatic H_2O_2 sensor based on rGO-Nafion@Ag6 (rGO-Nf@Ag6) nanohybrid using amperometric method (Yusoff et al., 2017). The rGO-Nf@Ag6 nanohybrid demonstrated a low detection limit of 0.5 μM with a sensitivity

of 0.45 $\mu\text{A } \mu\text{M}^{-1}$. Further, rGO-Nf@Ag6 nanomaterial can serve as a highly selective electrochemical sensor for the detection of H_2O_2 in presence of NaCl, urea, glucose, dopamine, uric acid, and ascorbic acid. In addition, the sensor was highly stable for ~5.0 days and showed high reliability with good accuracy and precision for H_2O_2 sensing in apple juice. Silver nanoparticles and their nanocomposites can significantly improve the electrochemical activity by exhibiting higher catalytic performance in comparison to their bulk material counterpart owing to large reactive surface area.

2.3. Platinum nanoparticles

Over the last decade, platinum based nanomaterials have attracted wide spread interest in the field of electrochemical biosensors for biomedical applications due to their distinctive electronic and electrocatalytic properties (Liu et al., 2016; Yan et al., 2016; Chen and Chatterjee, 2013; Dang et al., 2015). The electron-transfer process of the platinum nanoparticles can be drastically influenced by material compositions, surface reactive environment, crystalline plane and orientation, etc. Platinum derived nanocomposites provide as effectual electrode materials for the extension of their novel characteristics (Chen and Chatterjee, 2013; Dang et al., 2015; Rao et al., 2016a; Zhang et al., 2014; R.Z. Zhang and W. Chen, 2017; Zhu et al., 2015) toward development of reliable, fast and precise bioanalytical methods for the detection of various biomarkers and early-stage detection of diseases (Zhang et al., 2014; R.Z. Zhang and W. Chen, 2017; Singh et al., 2016; Imani et al., 2016).

Abellán-Llobregat et al. have developed a flexible electrochemical sensor for glucose determination in human perspiration based on platinum decorated graphite and glucose oxidase (GOx) (Abellán-Llobregat et al., 2017). The sensor was demonstrated for the detection of glucose with a linear range of 0.0 – 0.9 mM and a low detection limit (6.6 mM). This skin-worn sensor had been effectively applied to real human perspiration samples, verifying an appealing method for non-invasive glucose sensing. The real samples have been collected from volunteers without any diabetes history after an intense sport session, which were performed by chronoamperometry by applying at -0.35 V. Parrilla et al. developed paper-based high performance potentiometric sensor for sensing glucose in biological fluids in a wide linear range from 0.1 to 10 mM with a limit of detection of 0.1 mM (Parrilla et al., 2017).

The functional platinum nanomaterials based sensor platforms have been prepared to enhance the sensitivity and selectivity towards the biomolecules detection (Maiyalagan et al., 2014; Govindhan et al., 2016; Shahid et al., 2015). There are number of reports available for embedding multiplicity of nanomaterials for diverse electrochemical

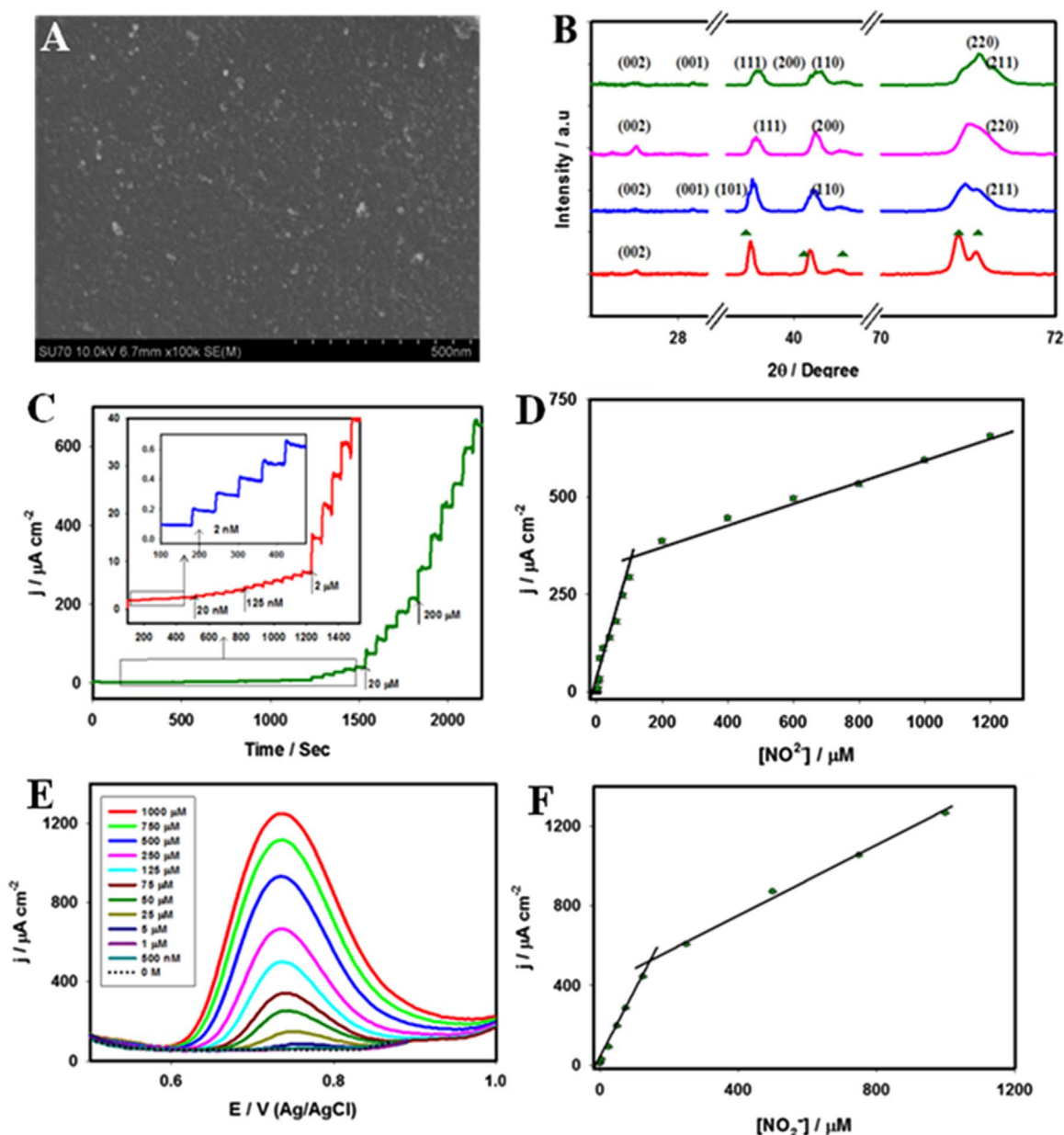


Fig. 3. FESEM image PtW/rGO-IL nanocomposite (A), XRD pattern of the rGO-IL (red), W/rGO-IL (blue), Pt/rGO-IL (pink) and PtW/rGO-IL (green) nanocomposites (B). Amperometry (C) and DPV (E) response of the PtW/rGO-IL nanocomposite electrode for sensing of NO and the corresponding calibration plots (D & F) (Govindhan et al., 2016).

sensing applications. Shahid et al. have established an electrochemical sensor using rGO–cobalt oxide (Co_3O_4) nanocube@platinum nanocomposite for the detection of NO (Shahid et al., 2015). The obtained impressive catalytic activity of the rGO– Co_3O_4 @Pt nanocomposite was ascribed to the synergistic effect of metal oxide nanocubes and platinum nanoparticles present in the rGO sheets. This sensor exhibited a low detection limit of 1.73 μM (S/N ratio of 3) with a wide linear range of 10 – 650 μM using the amperometric *i*-t curve technique. Govindhan et al. have fabricated an exceedingly sensitive electrochemical sensor for NO based on a nanocomposite made up of platinum-tungsten nanoparticles, rGO and IL (PtW/rGO-IL) (Govindhan and Chen, 2016). In this sensor design, there were no capping agents used, which are commonly present on the nanoparticles surface to avert the nanoparticles agglomeration and they might slab mass transport and electron transfer thereby lowering the sensor performance. As presented in Fig. 3A, the extensive distribution of PtW nanoparticles in the rGO-IL nanocomposite with an average particle size of ~ 7.3 nm exhibited high crystalline nature (Fig. 3B). The detection limit was found to be

0.13 nM with high sensitivity ($3.01 \mu\text{A } \mu\text{M}^{-1} \text{ cm}^2$) and good specificity against electroactive interferences. Fig. 3(C-F) depicts the sensing of NO on the PtW/rGO-IL electrode through *i*-t and DPV techniques. The NO sensor was also further demonstrated to selectively distinguish NO in genuine human serum and urine samples, confirming practical application.

2.4. Palladium nanoparticles

Palladium nanoparticles have engrossed much awareness in the field of biomedical applications due to their huge catalytic and sensor activities. The size and shape-controlled production of palladium nanoparticles is vital for facile selective catalytic and sensing properties towards various chemical and biological analytes (Chen and Ostrom, 2015; Cincotto et al., 2017; Majidi et al., 2015). The relatively large abundance of palladium over other noble metals such as gold and platinum makes it a cheaper substitute for application in various electrochemical sensing and biosensing platforms (Chen and Ostrom, 2015;

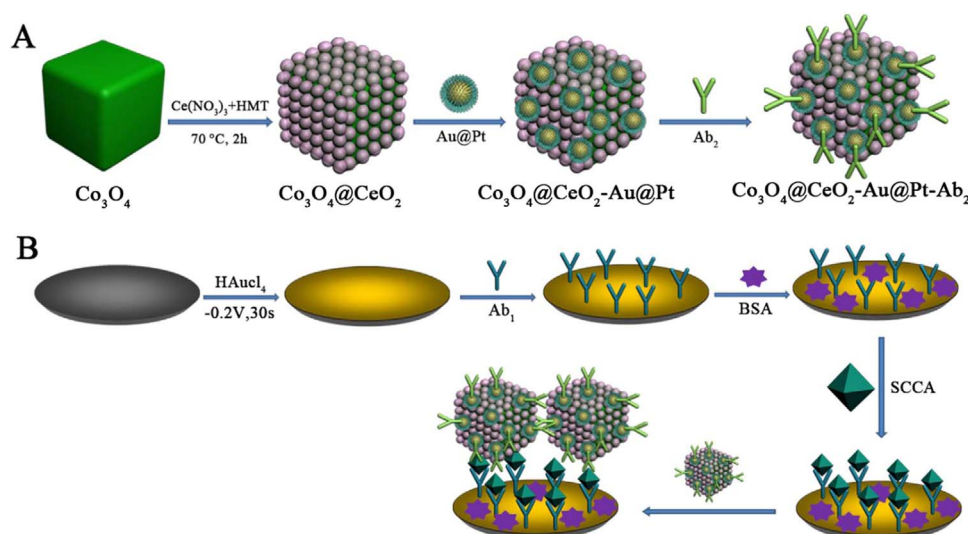


Fig. 4. Fabrication method for Co₃O₄@CeO₂-Au@Pt-Ab₂ label (A). Pictorial representation of sandwich-type electrochemical immunosensor for SCCA (B) (Y. Li et al., 2017a).

Kannan et al., 2014). Owing to unique electronic properties, improved catalytic and selective sensing performance, a variety of palladium nanomaterials such as nanocomposites, bimetallic nanoparticles, metal oxide nanomaterials, and carbon nanomaterials with variable composition have been investigated for the detection of numerous biomarkers over the last decade (Rahi et al., 2016; Shahrokhian et al., 2014; Rezaei et al., 2016).

Rahi et al. have demonstrated an electrochemical genosensor for *Brucella* using palladium nanoparticles deposited on a gold surface by applying constant potential (Rahi et al., 2016). Brucellosis, an infectious disease is affected by the gram-negative bacteria of the genus *Brucella* and this infection may be transmitted to people by contacts through bacteria contaminated animals products or animal (Rahi et al., 2016). Palladium nanoparticles are used as a transducer, which employed to immobilize a *Brucella*-specific probe. The method of immobilization and hybridization was achieved by voltammetric technique. This sensor exhibited a linear calibration range from 1.0 pM to 0.1 aM with a low detection limit of 27 zM while it showed excellent stability for 30 days if stored in the refrigerator at 4 °C. The synthesis of bimetallic gold-palladium nanoparticles is one of the most preferred alloys in catalytic and sensing studies which were effectively applied in sensing drugs (Shahrokhian et al., 2014; Rezaei et al., 2016). The electrochemical sensor with gold and palladium nanoparticles-modified nanoporous stainless steel (Au-Pd/NPSS) electrode for concurrent sensing levodopa (LD) and uric acid (UA) in urine, blood serum and levodopa C-Forte tablet was developed by Rezaei et al. (Rezaei et al., 2016).

In order to obtain better sensitivity and selectivity, the metal nanoparticles based nanocomposite containing graphene and IL have been established for sensing dopamine, nifedipine, hydroquinone, NO, DNA, etc. (Li et al., 2017a; Govindhan and Chen, 2016; Mao et al., 2015). Wang et al. have recently prepared a non-enzymatic glucose sensor using homogeneously dispersed palladium nanoparticles on graphene sheet and IL (C.H. Wang et al., 2017). A number of IL were used and optimized towards the detection of glucose and ascorbic acid using Pd NPs/GNss-IL electrode. Butyl methyl pyrrolidinium-bis(trifluoromethanesulfonyl) imide (BMP-TFSI) IL was more constructive for sensing glucose, whereas butylmethylpyrrolidinium-dicyanamide (BMP-DCA) IL was beneficial for high sensitivity towards the sensing of ascorbic acid with Pd NPs/GNss-IL electrode in 0.1 M NaOH. Noble metal nanoparticles may easily enhance the electrochemical sensing and biosensing performance as they show higher sensitivity, good specific catalytic activity, quick response time, and good biocompatibility, which may expedite the design of advanced applications in biological, pharmaceutical, clinical and point-of-care diagnostics.

3. Metal oxide nanomaterials

Metal oxide nanomaterials are widely employed in numerous fields such as electrochemistry, soft magnetism, catalysis, sensor, etc.. Due to tremendously reduced dimension, huge surface area to volume ratio, specific facet exposure, and the Debye length comparable to its dimensions, metal oxides nanomaterials may significantly improve sensitivity and/or selectivity (Kannan et al., 2016; Leung and Xuan, 2016; Galstyan et al., 2016; Gormley et al., 2016; Jahanbani and Benvidi, 2016; Lan et al., 2017). Metal oxide nanomaterials have been widely utilized as an effective electrocatalyst for sensing various analytes in the field of biology and biomedicine because of their strong electrocatalytic activity, low cost, and high organic capture ability (Tang et al., 2015; He et al., 2015; Mirzaei et al., 2015). A variety of metal oxide nanoparticles have been employed in electroanalysis, including cerium oxide (CeO₂), copper oxide (CuO), nickel oxide (NiO), iron oxide (Fe₂O₃), cobalt oxide (Co₃O₄), manganese oxide (MnO₂), zinc oxide (ZnO), titanium oxide (TiO₂), tin oxide (SnO₂), cadmium oxide (CdO), and, etc.

3.1. Cerium oxide nanomaterials

Cerium dioxide (CeO₂) nanomaterial is one of the central functional rare earth oxides and it reached momentous interest in the field of biosensors due to the easy immobilization of enzyme or protein on the surface of electrode and its tremendous catalytic activity. Recently, Bracamonte et al. have developed an electrochemical H₂O₂ sensor based on the integration of single walled carbon nanohorns with CeO₂ (CeO₂/SWCNH) catalysts (Bracamonte et al., 2017). The fabricated CeO₂/SWCNH electrode exhibited an excellent sensor performance towards H₂O₂ (LOD of 0.1 mM). The nanocomposite sensor displayed high stability over 2 weeks with high reproducibility. The versatility of the developed sensor was examined in commercial samples of milk and cleaning liquid, showing a remarkable selectivity toward H₂O₂ even in very complex matrices. In particular, the immobilization of primary antibody (Ab₁) in an immunosensor with sandwich-type is crucial point to increase of sensitivity. It has been shown that making a nanocomposite with other semiconductor oxides is an efficient mode to improve its sensing ability through synergistic effect. An electrochemical immunosensing for squamous cell carcinoma antigen (SCCA) based CeO₂ nanocomposite (Co₃O₄@CeO₂-Au@Pt) (Fig. 4) has been fabricated by Li et al. which exhibited high sensitivity and selectivity (Y. Li et al., 2017a).

3.2. Copper oxide nanomaterials

Copper oxide (CuO) nanomaterials offers versatile functions such as various valence states, tunable electron-transport performance, hierarchical nanostructures and high surface area. The exploration of CuO nanomaterials have been effectively employed in numerous sensing and biosensing applications. Yang et al. have demonstrated recently a non-enzymatic glucose sensing using of nanoneedle-like CuO on N-doped rGO (CuO/N-rGO) in 0.2 M NaOH (Yang et al., 2017). The CuO/N-rGO sensor demonstrated a rapid response to glucose with a wide linear range between 0.5 and 639.0 μM with a lowest detection limit of 0.01 μM . This three-dimensional nanohybrid architecture of the electrode may prominently increase the interfacial communicating area by offering high reactive sites for glucose housing, which condensed the diffusion length and improve the reactivity. In addition, this glucose sensor was effectively applied for the detection of glucose in human serum samples. Li et al. have developed $\text{Cu}_2\text{O}@/\text{CeO}_2\text{-Au}$ nanocomposites for the sensing of prostate specific antigen (PSA) (Pecher et al., 2017). Synergetic consequence displays in the $\text{Cu}_2\text{O}@/\text{CeO}_2$ core-shell decorated with gold nanoparticles ($\text{Cu}_2\text{O}@/\text{CeO}_2/\text{Au}$ NPs), showing superior electrocatalytic activity for H_2O_2 reduction than pure Cu_2O , Au NPs and $\text{Cu}_2\text{O}@/\text{CeO}_2$. This immunosensor demonstrated a wide linear range, 0.1 pg mL^{-1} – 100 ng mL^{-1} and showed a low detection limit of 0.03 pg mL^{-1} ($S/N=3$).

3.3. Magnetic nanomaterials

Owing to high accessible and active surface area and superior electron-transfer behaviour, magnetic nanomaterials such as NiO , Fe_2O_3 , Co_3O_4 , etc. have been measured as promising materials for superior electrochemical biosensors. Hierarchical porous metal oxide architectures with controlled surface structure and dimension have inward an ample range of fields. Hierarchical porous $\text{Co}_3\text{O}_4/\text{graphene}$ ($\text{Co}_3\text{O}_4/\text{GR}$) was also used as an effective enzyme free glucose sensor (M. Yang et al., 2017). Fig. 5A and B show SEM, TEM image and EDS of the $\text{Co}_3\text{O}_4/\text{GR}$ microsphere, revealing that graphene sheets were aggregated and interconnected with Co_3O_4 . The EDS mapping revealed the concurrence and regular dispersal of Co_3O_4 on graphene sheets. As presented in Fig. 5C-F, the $\text{Co}_3\text{O}_4/\text{GR}$ constructed electrode demonstrated high sensitivity and selectivity towards the glucose detection. The application of binary metal oxides has become progressively dominant due to lack of efficient protocols to upsurge the action of an individual metal oxide. Recently, it has been demonstrated that noble metal nanoparticles deposited on various semiconducting oxide provisions are catalytically energetic due to the noble metal nanoparticles polarization at the interface (Alammari et al., 2015; Govindhan et al., 2016b). In several cases, metal oxide nanomaterials are employed as backing materials for the dispersion of noble metal nanoparticles due to its much higher catalytic activity than the single-component nanomaterials (Zhang et al., 2013). The enhanced catalytic activity is often associated to the synergetic consequence that arises at the boundary of metal and oxide support (Albelda et al., 2017; Zhu et al., 2016).

Metal oxide nanoparticles offered a biocompatible atmosphere for the functionalization of the electrode by the immobilization of enzymes and augment the sensitivity of the electrode via easing electron transfer. The enzymes, acetylcholine esterase (AChE) and choline oxidase (ChO) were immobilized on the surface of Fe_2O_3 nanoparticles and poly(3,4-ethylenedioxythiophene) (PEDOT)-rGO nanocomposite were used as the sensing electrode materials for the sensitive detection of acetylcholine (Chauhan et al., 2017). This biosensor showed a linear range between 4.0 nM and 800.0 μM with a low detection limit of 4.0 nM. Han et al. have established a glucose biosensor based on genetically engineered M13@ MnO_2/GO_x nanowires (Han et al., 2016). This biosensor demonstrated a wide linear range from 5.0 μM to 2.0 mM with a low detection limit of 1.8 μM . Numerous advances have been made in the field of design and uses of electrochemical sensor based on the

metal oxides and their nanocomposites. The development of these sensor systems may lead to significant advantages in terms of simplicity, rapid response, cost, and robotics for various sensing applications toward the monitoring of biomolecules in cell.

4. Carbon nanomaterials

Carbon based nanomaterials (single-walled carbon nanotubes (SWNTs)), multi-walled carbon nanotubes (MWNTs), single-walled carbon nanohorns (SWCNHs), buckypaper, graphene, fullerenes (e.g., C_{60}), etc. afford many significant benefits because of their extraordinary surface-to-volume ratio, great electrical conductivity, chemical durability, biocompatibility, and strong mechanical strength (Zhang and Lieber, 2016; Erol et al., 2017; Kim et al., 2017; Teradal and Jelinek, 2017). These novel functionalities of carbon materials are accountable for the enlargement of a widespread variability of versatile carbon-based sensing electrodes, which exhibit great sensitivities and low sensing limits toward various biological and biomedical analytes. The morphology of functionalized carbon nanomaterials creates more appealing features that assist their enhanced sensitivity, selectivity and stable response. The reactive surface functional groups, edge-plane like sites, and impurities may also be responsible for the tremendous electrocatalytic and sensing performance of carbon nanomaterials (Jariwala et al., 2013; Marmisolle and Azzaroni, 2016). Many advances have been explored on carbon nanomaterials in recent years, both through continual development of existing or new fabrication techniques for the integration of sensor. For instance, Ali et al. recently established a sensor (Fig. 6) for low density lipoprotein (LDL) molecules based on antiapolipoprotein B 100 (AAB) functionalized carbon nanomaterials and NiO as nanocomposites for molecules and it showed a low detection limit of 5 mg dL^{-1} concentration with a linear range of 0–130 mg dL^{-1} (Ali et al., 2016a).

4.1. Carbon nanotubes

Carbon nanotubes (CNTs) have quite a lot of fascinating properties associated to their structure, functionality, morphology, and aptness in hybrid or composite materials due to their hollow cylindrical tubes comprising of graphitic carbon with a extraordinary aspect proportion and sp^2 hybridization. Carbon nanotubes can be mainly categorised as single-walled nanotubes (SWNTs), double-walled nanotubes (DWNTs), and multi-walled nanotubes (MWNTs) contingents on the number of graphite layers. In particular, CNTs have intensively explored to improve the performance of sensing and biosensing platforms due to their unique chemical and physical properties. The functionalized CNTs reveal distinctive properties which could enable diverse clinical, pharmaceutical and medical applications. The chemical functionalities can easily be conjugated and tuned for the modification of these tubular structures. Delivery of diverse therapeutic agents such as drugs, peptides, proteins, genes, and immune modulators via the biological membrane has easily achieved using the functionalized CNTs.

Venton and co-workers have demonstrated an electrochemical *in vivo* dopamine sensor based on metal microelectrodes modified with CNTs (Yang et al., 2016). It has been found that CNTs-coated niobium (CNTs-Nb) microelectrode exhibited higher sensitivity and lower ΔE_p value than the CNTs grown on CFs or other metal wires. The CNTs-Nb sensor demonstrated a low detection limit of 11 ± 1 nM for dopamine. The CNTs-Nb sensor was also employed to detect stimulated dopamine release in anesthetized rats and demonstrated high sensitivity with rapid measurements *in vivo*. The CNTs-Nb sensor was stable for more than 4.0 h of non-stop measurement and thus able to quantify the stimulated dopamine release in anesthetized rats. The design and synthesis of functional CNTs that focus on specific biological and biomedical applications are highly attractive because of high selectivity, accuracy, and long-term stability towards *in vivo* biosensing in live brains. Zhang et al. have designed an electrochemical ascorbic acid sensor for

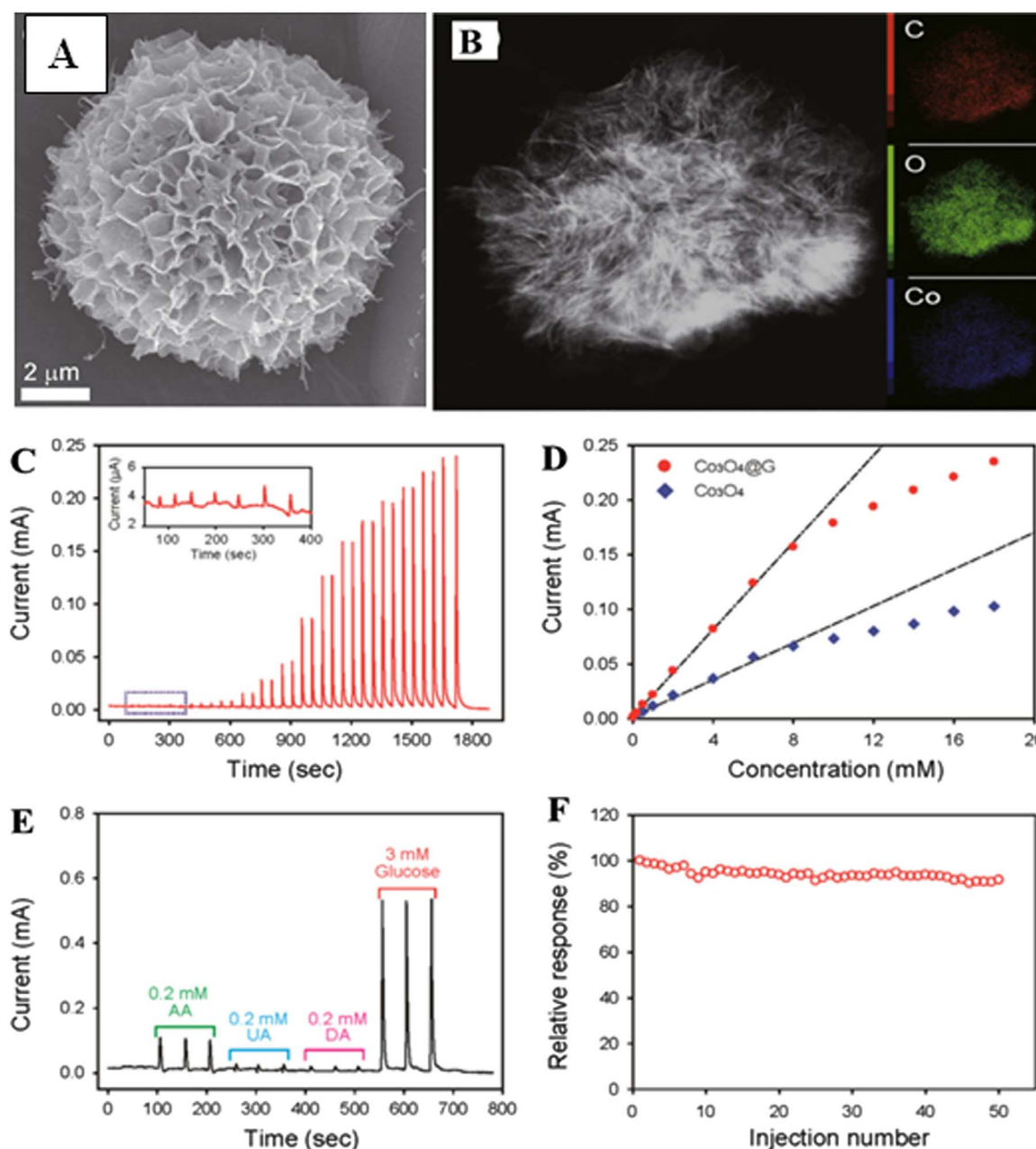


Fig. 5. SEM image (A) and TEM based EDS mapping (B) of hierarchical $\text{Co}_3\text{O}_4/\text{G}$ microspheres. (C) The i-t responses of $\text{Co}_3\text{O}_4/\text{G}$ electrode to flow injection of glucose (0.02 – 18.0 mM). (D) Corresponding calibration plot. (E) The i-t responses to the successive addition of interfering compounds, including 0.2 mM ascorbic acid (AA), uric acid (UA) and dopamine. (F) Variation of the response current of sensor to 5.0 mM glucose with injection number (M. Yang et al., 2017).

accurately measuring ascorbic acid levels in live brain using aligned carbon nanotube fiber (CNF) as a microsensor (L. Zhang et al., 2017). The sensor demonstrated that the ascorbic acid concentration was measured to be $259.0 \pm 6\ \mu\text{M}$ in cortex, $264.0 \pm 20\ \mu\text{M}$ in striatum, and $261.0 \pm 21.0\ \mu\text{M}$ in hippocampus, respectively, under normal conditions. Fig. 7 shows the pictorial representation, optical images and the DPV results of *in vivo* measurements for determining ascorbic acid in rat brain. This sensor provided a simple methodology for the integration of high-performance biosensors with other neurotransmitters, which might inspire new sensing techniques in brain medical research.

Nanocomposite of CNTs and various noble metal and metal oxide nanomaterials have been employed as electrocatalyst to enhance the sensing and biosensing performance towards the biomedical research (Baskaya et al., 2017; Bai et al., 2017; Rahman et al., 2016). Highly monodisperse Ni nanoparticles supported on functionalized MWCNT (Ni@f-MWCNT) based non-enzymatic glucose sensor had aimed by

Baskaya et al. (Baskaya et al., 2017). The Ni@f-MWCNT-based sensor showed a linear range of 0.05–12.0 mM and a low detection limit of $0.021\ \mu\text{M}$. The novel surface structure, the definite interfaces between Ni and f-MWCNT, and high surface area led to enhanced electrochemical sensing performance, which also showed high stability (over 10 weeks). In order to increase the biocompatibility of CNTs based nanomaterials, the biopolymer, chitosan (CS) has been used for electrochemical sensor application. Bal et al. have developed an electrochemical diethylstilbestrol (DES) sensor based on Au NPs/MWCNT-CS (Bai et al., 2017). It was found that DES offers many adverse effects to human body by causing damage of genetic elements which forwarded to transmutations in genes, and indorse cancers. The Au NPs/MWCNT-CS sensor exposed a low detection limit of $24.3\ \text{fg mL}^{-1}$ and the sensing range of $0.1\ \text{ng} - 10^{-6}\ \text{mg mL}^{-1}$. The combination of CNTs and graphene is reflected as an exceptional sensing candidate for production of sensitive, durable and low-cost electrochemical sensor due to the large

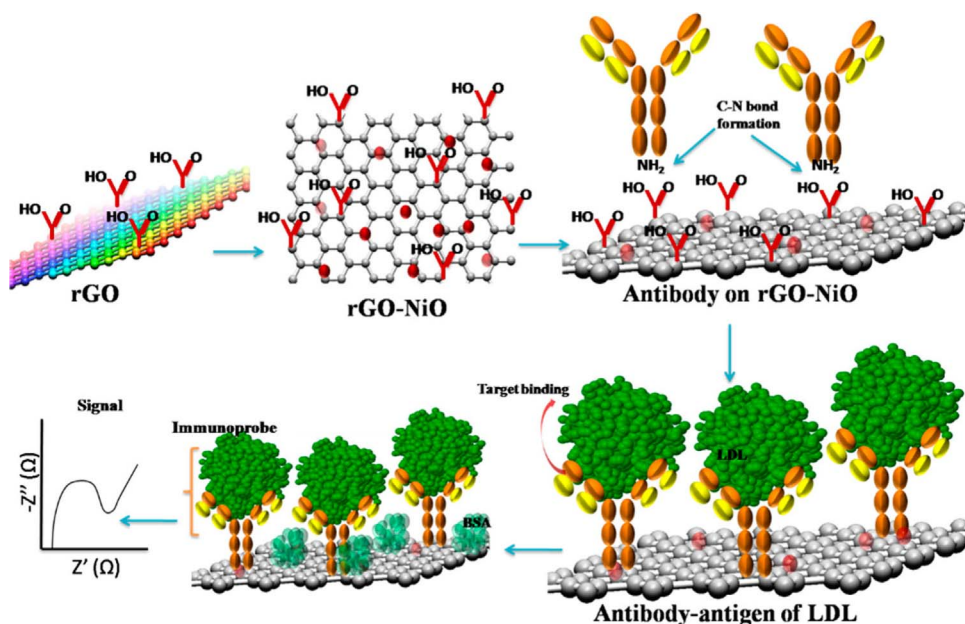


Fig. 6. Scheme for the functionalization of rGO-NiO nanocomposite with antibody for the sensitive detection of low density lipoprotein (Ali et al., 2016a).

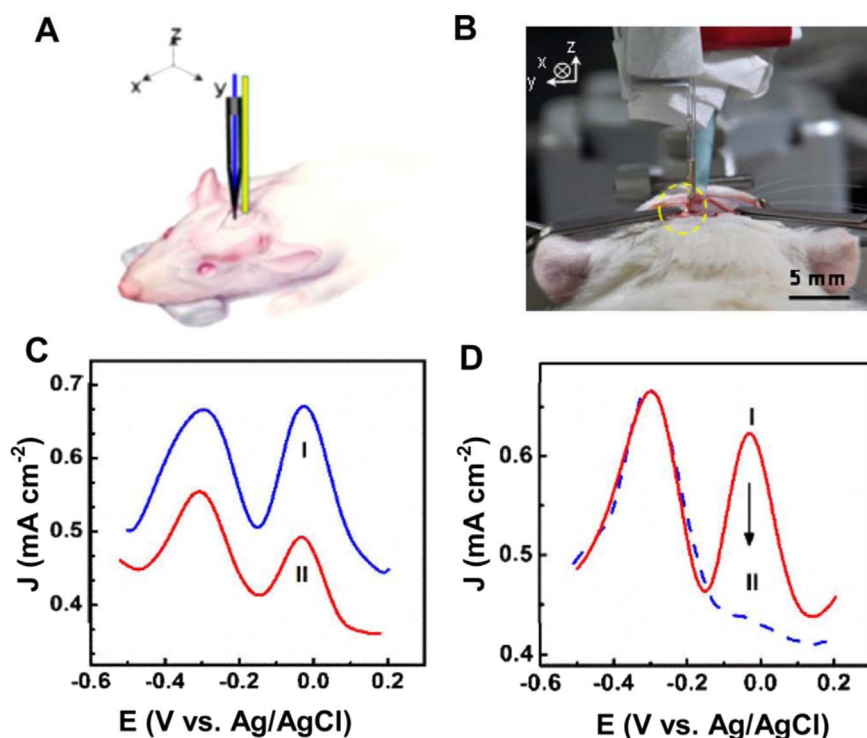


Fig. 7. (A) Scheme for the *in vivo* setup for the detection of ascorbic acid in rat brain. (B) Optical images before and after the stereotaxic implant into the brain. (C) DPV responses measured at the CNF microelectrode in the striatum of normal rat (I) and rat brain models of AD (II). (D) DPV responses recorded at the CNF microelectrode in the striatum of the rat brain model of AD before (I) and after (II) injection of AAox (L. Zhang et al., 2017).

number of carboxyl groups, reduced volumes, and upright electrical conductivity (Arvand and Hemmati, 2017; Rahimi-Nasrabadi et al., 2017; Mani et al., 2016; Asadian et al., 2017; Li et al., 2016). Recently, Arvand et al. have established nanocomposite of graphene quantum dots (GQDs), Fe₃O₄ nanoparticles and *f*-MWCNT (Fe₃O₄@GQD/*f*-MWCNT) for the sensitive detection of progesterone (P4) in human serum and pharmaceutical yields (Arvand and Hemmati, 2017).

The flexible and wearable electrochemical sensor can be able to quantify *in situ* sweat metabolites and secretions. It is considered to be a potential method for real-time monitoring of mechanically induced biochemical signals during mechano-transduction in sensitive cells and tissues. The great challenges still continue in constructing high performance flexible electrochemical sensors during repeated stretching for biological and biomedical applications. In particular, CNTs based

thin films onto or between stretchable substrates of highly elastic PDMS, Ecoflex was designed for electrochemical sensor. The real-time monitoring of NO level from mechanically sensitive cells is of great importance because NO generation from cells through mechano-transduction dramatically influenced by mechanical forces, including strain, tension, compression, and shear stress. Recently Jin et al. have developed a versatile approach to fabricate CNTs-based stretchable and transparent electrochemical NO sensors by binding SWCNT with conductive polymer of poly-(3,4-ethylenedioxythiophene) (PEDOT) to form composite films (Jin et al., 2017). CNTs still have vast potential in the field of biomedical applications due to their novel characteristics including high aspect ratio, catalytic properties, amenable to surface functionalization, conductive nature, and ability to maintain structural integrity. In addition, the capability to transfer electrons at a rapid pace

at the electrode and electrolyte interface permits them to be effectively applied in ultra-sensitive, discerning, and forceful chemical sensors and biosensors.

4.2. Graphene

Enormous research efforts have been dedicated on the graphene and graphene-based nanocomposite materials for various applications. Graphene is an indeterminately extended two-dimensional (2D) carbon network with a hexagonal lattice resembling a honeycomb structure which exhibit high sensitivity, great selectivity, good stability, low over potential, wide potential window, negligible capacitive current, and excellent electrocatalytic activity (Yu et al., 2017). It presents numerous interesting properties such as huge specific surface area, giant conductivity and transparency, excellent mechanical strength and flexibility, strong ambipolar electric field effect, good thermal and electrical conductivity, and excellent electronic properties. The various forms of graphene such as GO, rGO, graphene nanorippons (GNRs), etc. are possible after freeing the CNTs. The functionalized graphene using various materials, including organic and biomolecules, metal and metal oxide nanoparticles, polymers and enzymes are often employed for achieving improved sensing and biosensing performance towards biomedical applications (R. Zhang and W. Chen, 2017; Yu et al., 2017). Over the past few years, many researchers have reviewed on graphene based nanomaterials and their electroanalytical applications towards biological, biomedical, food safety, and environmental applications (R. Zhang and W. Chen, 2017; Yu et al., 2017; Zhu et al., 2017; L. Wang et al., 2017).

Adhikari et al. have developed a sensor using of electrochemically reduced graphene oxide (ERG) for sensitive sensing acetaminophen in pharmaceutical formulations and human body fluids (Adhikari et al., 2015). The superb electrical conductivity, great surface area, and oxygen-related defects of ERG create them as sensitive and rapid electrochemical sensing platforms toward acetaminophen detection. The ERG based sensor demonstrated a low detection limit of 2.13 nM and showed a linear range, 5.0 nM – 800.0 μ M. In addition, this sensor was productively smeared for the sensing of acetaminophen in human serum and pharmaceutical samples. The successful integration of graphene and metal nanoparticles has attracted much attention due to their great surface area, improved the kinesis of charge carriers, and firm electron transfer kinetics. Govindhan et al. have designed an electrochemical β -nicotinamide adenine dinucleotide (NADH) sensor using unscrewed Au nanoparticle/rGO nanocomposite (Au NPs/rGO) without using any redox mediators and enzymes (Govindhan et al., 2015). The Au NPs/rGO based sensor exhibited superior electrocatalytic activity towards the oxidation of NADH in neutral solution by offering a suitable atmosphere for electron transfer through the boosted electrical conductivity. This sensor showed high sensitivity (0.916 μ A/ μ M cm²) and wide linear range (50.0 nM – 500.0 μ M) with a low detection limit of 1.13 nM (S/N=3). In addition, the developed sensor was tested for the detection of NADH in human urine samples, displaying the Au nanoparticle/rGO nanocomposite device encouraging biomedical applications.

Three dimensional (3-D) porous graphene (3D GN) is recently considered as new support for immobilization to improve the enzyme-like activities towards the sensing of various biomolecules. The structural effects of metal oxide nanomaterials such as NiO, Co₃O₄, Fe₃O₄, etc. and peroxidase-like activity were examined. Wang et al. recently fabricated 3D GN decorated with Fe₃O₄ nanoparticles for the detection of glucose with a low sensing limit of 0.8 μ M (Q. Wang et al., 2017). Graphene possesses significant advantages such as rich anchoring sites, extraordinary surface area, brilliant biocompatibility, and low-priced production cost in comparison to other kinds of carbon nanomaterials, including CNTs, fullerene, carbon dots, and nano-diamond. The functionalization of graphene sheets can be easily attained using numerous approaches such as mechanical mixing, hybridization, co-deposition,

covalent or non-covalent interaction, etc.. The graphene based nanomaterials have been employed extensively in electrochemical sensors and biosensors for biomedical, health care and clinical applications. In addition, novel strategies for the fabrication of graphene nanocomposite based electrode materials with superbly meticulous designs are actual crucial.

5. Polymer nanomaterials

Electrochemical sensor and biosensor platforms based on polymer based nanomaterials such as homo- and co-polymers, polymeric structures with planned structure, and molecular shape-recognition materials have been employed widely in the detection of biomolecules due to its facile functionalization of biomolecules and long-term stability (Duncan and Pillai, 2015; Parisi et al., 2016; Qian et al., 2017; Yoon, 2013). The development of biomedical electrochemical sensor platforms trusts on manufacturing aspects of the biotic/abiotic interface. It has shown that electrochemical sensors and biosensors or biomedical devices comprise of a physical, mechanical, or electrical transducer attached to a bio-recognition element. The enhanced sensing performance of the polymer based sensors can be simply attained via tuning the following factors: (i) bio-functionalization – it depends on the exposed surface and nature of biomolecules; (ii) durability - covalent binding of the biomolecule, (iii) increased electrochemical signal transduction - fast kinetics of carriers/analytes, and (iv) high specificity – high recognition of bio-analytes. Due to the high sensitivity, linearity, hysteresis, and selectivity, polymeric nanomaterials based on dendrimers, conducting polymers (CPs), and molecular-imprinted polymers have used for the detection of DNA, enzymes, proteins, antigens, and metabolites. In this section, we highlight some recent examples of nanostructure functionalization, integration, and application of polymer nanomaterials based electrochemical sensors and biosensors related to biomedical applications.

5.1. Dendrimers

Dendrimers based electrochemical sensor/biosensor platforms have been extensively engaged for the sensing various bio-analytes because of their unique structural properties, including structural consistency, veracity, well-ordered composition and biocompatibility. Recent years, significant efforts were made toward the preparation and utilization of dendrimer-based electrochemical sensing electrodes. In particular, a huge number of biosensors were established on the direct electrochemistry of hemeoproteins and enzymes. The active biomolecules can easily be restrained on dendrimers without losing their biological activity that helps to produce efficient conducting interfaces useful in many fields. Dendrimers easily combine with a bulky number of bio-receptors because of their extraordinary quantity of amine groups, which significantly increase the sensitivity and detection limit of the target bio-analytes. Miodek et al. have developed a sensor for the detection of DNA using nanocomposite consisted of MWCNTs coated with polypyrrole (PPy) and redox poly-(amidoamine) dendrimers (PAMAM) (MWCNTs-PPy-PAMAM) for *Mycobacterium tuberculosis* (Miodek et al., 2015). This sensor showed a low detection limit of 0.3 fM (S/N = 3) with a linear range of 1 fM to 10 pM. Moreover, it was successfully applied to practical DNA samples from *Mycobacterium tuberculosis*. The similar PAMAM-G4 based sensor was developed for the sensitive detection of paracetamol in commercial tablets and human serum samples (Y. Zhang et al., 2016). Voltammetry technique was employed for the identifying of paracetamol using MWCNTs-PAMAM electrode and showed a low detection limit of 0.1 μ M (S/N = 3) with a linear range of 0.3 μ M – 0.2 mM. The CNTs-functionalized dendrimers based paracetamol sensor platform exhibited excellent permanence and specificity in presence of electrochemically active interferents.

5.2. Conducting polymers

Conducting polymers have been successfully applied in wide-ranging uses such as chemical sensing, biosensing, gas sensing, supercapacitors, etc. due to their unique electronic properties. The nanostructured polypyrrole (PPy), polyaniline (PANI), polythiophene (PTP) and their functionalized derivatives thereof have been studied intensely for sensing and biosensing applications because of their intrinsic conductivity. The rapid development of biosensor system has also motivated to investigate the communication of these polymers with biological tissues through *in vitro* assays and methods to improve biocompatibility. Recently, Au NPs patterned on polyaniline nanowires (PANI) based electrochemical neurotransmitter sensor in presence of ascorbic acid and uric acid was developed by Deveki and co-workers (Sadanandhan and Devaki, 2017). The deposition of Au NPs improved the conductivity of the PANI based hybrid system by offering significant electronic interactions with the polymer thereby enhancing charge transfer process. The developed sensor exhibited low detection limits of 0.08, 0.01, 0.025, and 0.04 μM for dopamine, ascorbic acid, serotonin, and uric acid, respectively. Wang et al. have constructed a non-enzymatic blood glucose sensor using poly(o-phenylenediamine)/Ag-NPs (PoPD/Ag-NPs) composite (J. Wang et al., 2017). The established glucose sensor disclosed a varied linear range of 0.15 – 13.0 mM with a low detection limit of 12.0 μM . The PoPD/Ag-NPs electrode was stable for more than ten weeks, showing great potential for bioanalysis. CPs based nanomaterials have been demonstrated to be decidedly well-matched with an extensive diversity of live cells, and cell components owing to well-defined polymeric materials without dangling surface bonds, causing in an operative interaction with cells surface, enabling adhesion and promoting ionic interactions (Strakosas et al., 2016). Recently, Liu et al. have designed a biosensor platform using cell membrane-mimic phosphorylcholine polymer film enabled microelectrode for *in vivo* electrochemical detection of dopamine (DA) (X. Liu et al., 2017). Fig. 8a shows the SEM images of the developed electrodes, which have been used for *in vivo* electrochemical detection of DA in the biological living system (Fig. 8b). Carbon fiber microelectrodes (CFEs) are entrenched into the animal's brain, but unfortunately electrode active materials in some cases perish by a non-specific adsorption of biomacromolecules and proteins onto the microelectrode surface during *in vivo* electrochemical detection of biomolecules (Fig. 8c). The design of next generation nanopolymer- or functionalized polymers based devices with controlled surface structure and morphology is required to investigate for improving selectivity and biocompatibility, which may further advance the sensing machineries in the extent of bioelectronics and healthcare.

5.3. Molecularly imprinted polymers

Molecularly imprinted polymers (MIPs) based sensor and biosensor platforms have been used for a variety of target chemical and biological molecules. The imprinting of organic or biomolecules including pharmaceuticals, pesticides, amino acids, peptides, nucleotide bases, steroids and sugars, even metal and other ions are well demonstrated to favor the selective organisation of functional groups in the imprinting network. It is still a challenging task for the imprinting of large or robust complex structures such as proteins through imprinting techniques. For the production of nanostructured MIPs, a variety of methods have been employed such as suspension, dispersion, precipitation, and emulsion seeded polymerization. Though the MIPs are normally organic solvent-compatible, the specific template binding of MIPs prepared in organic solvents is unusually decreased in aqueous environments, which dramatically limit the biotechnological applications. The combination of the self-assembly of an amphiphilic cross linkable copolymer and imprinting technology is effectively used for a series of molecularly imprinted nanoparticles in aqueous solution to fabricate several electrochemical sensors for biomedical application.

Liu et al. have prepared a sensitive electrochemical paracetamol sensor using a water-dispersible molecularly imprinted electroactive nanoparticle by a combination of macromolecular self-assembly and molecular imprinting technique employing paracetamol as a template molecule (Luo et al., 2016). This sensor exhibited two linear ranges from 1.0 μM to 0.1 mM and 0.1–10 mM with a low detection limit of 0.3 μM for sensing of paracetamol. Li et al. have established a sensor for salbutamol based on Ag NPs and N-doped rGO (Ag-N-rGO) (J. Li et al., 2017b). The developed sensor showed an active catalytic property and outstanding discrimination towards the sensing salbutamol in human urine and pork samples. The Ag-N-rGO composite electrode presented a linear range of 0.03 – 20.00 μM with a low detection limit of 7.0 nM for sensing salbutamol. The Ag-N-rGO composite based sensor not only enhances the sensitivity and selectivity of salbutamol, but also offers high stability and good reproducibility. Recently, Rao et al. have demonstrated an electrochemical creatinine sensor using of a magnetic-MIPs and a nanocomposite consisting of Ni NPs and PANI (Ni@PANI NPs) in urine-mimic and real urine samples which displayed a linear range from 40.0 to 800.0 nM with a low detection limit of 0.2 nM for sensing creatinine (Rao et al., 2016b).

The combination of metal nanoparticles into the MIP matrix permits to enrich the properties of inorganic nanoparticles and polymer, providing excellent materials with novel functions suitable for biomedical fields. Indeed, multicomponent nanomaterials involving carbon nanomaterials (such as CNT, graphene, etc.), metal oxide nanomaterials (such as TiO_2 , Fe_2O_3 , etc.), and noble metal nanoparticles (such as Au, Ag, Pt, Pd, etc.) clearly provide distinct added advantages. The MIP based science and technology has reached a new epoch where the molecular recognition capability of the imprinted polymers and the implementation of nanostructures license designing/constructing exclusive biomimetic sensor devices with unprecedented analytical performances. The development polymeric nanomaterials such as dendrimers, conducting polymers, molecular/ion imprinted polymers, etc. were successfully established for biological and biomedical applications.

6. Bio-nanomaterials

Numerous efforts have been made on the development of novel biomaterials such as proteins/enzymes, nucleic acids, biopolymers, etc. and their nanocomposite consisting of metal, semiconductor, carbon and CPs for applications in biosensors, cell targeting, bio-imaging, biomineralization, biocatalysts, and drug delivery because of their unique recognition, transport, electronic and catalytic properties (Saidur et al., 2017). The combination of biotechnology and nanotechnology has directed the growth of nanocomposite materials, towards novel electrochemical biosensor platform incorporating highly selective catalytic and recognition properties of biomaterials, including proteins/enzymes, peptides, nucleic acids, and biopolymers. Over the past two decades, bio-nanomaterials based electrochemical biosensor platforms have been successfully designed and attracted much attention due to their efficient sensing performances in terms of great sensitivity, selectivity and biocompatibility. With the advancement in synthesis, functionalization and integration of bio-nanomaterial, desired level of sensitivity and selectivity, rapid response, and speedy recovery can easily be achieved in the biological systems. A few selective biomaterial based electrochemical sensor platforms for the detection of biomolecules is highlighted in the following section.

6.1. Aptamers

Aptamers based biosensors have been focused much attention due to their high affinity, selectivity, and specificity which are equal to or even superior to antibodies. Aptasensors have shown an excessive assurance in protein sensing with high sensitivity, selectivity, and low-cost. Li et al. have developed a protein biosensor using a nanocomposite

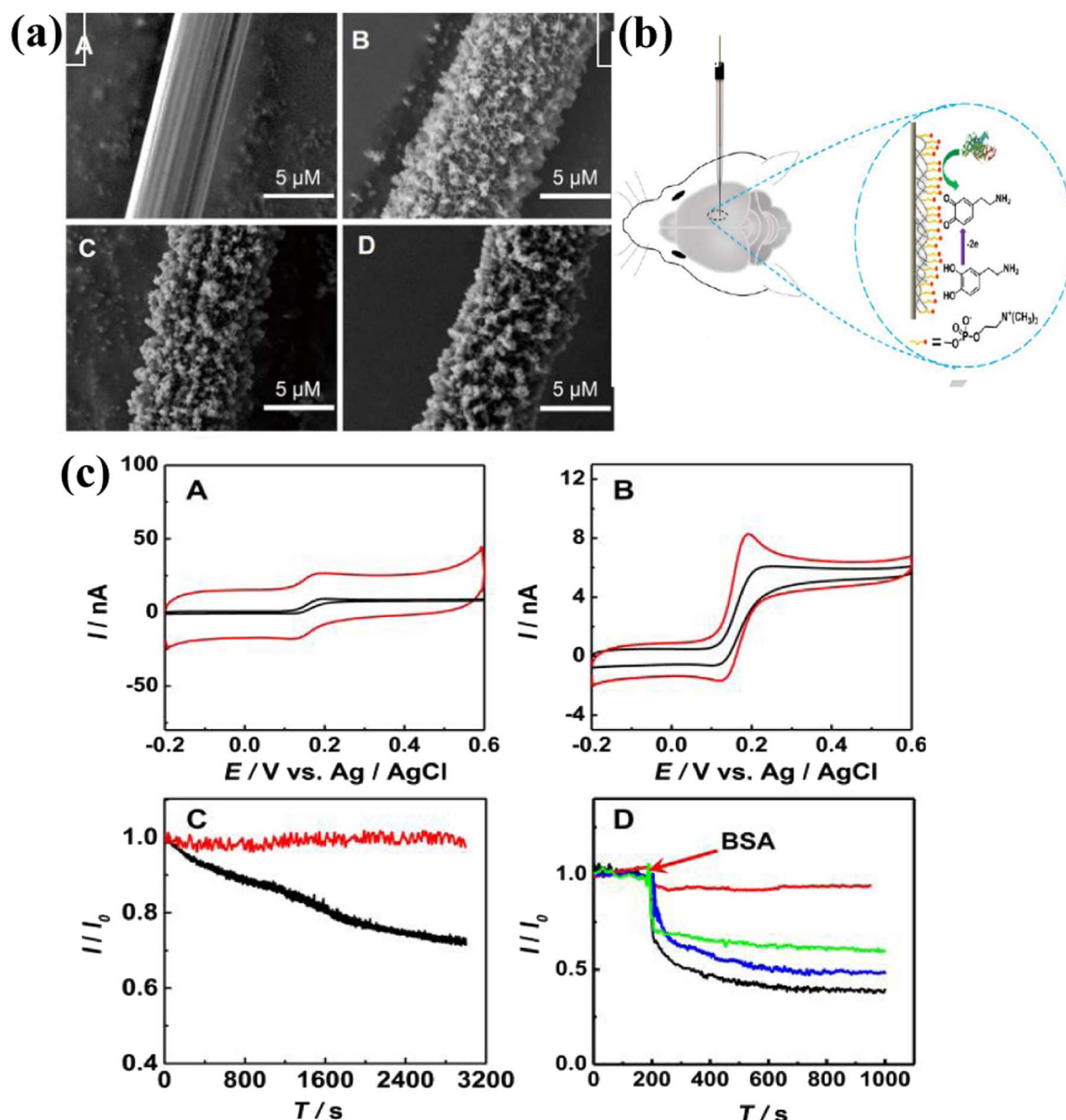


Fig. 8. (a) SEM images obtained for bare CFE (A), PEDOT/CFE (B), PEDOT-OH/CFE (C), and PEDOT-PC/CFE (D). (b) Schematic representation of *in vivo* monitoring of dopamine (DA) using microelectrode. (c) CVs recorded at PEDOT/CFE (red curve) (A), PEDOT-PC/CFE (red curve) (B), and bare CFE (black curves in A and B) in a CSF containing 20 μM DA. (D) *i-t* response towards 20 μM DA recorded with CFE (black) and PEDOT-PC/CFE (red). (D) *i-t* response towards 20 μM DA recorded with CFE (black), PEDOT/CFE (blue), PEDOT-OH/CFE (green), and PEDOT-PC/CFE (red) upon the addition 10 mg mL⁻¹ BSA (X. Liu et al., 2017).

of CNTs, aptamer, and horseradish peroxidase (HRP) (Li et al., 2015) for thrombin with a sensing limit of 0.05 pM. The amperometric aptasensor based on various sensing substrates of nanocomposites such as ferrocene-aptamer-CNTs, alkaline phosphatase-aptamer-SWCNTs, aptamer-Au NPs-SWCNTs, aptamer-MWCNTs-ionic liquid-chitosan, etc. have been established for thrombin detection. The microfluidic aptamer-based electrochemical biosensor for the detection of cardiac organoids was developed by Shin et al. (2016). Gold based microelectrode was functionalized with aptamers, which were highly selective to creatine kinase (CK)-MB (CK-MB) biomarker secreted from a damaged cardiac tissue. This biosensor was accessed to sense trace amounts of CK-MB secreted by the cardiac organoids upon drug treatments, agreeing well with the thrashing characteristics and cell feasibility scrutinises. In recent years, the advancements in microfluidics provide new tactics to construct biomimetic human organoid models that mimic both the biology and the physiological microenvironment of the human system.

6.2. DNA nanostructures

DNA triplex structure is very similar to the structure of aptamer, which has been employed for the design of biosensors due to its high selectivity, low cost, simple synthesis, reusability, and high affinity and flexibility. For instance, Fu et al. have recently demonstrated a melamine biosensor based on DNA on an indium tin oxide (ITO) electrode surface (Fig. 9A; Fu et al., 2016). This biosensor presented a low detection limit of 0.43 nM with a wide linear range from 1.0 nM to 0.5 μM (Fig. 9B&C). Deng et al. have demonstrated a dual signal-tagged hairpin structured DNA(dhDNA)-based ratiometric probe using the combination of ferrocene-labeled signal probe (Fc-sP) and methylene blue-altered internal orientation probe (MB-rP) in one hairpin-structured DNA for the detection of Mucin 1 (MUC1) (Deng et al., 2017). Mucin 1 (MUC1) is considered as a tumor marker model. This is very substantial for the initial diagnosis, distinguishing diagnosis, remedial consequence monitoring, and continuation inspections of patients with tumors or

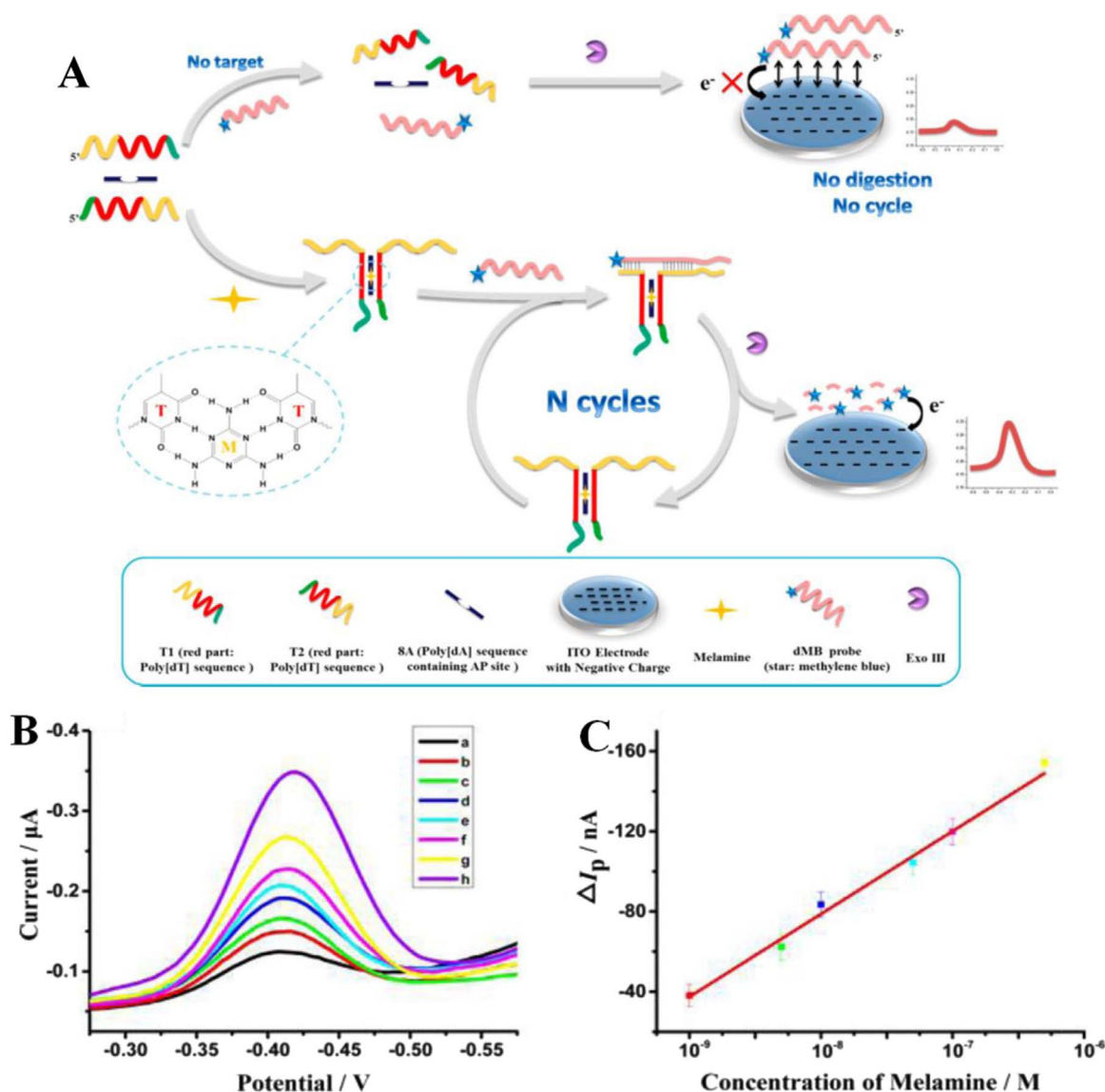


Fig. 9. Scheme for the melamine sensor based on DNA triplex structure and exo III-assisted recycling amplification (A). DPV curves (B) and corresponding calibration plot (C) for sensing of melamine in the range of 1.0 nM – 1.0 μM (Fu et al., 2016).

carcinomas. Hemagglutinin (HA) based electrochemical biosensors such as genosensors and immunosensors were developed for biomedical applications. Recently, neuroaminidase (NA) enzyme activity assessment based biosensor was designed for the detection of influenza A virus by Anik et al. (2016). Nanomaterial based signal amplification, enzyme-based signal amplification, and DNA facilitating amplified sensor have been employed to attain high sensitivity and selectivity. Electrochemical immunosensors based on functional nanomaterials are used for miniaturization of devices, creating them suitable for POC diagnosis, DNA/enzyme amplification approach, and new electro-analytical techniques.

7. Conclusions and outlook

Introduction of novel functional nanomaterials and analytical technologies signify a foremost opportunity for the development of electrochemical sensor and biosensor platforms. These novel sensor platforms are accomplished conceivably by offering new surface modifications, microfabrication techniques, and a diversity of new materials with unique properties. Low-cost, portable, energy efficient, easy fabrication, and simultaneous sensing performance are major advantages

of continued growth of electrochemical sensing and biosensing platforms, attracting the interdisciplinary research arenas spanning chemistry, material science, biological science and medical industries. This review highlights the importance of nanomaterials based electrochemical sensor and biosensor platforms for biological, biotechnological, and biomedical applications. Detailed electrochemical sensing and bio-sensing strategies based on wide range of nanomaterials such as noble nanomaterials, semiconducting metal oxide nanomaterials, carbon nanomaterials, polymeric nanomaterials, bio-materials, and their nanocomposites are described as unique and amplified functionality towards various applications. The application of electrochemical sensor and biosensor platforms have been much attracted for *in vivo* and *in vitro* analysis relating a judiciously planned electrode/solution interface. High sensitivity and selectivity, fast response, and excellent durability in biological media are all critical subjects to be addressed in-depth. As displayed in Table 1, diverse sensing nanomaterials are employed to progress the electrochemical sensing and biosensing performance towards biological and biomedical applications. An enormous research has been focused on the construction of nanocomposites based electrodes consist of noble metal nanoparticles or metal oxides with carbon nanomaterials or polymer materials. The advanced

Table 1

A list of advanced nanomaterials based electrochemical sensor and biosensor platforms for biological and biomedical applications.

Material	Analyte	Detection limit	Linear range	Reference
Au-Cys-Bt	Ascorbic acid	87.0 nM	1.0 μ M - 25 mM	(Yadav et al., 2017)
	Uric acid	93.0 nM	1.0 μ M - 0.2 mM	
	Folic acid	78.0 nM	5.0 μ M - 1.5 mM	
Au NPs	RSNOs	100.0 nM	100.0 nM - 1.0 μ M	(Baldim et al., 2016)
Au-MSM	Ascorbic acid	165.0 nM	50.0 μ M - 15.0 mM	(Gupta et al., 2015)
	Uric acid	214.0 nM	20.0 μ M - 17.0 mM	
Au NPs/MMPF-6(Fe)	Hydroxylamine	4.0 nM	10.0 nM - 4.0 μ M	(Wang et al., 2016a)
Au NPs/GO	ATP	6.7 fM	0.02–200.0 p.M.	(Dong et al., 2016)
Au NPs/GR	HbA1c	0.2 μ M	0.3–2000.0 μ M	(Jain and Chauhan, 2017)
Au NPs/GO-IL	Dopamine	2.3 nM	7.0 nM - 5.0 mM	(J. Li et al., 2017a)
Ni/Ag@C	H ₂ O ₂	10.0 μ M	0.03–17.0 mM	(Sheng et al., 2017)
Ag NPs/CP	MOXI	2.9 nM	0.7 μ M - 0.2 mM	(Fekry, 2017)
Ag NPs/rGO	NO	2.8 μ M	10–220 μ M	(Ikhsan et al., 2016)
Ag-P(MMA-co-AMPS)	Isoniazid	10.0 nM	50–150000 μ M	(Rastogi et al., 2016)
Ag ₆ @rGO-Nf	H ₂ O ₂	0.5 μ M	1.0–300.0 μ M	(Yusoff et al., 2017)
Ag-Bt	H ₂ O ₂	9.1 μ M	10.0–15000 μ M	(Yadav et al., 2016)
Ag NPs/HNTs	Glucose	0.2 mM	0.2–6.0 mM	(K.-Krishnan et al., 2016)
Pt NPs/GR-GO _x	Glucose	0.6 mM	0.0–0.9 mM	(A.-Llobregat et al., 2017)
Pt NPs/Nf-GO _x	Glucose	0.1 mM	0.1–10 mM	(Parrilla et al., 2017)
Pt NPs/WC NTs	Oxalic acid	12.0 nM	0.0–125.0 nM	(Maiyalagan et al., 2014)
Pt NPs/Co ₃ O ₄ /rGO	NO	1.7 μ M	10.0–650.0 μ M	(Shahid et al., 2015)
PtW NPs/rGO-IL	NO	0.13 nM	2.0 nM - 1.2 mM	(Govindhan and Chen, 2016)
Pd NPs	Brucella	27.0 zM	1.0 p.M. - 0.1 a.M.	(Rahi et al., 2016)
Pd NPs-GO	Ascorbic acid	20.0 μ M	0.02 – 2.3 mM	(Wu et al., 2012)
Pd-Au NPs/NPSS	Levodopa	0.2 μ M	5.0 – 55.0 μ M	(Rezaei et al., 2016)
	Uric acid	15.0 μ M	100.0 – 1200 μ M	
PdCu NPs/SWCNHs	NT-proBNP	0.05 pg mL ⁻¹	0.001 – 25.0 ng mL ⁻¹	(Liu et al., 2017b)
Pd NPs/SH- β -CD-GR	Rutin	0.3 nM	1.0 nM – 30.0 μ M	(Z. Liu et al., 2017)
	Isoquercitrin	1.6 p.M.	5 p.M. – 5.0 μ M	
	H ₂ O ₂	0.1 mM	0.1–1.0 mM	
CeO ₂ /SWCNH	Glucose	0.01 μ M	0.5 – 639.0 μ M	(Bracamonte et al., 2017)
CuO/N-rGO	Glucose	0.04 mM	0.02 – 8.0 mM	(S. Yang et al., 2017)
Co ₃ O ₄ /GR	PSA	0.03 pg mL ⁻¹	0.0001–100.0 ng mL ⁻¹	(M. Yang et al., 2017)
Cu ₂ O@CeO ₂ /Au NPs	Dopamine	0.13 nM	100.0 nM– 1.0 mM	(Pecher et al., 2017)
α -Fe ₂ O ₃ @AuPd NPs	Uric acid	1.8 μ M	1.0 μ M – 1 mM	(Sumathi et al., 2016)
	SCCA	33.0 fg mL ⁻¹	100fg – 80 ng mL ⁻¹	
Co ₃ O ₄ @CeO ₂ -Au@Pt	Glucose	2.0 μ M	0.005–8.6 mM	(Y. Li et al., 2017a)
NiCo ₂ O ₄ NWs-rGO	Lipoprotein	0.02 μ M	0.02–0.4 mM	(Ma et al., 2016)
CysCdS-NiO	Glucose	0.1 mg dL ⁻¹	0.01–200 mg dL ⁻¹	(Ali et al., 2016c)
ZnO/Au NPs	Glucose	1.8 μ M	5.0 μ M – 2.0 mM	(Munje et al., 2017)
M13@MnO ₂ /GO _x	Acetylcholine	4.0 nM	4.0 nM – 800.0 μ M	(Han et al., 2016)
Fe ₂ O ₃ NPs/rGO/PEDOT	H ₂ O ₂	10.0 nM	0.1 – 360.0 μ M	(Chauhan et al., 2017)
TiO ₂ /rGO/Hb	Dopamine	11.0 nM	–	(H. Liu et al., 2017)
CNTs-Nb	NO	10.0 nM	10 – 200 nM	(Yang et al., 2016)
SWMT/PEDOT	Ascorbic acid	50 μ M	0 – 1.0 mM	(Jin et al., 2017)
CNF	Glucose	0.021 μ M	0.05–12.0 mM	(L. Zhang et al., 2017)
Ni@f-MWCNT	PDGF-BB	60 pg mL ⁻¹	0.1–100 ng mL ⁻¹	(Baskaya et al., 2017)
Ag NPs/MWCNT	Diethylstilbestrol	24.3 fg mL ⁻¹	0.1 ng–0.1 mg mL ⁻¹	(Song et al., 2016)
Au NPs/MWCNT-CS	5-Hydroxytryptophan	77.0 nM	2.0–400 μ M	(Bai et al., 2017)
PdNPs/MWCNT	Progesterone (P4)	2.2 nM	0.01–0.5 μ M	(Kumar et al., 2017)
Fe ₃ O ₄ /GQD/f-MWCNT	Dopamine	50 nM	0.1 – 100 μ M	(Arvand and Hemmati, 2017)
GNS-CNTs/MoS ₂	Diazepam	87.0 nM	0.3–700.0 μ M	(Mani et al., 2016)
CNTs/IL	Acetaminophen	2.1 nM	5.0 nM – 0.8 mM	(Rahimi-Nasrabadi et al., 2017)
ERG	NADH	1.1 nM	50 nM - 500 μ M	(Adhikari et al., 2015)
Au NPs/rGO	H ₂ O ₂	16.0 nM	0.05–518.2 μ M	(Govindhan et al., 2015)
Au NPs/rGO	LDL	5 mg dL ⁻¹	0 – 130 mg dL ⁻¹	(Thirumalraj et al., 2016)
NiO/rGO	α -Fetoprotein	0.2 pg mL ⁻¹	0.5 pg – 10 ng mL ⁻¹	(Ali et al., 2016b)
Cu ₂ SnZnS ₄ /CD/GR	Tetracycline	1.0 pg mL ⁻¹	2.0 pg – 20 ng mL ⁻¹	(L. Liu et al., 2017)
GO/AP	Lactate	2.5 μ M	2.5–90 μ M	(Tang et al., 2017)
rGO/LDH	Glucose	0.3 μ M	1.0 μ M – 3.6 mM	(Manna and Raj, 2016)
rGO/PDA/MOF/GOx	DNA	0.3 fM	1.0 fM – 10.0 p.M.	(Wang et al., 2016b)
MWCNTs-PPy-PAMAM	Paracetamol	0.1 μ M	0.3 μ M – 0.2 mM	(Miodek et al., 2015)
MWCNTs-PAMAM	Acetaminophen	0.2 μ M	0 – 17.0 mM	(Y. Zhang et al., 2016a)
Pt NPs-PAMAM	H ₂ O ₂	25 μ M	50 – 800 μ M	(Armada et al., 2016)
GR-PAMAM	α -fetoprotein	0.3 fg mL ⁻¹	1fg mL ⁻¹ –80 ng mL ⁻¹	(Rao Vusa et al., 2016)
PAADs@CNDs	Dopamine	80.0 nM	20.0–750 μ M	(S. Zhang et al., 2016)
PANI/Au NPs	Ascorbic acid	10.0 nM	50.0–1550 μ M	(Sadanandhan and Devaki, 2017)
	Serotonin	25.0 nM	50.0–540 μ M	
	Uric acid	40.0 nM	50–550 μ M	
	Glucose	12.0 μ M	0.15 – 13.0 mM	
	Dopamine	3.5 nM	0.01– 40 μ M	
PoPD/Ag-NPs	H ₂ O ₂	2.2 μ M	5.0 – 50.0 μ M	(J. Wang et al., 2017)
rGO-poly(Cu-AMT)	Dopamine	2.0 nM	0.05–100 μ M	(Y. Li et al., 2017b)
SBP-PANI-PAA	5-Hydroxytryptamine	3.0 nM	0.05–150 μ M	(Torres et al., 2017)
GR/p-AHNSA				(Raj et al., 2017)

(continued on next page)

Table 1 (continued)

Material	Analyte	Detection limit	Linear range	Reference
PVA/PEI NFs	Glucose	0.9 μM	10–200 μM	(Sapountzi et al., 2017)
LP/PC	Leukemia cells	68 cells mL^{-1}	1.0×10^3 – 2.5×10^5	(Gurudatt et al., 2016)
G-QDOD	PARP	0.003 U	0.01–1.0 U	(Xu et al., 2016)
NVC-EHA-AA	Paracetamol	0.3 μM	1.0 μM –10 mM	(Luo et al., 2016)
Ag-N-rGO	Salbutamol	7.0 nM	0.03–20.0 μM	(J. Li et al., 2017b)
Ni@PANI NPs	Creatinine	0.2 nM	40–800 nM	(Rao et al., 2016b)
CAR-SWNTs	Carvedilol	16.1 μM	50–325 μM	(Coelho et al., 2016)
AuNPs/MWCNTs-CS	Diethylstilbestrol	24.3 fg mL^{-1}	0.1 pg–1.0 ng mL^{-1}	(Bai et al., 2017)
CNTs/APT/HRP	Thrombin	0.05 p.M.	0.05 p.M.–50 nM	(Li et al., 2015)
Au/APT	Creatine kinase	1.0 ng mL^{-1}	10.0 pg–100 ng mL^{-1}	(Shin et al., 2016)
Fe-A/NA	Influenza A	–	–	(Anik et al., 2016)
DNA/ITO	Melamine	0.43 nM	1.0 nM–0.5 μM	(Fu et al., 2016)
dhDNA/ Fc-sP/MB-rP	MUC1	0.8 nM	0.0 nM–0.1 mM	(Deng et al., 2017)
HAP/ALP	BACE1	5.0 nM	5.0–150 nM	(Qu et al., 2016)
SWCNT-Polytyr	NADH	7.9 nM	0.2–83.0 μM	(Eguilaz et al., 2016)
DNA-L-Au NPs	Telomerase-A	2.3×10^{-9} IU	0–32000 cells mL^{-1}	(Feng et al., 2017a)
GO-ssDNA	VEGF	1.0 ng mL^{-1}	1.0–100 ng mL^{-1}	(Pan et al., 2017)
	PSA	0.05 ng mL^{-1}	0.05–100 ng mL^{-1}	
MoS ₂ -Au-PEI-hemin	Clenbuterol	1.9 ng mL^{-1}	10.0 ng–2.0 $\mu\text{g mL}^{-1}$	(Y. Yang et al., 2017)
anti-CTV/MUA-MPA/Au	CTV	0.3 nM	1.0 nM–5.0 μM	(Liu et al., 2014)
PtCu@rGO/g-C ₃ N ₄	PSA	16.6 fg mL^{-1}	50 fg mL^{-1} –40 ng mL^{-1}	(Feng et al., 2017b)
N-GR/CEA	Tumor	0.01 ng mL^{-1}	0.02–12 ng mL^{-1}	(Feng et al., 2017b)
MoS ₂ /AuNRs/HRP-Ab ₂	Microcystin-LR	5.0 ng L^{-1}	0.01–20 g L^{-1}	(Y. Zhang et al., 2017)

nanocomposites favor the immobilization enzyme or bioactive molecules thereby enhances the catalysis due to their synergistic effect. In certain noble metal nanoparticles, especially gold nanoparticles show intrinsic characteristics and played a key responsibility in designing sensitive biosensors. Advanced nanomaterials constructed electrochemical sensing and biosensing platforms have potential for improving the scope of present neuroscience diagnostics, clinical, and point-of-care diagnostics.

Fabrication of robust device with rapid, sensitive, selective, stable, inexpensive, high throughput, and miniaturized features for the detection of biological analytes is yet to be established and thus the research on *in vivo* and *in vitro* sensing has a great potential. There are several opportunities to integrate the high-performance electrochemical sensing and biosensing platforms with analytical methods for biological, biotechnological, and biomedical applications. (i) The development of prime electrochemical active sites by tuning size and shape controlled nanomaterial synthesis; (ii) the establishment of enhanced sensitivity and selectivity by optimizing the bi- or tri-metallic nanomaterials with exceptional catalytic properties; (iii) the ease of functionalization of nanomaterials using appropriate functional organic or biomolecule, offering high selectivity to the sensor; (iv) the enhancement of electrochemical properties by designing nanocomposites consisting of high conductive and chemically stable substrate materials with huge surface to volume ratio; (v) the integration of *in situ* electrochemical methods with physiological techniques and (vi) the development of multiple sensing measurements in a complex situation by designing layer of excellent sensitive and selective nanomaterials on the electrode surface. Finally, the integration of micro- or nano-scale electrodes or array of electrodes to expedite the brain or other biological mapping studies has to be developed. In summary, the online *in vivo* and *in vitro* monitoring of analyte signals using electrochemical sensor remains a challenging task and it is believed that electrochemical sensor and biosensor platforms hold an excellent potential by captivating merits of latest developments in electrochemistry, electric/electronic engineering, and biochemistry. Further advances in novel synthetic approaches of functional nanomaterials and analytical sensing strategies will certainly influence the discovery of unique physicochemical properties of nanomaterials towards biomedical applications.

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