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REVIEW ARTICLE

Electrochemical sensors based on metal and semiconductor nanoparticles

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Abstract Metal and semiconductor nanoparticles exhibit unique optical, electrical, thermal and catalytic properties. Therefore, they have attracted considerable interest and have been employed for construction of various electrochemical sensors. This minireview gives a general view of recent advances in electrochemical sensor development based on metal and semiconductor nanoparticles covering genosensors, protein and enzyme-based sensors, gas sensors and sensor for other organic and inorganic substances. Different assay strategies based on metal and semiconductor nanoparticles for biosensor and bioelectronic applications are presented, including electrochemical, electrical, and magnetic signal transduction techniques. Electrochemical transduction principles provide signal changes in conductance, charge, potential and current. We have paid much attention to the potential-based and current-based sensors herein. Lastly, a brief introduction is given into advances concerning the role of nanoparticles, quantum dots and nanowires for nanomedicine, such as drug delivery and discovery.

Keywords Electrochemistry · Sensors · Biomolecules · Metal and semiconductor nanoparticles · Nanomedicine

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Introduction

With the development of nanotechnology the nanoparticles attract substantial interest because they exhibit unique optical, electrical, thermal and catalytic properties. These properties originating from quantum-size dimensions could change with their sizes and shapes. Nanosized particles have a chemical behavior similar to small molecules and can be used as specific electrochemical label, and yet if the particles are excessively small the high surface energy and the large curvature can make them unstable [1–6]. Generally, the particles size can be controlled by kinds of synthesis methods including physical and chemical methods, then further characterized by various types of devices and applied to various fields involving in biological medicine, environment engineering, information technology, aerospace industry, food analysis and so on. In recent years, the utilizing superstructure of metal and semiconductor nanoparticles for electrochemical sensors organization is an extremely promising prospect [7, 8].

Metal and semiconductor nanoparticles as sensing elements could be immobilized on working electrode surface by kinds of methods including physical adsorption, chemical covalent bonding, electrodeposition, electropolymerization with redox polymers and so on. Multilayers of conductive nanoparticles modified electrode could give a porous film with high specific surface area where the local microenvironment of metal and semiconductor nanoparticles could be controlled by the crosslinking elements. The porous property endues the modified electrodes with strong adsorption ability to most of substrates. That is to say, substrates could be accumulated on the surface of the electrode. In addition to this accumulation effect, this kind of modified electrode may lead to specific and selective interactions with substrates [9–11]. Mono- or multilayer arrays of conductive nanoparticles assembled on the electrode surfaces may be considered as assemblies of nanoelectrodes of controllable active areas [12]. The catalytic properties of metal and semiconductor nanoparticles could decrease overpotential of some important reactions in electrochemical analysis and even provide electrochemical reversibility for redox reactions which are irreversible at traditional bulk electrodes [2], sometimes, could further enhance the electrochemical responses greatly. Recently, the molecule- and polymer-functionalized sensing surface of metal and semiconductor nanoparticles have been employed for developing all kinds of electrochemical sensors and nano-devices. The constructed sensors have special functions and could be applied to related sensing or biosensing and bioelectronics research area, covering deoxyribonucleic acid (DNA) hybridization, protein–protein interaction and small molecules determination, cell and microbe analysis, nanomedicine and so on.

It is the aim of this minireview to summarize the recent advances in metal and semiconductor nanoparticles-based electrochemical sensors. We will discuss: (i) Genosensors including rarely direct DNA determination based on the redox of bases or sugar residues using nanoparticles and mainly indirect analysis using metal and semiconductors as electrochemical labels for amplifying detection or hydridization analysis. (ii) Protein sensors and enzyme based sensors. (iii) Electrochemical sensors for small molecules such as neurotransmitter based on the electrocatalytic properties of metal and semiconductor nanoparticles. (iv) Electrochemical detection of metal ions, gas and other inorganic substrates. (v) Roles of metal and semiconductor nanoparticles in medicine. This review attempts to present a relatively good coverage of recent review articles and a selection of original research articles emphasizing new developments or principles for metal and semiconductor nanoparticles-based electrochemical sensors. But only a fraction of relevant works could be covered here, and not all excellent works being done in this field could be given due credit. So the authors apologize to anybody who feels that some key papers have been left out.

Genosensors

Deoxyribonucleic acid (DNA) analysis is helpful to understand many diseases on a molecular level and promise new perspectives for medical diagnosis in future. DNA bearing the genetic information is a double helix molecule and the double helix is held together by two sets of forces, as described earlier: hydrogen bonding between complementary base pairs and base-stacking interactions. Pioneer research about electroactivity of nucleic acid began in 1960, and electrochemical devices have been considered as promising tools for these purposes [13]. Direct electrochemistry of nucleic acids based on the redox of bases or sugar residues is poorly developed with very high overpotential and limited voltammetric peaks. Several methods to improve the signal response have been reported via CNTs or its composite film modified electrode [14], but indirect methods for DNA analysis based on determination of electroactive indicators that intercalate or otherwise associate with DNA has witnessed tremendous growth. Powerful metal and semiconductor nanoparticles or their functional complexes offer excellent prospects for chemical and biological sensing because of their unique optical and electrical properties.

On one hand, with the development of electrochemical DNA sensors, it is necessary to search for new efficient surface-immobilization techniques to enhance immobilization amount and ultimate detection capacity of sequence-specific DNA. Metal and semiconductor nanoparticles with a large surface area have been used to enhance ssDNA immobilization capacity on an electrode, and develop a sensitive electrochemical DNA sensor with an improved sequence-specific DNA detection capacity [15, 16]. For example, Fang's group has early developed an electrochemical DNA biosensor utilizing colloidal Au to enhance the DNA immobilization amount and ultimately lower its detection limit [17]. Self-assembly of approximately 16-nm diameter colloidal Au onto a cysteamine modified gold electrode resulted in an easier attachment of an oligonucleotide with a mercaptohexyl group at the 5′-phosphate end, and therefore an increased capacity for nucleic acid detection. Quantitative results showed that the surface densities of oligonucleotides on the Au colloid modified gold electrode were approximately 1.0×10^{14} molecules cm^{-2}. A detection limit of 5×10^{-10} $\mathrm{mol{\cdot}L^{-1}}$ of complementary ssDNA could be obtained, which was much lower than many electrochemical DNA biosensors.

On the other hand, because of their special characteristics metal and semiconductor nanoparticles are widely used as effective labels of DNA or relative markers for amplifying electric sensing signals, especially gold and silver nanoparticles [18–25]. Mirkin [26] has exploited the silver-deposition technique to construct a sensor based on conductivity measurements. A sharp drop in the resistance of the circuit could be carried out. Subsequently, as 'tracer amplification', deposition of colloidal gold and silver on the gold nanoparticles after DNA hybridization have been used to signal amplification in various DNA detection assays and three strategies for the detection of gold tracers have been reported, which are integrated by Merkoçi and co-workers [27]. Anodic-stripping voltammetry (ASV) was employed to determine the gold (III) ions dissolving with HBr/Br_2 [28] and enhanced electrochemical signal was obtained [29, 30]. Merkoçi and co-workers have reviewed recent important achievements on the electrochemical sensing of DNA concerning Au nanoparticles (AuNPs) [31]. Some novel strategies for AuNP based genosensors have been discussed. As shown in Fig. 1, these strategies consist of: (a) the electrochemical detection of AuNPs label by detecting the gold ions released after acidic dissolving; (b) direct detection of AuNPs anchored onto the surface of a conventional genosensor (based on stripping voltammetry); (c) silver enhancement using conductometric technique; (d) enhancement of AuNPs anchored to conventional genosensor surface by using silver or gold; (e) AuNPs as carriers of other AuNPs; (f) using AuNPs as carriers for other electroactive labels.

In addition to above-mentioned nanoparticles-labeled DNA sensor, quantum dot (QD) has also attracted the attention of research workers. QD is one kind of semiconductor particle that has all three dimensions confined to the 1–10 nm length scale [32]. Compared with existing labels, nanoparticles in general and QD in particular are more stable and cheaper. They allow excellent flexibility, fast binding kinetics (similar to those in a homogeneous solution), high sensitivity and reaction rates for many types of multiplexed assays, ranging from immunoassays to DNA analysis. A detection method of DNA hybridization based on labeling with QD tracers has been developed with electrochemical-stripping measurements of the nanoparticles [33–37]. Wang's group reported a new multi-target sandwich hybridization assay involving a dual hybridization event, with probes linked to three tagged inorganic crystals and to magnetic beads [37]. The DNA-connected QD yielded well-defined and resolved stripping peaks at −1.12 (Zn), −0.68 (Cd) and −0.53 V (Pb).

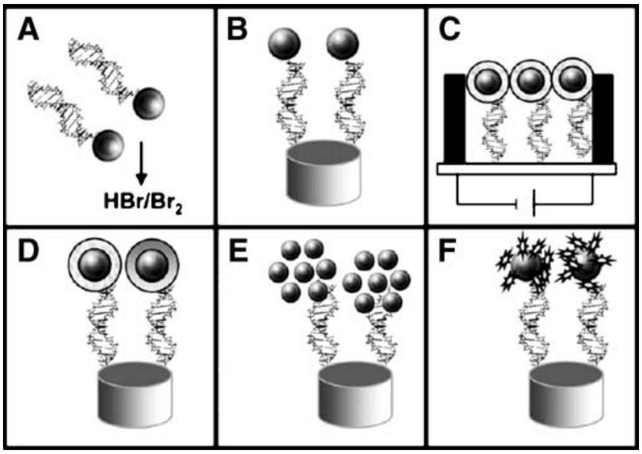

Fig. 1 Schematic (not in scale) of the different strategies used for the integration of gold nanoparticles (AuNPs) into DNA sensing systems: **a** Previous dissolving of AuNP by using HBr/Br$_2$ mixture followed by Au(III) ions detection; **b** direct detection of AuNPs anchored onto the surface of the genosensor; **c** conductometric detection, **d** enhancement with silver or gold followed by detection; **e** AuNPs as carriers of other AuNPs; **f** AuNPs as carriers of other electroactive labels. Reprinted from [31]

Following similar amplification strategy as mentioned above, many methods based on other composite/functionalized metal and semiconductor nanoparticles have also been developed for the sensitive quantification of DNA [35, 38–41]. A method for amplified voltammetric detection of DNA hybridization via oxidation of ferrocene caps on gold nanoparticle/streptavidin conjugates was developed by Zhou [42]. In this work, Gold nanoparticle/streptavidin conjugates covered with 6-ferrocenylhexanethiol were attached onto a biotinylated DNA detection probe of a sandwich DNA complex. The amplification of the voltammetric signals was attributed to the attachment of a large number of redox (ferrocene) markers per DNA duplex formed. A detection limit for oligodeoxynucleotide samples, down to 2.0 pM (10 amol for the 5 μL of sample needed) was obtained. The amenability of this method to the analyses of polynucleotides (i.e., PCR products of the pre-S gene of hepatitis B virus in serum samples) was also demonstrated. This method did not require labeling of the DNA targets. Because this approach was shown to be simple, selective, reproducible, and cost effective and it was used for real sample analysis. PCR products of hepatitis B virus pre-S gene extracted from serum samples were measured.

Magnetic nanoparticles (e.g., Fe_3O_4), biomaterial-functionalized magnetic particles and related techniques have been applied in a broad variety of bioelectronic applications because they permit easy separation, efficient concentration and rapid biospecific binding [2, 43, 44]. A number of works focusing on magnetic based electrochemical sensors have been reported [30, 45–48]. Li's group [47] reported the electrochemical detection of hybridized DNA strands with a magnetic nanoparticles modified electrode using commonly electrochemical couple $K_3[Fe(CN)_6]$/$K_4[Fe(CN)_6]$ as probe. The detection was proved to be fast and very simple and magnetic nanoparticles could be employed to control the DNA hybridization process. An inhibited or an enhanced degree of hybridizing could be produced. Wang et al. reported a protocol for detecting DNA hybridization based on a magnetically induced solid-state electrochemical stripping detection of metal tags [30]. The bioassay involved the hybridization of a target oligonucleotide to probe-coated magnetic beads, followed by binding of the streptavidin-coated gold nanoparticles to the captured target, catalytic silver precipitation on the gold-particle tags, a magnetic "collection" of the DNA-linked particle assembly and solid-state stripping detection. The magnetic triggering of the electrical DNA detection was realized through a "magnetic" collection of the magnetic-bead/DNA-hybrid/metal-tracer assembly onto a thick-film electrode transducer to allow direct electrical contact of the silver precipitate. The resulting solid-state electrochemical transduction offered highly sensitive and selective detection of DNA hybridization. At the same time, the reversible magnetically controlled oxidation of DNA was accomplished in the presence of nucleic acid-modified magnetic particles [45]. Avidin modified magnetic particles were functionalized with the biotinylated probe nucleic acid, and subsequently hybridized with the complementary DNA. Two carbon-paste electrodes were patterned on a surface and applied as working electrodes. Spatial deposition of the functionalized magnetic particles on the right or left electrode enabled the magneto-controlled oxidation of the DNA by chronopotentiometric experiments (potential pulse from 0.6 to 1.2 V). Changing the position of the magnet was thus used for ON and OFF switching of the DNA oxidation (through attraction and removal of DNA functionalized-magnetic particles). Such magnetic triggering of the DNA oxidation holds great promise for the analysis of DNA on arrays. Functionalized magnetic particles were employed for the ON–OFF switching of bioelectrocatalytic processes [43, 49, 50]. Also, the rotation of functionalized magnetic particles on electrode supports was used to amplify bioelectrocatalytic reactions [51, 52] and biosensing analysis of DNA [53]. Willner reported on the reversible blocking of the electrochemical and bioelectrocatalytic processes at electrodes by attraction of the hydrophobic magnetic NPs to the electrode surface [54–56].

Compared to enzymes/protein, Au nanoparticles show better long-term stability and are more easily prepared. In addition to the protocols for DNA detection that were described above, Chen has recently reported an electrical detection method on a DNA biochip that employed a novel approach for ultra sensitive detection of DNA using self-assembled gold nanoparticles and bio-bar-code-based amplification (BCA) DNA [57]. The experimental study relied on three-components oligonucleotide-modified gold nanoparticles, single-component oligonucleotide-modified magnetic nanoparticles and subsequent detection of amplified target DNA in the form of bio-bar-code ssDNA (single strand DNA) using a chip-based detection method. In this way, magnetic nanoparticles and bio-bar-code DNA were used to amplify obtainable current through nanogap electrodes from the extremely low concentration of target DNA. The detective concentration of target DNA with electrical DNA biosensor was as low as 1 fM for the analysis of current–voltage curves [57]. Also, a novel nanoparticle-based detection of DNA hybridization has been performed based on magnetically induced direct electrochemical detection of the 1.4 nm Au_{67} QD tag linked to the target DNA [j1]. The Au_{67} nanoparticle tag was directly detected after the DNA hybridization event, without need of acidic (i.e., HBr/Br_2) dissolution. The characterization, optimization, and advantages of the direct electrochemical detection assay for target DNA were demonstrated. The two main highlights of presented assay were (1) the direct voltammetric detection of metal QDs obviates their chemical dissolution and (2) the Au_{67} QD-DNA_1/DNA_2-paramagnetic bead conjugate did not create the interconnected three-dimensional network of Au-DNA duplex-paramagnetic beads as previously developed nanoparticle DNA assays, pushing down the achievable detection limits [58].

Recently, Yang described an Au nanocatalyst-based assay for electrochemical DNA detection that combined the advantages of magnetic beads (MBs, coated with streptavidin) and AuNPs (modified with a thiolated DNA monolayer). Capture-probe-conjugated magnetic beads and a ferrocene (Fc)-modified indium-tin oxide (ITO) electrode were used as the target-binding surface and the signal-generating surface, respectively [59]. Figure 2 shows a schematic diagram of a sandwich-type electrochemical DNA sensor using AuNPs as catalytic labels. Biotinylated capture probes were biospecifically immobilized onto streptavidin-coated MBs [59]. After target DNAs were hybridized to capture-probe-conjugated MBs, detection-probe-conjugated AuNPs were hybridized. The resulting target DNA-linked MB-AuNP assemblies were attracted to an Fc-D-modified ITO electrode by an external magnet. The MB-AuNP assemblies were incubated for 15 min to generate a large amount of pAP from pNP in the presence of $NaBH_4$. The generated pAP near an Fc-D-modified ITO electrode is electrooxidized to *p*quinoneimine (pQI) via the electron transfer mediated by Fc. pQI is then reduced back

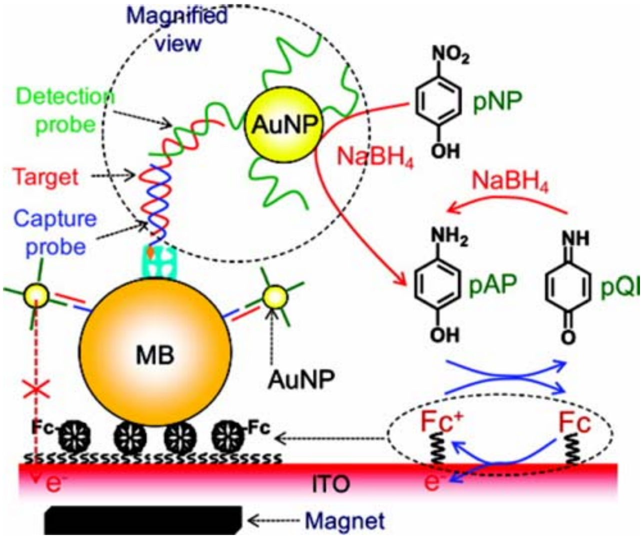

Fig. 2 Schematic view of the attraction of DNA-linked MB-AuNP assemblies to an Fc-D-modified ITO electrode and the electrochemical detection of target DNA. *MB* magnetic bead, *AuNP* gold nanoparticle, *Fc* ferrocene, *Fc-D* ferrocenemodified dendrimer, *ITO* indium-tin oxide, *pNP* *p*-nitrophenol, *pAP* *p*-aminophenol, *pQI* *p*-quinoneimine. Reprinted from [59]

to pAP by $NaBH_4$. Some of the regenerated pAP is reelectrooxidized. As a result, pAP redox cycling by $NaBH_4$ occurs [60, 61] and this considerably increases electrochemical signals. Importantly, pAP is electroactive within normal potential windows, whereas pNP is not [60, 61], this plays a crucial role in achieving a high signal-to-background ratio. The high signal amplification and low background current enable the detection of 1 fM target DNA.

Actually, genosensors are designed according to not only sorts and properties of nanoparticles but also demand of sensor performance. Rapidly increasing information about the human genome requires a fast and simple method for the detection of single-nucleotide polymorphisms (SNPs). A novel method to discriminate and code all possible combinations was described by Tamiya [62]. This versatile nanoparticle-based electrochemical protocol was a promising candidate for coding all mutational changes. The favorable signal-to-noise ratio (S/N) characteristics of these data indicated a detection limit of 0.02 OD (S/N=3). Additionally, one protocol offered great promise for decentralized genetic testing was proposed by Authier [28]. In this protocol, signal amplification, and lowering of the detection limits to the nanomolar and picomolar domains was achieved.

An explosion of interest in the use of metal and semiconductor nanoparticles in assays for DNA analysis has resulted in the great increase of corresponding works on DNA electrochemical detection [63, 64]. For examples, Hsing's group researched enhanced electrochemical detection of DNA hybridization based on electrode-surface modification [65]. The preparation and advantages of indium microrod tracers for solid-state electrochemical detection of DNA hybridization were described by Wang [66]. The resulting micrometer-long rods thus offered a significantly reduced detection limit (250 zmol), as compared to common bioassays' spherical nanoparticle tags. Recently, Merkoci and co-workers summarized some of analytical parameters of ongoing strategies described in Table 1. The data in Table 1 demonstrate that low detection limits could be obtained for metal and semiconductor nanoparticles-based assays, and clearly, nanoparticles have a promising future in designing electrochemical sensors.

Protein sensors

Because DNA contains lots of genetic information, they have always attracted a widespread attention from researchers. Proteins, molecular expression of this genetic information, are not only responsible for directing cell metabolism through their activity as enzymes but also at the very core of biological function. They are the centre of most pathological conditions and biomarkers of most diseases.

Table 1 Reported nanoparticle labels and analytical parameters of the assays developed

Nanoparticle label	Labels connection with DNA	Detection technique	Hybridization separate from detection	DNA detection limits	RSD	Reference
Au 0.78 fmol·mL^{-1}	Au-SH-DNA ~8%	DPV at pencil-graphite electrode [52]	No			
Au	Au-SH-DNA	PSA and silver catalytic enhancement at screen-printed electrodes	Yes	150 pg·mL^{-1}	7%	[30, 40]
Au	Au-SH-DNA	Conductivity at microelectrodes	No	500 fM	_	[41]
Au carried into PVC beads	PVC(Au) streptavidin–biotin-DNA	PSA and silver catalytic enhancement at screen-printed electrodes	Yes	40 pg·mL^{-1}	13%	[53]
CdS QDs	Cd-NH-DNA	EIS with gold electrode	No	1.43×10^{-10} M	_	[43]
CNTs loaded with CdS QDs	CNT-CdS-streptavidin–biotin-DNA	DPV at Hg-film electrode	Yes	40 pg·mL^{-1}	6.4%	[44]
Au-Fe (core/shell)	Fe-Au-SH-DNA	DPV at Hg-film electrode	Yes	50 ng·mL^{-1}	6.3%	[45]
CdS QDs	CdS-SH-DNA	PSA and catalytic enhancement with Cd at screen-printed electrodes	Yes	20 ng·mL^{-1}	6%	[46]
CdS QDs PbS QDs ZnS QDs	CdS-SH-DNA PbS-SH-DNA ZnS-SH-DNA	Simultaneous detection with SWV at Hg-film electrode	Yes	5 ng·mL^{-1}	9.4%	[47]

Reprinted from [27]

PSA potentiometric stripping analysis, *DPV* differential pulse voltammetry, *SWV* square wave voltammetry, *EIS* electrochemical impedance spectroscopy

Electrochemical sensors technology has emerged as one of the most promising platforms for proteins analysis. As for developing electrochemical protein sensor there are basically five different pathways summarized by Tamiya [67]: a change in the electrochemical signal of (i) a label, which selectively binds with the target protein, (ii) electro-active amino acids of antibody or target protein, (iii) a secondary antibody-tagged probe, (iv) aptamers- and (v) an enzyme-tagged probe can be monitored [68, 69]. Here, the author gives particular focus to the metal and semiconductor nanoparticles-based electrochemical protein sensors falling into two categories: direct and indirect detection system.

In the early 1970s, a relatively small group of proteins containing a metal center with reversible redox-activity (metalloproteins) has attracted a lot of the attention from researchers [70]. Nowadays, a few electro-chemists focus on the fact that most of the proteins without a metal center could show electrochemical activity too, depending on their amino acid structure. Because these proteins molecules are very large, current responses of direct electrochemical detection are very poor. Few works on nanoparticles-based direct electrochemical protein sensors has been reported.

As far as indirect detection system is concerned, several modes would be involved in discussion including antibody-based protein detection, aptamer-based protein detection and so on. Firstly, metal and semiconductor nanoparticles have been extensively used in electrochemical immunoassay [40, 71–80]. A fast, simple, sensitive, and low-cost method for electrochemical multianalyte immunoassay was developed via combining newly designed electric field-driven incubation with a screen-printed reagentless immunosensor array by Ju's group [71]. This disposable immunosensor array and simple detection system for fast measurement of panels of tumor markers (protein) showed significant clinical value for application in cancer screening and provided great potential for convenient point-of-care testing and commercial application. Similarly, AuNPs/streptavidin conjugates capped with multiple ferrocene (Fc) groups were used for detection P53 which is a tumor suppressor protein [40]. Meanwhile, Zhu's group developed a novel label-free immunosensor for the detection of C-reactive protein (CRP) based on a three-dimensional ordered macroporous (3DOM) gold film modified electrode by using the electrochemical impedance spectroscopy (EIS) technique [62]. The detection of CRP levels in three sera obtained from hospital showed acceptable accuracy. Additionally, magnetic nanoparticles have also been widely used in the fabrication of immunosensor [71, 81, 82]. For example, Yuan's group demonstrated a novel approach toward development of advanced immunosensors based on chemically functionalized core–shell Fe_3O_4@Ag magnetic nanoparticles. The preparation, characterization, and measurement of relevant properties of the immunosensor were useful for the detection of carcinoembryonic antigen (CEA) in clinical immunoassay. The immunosensor based on the combination of a magnetic nanocore and an Ag metallic shell showed good adsorption properties for the attachment of the CEA antibody selective to CEA. The core–shell nanostructure presented good magnetic properties to facilitate and modulate the way by which it was integrated into a carbon paste. Under optimal conditions, the resulting composite presented good electrochemical response for the detection of CEA, and allows detection of CEA at a concentration as low as 0.5 $ng \cdot mL^{-1}$. Importantly, the proposed methodology could be extended to the detection of other antigens or biocompounds [81].

Secondly, recent studies show that aptamer can be employed in molecular recognition instead of antibodies. Aptamer is generally single-stranded DNA or RNA oligonucleotides that can bind with high affinity and specificity to a wide range of target molecules, such as drugs, proteins or other organic or inorganic molecules. It was obtained by an in vitro selection process known as systematic evolution of ligands by exponential enrichment (SELEX) [83, 84]. Aptamer is easily synthesized, labeled, and modified with low cost and high stability. Ikebukuro firstly reported construction of the model of the aptamer-based protein sensor system. Thrombin was detected through sandwiching by a GDH-labeled antithrombin aptamer for detection and another aptamer immobilized onto the gold electrode for capturing the thrombin [85]. Since then there have been a steady flow of publications about aptamer-based electrochemical protein sensors instead of antibodies [85–94]. Generally speaking, sandwiching is the most popular and useful mode for the detection of protein, because it does not require the labeling of the target DNA. At the present day, most of aptamer-based protein sensors focus on conventional electrodes and more attention has been paid to thrombin, PDGF, cocaine and so on. Hansen [93] firstly reported the coupling of aptamer with the coding and amplification features of inorganic nanocrystals for highly sensitive and selective simultaneous bioelectronic detection of several protein targets. This was accomplished in a single-step displacement assay in connection to a self-assembled monolayer of several thiolated aptamer conjugated to proteins carrying different inorganic nanocrystals as shown in Fig. 3. Electrochemical stripping detection of the nondisplaced nanocrystal tracers resulted in a remarkably low (attomole) detection limit, that is, significantly lower than those of existing aptamer biosensors. The new device offered great promise for measuring a large panel of disease markers present at ultralow levels during early stages of the disease progress. Recently, the first potentiometric sandwich assay of thrombin has been reported based on CdS quantum dot labels of the secondary aptamer. As a prototype example,

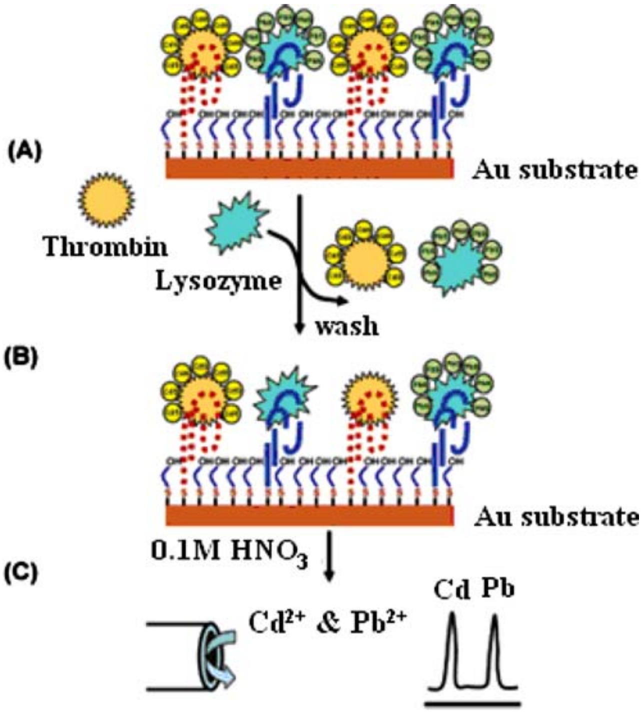

Fig. 3 Operation of the aptamer/quantum-dot-based dual-analyte biosensor, involving displacement of the tagged proteins by the target analytes. *A* Mixed monolayer of thiolated aptamers on the gold substrate with the bound protein-QD conjugates; *B* sample addition and displacement of the tagged proteins; *C* dissolution of the remaining captured nanocrystals followed by their electrochemical-stripping detection at a coated glassy carbon electrode. Reprinted from [93]

thrombin was measured in 200 μL samples with a lower detection limit of 0.14 nM corresponding to 28 fmol of analyte. The results showed great promise for the potentiometric determination of proteins at very low concentrations in microliter samples [94]. In the future, more novel aptamer-based protein sensors will be fabricated with the appearance of new aptamer.

Enzyme based sensors

Except above-introduced works concerning protein sensors more enzyme/protein-based sensors based on the metal and semiconductor nanoparticles have also been widely reported. This kind of sensor does not focus on the determination of protein but is developed for sensing related substrate, which are performed by establishing electrical communication between the enzyme/redox-protein and the electrode making good use of metal and semiconductor nanoparticles. As we know, proteins are very large molecules. Their metal redox centers are easy to be buried inside and far away from the electrode surface. Furthermore, considering the low diffusion coefficient of enzyme/protein and denaturation of enzyme/protein adsorbed on the electrode surface electrical contacting of the metal redox centers with electrodes is a key process in the tailoring of enzyme/protein-electrodes for electroanalytical applications. It is the special characteristics of metal and semiconductor nanoparticles that make them to carry out the effective electrical contacting and heterogeneous electron-transfer reaction of metalloproteins with electrodes [95–103]. These nanoparticles can act as electron-conducting pathways between prosthetic group and the electrode surface. Therefore efficient electrical communication between redox-proteins and electrodes was achieved by the facilitated electron transfer process between prosthetic group and the electrode surface based on the effect of nanoparticles or the optimal alignment of the proteins on the electrode surface. Furthermore these sensors are satisfying because of good stability and high sensibility. Nowadays, researchers attach much importance to this enzyme/protein-based sensor.

A number of works have shown that several enzyme/protein maintain their enzymatic and electrochemical activity when immobilized on AuNPs. Natan's group described the direct electron transfer between SnO$_2$ electrodes modified with 12-nm-diameter colloidal Au particles and horse heart cytochrome c. The experiment data indicated that nanometer-scale morphology of metals played a key role in protein electrochemistry, and suggested that isolated, surface-confined colloidal Au particles might be useful building blocks for macroscopic metal surfaces for biological applications [104]. Willner and co-workers reported a method carrying out a highly efficient electrical contacting of the glucose oxidase through a single Au NP by the reconstitution of the flavoenzyme, glucose oxidase, with a 1.4 nm Au NP functionalized with N^6-(2-aminoethyl)-flavin adenine dinucleotide (FAD cofactor aminoderivative) as shown in Fig. 4 [105, 106]. This electric wiring not only greatly improved and enhanced the electric contacting efficiency between the protein and the electrode surface but also made the modified electrode have a good electrocatalytic response to glucose.

The ability of external magnetic fields to control bioelectronic processes, such as biocatalytic transformations of redox enzyme/protein, has been documented by Willner [49, 107]. In recent years, a large numbers of publications concerning biosensing and biocatalysis devices based on the magnetic nanoparticles appeared [50, 108–113]. For example, Katz developed a novel procedure to architecture nanoelectrode arrays with enhanced electrochemical properties. Magneto-assisted formation of conducting nanowires upon self-assembling of Au-shell/CoFe$_2$O$_4$-magneticcore nanoparticles (18±3 nm diameter) was demonstrated on a Au electrode surface by application of an external magnetic field. The conducting nanowires

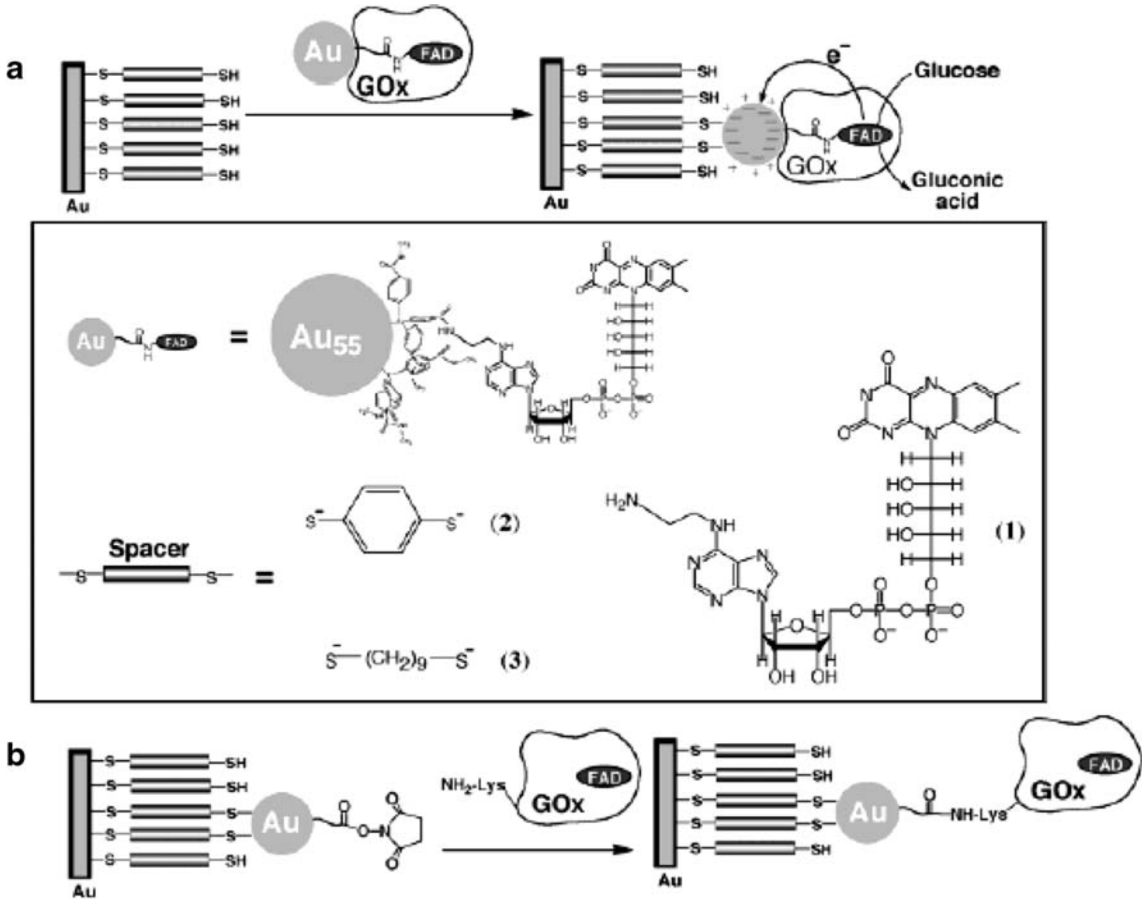

Fig. 4 *A* Assembly of the electrically contacted reconstituted GOx/Au-NP systems on Au-electrodes by means of dithiol bridging units; *B* Assembly of the random covalently linked GOx/Au-NP system on the Au-electrode. Reprinted from [105]

caused an increase of the electrode surface area yielding an electrochemical response to a diffusional redox probe (ferrocenemonocarboxylic acid) enhanced by ~6.5 fold after 120 min. The enhancement factor for the electrochemical process was controlled by the time intervals allowed for the nanoelectrode array formation. The primary electrochemical reaction of the electron relay was coupled with the bioelectrocatalytic oxidation of glucose in the presence of soluble glucose oxidase resulting in the amplification of the biocatalytic cascade controlled by the growth of the nanostructured assembly on the electrode surface. The studied nanoelectrode array was suggested as a general platform for electrochemical biosensors with the enhanced current outputs controlled by the structure of the self-assembled nanowires as showed in Fig. 5 [108].

Thin film of nanoparticles and enzyme/protein assembled layer by layer on electrodes can provide favorable microenvironments for enzyme/protein to exchange electrons with underlying electrodes. On one hand, the efficient electron transfer between the enzyme/protein active sites and the electrode support is allowed without electron transfer mediators. On the other hand, if the positioning of redox enzyme/protein on the conductive nanoparticles is random and non-optimized effective electron-conducting between proteins and electrodes can not be accomplished. It has been reported that hemoglobin (Hb), myoglobin (Mb), horseradish peroxidase (HRP), and cytochrome c (Cyt c) exhibited excellent electrochemical responses at film electrode constructed with nanoparticles such as clay, SiO_2, MnO_2 and TiO_2 [114–121]. Moreover, the constructed film electrodes showed high catalytic activity to some small molecules and then were used as sensors in food analysis and so on [122]. For instance, Myoglobin (Mb) has been successfully immobilized in alternation with oppositely charged poly (dimethyldiallylammonium chloride) via the sequential layering approach on the biocompatible Fe_3O_4@SiO_2 nanoparticles. The bound Mb could be easily separated by an external magnetic field and used as less costly, more stable, and reusable alternatives to the soluble ones. Direct electron transfer between the immobilized Mb and the electrode was observed. Moreover, the immobilized Mb provided remarkable thermostability up to 70°C and high electroactivity with the apparent Michaelis–Menten constant (K_M) of 45 μM [123].

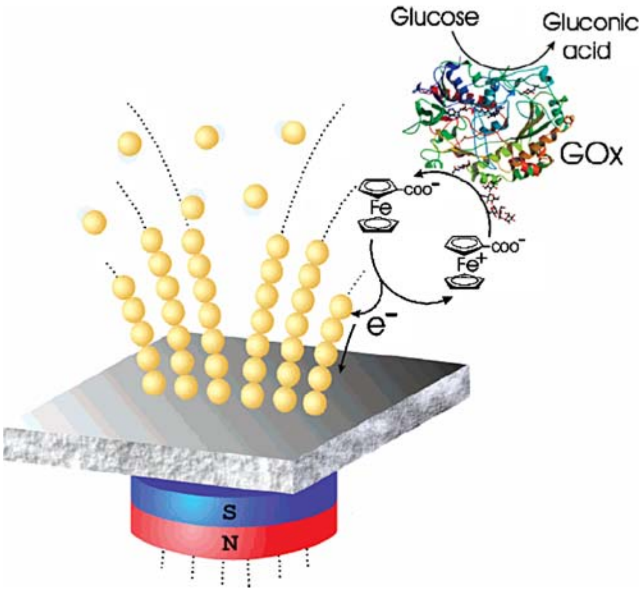

Fig. 5 Formation of the conducting nanowires upon self-assembling of the Au-coated magnetic NPs along the magnetic field lines and their use as a nanostructured electrode for electrochemical oxidation of ferrocenemonocarboxylic acid coupled with the glucose oxidation biocatalyzed by GOx. Reprinted from [108]

Now sol–gel technology provides a unique means to prepare a three-dimensional network suited for the encapsulation of a variety of biomolecules and nanoparticles [124, 125]. Sol–gel-derived inorganic materials are particularly attractive for biosensor fabrication, because they can be prepared under ambient conditions and they exhibit tunable porosity, high thermal stability, and chemical inertness, and they experience negligible swelling in aqueous solution. Combining sol–gel and self-assembly technologies many novel methods for fabrication of protein/enzyme-based sensors have been developed by wrapping metal or semiconductor nanoparticles to sol–gel network by chemists [126, 127].

In conclusion, these enzyme/protein based sensors based on the metal and semiconductor nanoparticles focus on sensing of some small molecules or relative substrates including peroxide, oxynitride (such as NO), cholesterol, glucose, phenolic compounds (phenol, catechol, caffeic acid, chlorogenic acid, gallic acid and protocatechualdehyde) and so on [100, 110–112, 128–148]. The works could not be list here one by one. It is undoubted that more applications of metal and semiconductor nanoparticles to development of protein/enzyme-based sensors will be further investigated.

Other organic substances

The determination of organic substances including biochemical, biological and other substances is of considerable importance because it is widely used in various fields including those concerned with biological, chemistry, environmental, clinical, and food analysis. Biochemical and biological substances, dopamine (DA), ascorbic acid (AA), uric acid (UC), epinephrine, norepinephrine and so on, are close to our life. For examples, Low levels of dopamine (DA) have been found in patients with Parkinson's disease. Uric acid (UA) and ascorbic acid (AA) are commonly found in biological fluids, such as blood and urine. Other organic substrates, methanol, formaldehyde, ethanol, other π-donor molecules and so on, have been widely studied too, associated with the electrochemical sensors. As to the electrochemical method, a major problem encountered in voltammetric detection is the coexistence of many interfering compounds. For instance, the existence of ascorbic acid (AA) and uric acid (UA) would interfere with the detection of many biomolecules like that. Generally, voltammetric differentiation of these biomolecules is not possible on bare metal or carbon electrodes due to the overlap of oxidation voltages for these species. Major efforts in sensor research essentially involve elaborate surface modification steps to impart perm-selection or electrostatic selection on these electrodes toward dopamine (DA), ascorbic acid (AA), uric acid (UA) and other biomolecules. Therefore, searching of the stable, easy to preparation, and highly biocompatible labels, which influence their selective response to the substrates molecules, is of critical importance for the analysis of biological substrates or other organic molecules.

Metal and semiconductor nanoparticles have been widely used as electro-catalyst to achieve the electrochemical detection of some organic molecules because of their high biocompatibility and catalytic activity [149–160]. Luong's group reported the interfacial interactions between immobilized DNA probes and DNA-specific sequence binding drugs using impedance spectroscopy and the development of a novel biosensing scheme [161]. They pointed that, electrochemical deposition of gold nanoparticles on a gold electrode surface showed significant improvement in sensitivity. The immobilization of DNA and then the DNA drug interaction on the electrode surfaces altered the capacitance and the interfacial electron resistance and thus diminished the charge-transfer kinetics by reducing the active area of the electrode or by preventing the redox species from approaching the electrode compared to bare gold surfaces. DNA-capped gold nanoparticles on electrodes act as selective sensing interfaces with tunable sensitivity due to higher amounts of DNA probes and the concentric orientation of the DNA self-assembled monolayer. The specificity of the interactions of two classical minor groove binders, mythramycin, a G-C specific-DNA binding anticancer drug, netropsin, an A-T specific-DNA binding drug and an intercalator, nogalamycin on AT-rich DNAmodified substrate and GC-rich DNA-modified substrate are compared. The gold nanoparticle-modified sensing device resulted in detection limits of 5 nM for nogalamycin, 10 nM for mythramycin, and 40 nM for netropsin, respectively, which are 15–40-fold lower compared to flat gold substrates. The enhanced sensitivity might be simply explained in terms of changes in the geometry of the electrode surface affecting the binding efficiency of the DNA-drug interaction and hence direct the improvement of impedance signal changes illustrated in Fig. 6 [161].

A similar norepinephrine (NE) biosensor was fabricated via layer-by-layer deposited multilayer films containing DNA and gold nanoparticle by Lin's group early [162]. The gold nanoparticles were deposited on the surface of DNA layer to build a hybrid device of nanoscale electrode array but not on a gold electrode surface. This electrode was successfully used for selective determination of norepinephrine (NE) in the presence of ascorbic acid (AA). The reversibility of the electrode oxidation reaction of NE was significantly improved in result of 200 mV negative shift of the voltammetric peak potential on the electrode, and a large increase in the peak current. A detection limit of 5 nM NE was obtained by using DPV in static solutions. The co-existence of a large excess of AA did not interfere with the detection. This electrode showed excellent sensitivity, good selectivity and antifouling properties. In fact, the relevant works can not be listed one by one. More and more kinds of metal and semiconductor nanoparticles have been used as ideal labels for recognition and sensing processes [130, 162–169], especially gold nanoparticle. Yuan's group fabricated a novel glucose sensor based on self-assembled gold nanoparticles and double-layer 2 d-network (3-mercaptopropyl)-trimethoxysilane polymer onto gold substrate [170]. With the aid of $\mathrm{Co(byp)_3}^{3+}$ as a mediator in the solution, the electrode displayed excellent electrocatalytical response to the glucose and exhibited a good stability and sensitivity. The detection of paraoxon and dopamine based on gold nanoparticles has been studied by Shen and Ohsaka's groups [171, 172]. In the later system, gold (Au) nanoparticles immobilized on an amine-terminated self-assembled monolayer (SAM) on a polycrystalline Au electrode were successfully used for the selective determination of dopamine (DA) in the presence of ascorbate (AA). At this nano-Au electrode well-separated voltammetric peaks were observed for DA and AA. The oxidation potential of AA was negatively shifted due to the high catalytic activity of Au nanoparticle. The reversibility of the electrode reaction of DA was significantly improved at the nano-Au electrode, which resulted in a large increase in the square-wave voltammetric peak current with a detection limit of 0.13 mM. The coexistence of a large excess of AA did not interfere with the voltammetric detection of DA. The nano-Au electrode showed excellent sensitivity, good selectivity and antifouling properties. This resulted in the effective separation of the oxidative potentials of ascorbic acid and dopamine, thus allowing their selective electrochemical analysis. More references about the detection of DA in the presence of AA and UA or other molecules could be consulted based on metal and semiconductor nanoparticles including gold, silver, $\mathrm{LaFeO_3}$, silver–titanium dioxide core–shell nanoparticles and so on [173–176].

Other electrochemical sensors have been reported frequently, such as pulsed amperometric detection of histamine at glassy carbon electrodes modified with gold nanoparticles. Recently, copper nanoparticles have been employed in the applications of electrochemical sensors [177–180]. Luong's group achieved the electrochemical detection of carbohydrates using copper nanoparticles and carbon nanotubes [179]. The response time and the detection limit (S/N=3) of the sensor for glucose were

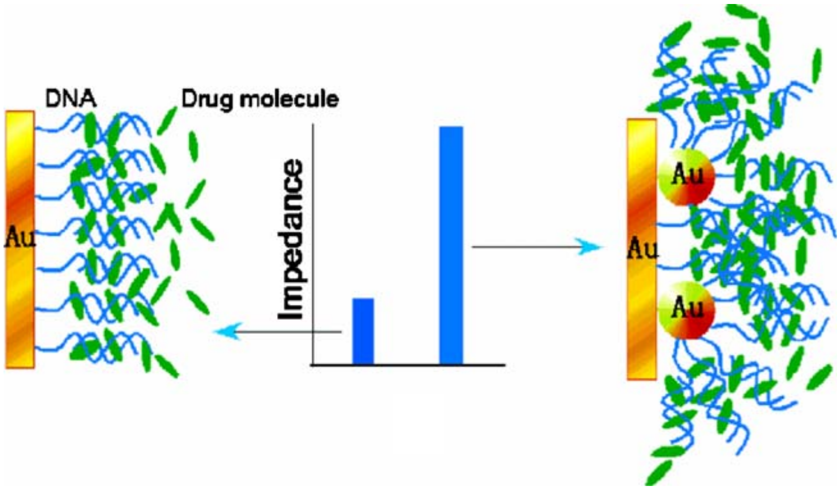

Fig. 6 Schematic representations of the drug interactions with the DNA monolayer with different orientations on (a) flat substrate and (b) gold nanoparticle-deposited substrate, 1 mm. Reprinted from [161]

10 s and 250 nM, respectively. Willner's group has achieved the electrochemical detection of NADH and of NAD^+-dependent biocatalyzed processes by the catalytic deposition of copper on gold nanoparticles [180]. In addition, Yu's group invented a phenol biosensor based on immobilizing tyrosinase to modified core–shell ($MgFe_2O_4$-SiO_2) magnetic nanoparticles supported at a carbon paste electrode [181]. The linear range for phenol determination was from 1×10^{-6} to 2.5×10^{-4} $mol\cdot L^{-1}$ with a detection limit of 6.0×10^{-7} $mol\cdot L^{-1}$ obtained at a signal-to-noise ratio of 3. The stability and the application of the biosensor were also evaluated. Recently, Vonna had also reported magnetic nanoparticles based sensing devices. The magnetic particles were immobilized on PPy films under appropriate magnetic field in order to control their organization on the PPy film and finally to improve the sensitivity of the system in potential sensing applications. The designed biosensor had been successfully applied in rapid, simple, and accurate measurements of atrazine concentrations, with a significantly low detection limit of 5 $ng\cdot ml^{-1}$ [182]. Moreover, semiconductor nanoparticles were also used to develop electrochemical sensor for toxic substrates. Lin presented an electrochemical sensor for detection of organophosphate (OP) pesticides and nerve agents using zirconia (ZrO_2) nanoparticles as selective sorbents [183]. The promising stripping voltammetric performances open new opportunities for fast, simple, and sensitive analysis of OPs in environmental and biological samples. These findings can lead to a widespread use of electrochemical sensors to detect OP contaminates. Also, they had reported a poly (guanine)-functionalized silica nanoparticle (NP) label-based electrochemical immunoassay for sensitively detecting 2,4,6-trinitrotoluene (TNT) recently [184]. As we know that some organic molecules can be electrostatic crosslinked with metal or semiconductor nanoparticles to modify electrodes and then get the sensoric applications. Willner's and coworkers have summarized main advances about this topic [9, 11, 185].

Besides these applications discussed above, metal and semiconductor nanoparticles have an important application, which are used in fuel cell systems. For instance, the oxidation of methanol has been investigated widely based on the metal or semiconductor nanoparticles catalysis [186, 187]. One problem is that the intermediate species such as CO remain adsorbed on the surface and inhibit the oxidation reaction. Significant efforts are being dedicated to the development of new electrocatalytic materials to resolve the oxidation of CO. Metal and semiconductor nanoparticles are good choice because their excellent catalytic activity. Therefore, further progress in fuel cell catalysis, especially on a nanoparticle surface, and the catalyst optimization are needed [188]. We don't discuss this topic here.

Inorganic substances

Trace metals ions, such as $Fe^{2+/3+}$, Co^{2+}, Ni^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+}, As^{3+} and Cu^{2+}, have threatened both human and environmental health through their greatly increasing presence in environmental matrixes because of their toxic effects to plants and humans, especial the environmental heavy metal ions. A number of researches show that low levels of long-term exposure to these trace metal ions can attribute to an increased risk of cancer. Thus, monitoring and removal of environmental trace metal ions are increasingly important and has become a major focus of waste treatment and cleanup efforts [189, 190]. Electrochemical techniques such as anodic stripping voltammetry (ASV) [191] provide accurate measurements of low concentrations of trace metal ions at the ppb levels with rapid analysis times and low-cost instrumentation. In the past years, hanging drop mercury electrodes (HDMEs) and thin mercury film electrodes (MFEs) were widely used in association with ASV. With development of chemically modified electrode (CME) nano-materials has been applied to the trace metal ions analysis, especially metal or semiconductor nanoparticles [192–199].

Specific interactions between analyte ions and organic shell functional groups on nanoparticles could enhance sensitivity and increase selectivity of the electroanalytical sensors. For example, electrochemical analysis of Cu^{2+} ions with sensitivity below 1 ppb was achieved using a glassy carbon electrode (GCE) functionalized with thin films assembled from thiolate-encapsulated gold nanoparticles of 2 nm core size ($Au_{2\text{-}nm}$) and a carboxylic functionalized alkyl thiol linker, i.e. 11-mercaptoundecanoic acid (MUA) [200]. The high surface-to-volume ratio and the 3-D ligand network properties were potentially useful as sensitive and selective nanomaterials for the monitoring and removal of environmental heavy metals. The selectivity of the electroactivity was also probed using mixed-metal systems such as Cu^{2+} and Fe^{3+}, Cu^{2+} and Zn^{2+}. The results also revealed that the ion-binding affinity of the film was more selective to Fe^{3+} than Cu^{2+}, and more selective to Cu^{2+} than to Zn^{2+}. Issues related to the electrochemical activity of these metal ions were also discussed. Compton's group firstly studied electrochemical detection of arsenic (As^{3+}) at a gold nanoparticle-modified electrode by electrodeposition method [201]. After optimization, a limit of detection of 0.0096 ppb was obtained with LSV.

Hu's group has reported the simultaneous determination of cadmium (Cd^{2+}) and lead (Pb^{2+}) using anthraquinone (AQ) improved Na-montmorillonite nanoparticles (nano-SWy-2) clay nanoparticles-beased sensor by differential pulse anodic stripping voltammetry (DPASV) [202]. Corresponding data can be observed in Fig. 7. The authors pointed out that this method was based on a non-

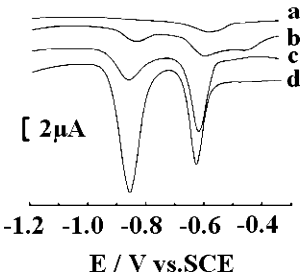

Fig. 7 Differential pulse voltammograms of 2×10^{-7} mol·L^{-1} Cd^{2+} and 1×10^{-7} mol·L^{-1} Pb^{2+} in pH 5.6 NaAc–HAc buffer. Accumulation potential: −1.20 V; accumulation time: 5 min; scan rate: 50 mVs^{-1}; pulse amplitude: 100 mV; pulse width: 50 ms. Reprinted from [202]

electrolytic preconcentration via ion exchange model, followed by an accumulation period via the complex formation in the reduction stage at a constant potential, and then by an anodic stripping process. Many inorganic species did not interfere with the assay significantly. The applications for the detection of trace levels of Cd^{2+} and Pb^{2+} in milk powder and lake water samples indicated that it was a satisfying method.

Urine is universally recognized as one of the best non-invasive matrices for biomonitoring exposure to a broad range of xenobiotics, including toxic metals. Detection of metal ions in urine has been problematic due to the protein competition and electrode fouling. For direct, simple, and field-deployable monitoring of urinary Pb, an electrochemical sensor employing superparamagnetic iron oxide (Fe_3O_4) nanoparticles with a surface functionalization of dimercaptosuccinic acid (DMSA) has been developed by Yantasee [203]. The metal detection involved rapid collection of dispersed metal-bound nanoparticles from a sample solution at a magnetic or electromagnetic electrode, followed by the stripping voltammetry of the metal in acidic medium. The sensor could detect background level of Pb (0.5 ppb) and yielded linear responses from 0 to 50 ppb of Pb, excellent reproducibility (%RSD of 5.3 for seven measurements of 30 ppb Pb), and Pb concentrations comparable to those measured by ICP-MS. The sensor could also simultaneously detect background levels (<1 ppb) of Cd, Pb, Cu, and Ag in river and seawater. With the use of DMSA-Fe_3O_4 as metal collector from biological samples, The authors claimed that heavy metals like Pb could be directly detected in the samples using electrochemical sensors with high accuracy and sensitivity without (1) sample pretreatment by acid elution or solvent extraction to release metals from proteins into a pure medium followed by metal preconcentration at a mercury-film electrode, (2) the use of internal standards at Hg-based electrodes, or (3) the use of sonication at the polymeric film-coated mercury-film electrode coupled with large sample dilution to minimize protein adsorption and promote mass transport of metals to the sensor surface [203].

Additionally, carbon-based nanoparticles have been used in the metal ions analysis too. Mascaro and co-workers succeed in fabricating a new electrode obtained by the dispersion of template carbon nanoparticles onto polyanline [204]. This new electrode exhibited excellent chemical and physical stabilities. ASV measurements revealed that the new electrode presented a noteworthy linear response to very low concentrations of copper (Cu^{2+}) and lead (Pb^{2+}) ions under few minutes of pre-concentration. In Marken's group study [205], nanocomposite electrodes made of carbon nanofibers and black wax were characterized and investigated as novel substrates for metal deposition and stripping processes. The resulting nanocomposite electrodes showed (i) low background current, (ii) a wide potential window in aqueous solutions, (iii) good conductivity, (iv) near steady state voltammetric responses with substantial Faradaic currents and (v) sharply peaked fast scan metal stripping responses [205]. They used this electrode to achieve ASV analysis for zinc and lead ions and the resulting were satisfying. Finally, some researchers have utilized the adsorption properties of metal ions on the chitosan-bound nanoparticles to remove the trace metal ions [206, 207], but not to detect quantificationally.

As to other inorganic substrates such as H_2O_2, NO_2^-, and NaClO, they have been reported, too [163, 208–212]. Hirono's group developed a platinum nanoparticle-embedded carbon film electrode which was used for the detection of hydrogen peroxide [212]. Additionally, in this part, it can not be neglected that pH sensor (H^+ measurement) has been fabricated using the metal and semiconductor nanoparticles [213, 214].

Gas sensor

The growing concern worldwide about air pollution on environment, industrial safety and hygiene applications has made the monitoring of gaseous species, such as SO_2, H_2S, ozone, H_2, NO_x, CO, Cl_2, NH_3, formaldehyde, ethanol, propane or ethylene oxide is of wide interest. Electrochemical sensors are the most attractive instrumentations because the electronic signals (resistance, potential and current etc.) can be obtained directly. The design of electrochemical gas sensors presents a challenge as the gas phase has to be brought into contact with a solid electrode as well as an electrolyte phase which usually is liquid [215]. Nevertheless, in order to improve sensitivity and selectivity many new methods of sensors construction have been developed in recent as well as approaches to miniaturization. It is certainly that metal and semiconductor nanoparticles will be widely used as conducting materials for construction of electrochemical gas sensor.

Chiou have developed a dispersed catalyst gas-diffusion electrode for SO_2 sensing [216]. The electrode was a composite material with gold as catalyst. Gold particles catalyzed the electrochemical oxidation of SO_2 when this gas diffused through the porous working electrode. This

SO_2 sensor resulted in a stable device with a very fast response time. The application of different kinds of metallic nanoparticles integrated in different organic matrices allowed the tailoring of controllable interactions with variable vapor materials and the development of chemiresistors with sensitive and specific functions. For example, lead nanoparticles incorporated into a ploy (p-xylylene) film demonstrated sensoric functions for NH_3 vapor [217]. In fact, as we described above, the gas sensor does not focus on the chemically modified conventional electrode but the replace semiconductor materials of porous or membrane electrode by semiconductor nanoparticles because the grain size and surface reactivity of these particles can rapidly increase their catalysis effect and the sensitivity of relative sensors. So many reports focusing on this gas sensor have appeared such as the CO sensor [218, 219].

Of course, the chemically modified conventional electrode-based gas sensors are also investigated in recent years, especially for the studies of dissolved gas species such as O_2 and NO using metal and semiconductor nanoparticles. However, almost all studies on dissolved O_2 are focusing on the mechanism of O_2 reduction or the catalysis researches of nanoparticles materials and not the sensing applications [220]. On the contrary, a large quantity of NO sensors has been designed utilizing the special characteristics of metal and semiconductor nanoparticles. NO, a radical-like diatomic molecule, has been established recently as one of the most important cellular messengers. It has been associated with many physiological and pathological processes. The measurement of NO in the biological media is a very challenging task because of its short lifetime (a few seconds), low concentration, and high fugacity. The demand to measure the small amount of NO released in situ in real time has led to an extensive effort in developing nanoparticles-based electrochemical sensors with excellent sensitivity. Besides the protein-based sensor in Part 3, many other new sensing methods have been introduced. Several years ago, a sensitive, selective and stable NO microsensor was described, which was modified by nano-Au colloid and Nafion [221]. A low detection limit, high selectivity and sensitivity for NO determination could be obtained using this microsensor. The microsensor was successfully applied to the measurement of the direct real time production of NO in the smooth muscle cells continuously. After that, Caruso's group [222] prepared a novel sensor by infiltrating 4-(dimethylamino) pyridine-stabilized gold nanoparticles (DMAP-AuNP) into PE multilayers preassembled on indium tin oxide (ITO) electrodes. The results showed that gold nanoparticles in the PE multilayers showed high electrocatalytic activity to the oxidation of NO. The sensitivity of the composite films for measuring NO could be further tailored by controlling the gold nanoparticle loading in the film. Subsequently, gold nanoparticle arrays, Pt-Fe(III) nanoparticle, carbon nanotube-gold nanoparticle and copper nanoparticle were also used to design NO sensors [92, 223–226].

Nanomedicine

Nanomedicine is the medical application of nanotechnology [227]. The approaches to nanomedicine range from the medical use of nanomaterials, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology. Current medicinal uses of nanosensors mainly revolve around the potential of nanosensors to accurately identify particular cells or places in the body in need. By measuring changes in volume, concentration, displacement and velocity, gravitational, electrical, and magnetic forces, pressure, or temperature of cells in a body, nanosensors may be able to distinguish between and recognize certain cells, most notably those of cancer, at the molecular level in order to deliver medicine or monitor development to specific places in the body (http://en.wikipedia.org/wiki/Nanosensor) [228, 229]. In addition, they may be able to detect macroscopic variations from outside the body and communicate these changes to other nanoproducts working within the body. The design of nucleic acid machines based metal and semiconductor nanoparticles/QDs has attracted increasing interest in the last few years [230]. DNA-based scissors [231], motors [232], walkers [233], and transporters [234] have been developed. The possible use of DNA-based machines for sensing purposes has recently become an emerging research area. Recently, Willner has reported on an autonomous DNA-based machine that amplified the DNA biorecognition event by the generation of a nucleic acid product that induces aggregation of Au NPs. The optical features of the Au NP aggregates allowed the colorimetric imaging of the machine functions and the optical readout of the biosensing event. Besides the important demonstration of the machine-induced amplified detection of DNA with visual imaging, the system revealed an approach for the "sensing" of NP aggregates that included a controlled number of Au NPs in aggregated clusters. Such aggregates might be building blocks for assembling nanodevices [235]. Many similar works have been also reported by them [236, 237]. In the field of electrochemical analysis, more and more publications concerning the recent but very important role of metal and semiconductor nanoparticles/QDs for nanomedicine appeared [238–241], such as cell analysis, microbe detection and drug discovery.

Ju has reported the electrochemical study of K562 leukemia cells based on chitosan nanocomposite gel encapsulated Au NPs [242]. A novel nanocomposite gel was prepared by neutralizing a designer nanocomposite solution of chitosan encapsulated Au NPs formed by reducing in situ tetrachloroauric acid in chitosan. The bio-inspired gel was designed for immobilization and electrochemical study of cells and monitoring adhesion, proliferation, and apoptosis of cells on electrodes. Using K562 leukemia cells as a model, an impedance cell sensor was constructed. The living cells immobilized on glassy carbon electrode exhibited an irreversible voltammetric response and increased the electron-transfer resistance with a good correlation to the logarithmic value of concentration ranging from 1.34×10^4 to 1.34×10^8 cells/mL with a limit of detection of 8.71×10^2 cells/mL at 10σ. As shown in Fig. 8a, K562 cells were capable of not only adhering to GNPs-CHIT gel film but also proliferating on the film upon extended culture. With an increasing incubation time, the density of cells adhered on the film increased. After incubation for 72 h, K562 cells apparently spread evenly over the entire surface (photo c, Fig. 8a). The cells were alive, as evidenced by the morphology of the distinguishable filopodia, a good indicator of cell adhesion to material surfaces and cell viability. A longer incubation time caused the loss of cell normal characteristics and viability, presenting an abnormal morphology on the film (photo d, Fig. 8a). These observations could be monitored with impedance measurements. With an increasing incubation time of cells/GNPs-CHIT gel/GCE, *R*et increased (curves a–c, Fig. 8b), resulting from the cell proliferation on the electrode, which introduced a barrier for electrochemical process. The inset in Fig. 8b indicates that the *R*et of the probe increased gradually up to the incubation time of 50 h and then tended to a relatively steady value during the incubation time of 50–70 h. After the incubation time of 70 h, drastically increased resistance was observed (curve d, Fig. 8b). This change might be related to the apoptosis of cells, which were congregated on the electrode surface [243]. These results were consistent with the observation from optical microscopy. They have also researched tumor cell adhesion and viability based on Colloidal gold nanoparticle modified carbon paste interface. This simple and rapid method could be applied for the electrochemical investigation of exogenous effect and characterization of the viability of living cells [244]. Thus, besides the detection of cell immobilization, this method could be employed to monitor both proliferation and apoptosis of cells on electrode surface. This work implied that the nanocomposite gel based on biopolymer and nanoparticles possessed potential applications for biosensing and provided a new avenue for electrochemical investigation of cell adhesion, proliferation, and apoptosis.

Recently, the use of super-paramagnetic particles or magnetic beads (MB) as labels in biosensing has become a very important tool in nanomedicine research. These magnetic particles are especially designed for labeling cells [245]. For example, magnetic particles coated with immunospecific agents have been successfully used to lung cancer cells [246]. Polyethyleneimine (PEI) conjugated magnetic beads were used as novel virus concentration method to enhance the sensitivity of virus detection by PCR. PEI has the possibility of adsorbing viruses [247]. Hassena [248] developed a biosensor based on streptavidin functionalized magnetic nanoparticles for HIV and HBV DNA detection. The magnetic layer is composed of the streptavidin functionalized magnetic nanoparticles immobilized on a gold electrode via a 300 mT magnet. The biotinylated HBV and HIV DNA probes were then linked through a strong biotin–streptavidin interaction (*K*a~10^{15} M) and finally DNA hybridization detection was conducted by impedimetric measurements. Non-faradic impedance spectroscopy allowed to detect 50 pmol of HBV DNA and 160 pmol of HIV DNA on sample of 20 μL. Saturations were reached for the same concentration 12.65 nmol·mL^{-1} for a same quantity of immobilized DNA probes.

The detection of pathogenic bacteria remains a challenging and important issue for ensuring food safety and security, for controlling water and soil pollution, and for

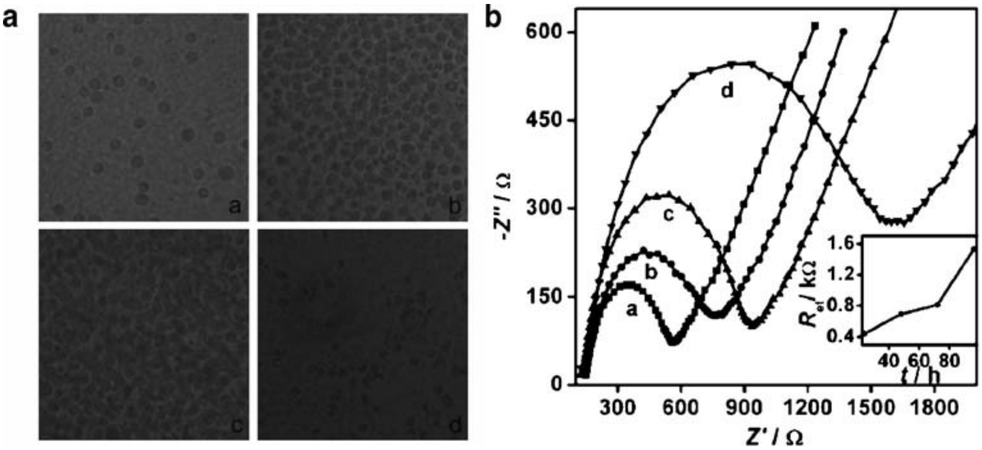

Fig. 8 Photos of K562 cells proliferated on GNPs-CHIT gel film coated on glassy dishes at *a* 24, *b* 48, *c* 72, and *d* 96 h (**a**), and EIS measurements of K562 cells proliferated on GNPs-CHIT gel/GCE after cell incubation for *a* 24, *b* 48, *c* 72, and *d* 96 h (**b**). *Inset* in **b**: relationship between electron-transfer resistance and proliferation time of K562 cells on GNPs-CHIT gel/GCE. Reprinted from [240]

preventing bioterrorism and nosocomial diseases [249]. Both Jaffrezic-Renault and Wang reported the works concerning the E. coli detection based on metal and semiconductor nanoparticles [249–251]. Moreover, Jaffrezic-Renault showed the results of comparison of two innovatives approaches for bacterial detection: paramagnetic nanoparticles and self-assembled multilayer processes [248]. In view of their results, the authors hypothesized that the immunomagnetic sensor elaborated for E. coli detection was much more sensitive than the biosensor based on the self assembled multilayer system. In fact, paramagnetic beads are among the new technologies greatly needed to improve laboratory tests that can be used in point-of-care clinical settings. With their ease of use and affordability, they would become a popular choice for biomolecule selection and purification [250].

Additionally, applications of nanoparticles in nanomedicine are also involved in the detection of RNA, drug analysis, nonviral transfection in vitro and so on [252–254]. On the whole, many approaches to nanomedicine being pursued today are already close enough to fruition that it is fair to say that their successful development is almost inevitable, and their subsequent incorporation into valuable medical diagnostics or clinical therapeutics is highly likely and may occur very soon.

Conclusions and perspective

The integration of nanotechnology with biology and electrochemistry is expected to produce major advances in the field of electrochemical sensors. This review has mainly addressed recent advances of electrochemical sensors based on metal and semiconductor nanoparticles. Recent progress focused on, on one hand, the development of functional nanoparticles that are covalently linked to biological molecules, such as peptides, proteins and nucleic acids, on the other hand, the chemically modified electrode using the metal and semiconductor nanoparticles or their functionalized particles. Throughout this review the metal and semiconductor nanoparticles are attractive materials for electrochemical sensors applications, maybe for electroanalytical and bioelectroanalytical applications, because of their several advantages [2, 3, 63]: (i) Their small size (1–100 nm) and correspondingly large surface-to-volume ratio could generate a roughened conductive-high-surface area interface after they have been immobilized on the electrodes surface, which can enables the sensitive electrochemical detection of organic or inorganic molecules or other analytes. (ii) Chemically tailoring for metal and semiconductor nanoparticles of physical properties which directly relate to size, composition, and shape, and their functionalization with molecular, polymer, biomatetial or other nanomaterial coatings reveal that different electrochemical sensors could be tailored on kinds of electrode surface using such functional nanoparticles discussed above. We could functionalize different nanoparticles with different modifiers according to the characteristics of different analytes and develop corresponding electrochemical sensors. (iii) Because the size of metal and semiconductor particles mentioned in this chapter is nano-scaled, the overall structural robustness and their conductive perspective enable the design of electroanalytical and bioelectroanalytical systems with pre-designed and controlled electrochemical functions. (iv). The unusual target binding properties can make nanoparticles act as effective labels for the amplified electrochemical analysis of the respective analytes, such as DNA, protein, and the others.

In most cases, the extension of the concept for nanoparticles has provided more chances to accomplish design new sensing devices. Generally the integration of metal and semiconductor nanoparticles with other nanowires or nanotubes is advantageous to the design new sensors with kinds of functions. Certainly this topic includes one kind of excellent nanocrystals, quantum dots (QDs) [255]. The unique properties of QDs may allow the design of simple, inexpensive electrochemical systems for detecting ultrasensitive, multiplexed assays. The electrochemical properties of QD nanocrystals make them extremely easy to detect using simple instrumentation. QDs nanocrystals are made of a series of semiconductor nanoparticles that can easily be detected by highly sensitive techniques, such as stripping methods. In addition, these electrochemical properties may allow the design of simple, inexpensive electrochemical systems for detecting ultra-sensitive, multiplexed assays. The electrochemical coding developed could be adapted to other multi-analyte biological assays, particularly immunoassays. The use of semiconductor nanoparticles or nanocrystals in photoelectrochemistry would sometimes enlarge their applications in electroanalytical chemistry and bioanalytical chemistry. Although the unique properties of nanoparticles have offered many advantages for their applications in electrochemical sensors, nanoparticles need to have surface functionality amenable to biological modification, solubilization solubility and long-term stability in a range of buffered saline solutions and pH values, and limited non-specific binding to fabricate more analysis systems with better sensitivities and simple process. Further efforts should be made focusing on this aim.

To date, with the development of the electroanalytical applications of functionalized nanoparticles, it is mature to fabricate bulky sensors according to the collective properties of the metal and semiconductor nanoparticles ensembles. Now, in order to fully use the unique properties and other advantages in our day life we must be in the face of a challenging topic, which is the miniaturization of the metal and semiconductor nanoparticles ensembles with the ultimate goal of using a single functionalized nanoparticle for the electronic sensing events. So based on the unique properties of nanoparticles and the nanoscale dimension of the active sensing elements future advances will require continued interdisciplinary efforts by of chemists in close collaboration with experts in physics, biology, material science and medical fields, which future could yield new generations of miniaturized sensing devices.

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