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Review

Nanomaterial-based electrochemical DNA sensing strategies

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In honor of Prof. Joseph Wang's 60th birthday who is the pioneer of electrochemical (bio)sensors.

Abstract

DNA sensing strategies have recently been varieted with the number of attempts at the development of different biosensor devices based on nanomaterials, which will further become DNA microchip systems. The investigations at the side of material science in connection with electrochemical biosensors open new directions for detection of specific gene sequences, and nucleic acid–ligand interactions.

An overview is reported here about nanomaterial-based electrochemical DNA sensing strategies principally performed for the analysis of specific DNA sequences and the quantification of nucleic acids. Important features of electrochemical DNA sensing strategies, along with new developments based on nanomaterials are described and discussed.

Keywords: Nanomaterials; Biosensors; DNA; Electrochemical transducers; Nanoparticles; Carbon nanotubes; Guanine; Adenine

Contents

1. Introduction

Recent progress in biosensing technologies based on nanomaterials has resulted by the development of several novel sensor devices with their challenging applications. Modern biomedical sensors developed with advanced microfabrication and signal processing approaches are becoming inexpensive, accurate, and reliable. This progress in miniature devices and instrumentation development will significantly impact the practice of medical care as well as future advances in the biomedical industry [1]. Electrochemical, optical, and acoustic wave sensing technologies have currently emerged as some of the most promising biosensor technologies.

The use of nucleic acid technologies has significantly improved preparation and diagnostic procedures in life sciences. Various combination of DNA associated with different types of transducers are an attractive subject of research. Nucleic acid layers combined with electrochemical or optical transducers produce a new kind of affinity biosensors as DNA biosensor for small molecular weight molecules [1–6]. The detection of DNA has a particular interest in genetics, pathology, criminology, pharmacogenetics, food safety and many other fields.

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After discovery of electroactivity in nucleic acids at the beginning of the 1960s [7], many approaches in combination with electrochemical nucleic acid sensors have been developed for analyzing or quantification of nucleic acids and DNA interactions and recognition events in solution and at solid substrates [1–3,8–31]. Electrochemical DNA biosensors are attractive devices especially for converting DNA hybridization event into an analytical signal for obtaining sequence-specific information in connection with clinical, environmental or forensic investigations. Such fast on-site monitoring schemes are required for quick preventive action and early diagnosis.

Nucleic acid hybridization is a process in which inconsonant nucleic acid strands with specific organization of nucleotide bases exhibiting complementary pairing with each other under specific given reaction conditions, thus forms a stable duplex molecule. This phenomenon is possible because of the biochemical property of base pairing, which allows fragments of known sequences to find complementary matching sequences in an unknown DNA sample [6]. An increasing interest has appeared in the development of simple, rapid and user-friendly electrochemical detection systems based on DNA sequence and mutant gene analysis, for instance early and precise diagnosis of infectious agents, for routine clinical tests [8,10–17,23,29]. Thus, DNA hybridization biosensors can be employed for determining early diagnoses of infectious agents in various environments [1,2] and these devices can be exploited for monitoring sequence-specific hybridization events directly [9,13–17] based on the oxidation signal of guanine/adenine or using DNA intercalators (some antibiotics, metal coordination complexes, etc.) which contain several aromatic condensed rings and often bind dsDNA in an intercalative mode [8,18,19,21,23,27,29,30].

Material science has recently a growing interest since it can present the possibilities how to apply novel materials from micro- to nanoscales, such as nanoparticles, nanotubes, nanowires into optical, electrical, magnetic, chemical and biological applications [32–44]. The novel surfaces modified with nanomaterials have recently presented an excellent prospect for biological recognition surfaces in order to develop a more selective and sensitive DNA sensor technology.

In the following section, the important features of electrochemical DNA sensing strategies, along with new developments based on nanomaterials are described and discussed.

2. Nanomaterial-based electrochemical DNA sensing strategies

Progress in synthesis and characterization of nanostructured materials and continuously emerging nanotechnologies promise dramatic changes in sensor design and their capabilities. Various nanostructured and advanced electronic materials with remarkable electrical, optical, and mechanical properties have recently been developed, with numerous unique applications [45].

Electrochemical DNA biosensors can normally be employed for determining the possible interaction between drug and DNA, or early and precise diagnoses of infectious agents in various environments [1–5] by using different electrochemical techniques; differential pulse voltammetry (DPV), potentiometric stripping analysis (PSA), square wave voltammetry (SWV), cathodic stripping voltammetry (CSV), adsorptive transfer stripping voltammetry (AdSTV), linear voltammetry (LV) and linear square voltammetry (LSV), etc. The reported studies utilized in DNA sensing strategies combined with different electrochemical transducers; carbon paste electrode (CPE)/magneto carbon paste electrode (MCPE), hanging mercury drop electrode (HMDE), screen printed electrode (SPE), pencil graphite electrode (PGE), pyrolytic graphite electrode (PrGE), mercury film electrode (MFE), gold electrode (AuE), platinum electrode (PtE), include:

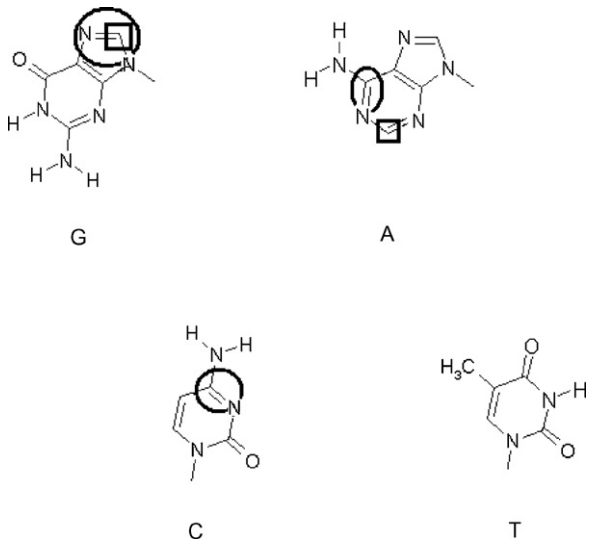
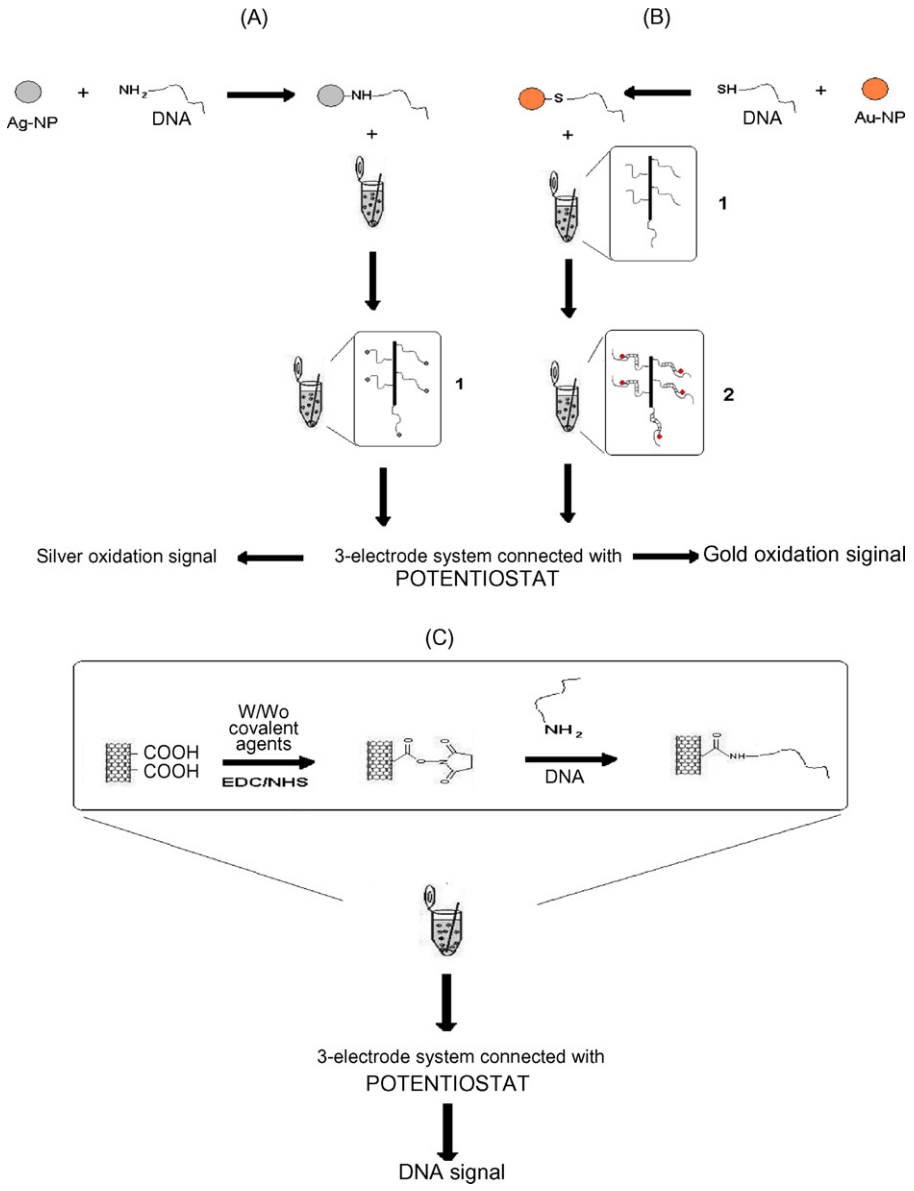


Fig. 1. All purine and pyrimidine bases of DNA and their electroactive sites; the circles representing the reducible (Red) groups and the squares representing the oxidizable (Oxi) groups.

(1) label-free DNA detection system called for sequence-specific hybridization processes based on the redox signal of most electroactive DNA bases, guanine and adenine [9,13–18,34,35,37,40,41] (all purine and pyrimidine bases of DNA, and their electroactive sites have also been shown in Fig. 1);
(2) electroactive indicator-based system (a) in the presence of any DNA intercalators (metal coordination complexes, antibiotics, etc.) [8,19,23,27,30], and (b) in the presence of some metal tags labelled nanoparticles, such as gold and silver nanoparticles, etc. [32,36,38,39,43,44].

In recent years, different electrochemical DNA sensing strategies developed in principle of nanotechnology have become one of the most exciting forefronts fields in analytical chemistry due to the challenging advances of various nanomaterials, e.g., magnetic particles/nanoparticles labelled with metal tags [14–17,36–39,41–44,46,47], nanotubes [34,35,40,48,49] and nanowires [33,50–52] by using different electrochemical transducers. Especially, after the pencil lead electrode (PGE) was introduced by Wang et al. [53] under the principles of development for a single-use nucleic acid sensor technology, the



Scheme 1. Representative schemes for presenting the simple applications of nanomaterial-based electrochemical strategies performed using disposable graphite electrodes, PGE. (A) Silver nanoparticles (Ag-NPs) and amino-linked DNA are used. Step 1 represents the immobilization of Ag-NPs labelled DNA onto the surface of PGE. (B) Gold nanoparticles (Au-NPs) and thiol-linked DNA are used. Step 1 represents the immobilization of DNA probe onto the surface of PGE and step 2 represents the hybridization between probe and its complementary labelled with Au-NPs. (C) Carbon nanotubes (CNTs), covalent agents (EDC/NHS) and amino-linked DNA are used.

numerous electrochemical DNA sensing routes have been created and then, progressed using disposable graphite electrodes. In comparison to the strategies performed using other electrochemical transducers, AuE, GCE, CPE and HMDE, etc. the applications of different nanomaterials-based electrochemical DNA sensing strategies using disposable graphite electrodes, PGE (representative simple procedures shown in Scheme 1) have been found simpler and faster. For example, to develop electrochemical DNA sensing approaches using AuE, GCE or GEC electrodes, the time-consuming cleaning procedure and complicated surface chemistry process are required for the preparation of these electrodes. Consequently, these strategies based on various nanomaterials in combination with PGEs bring some important advantages such as being inexpensive, simple and direct electrochemical assay for DNA detection in more reproducible and more sensitive results with a good degree of selectivity.

2.1. Electrochemical DNA sensing strategies using magnetic particles/nanoparticles connected with biological molecules labelled with metal tags

The use of magnetic particles/nanoparticles labelled with metal tags can bring novel capabilities to bioaffinity assays and sensors, especially after the electrochemical DNA detection strategies on nanoparticles have recently been introduced.

Table 1
A summary of the recent electrochemical investigations for DNA detection strategies based on various type of particles

Technique	Working electrode	HT (min)	Response	DL	Reference
PSA	PGE, CPE, m-CPE	10	Guanine	60 pM	[14]
DPV	GECE, m-GECE	20	Guanine	9.68 fmol/mL	[15]
DPV	PGE	20	Guanine	74.8 fmol/mL	[17]
PSA	SPEs	30	Silver	1.2 fmol	[37]
PSA	MFE	10	Cadmium	100 fmol in 50 μL sample	[38]
CSV	HMDE	15	Iron	10 ng in 50 μL sample	[39]
DPV	PGE	20	Guanine	43.11 pmol/mL	[41]
DPV, SWV, LV	SPEs	20	α-Naphthol	500 pg in 50 μL sample	[42]
DPV	CPE, PGE	60	Gold	0.78–0.83 fmol/mL	[43]
	m-GECE	15		33 pmol	[62]
AdTS-SWV	PrGE	30	Guanine/adenine	Higher than ppb level	[47]
LSV			1-Naphthol	3 fmol	
DPV	PGE	–	Silver	–	[44]
CSV	HMDE	30	Adenine	Below 2 nM for adenine	[54]
PSA	CPE, MCPE	–	Guanine	–	[55]

Working electrodes: carbon paste electrode (CPE)/magneto carbon paste electrode (m-CPE), hanging mercury drop electrode (HMDE), graphite epoxy composite electrode (GECE)/magneto graphite epoxy composite electrode (m-GECE), screen printed electrode (SPE), pencil graphite electrode (PGE), pyrolytic graphite electrode (PrGE) and mercury film electrode (MFE). Voltammetric techniques: differential pulse voltammetry (DPV), potentiometric stripping analysis (PSA), square wave voltammetry (SWV), cathodic stripping voltammetry (CSV), adsorptive transfer stripping voltammetry (AdSTV), linear voltammetry (LV) and linear square voltammetry (LSV). DL: detection limit, HT: hybridization time and Ref: related reference.

In the majority of earlier reports (also summarized in Table 1) it was shown that different types of transducers in connection with a number of voltammetric techniques were used for the development of efficient tools on electrochemical DNA sensing technology in combination with various type of particles. Such protocols have been developed by using the colloidal gold tags, semiconductor quantum dot tracers, polymeric carrier beads, or magnetic particles (summarized in Fig. 2).

In table, an overview about DNA sensing strategies by using magnetic particles and nanoparticles labelled with metals is briefly summarized, and their applications for the development of electrochemical sensor technology are discussed.

The electrochemical DNA detection using magnetic particles [14–17,41,42,46,47,55] brings the sequence-specific detection of DNA hybridization observed in exceedingly low detection limits as resulting in efficient magnetic separation. For example, Wang et al. [14] was reported a novel genomagnetic electrochemical assay related to BRCA1 breast-cancer gene based on label-free detection by using different transducers, PGE, CPE, and also m-CPE. An enzyme-linked sandwich hybridization was also studied combined with electrochemical detection of DNA sequences related to BRCA1 gene by using magnetic particles labelled with probe hybridizing to a biotinylated DNA target capturing a streptavidin-alkaline phosphatase (AP) enzyme, and consequently, 1-naphthol was measured as a product of enzymatic reaction in the presence of DNA hybridization [42]. Another study on enzyme-linked immunoassay coupling with magnetic particles for the detection of the DNA hybridization by using linear square voltammetry (LSV) technique and pyrolytic graphite electrode (PrGE) was reported by Palecek et al. [47]. Recently, there have been two reports performed by Erdem et al. [15,17] representing the electrochemical detection routes for DNA hybridization related to specific sequences using different transducers. A label-free genomagnetic assay for the electrochemical detection of *Salmonella* spp. sequence has been presented by using graphite-epoxy composite electrode (GECE) and magneto-GEC electrodes as electrochemical transducers [15]. Another genomagnetic assay developed by Erdem et al. [17] by using commercial magnetic particles for the electrochemical monitoring of detection of wild type hepatitis B virus (HBV) DNA in polymerase chain reaction (PCR) amplicons in length 437-bp has been described.

In contrast to other similar methodologies earlier reported in the literatures, as the first time, the streptavidin-coated magnetic nanoparticles were produced in the average diameter of 125 and 225 nm, and their performance was studied for the development of electrochemical DNA sensor technology [41]. Thus, it was exhibited that DNA hybridization can be realized onto magnetic nanoparticles carrying the probe oligonucleotides with the target sequences within the medium, and it can be effectively followed by the measurement of guanine oxidation signal using an electrochemical nucleic acid sensor in order to detect specific DNA sequences related to hepatitis B virus (HBV) quite sensitively and selectively, with this less time-consuming, and cheaper label-free electrochemical technique as the first time using home-made magnetic nanoparticles by Erdem et al. [41] in comparison to other traditional techniques [29,56,57] reported in literatures, where several external indicators $[Co(phen)_3]^{3+}$, di(2,2′-bipyridine)osmium(III) complexes, methylene blue, etc. have been used.

Recent developments have led to the progress of functional nanoparticles that could bind to nucleic acids, peptides, and proteins by applying the principles of surface chemistry. The electrochemical signal coming from nanoparticles labelled with gold (Au) tags were mostly used for the development of many strategies on electrochemical DNA detection

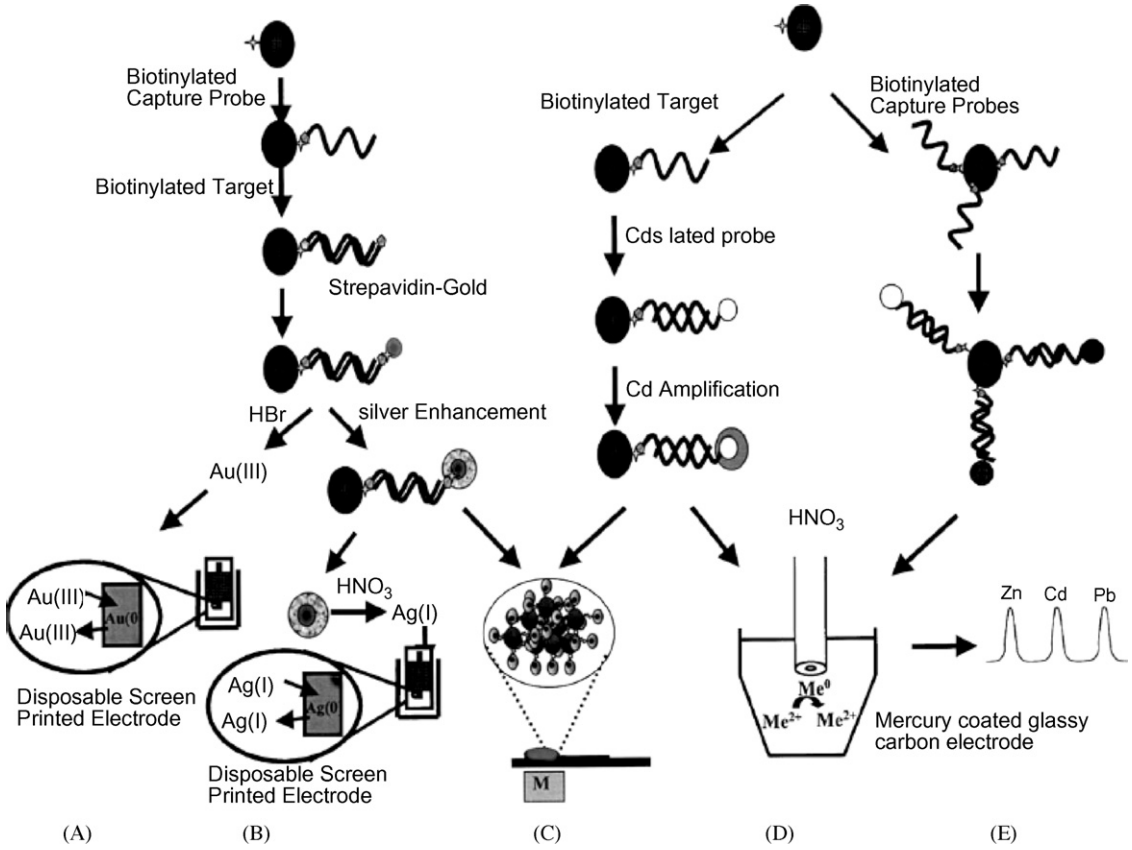


Fig. 2. Particle-based protocols for electrochemical detection of DNA. These assays involve the introduction of the probe-attached onto the magnetic particles, addition of the target/hybridization event, magnetic removal of unwanted materials, binding of the metal and amplified electrochemical detection of the dissolved gold (Au) (A), silver (Ag) (B) and cadmium sulfide (CdS) (D) nanoparticles. Me: metal tag. Also shown are solid-state stripping (C) and multi-target (E) detection protocols. (Reprinted from [5], Copyright (2003) with permission from Elsevier.)

[43,46,58,59]. The electrochemical detection and amplification of DNA hybridization based on streptavidin-coated Au nanoparticles was reported as the first time by Wang et al. [58]. The acid dissolution of Au tags was monitored by chronopotentiometric stripping analysis at disposable electrodes. Authier et al. [46] presented a method using Au labelled probes for the detection of human cytomegalovirus in PCR amplicons. After the release of gold atoms by oxidative metal dissolution using acidic bromine–bromide solution, the signal of gold was measured by anodic stripping voltammetry (ASV).

A sensitive electrochemical detection assay for DNA hybridization using silver nanoparticles and ASV method connected with carbon fiber ultramicroelectrode was reported by Cai et al. [60]. In this study, the determination of solubilized Ag(I) ions was successfully performed after the release of silver atoms by oxidative metal dissolution. Zhu et al. [61] reported a method for the detection of DNA hybridization in connection to lead sulfide (PbS) nanoparticles by measuring the lead signal in combination with ASV technique and polymer-modified glassy carbon electrode.

A novel nanoparticle-based protocol for detecting DNA hybridization was performed using a strategy based on a magnetically induced solid-state electrochemical stripping detection of silver in connection with single-use electrodes [37]. The selectivity of this assay was also checked in co-existing of a number of mismatched oligonucleotides and noncomplementary oligonucleotides beside the complementary of probe. Another strategy for the detection of DNA hybridization in a higher sensitivity with the shortest time (i.e., 10 min hybridization time) followed by the genomagnetic assay – magnetic-bead/ DNA hybrid/ cadmium sulfide nanoparticle – was performed successfully using mercury-film electrode [38]. Two different particle-based electrochemical schemes were reported for monitoring DNA hybridization based on PSA detection of an iron tracer [39]. The probes labelled with gold-coated iron core-shell nanoparticles were used, and thus, the captured iron-containing particles are dissolved following hybridization step, the released iron is quantified by cathodic-stripping voltammetry by using HMDE, in the presence of the 1-nitroso-2 naphthol ligand and a bromate catalyst. The results showed that this approach offers a novel DNA sensing strategy in a high sensitivity with minimal contributions from noncomplementary nucleic acids.

In the one of recent studies [43], the electroactivity of Au nanoparticles was used for the detection of hybridization without using any external indicators, or the need for any acidic dissolution of Au tag. Thus, DNA-specific sequences related to factor V Leiden mutation were detected electrochemically in this study by tagging a probe with gold colloid, and immobilizing the tar-

get onto the disposable electrode followed by anodic stripping analysis of Au colloid in a higher sensitivity and selectivity. The work also has a realistic potential application, since the experiments were carried out using real PCR amplicons. Pumera et al. described two gold nanoparticles-based genomagnetic sensors for detection of DNA hybridization related to specific DNA sequences, i.e., BRCA1 and cystic fibrosis. Consequently, the direct electrochemical detection of gold tags in the presence of hybridization was performed successfully by using magnetic graphite-epoxy composite electrodes (m-GECE). In contrast to the detection limit reported in the study of Pumera and coworkers [62], the lower detection limit as fM concentration level was obtained in this study [43] with a higher hybridization time (i.e., 60 min) and using PCR amplicons.

Some literatures have shown that the quantum dots (QD) can be used in a variety of bioanalytical formats with electrochemical detection, especially for DNA [63]. In this study, a novel gold nanoparticle-based protocol for detection of DNA hybridization based on a magnetically trigged direct electrochemical detection of gold quantum dot tracers by using m-GECE was described. Au67 quantum dot tag in the size of 1.4 nm linked to the target DNA was directly detected after the DNA hybridization event, without need of any acidic dissolution.

A novel electrochemical assay for the improved electrochemical sensing of DNA based on both oxidation signals of silver (without any external catalyst for metal ion or any acidic dissolution) and also guanine by using disposable pencil graphite electrodes (PGE) was introduced to the literatures [44]. The easy surface modification of disposable electrodes with nucleic acids was performed in this study by passive adsorption using amino-linked DNA oligonucleotide attached onto the surface of silver nanoparticles (Ag-NPs). This electrochemical approach for DNA detection has presented some important advantages in comparison to other earlier studies [37–39,58–61] such as, low preparation cost and easy modification of surface materials in higher sensitivity and selectivity.

2.2. *Electrochemical DNA sensing strategies using carbon nanotubes and other nanomaterials*

The versatility of the carbon–carbon bond presents the opportunity for attaching different functional groups to the end of the carbon nanotube (CNT) that offers potential for CNTs to be used as a new material for sensors in (bio)chemical applications [64].

The modification of electrochemical transducers with carbon nanotubes (CNTs) has recently attracted considerable attention in the field of DNA sensing technology and thus, many different schemes for electrochemical DNA sensing based on CNTs have been presented in the literatures [34,35,40,48,49,64].

Direct electrochemistry of DNA electroactive bases, guanine and adenine at a multiwalled carbon nanotube (MWNT)-modified glassy carbon electrode (GCE) provided significantly enhanced voltammetric signals (with calculated detection limit as 100 fmol of breast cancer BRCA1 gene) in comparison to unmodified GCE by Wang et al. [34].

The fabrication of CNT riched paste electrode was fabricated by Pedano et al. [35], and it was used for adsorption and electrochemical oxidation of nucleic acids. Incorporation of multiwalled nanotubes (MWNT) into carbon paste matrix provided 29 and 61 fold larger current values than the ones obtained from a carbon paste electrode for single stranded DNA (ssDNA) and short oligonucleotide. Additionally, the use of CNTs was reported for enzyme amplification of electrochemical DNA sensing strategy by Wang et al. [48].

A nanoelectrode array based on vertically aligned multiwalled carbon nanotubes, MWCNTs with controlled density, embedded in a SiO_2 matrix was reported by Li's group to be useful for detecting DNA hybridization [49]. Oligonucleotide probes were selectively functionalised to the open ends of the MWNTs and thus, DNA targets could be detected by combining the nanoelectrode array with ruthenium bipyridine mediated guanine oxidation.

A simple and sensitive electrochemical method based on CNT-modified disposable graphite electrodes for the detection of DNA and label-free DNA hybridization was performed by using the signal enhancement of the guanine oxidation signal without any modifications in the native bases or any external labelling by Erdem et al. [40]. Both CNT-modified transducers displayed an attractive voltammetric performance over their bare ones, the modified PGE compared favorably to the commonly used CNT-modified GCE electrode.

The specific properties of other nanomaterials, such as nanowires also offer an excellent prospect for biological recognition surfaces in order to develop a more selective and sensitive biosensor technology [33,50–52]. Li et al. [51] reported a novel method using a sequence-specific label-free DNA sensors based on silicon nanowires (Si-NWs) by measuring the change of the conductance. Kelley and coworkers [52] developed a gold nanowire array (Au-NW) in 15–20 nm in diameter, and this array was used for electrochemical DNA detection by the help of the electrocatalytic reporter systems, $Ru(NH_3)_6^{3+}$ and $Fe(CN)_6^{3-}$.

3. Conclusions and future perspectives

Nanotechnology refers to research and technology development at the atomic, molecular, and macromolecular scale, leading to the controlled manipulation and study of structures and devices with length scales from 1 to 100 nm range [65]. Nanomaterials have unique chemical and physical properties that offer important possibilities for analytical chemistry. For example, nanoparticles represent an excellent biocompatibility with biomolecules, and display unique structural, electronic, magnetic, optical and catalytic properties which have made them a very attractive material [66] as labels in the detection of DNA hybridization [67] using optical methods, e.g., surface plasmon resonance [68] or different electrochemical techniques [5] between other applications.

The integration of nanotechnology in combination with molecular biology and electrochemistry has been expected to create major advances in the area of electrochemical DNA sensor technology. The development of advanced electrochemical DNA sensing strategies based on nanomaterials have recently been considered as important tools in the field of genomics, medical diagnosis, and drug–DNA interactions [36,50,64].

The electrochemical schemes for DNA detection based on magnetic particles assay in combination with metal nanoparticles or enzyme labelling, or using label-free system, brings the sequence-specific detection of DNA hybridization observed in exceedingly low detection limits as resulting in efficient magnetic separation.

Such coupling of DNA hybridization surfaces with electrochemical transducers and metal nanoparticles eliminates the needs for external indicators and advanced surface modification or other regeneration schemes.

The modification of transducers with carbon nanotubes has recently attracted considerable attention in the field of electro-analytical chemistry. The high-surface area, and hollow geometry, the useful mechanical properties of CNTs combined with their electronic conductivity and ability to promote electron transfer reactions provide novel challenging transducers for the catalysis of biomolecules and inorganic compounds [69].

The exploitation of carbon nanotubes for the development of electrochemical DNA sensing strategies has been still in progress. Beside this progress on the development of nanotube-based electrochemical transducers, there have been available reports in the literatures that represent the results obtained by (1) any external time-consuming step required expensive agents (e.g., enzyme labelling of CNT for specific binding of DNA onto the surface), or (2) any fluorescence labels for detection of DNA, and DNA hybridization.

The development of DNA sensing strategies or gene detection has been increasing its practical importance, especially in conjunction with the development of microfabrication technology toward chips and arrays. It is hoped that continued development through combined efforts in microelectronics, surface/interface chemistry, molecular biology, and analytical chemistry will lead to the establishment of genosensor technology based on DNA sensing strategies combined with the advantages of nanotechnology.

Nanomaterial-based genoelectronics, the molecular interfacing approach into exploiting DNA recognition events is important in coming perspective, that can bring us the term as “DNA microarray” to measure the expression patterns of thousands of genes in parallel, generating clues to gene function that can help to identify appropriate targets for therapeutic intervention, and to monitor changes in gene expression in response to drug treatments [70–72].

Congratulations

I feel very, very lucky to have been able to work with Prof. Wang at his senso-chip lab. His outstanding example of scientific excellence allows us always to work in a successful and challenging atmosphere. In addition, his happy and friendly personality encourages us to join with the scientific community in becoming a good and close friend.

I would like to congratulate Prof. Wang on his 60th birthday and I wish him with his family more and more wonderful years filled with health, happiness and continued success in all of his endeavors!

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