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DNA conformational polymorphism for biosensing applications

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ABSTRACT

In this mini review, we will briefly introduce the rapid development of DNA conformational polymorphism in biosensing field, including canonical DNA duplex, triplex, quadruplex, DNA origami, as well as more functionalized DNAs (aptamer, DNAzyme etc.). Various DNA structures are adopted to play important roles in sensor construction, through working as recognition receptor, signal reporter or linking staple for signal motifs, etc. We will mainly summarize their recent developments in DNA-based electrochemical and fluorescent sensors. For the electrochemical sensors, several types will be included, e.g. the amperometric, electrochemical impedance, electrochemiluminescence, as well as field-effect transistor sensors. For the fluorescent sensors, DNA is usually modified with fluorescent molecules or novel nanomaterials as report probes, excepting its core recognition function. Finally, general conclusion and future perspectives will be discussed for further developments.

1. Introduction

1.1. General duplex DNA

The deoxyribonucleic acid (DNA) is generally regarded as the carrier of gene in a broad range of animals, plants, and viruses. Since the early model of B-DNA structure, which proposed in 1953 by Watson and Crick, it has sparked tremendous interest on the horizons of biological science and bioapplications. The classic B-form DNA owns a right-handed double helix, with two antiparallel sugar phosphate backbones and the base pairs locating at the center of helix axis. The formed major and minor grooves are important to mutual recognition of DNA and proteins (Watson, 1953). Moreover, different from the Watson-Crick double helix, DNA also could adopt some other structures, such as A-/Z- form, quadruplex and i-motif etc. (Langridge et al., 1965). A-DNA is also the right-handed double helix. In contrast to B-DNA, it is narrower and has 11 base pairs per helical turn resulting in a deep and narrow major groove (Mirkin, 2008; Kulkarni and Mukherjee, 2017). And other deviations that have different base pairs, including C-form, D-form and T-form, etc., existed in the right-handed double helical family of structures (Mirkin, 2008). The B-form is well-acknowledged the most frequently observed conformation of DNA. Later, a special kind of left-handed DNA helix is reported in DNA crystals, called Z-DNA (Wang et al., 1979). Its structure is formed by specific sequences composed of alternating purines and pyrimidines. Opposed to B-DNA, its helical turn was 12 base pairs so that it had only one deep and narrow groove, corresponding to the minor groove in B-form. And Z-form can be transited from B-form under some conditions, considering as a transient structure occurred during transcription (Feng et al., 2013). DNA B-Z transition has attracted much because of not only Z-DNA biological important but also their relation to disease and DNA nanotechnology. In general, duplex DNA is the most common and classic DNA structure, as well as the basis of DNA conformation polymorphism. However, simply duplex conformation has also highly limited by the susceptibility to enzymatic degradation, low resistance to heat or denaturing reagents, etc, thus diverse conformations are necessary with varied roles during the fabrication of nanostructures and nanodevices.

1.2. Triplex DNA

The views on DNA structure has developed along with the discovery of multistranded DNA structures. Much attention has paid on these structures due to their potential use of therapeutics and specific significant roles in vivo. Triple-helical structure is formed by a duplex DNA and a third strand, via Hoogsteen or reverse Hoogsteen hydrogen base pairing. Triplex has initially discovered in the regulatory parts of eukaryotic promoters and regarded as transcription regulatory signal (Johnston, 1988). There are two types of DNA triplex structures, the parallel and the antiparallel, determined by the studies of NMR spectroscopy according to the third strand binding ways (Frankkamenetskii and Mirkin, 1995). In the parallel form, the third strand with

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homopyrimidine binds parallel to the complementary strand via Hoogsteen hydrogen bonds, reaching the triplex TA.T and $CG.C^+$ (Valery and Vladimir, 1996). Differently, the third strand in antiparallel form contained homopurine binds antiparallel to duplex homopurine via reverse Hoogsteen pairing and mainly forms triplex TA.T, CG.C and TA.A (Gee and Miller, 1992; Hanvey et al., 1988). In the efforts to improve the triplex stability, Ihara et al. reported that silver ions (Ag^+) can stabilize triplex DNA, and found that Ag^+ could specifically displace an N3 proton of a cytosine in the $CG.C^+$ base site of triplex DNA to form a new triplet (CG. CAg^+). This novel triplet could stabilize the parallel-motif triplex, even at neutral pH (Ihara et al., 2009). Motivated by the unique feature that Ag^+ could only work on Hoogsteen hydrogen bonding in the $CG.C^+$ within triplex DNA, we further created site-specific, homogeneous, and bright silver nanoclusters (AgNCs) with high-stability using triplex as novel nanoscaffold for sensitive and label-free biotiols detection (Feng et al., 2012a, 2017). Triplex DNA, formed with the duplex and triplex forming oligonucleotide, has become a powerful and alternative motif in the design of new molecular biology tools. However, few triplex compositions have been utilized, except the typical TA.T and $CG.C^+$ triplets. In recent years, the wide applications of triplex in diagnostic agent and sophisticated DNA-based nanomaterials have been proposed (Hu et al., 2017).

1.3. Quadruplex DNA

Apart from triplex DNA conformation, the four-stranded DNA structure is the other example of multistranded DNA structures, including G-quadruplexes and i-motif quadruplexes (Guschlbauer et al., 1990; Manzini et al., 1994). G-quadruplexes can form from DNA oligomers with G-cluster through a cyclic Hoogsteen hydrogen bonding. Due to the various molecularity and strand orientations, there exists a variety of quadruplex structures in vitro (Sundquist and Klug, 1989). A typical duplex region composed of hundreds of TTAGGG repeats exists in human telomeric DNA, also with an end of G-rich single-stranded protrusion, folding into highly stable four-stranded helices. G-quadruplex structure is stable and detectable in human cells, as well as potential anticancer agents, since it is activated and involved in the telomerase activity regulation (Lam et al., 2013; Xu, 2011). Furthermore, the telomeric terminal overhang can form more-complex, higher-ordered G-quadruplex dimer or multimer, and TTA linkers are usually adopted to connect the consecutive units. Except parallel motifs, antiparallel intramolecular quadruplex can obtain from DNA sequences with four guanine-rich repeats or long guanine tracts folding. Various DNA sequences and strand orientations produce a variety of groove sizes among different G-quadruplexes, which may provide the specific recognition of multiple G-quadruplexes structures (Gilbert and Feigon, 1999). Quadruplexes supply rich changes in target binding and signal probe linking. Moreover, the important function of cations in the stability and folding of G-quadruplexes are studied, which are sensitive to the presence of cations and their concentrations. For instance, the GC.CG quartets form different quadruplexes structures in the presence of K^+ verse Na^+(Debmalya et al., 2016). There is also report that a G-quadruplex is selectively stabilized by K^+ but not by Li+, which is partially attributable to size matching (Creze et al., 2007). Classic human G-quadruplexes have been reported to inhibit telomere elongation, much effect has gone into the study of G-quadruplexes' potential capability in cancer diagnosis and therapy (Zahler et al., 1991).

Cytosine-rich DNA strands can form the i-motif quadruplexes under acidic conditions (Manzini et al., 1994). A four-stranded i-motif structure is usually generated from two parallel-stranded duplexes within hemiprotonated C^+C pairs intercalates into a second antiparallel duplex. The presence of i-motif also indicates conformation polymorphism of DNA. Like G-quadruplex sensitive to K^+ ions, Waller et al. has reported that i-motifs can be stabilized by Ag^+ under physiological pH. Then a label-free i-motif DNA sensor for Ag^+ detection has developed (Bei et al., 2016; Day et al., 2013). No matter triplex, G-quadruplex or i-motif structures, the mentioned work about interactions between DNA and metal ions open up the door to adopt novel DNA structures for special ions detection. Interestingly, Qu's group has reported that single-walled carbon nanotubes (SWNTs) can inhibit DNA duplex association and selectively induce human telomeric i-motif DNA formation. The nanomaterials bind to the 5′-end major groove under physical conditions or even at pH 8.0 conditions (Li et al., 2006). Recently years increasing concern about how to safely develop and use carbon nanotubes requires a simple and highly sensitive detection method for their toxicological evaluation and environmental monitoring. A novel and low-cost electrochemical DNA-based sensor has designed to distinguish single- or multi-walled carbon nanotubes, providing new insights into how to design a biosensor for nanomaterials detection (Peng et al., 2009). DNA quadruplexes provide interesting advantages over canonical other structures, including high stability, flexibility and selectivity to various molecules under selected conditions, promising a greater diversity of DNA-based building blocks in combining with multiple nanomaterials and nanodevices.

1.4. DNA nanomaterials

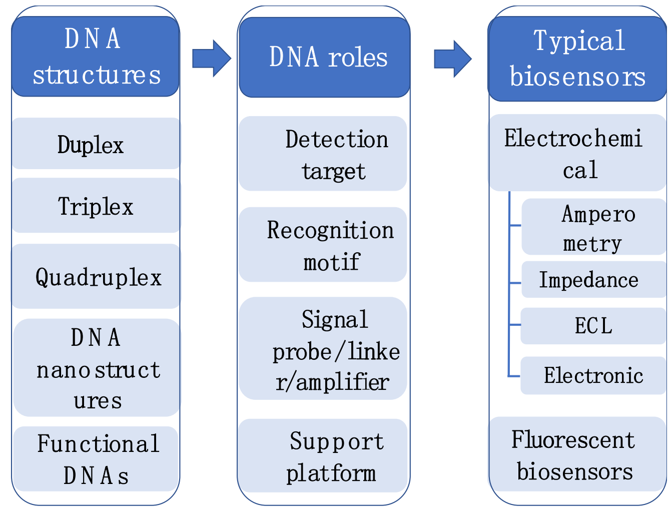
DNA itself is also a typical nanomaterial, and in the past decades DNA nanotechnology offers a variety of possibility to the biodevice design and research (Kallenbach, 1983). Rigid branched DNA motifs can be constructed through the complementary Watson-Crick base pairing, then further assembled into discrete finite object or infinite periodic lattices through sticky-end cohesion. Fan's group have successfully constructed three-dimensional (3D) DNA tetrahedral nanostructures, and studied that they can easily enter live cells and release carried drugs, which are ideal molecular scaffolds with high mechanical rigidity and structural stability for various application from molecular sensing to therapeutics(Li et al. (2011)). Further, they have developed series work with DNA tetrahedral structure for the construction of sensing platform and, the investigation of DNA-mediated charge transport (CT) through duplex or space.

Another typical DNA self-assembled nanostructures, the scaffold DNA origami, have also been successfully applied into biosensing, smart drug delivery, enzyme cascades and analysis platforms, etc (Hong et al., 2017; Song et al., 2017). DNA origami is usually obtained from a straightforward self-assembly process in which a long single-stranded scaffold is folded into special desired shape, and a multitude of short helper strands are needed. It is easily fabricated with finite-size, highly molecular weight, and highly addressable pixel in nanoscale, working as a versatile platform for other molecules immobilization (Saccà and Niemeyer, 2012). In short, DNA nanomaterials have avoided the disadvantages of separate structures, and greatly expanded the potential of DNA nanotechnology development. As discussed below, the typical study of DNA origami offers a novel proof-of-concept nanofabrication mechanism and stable pathway for in-vivo biosensing (Suo et al., 2018).

1.5. DNA aptamer and DNAzyme

In addition, functionalized DNAs, such as aptamers and DNAzymes, have also developed quickly in biosensor fields due to their special recognition abilities and excellent biocompatibility with the cellular environment. In general, both of them are obtained from the method called in vitro selection or SELEX (systematic evolution of ligands by exponential enrichment)(Tang et al., 2014). DNA aptamers are a class of oligonucleotides that can recognize specifically to target molecules (including metal ions, organic dyes, proteins, amino acids, and even whole cells). Since aptamers were firstly reported, they have been widely applied as building elements with high affinity for biosensors (Nguyen et al., 2017; Poolsup and Kim, 2017). For example, DNA aptamers show a strong recognition ability to some special cellular surface receptors, which is in the form of proteins, for sensitive and label-free cancer cell sensor design (Shangguan et al., 2006). And DNAzymes are new members of the enzyme family, basing on DNA enzymatic molecules, which catalyze biochemistry related reactions including nucleic acid cleavage, ligation and peptide bond formation (Tang et al., 2014). Comparing to conventional protein enzymes, DNAzymes take advantages of cost-effective synthesis, high chemical stability, and easy molecular modification and have been extensively explored in diverse areas for versatile applications such as biosensing and nanoelectronics (Lan and Lu, 2012; Zhao et al., 2013). DNAzymes can be used as amplifying label when developing biosensors. Its catalytic function is always accomplished to design aptamer-DNAzyme conjugate which can combine the recognition property of aptamer and amplification signal. Both of DNA aptamer and DNAzyme are selected and functionalized sequences with special properties that provide more possibilities for biosensor fabrication, to date against targets as diverse as DNA, RNA, proteins, small molecules/ions and nanomaterials, which are significant to the promotion of DNA sensing performance with various structures above.

Furthermore, some DNA analogues, like peptide nucleic acids (PNA) and locked nucleic acids (LNA), have also been utilized for the development of high-performance affinity biosensors (Briones and Moreno, 2012). These two artificial polymers have inimitable physicochemical properties and are able to bind strongly and specifically to complementary targets.



Scheme 1. Representation of DNA conformational polymorphism with various roles in electrochemical/fluorescent biosensor designs.

2. The roles of DNA in biosensors

Biosensors are a class of analytical devices integrating biological or biologically derived sensing element, converting a biological response into an analytically useful signal via a physicochemical transducer (Thevenot et al., 2001). Since biosensors began in the 1960s, there are various types of biosensors being developed, such as enzyme-based biosensor, immunosensor, nucleic acid-based biosensors, as well as optical/electrochemical/thermal and piezoelectric biosensors, etc., according to different classification methods. Generally, one typical biosensor is composed of several factors: (1) the targets to be detected, such as metal ions, DNA/RNA, proteins or whole cells, etc., depending on various application fields; (2) the molecular recognition motif to realize selective responses, like antibodies in immunosensor or DNA/RNA for nucleotide-based sensor; (3) For process between different interfaces, sensor platform or scaffold where the detection processes constructed. For example, one sensitive electrode surface is necessary in electrochemical biosensor. Also, DNA origami as a novel sensor platform would be mainly discussed in the following part; (4) finally, what kind of output signal obtained. Different biosensors have been designed with signals of electrochemical, optical, mass, and so on, and widely applied in biological/medial field, environment testing and food industry due to their excellent stability and sensitivity.

There is no doubt that DNAs play important roles in biosensor development and application by involving different aspects as discussed above. A significant progress has been achieved, particularly in heavy ion, cancer and genetics biomedicine etc.(Mehrotra, 2016). The conformational polymorphism of DNA provides a variety of possibilities in sensor design, herein, we mainly classify DNA from the four general roles as detection target, recognition motif, staple strand for linking or platform, as well as signal report probes by itself or functionalized materials. Noticeable, the functions of DNA are not single but diverse depending on the sensor principle in most cases. Later in Section 3, recent publications of DNA-based sensors with electrochemical and fluorescent signal readout will be mainly summarized according to the output display (Scheme 1).

2.1. DNA as detection target

Nucleic acid assays are important for the detection of microorganism, genotyping and gene expression profiling. Traditional hybridization protocol has been developed on solid substrate, usually glass, plastic, silicon, or even cheaper paper (Lawn et al., 2013; Song et al., 2014). In many proof-of-concept DNA biosensor, one short DNA sequence is often chosen as model target. Such target DNA can be disease-related strand with genetic information. For example, 11mer-HIV virus-related ssDNA molecule has been detected in our recent publications (Fu et al., 2017). We have operated a graphene transistor in an ambipolar mode near its neutrality point, and recorded the target DNA binding response with achieved detection at picomolar level. Traditional DNA analysis always needs polymerase chain reaction (PCR) and microarray techniques, which is comparably complicated procedures and high cost (Niemeyer and Blohm, 1999). Besides the common PCR, the signal amplification for DNA detection can generally be realized by amplifying the signal label using enzymes or nanomaterials. The cycling method after target DNA binding through various nuclease, such as nicking endonuclease (Xu et al., 2010), polymerase (Guo et al., 2009), exonuclease etc., have been applied for sensor design (Su et al., 2011). By further combining with rolling circle amplification (RCA) protocol, it can prolong the enzyme cleaved molecular beacon fragment to realize high sensitive detection after the hybridization events occurred (Ji et al., 2012; Wu et al., 2010). Recently years, some enzyme-free amplification methods have also been applied for DNA detection, which can be realized using catalyzed hairpin assembly with nearly zero background and a high catalytic efficiency. And it usually been applied to multiple different analytical formats, like fluorescent, colorimetric and electrochemical signaling (Li et al., 2011). To realize high-throughput multiplex detection is an important issue, in which DNA chips have been achieved great process. It always needs distinguishable signal readouts for different target DNAs through labeling with different fluorescent or electroactive probes. Except these common methods, some other technique, for example surface-enhance raman spectroscopy (SERS) has been recently reported to realize sensitive DNA detection with single-base sensitively (Xu et al., 2015a). An iodide-mediated Ag nanoparticle was synthesized to prevent the DNA direct interaction on surface. The DNA phosphate backbone signal works as an internal standard to calibrate each base signal produced, therefore a more reliable DNA structure determination is realized.

2.2. DNA as recognition motif

DNA is also commonly used as recognition motif due to its high bioaffinity and specificity in biosensor design. It can bind to various targets by diverse modes, including hydrophobic, electrostatic interactions, hydrogen bond and covalent binding, etc. A designed single

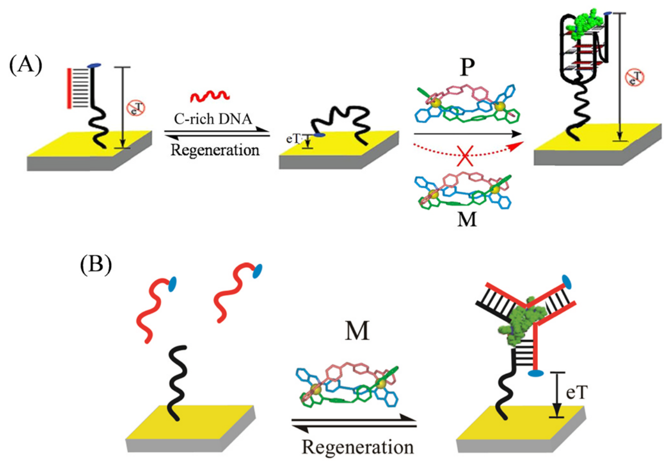


Fig. 1. Novel chiral biosensors design with (A) G-quadruplex and (B) three-way junction DNA as recognition probes [72, 73].

strand DNA (ssDNA) is usually exploited as capture probe, which can immobilize on special surfaces in the sample solution (Labuda et al., 2010). Due to its easily modification and functionalization, DNA can be easily immobilized onto the surface of transducers and act as staple strand for linking at the same time (William and Ronkainen, 2014). The groups, like SH-, OH-, COOH- etc., can be modified at 3′ or 5′ terminus of DNA probes, and they can be further immobilized on special platform through covalent bonding or electrostatic interaction. DNA hybridization is a typical biorecognition process, in which the ssDNA can specifically recognize its complementary sequence through Watson- Crick's way into a double helix. This is the principle that DNA biosensors used for nucleic acid sequences detection (Yola et al., 2014; Zhang and Huang, 2012).

Moreover, DNA conformational polymorphism supply much opportunities for biosensor design for other targets. For example, chirality is of central importance in biomolecular recognition, and previously various techniques have developed for distinguishing enantiomers. Considering the intrinsic chiral binding property of DNA, we has designed one novel G-quadruplex to distinguish different chiral metallo-supramolecular enantiomers (Fig. 1) (Feng et al., 2012b, 2012c). The human G-quadruplex strand has been immobilized on electrode surface to construct a chiral surface, on the basis of one enantiomer of G-quadruplex ligand can selectively induce the folded structure formation, while the other enantiomer cannot (Fig. 1**A**). We further expanded the design with well-designed three-way junction DNA structure as binding motif for chiral molecular distinguishment. Since previous such chiral sensors are usually using cyclodextrins or molecularly imprinted polymer as recognition substrate, here our work taking DNA as recognition probe supplied another thinking way (Fig. 1**B**). Interestingly, with complementary DNA as competitive agent, we can also realize highly efficient sensor regeneration.

DNA aptamer and DNAzyme are also two typical recognition probes in hundreds and thousands of sensor work. This ability is based on their novel SELEX selection process with high sensitivity and selectivity. In SELEX rounds, it comprises repeated steps of incubation, separation, and amplification until sequences with highest affinities selected. In addition, negative selection are also subjected to further rounds, in which the DNA libraries are mixed with negative targets to ensure highly selectivity. Till now, a lot of review has summarized their special recognition functions for various targets, and readers can easily get relevant information from recent detailed summary work (Peng et al., 2017; Zhou et al., 2014). Noticeably, for metal ions (Pd^{2+}, Zn^{2+}, Cu^{2+}, UO^{2+}, Cd^{2+} and Hg^{2+} etc.) detection, previous work has mainly utilized in aqueous buffers by using aptamer and DNAzyme as recognition motifs.

2.3. DNA as signal probe or as probe linker/amplifier

DNA itself is electrochemically active due to their electrochemically oxidizable or reducible nucleobases, and they exhibit specific surface activity as signal probe. Among the four nucleotides, guanine shows the strongest and most sensitive electrochemical signal. The electrochemical properties of single base can be detected on different platform, for example, on graphene surface (Zhou et al., 2009). Furthermore, the different DNA structure can also been examined on graphene modified electrode surface, which is sensitive enough to detect single nucleotide polymorphism (Bonanni et al., 2012). Triplex is an unusual DNA structure as we discussed above, and it is important to distinguish triplex from different forms of DNA. These different DNA structures can be detected on graphene modified electrode (Feng et al., 2014). Based on the interactions between nucleotides and graphene surface and another sensitive redox probe, $Ru(bpy)_3^{2+}$ mediated guanine oxidation, it has produced distinguished electrode responses for different DNA structures. Especially for triplex, guanine bases are hidden inside the folded form, making it less susceptible to be oxidized on electrode. Also the conjoint way of several guanines strongly influenced their electrochemical responses on electrode surface. These information can be obtained with different electrochemical techniques, such as cyclic voltammetry, impedance spectroscopy, and electrochemiluminescence methods.

Except DNA nucleotides intrinsic signal, most of the biosensor design use DNA as linker to modify electroactive/fluorescent molecules. Depending on the techniques, the signal or immobilization probes can be modified on 3′- or 5′- DNA terminals, as well as on any nucleotide inside the sequence. In a biosensor, DNA can act as staple strand for linking, which can be regarded as a bridge between sensing element and transducer (Shen et al., 2008; Yu et al., 2013). And different signal molecules, such as redox-label or external fluorescent groups, have been applied in electrochemical sensors and fluorescent sensors (Chen et al., 2017; Li et al., 2017). A number of detections have employed label DNA probe for improving sensitivity of biosensors, including using redox-active methylene blue and fluorescent molecules (Hvastkovs and Buttry, 2010).

The ease of DNA modification further promotes other molecules or nanomaterials binding. For example, folate can be linked to DNA allows it targeting cancer cells. Labeling with fluorophores makes the designed sensor sensitive and optical observation. Nanomaterials are also easily modified at DNA end, which further bring more redox probe close to surface with enhanced signal. (Qiu et al., 2014). (Kang et al., 2010)

With the highly development of carbon nanomaterials (CNMs), there are also much researches focused on the binding of modified DNA with CNMs, such as single walled nanotubes, graphene/graphene oxide, carbon quantum dots, etc., aiming to achieve improved biocompatibility and biomolecular recognition capabilities (Liu, 2014). The diverse interactions between CNMs and DNA of different structures, such as single-stranded, duplex, triplex and quadruplex, have been systematically studied in one recent review (Sun et al., 2016).

Based on the highly programmable and predictable nature of DNA nanotechnology, Fan's group has demonstrated to construct valency-controlled signal amplifiers on which signaling molecules can be quantitatively recruited (Fig. 2) (Liu et al., 2018). The modification property of DNA makes it easily link protein, DNA or different nanoparticles (Fig. 2**A**). In the sensor structure, a thiol-modified tetrahedral DNA as framework nucleic acids (FNAs) can be firstly modified on gold surface, and the long linker DNA is adopted to design concatenating FNAs as valence-controlled signal amplifiers. As shown in Fig. 2**B**, a pendent probe was designed at one vertex of each FNAs to hybridize to the long linker DNA with high modularity for ultrasensitive biosensing. More horseradish peroxidase (HRP) modified at the end of FNAs can be brought close to electrode surface, which could catalyze enzyme substrates reaction. With this design, biomolecular recognition events can be amplified by recruiting multiple regulatory target to the action site

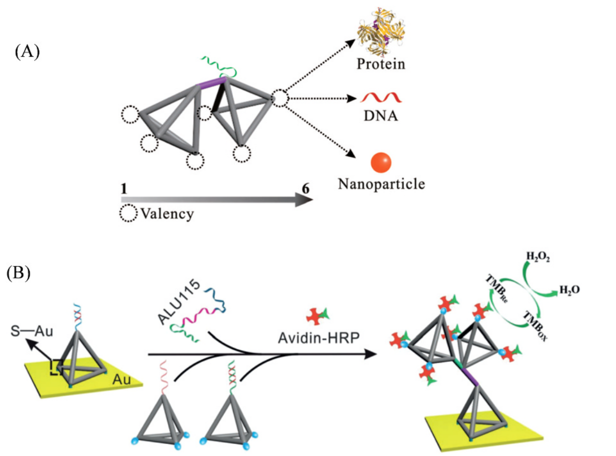


Fig. 2. (A) Schematic illustration of FNAs construction, which was designed to hybridize tetrahedral DNA nanostructures to a long DNA linker, with the end modification of recruit DNA, protein avidin and gold nanoparticles; (B) electrochemical biosensor design for *cf*DNA detection based on valence-controlled amplifier.

to realize signal amplification detected. With this valence-controlled signal amplifier, the electrochemical biosensor detection sensitivity is enhanced with nearly 5 orders of magnitude for target tumor-relevant circulating free DNA (*cf*DNA), with an improved dynamic range at the same time. In this typical biosensor, DNA functions are various as staple strand for surface immobilization, linker strand for FNAs, signal enzyme probe modification on DNA nanostructures, as well as the detection target *cf*DNA.

2.4. DNA as support platform

In this section, we mainly take DNA origami as model for following discussion. DNA origami is a versatile platform for the self-assembly of other molecules, therefore novel nanoscale devices can be created on it for biosensor applications. Especially at the single-molecule level with atomic force microscopy (AFM) technique to design nanosensors. For example, Yan et al. has developed a label-free sensor or RNA hybridization detection using DNA origami as an addressable support (Fig. 3) (Ke et al., 2008). On this origami nanostructure, multiple probe tiles have been used to target RNA with a specific sequence. The whole hybridization events can be positioned on nanoscale area, and detected under AFM observation before and after target RNA binding. Furthermore, different probes' bar-coded tiles have also introduced on the origami surface to realize multiplex detection simultaneously. DNA origami-based nanosensor supply a promising way to profile gene expression of single cells. Seeman's group has reported a novel nanosensor to detect single nucleotide polymorphism (SNP) (Subramanian et al., 2011). Tintore et al. further developed a DNA repair naosensor at the single-molecule level, taking the spatial addressability of DNA origami in combination with DNA G-quadruplex. AFM method can visually detect the DNA change conformation after its binding of thrombin protein. The enzymatic activity of Human O^6-alkylguanien-DNA alkyltransferase (hAGT) has been visualized on an origami platform (Tintoré et al., 2013). In this typical work, the roles of DNA are various. Except sensor platform for binding other molecules, it also combined the ability of thrombin aptamer recognition to its target protein, with DNA aptamer working as probe motif. The identification of different enzyme inhibitors are expected to realize on such DNA origami assays, opening the door for developing new biosensor of protein activity.

In all, the functions of DNA in sensors demonstrate the important roles that DNA polymorphism act as, which greatly inspire the researchers' thinking and extend the novel applications of DNA-based biosensors. We would later summarize the recent development of DNA biosensors, including mainly the electrochemical sensors and fluorescent sensors in Section 3.

3. DNA polymorphism in electrochemical sensors

Electrochemical biosensors are a class of biosensors, integrating with electrochemical transducers, which are capable for providing selective quantitative analytical information by using a biological recognition element. With the characteristics of low fabrication costs, convenient to operation, portability and simplicity of construction, use of electrochemical detection for monitoring the transducers is becoming more common in most biosensors (Shehata et al., 2016; Fekry, 2017). Thus, the development and application of electrochemical biosensors are significant to a wide fields. Due to their rich structural polymorphism and ability to bind particular targets with sensitivity and specificity, DNA has attracted much attention in the construction of electrochemical biosensors (Rothlisberger et al., 2017). The high specificity for analytical molecules makes DNA capable for acting as recognition element and the electrochemical activity of DNA promises to provide a useful electrical signal in the detection process. These biosensors based on DNAs are playing indispensable roles in environmental monitoring, biomedical and food industry (Huang et al., 2017).

The measurement techniques of electrochemical biosensors can be divided into different types according to the detection principle. Herein, we focus primarily on those techniques since they are the most commonly applied in electrochemical biosensors, including amperometry, electrochemical impedance spectroscopy (EIS), electrochemiluminescence (ECL) and field-effect transistor (FET). The DNA polymorphism integrated with diverse measurement techniques expand the application range of electrochemical biosensors. We will summarize the recent researches about DNA-based electrochemical biosensors involving in those measurement techniques to indicate the DNA polymorphism in sensing platforms (Table 1).

3.1. Amperometry sensors

Amperometry is a typical measurement in electrochemical sensors. The characteristic of this technique is adding a potential to a working electrode versus a reference electrode, and the result of measuring current is the indicator of electrochemical reduction or oxidation at the working electrode and is directly correlated to the concentration of the electroactive species. So the current response, usually a peak or a plateau, is corresponding to the concentration of analyte (Ronkainen et al., 2010). Currently, the current measured at a constant potential refers to amperometry, while the controlled variations of the potential refers to voltammetry. The latter includes the linear sweep voltammetry, cyclic voltammetry, differential pulse voltammetry and square-wave voltammetry, etc. With the development of DNA electrochemical biosensors, these methods represent a significant tool in measurement process.

A typical electrochemical DNA-based (E-DNA) sensing platform, which involves a redox-labeled single strand DNA(ssDNA) probe immobilized on an electrode surface, provides a typical approach for the application of amperometry in DNA-based sensors (Fan et al., 2003). The hybridization of probe with the complementary sequence leads to a duplex formation that alters electron transfer efficiency between redox label and electrode surface. Then a measureable current response that is proportional to the analyte can be obtained. Plaxco and co-workers have applied this platform for detection of specific nucleic acid sequences (Rowe et al., 2011) and protein marker (Bonham et al., 2013). Recently, using this platform Yang et al. developed a biosensor for PML/RARA fusion gene detection (Yang et al., 2016), and Yin et al. prepared a functionalized locked nucleic acid (LNA) probe to detect micro-RNA21 (Yin et al., 2012). Besides the specific sequence detection, Huang et al. (2016) employed this platform and aptamer for the sensitive detection of ochratoxin A based on a competitive mechanism.

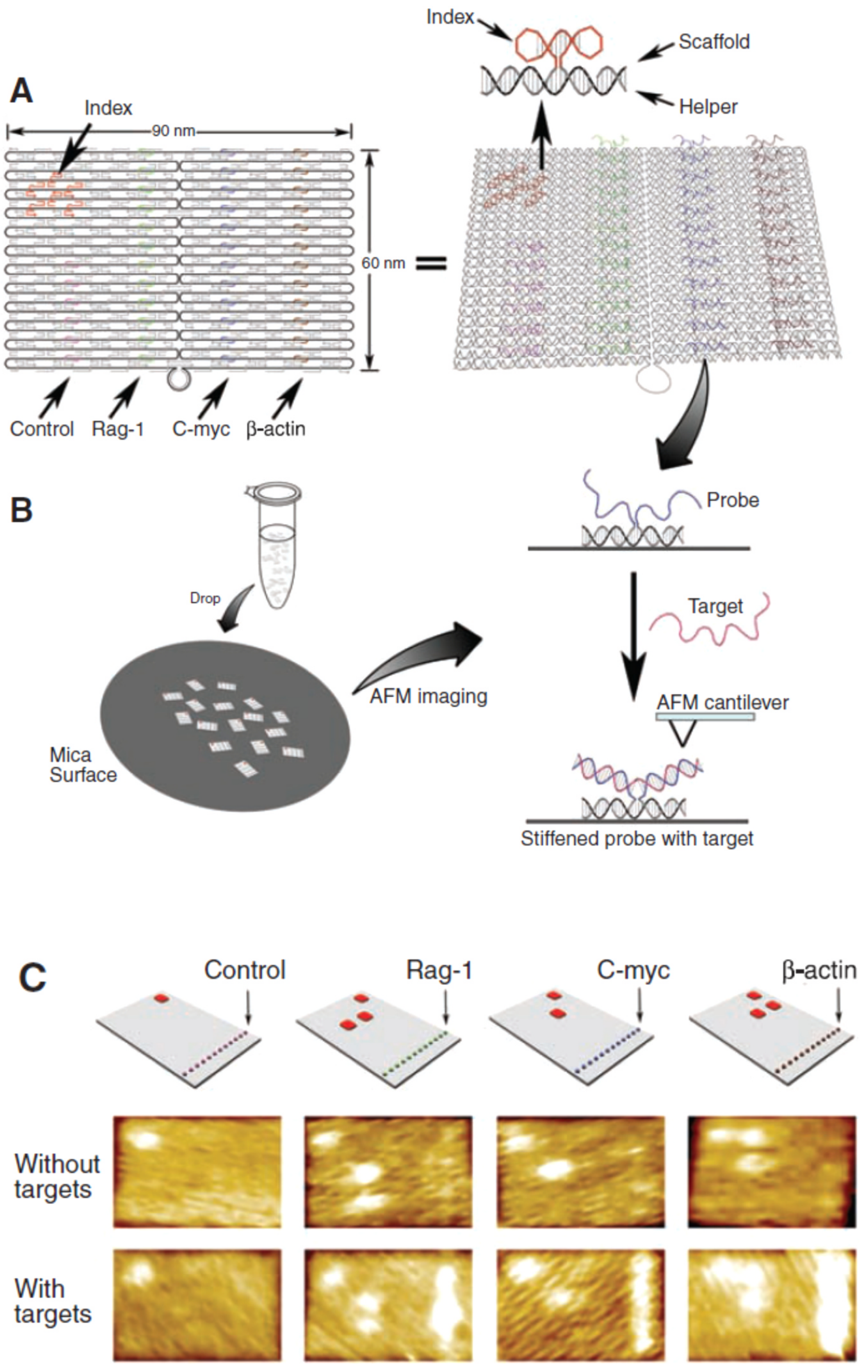


Fig. 3. (A) Schematic layout of the indexed nucleic acid probe tiles bearing three different probes and a control probe. (B) Illustration of the process for the use of probe tiles for target detection. Probe tiles are self-assembled in solution, hybridized with targets, and then dropped onto the mica surface for AFM imaging. (C) (Top) the bar-coded tile designs. (Middle and Bottom) Typical zoom-in AFM images of the bar-coded tiles without targets (Middle) and with targets (Bottom); each type of tile is readily identified by its bar code.

Further typical CdSe quantum dots are labeled on the DNA signal strand as probe to detect streptavidin (Wei et al., 2017).

In addition to the double strand formation, the triplex-forming oligonucleotide (TFO) immobilized on electrode surface can be introduced into this platform. A clamp-like DNA probe was investigated to recognize and bind complementary target sequence. Through two distinct and sequential events, the target and probe formed a triplex DNA conformation which brought the redox label into close with the electrode surface, increasing electron transfer efficiency and resulting in an increase in the observed current (Idili et al., 2014). As the natural state of DNA is double helix, the direct detection of double-stranded DNA (dsDNA) represents great significance in disease diagnosis and gene therapy. Utilizing the interaction of TFO with double-helix DNA to form triplex formation through Hoogsteen, Miao et al. developed a Fc modified molecular beacon as the TFO, the presence of target dsDNA induced the formation of parallel triplex DNA and opened the stem-loop structure of it, which resulted in the redox probe away from the electrode and triggered the decrease of current signals (Miao et al., 2014).

As we have mentioned above, the monovalent cation ions are essential for the stability of G-quadruplex formation. Under specific conditions,cations can change the G-rich DNA sequence into G-Quadruplex (Li et al., 2013). The presence of Pb^{+} induced its G-rich

Table 1
DNA conformational polymorphism in electrochemical biosensors.

DNA design	Roles in sensor	Target	LOD	Range	Recovery	Complexity	Ref.
Duplex	Recognition	PML/RARA fusion gene	0.66 fM	1 fM to 1 μM	Yes	No	(Yang et al., 2017)
Duplex	Recognition/linker/signal probe	microRNA-21	0.06 pM	0.1–70 pM	No	Yes	(Yin et al., 2012)
Triplex	Recognition/signal probe	dsDNA	275 pM	350 pM to 25 nM	No	No	(Miao et al., 2014)
Triplex	Recognition	p53 gene	4.15 pM	0.01–10 nM	No	No	(Hamidi-Asl et al., 2013)
Triplex	Support platform	Biothiols	0.5 μM	0.5–50 μM	No	No	(Feng et al., 2017)
Tetrahedron	Recognition/linker	ATP	0.2 nM	0.5–1000 nM	Yes	Yes	(Bu et al., 2013)
Tetrahedron	Linker/amplifier	microRNA	10 aM	1 fM to 100 pM	No	No	(Chem et al., 2014)
Quadruplex (G4)	Recognition	Amino acids	0.5 pM	0–0.15 μg/mL	No	Yes	(Carter and Kataky, 2017)
Quadruplex (G4)	Recognition/signal probe	α-naphthol	0.1 nM	1 nM to 100 mM	Yes	Yes	(Liang et al., 2013)
Quadruplex (G4)	Signal probe	ATP	7.6 nM	8–2000 nM	Yes	Yes	(Liu et al., 2014)
Aptamer	Recognition	Ochratoxin A	0.08 pM	0.0001–1 nM	Yes	Yes	(Huang et al., 2016)
Aptamer	Recognition	Malaria	0.84 pM	0.01–100 pM	Yes	Yes	(Figueroa-Miranda et al., 2018)
Aptamer	Recognition	Thrombin	1.2 aM	3.0–300 aM	No	Yes	(Jin et al., 2015)

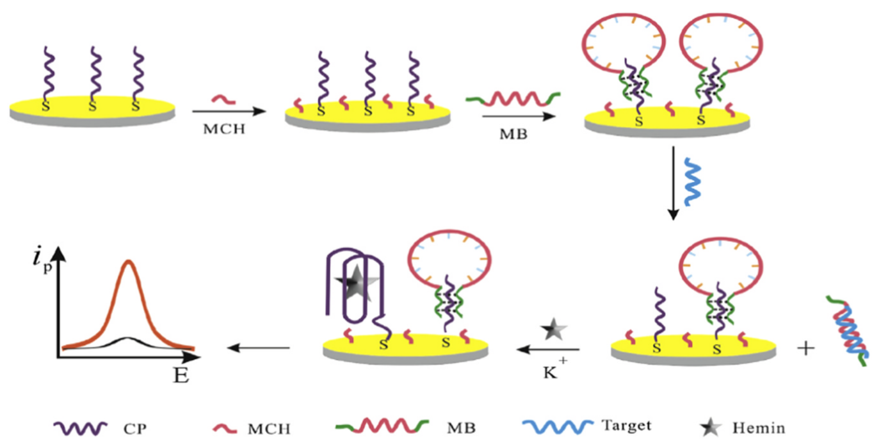


Fig. 4. Scheme of indirect detection of DNA sequence based on G-quadruplex formation. Different DNA structures are involved in this typical design, with hairpin molecular beacon as receptor DNA, triplex formed as staple strand, as well as the quadruplex with hemin as signal reporter.

aptamer to form G-quadruplex. After the catalysis of HRP-mimicking DNAzyme at the structure, a linear response toward Pb^{2+}concentration was observed by DPV. The similar principle has also been applied on electrochemical biosensors for detection of K^+ (Wu et al., 2008) and Hg^+ (Zhang et al., 2013). Besides the cations, G-quadruplex for indirect detection of DNA sequence was described in Fig. 4 (Wang et al., 2015). The hairpin molecular beacon and hemin aptamer form a triple-helix structure through DNA hybridization. Upon target sequence introduced, the triple-helical dissembled and exposed the hemin aptamer. The formation of G-quadruplex hemin complex in the presence of K^+ will lead to an electrochemical response that confirm the presence of target. Furthermore, taking advantage of the tetrahedral structure, a three-dimensional tetrahedral DNA nanostructure has been introduced to microRNA detection with signal amplification (Chem, 2014).

3.2. Electrochemical impedance sensors

Electrochemical impedance spectroscopy(EIS) has been firstly described in 1975 and has been employed widely in electrochemical systems (Lorenz and Schulze, 1975). Typically, a small sinusoidal AC voltage (approximately 2–10 mV) and a wide range frequency are applied for determining the resistive and capacitive properties of materials via current responses in EIS technique. In biosensors, EIS can be used to monitor analyte binding events which alters the electron transfer resistance on the sensing interface. Thus the result of changed impedance has usually a linear relationship with the concentration of the measured species (Ronkainen et al., 2010). Since amperometric detection required the active site must be easily accessible to the analyte solution and in close proximity to the electrode surface, EIS shows label-free advantage and has gained much interest in electrochemical biosensors (Elhakim et al., 2018).

EIS exhibits a favorable choice that DNA biorecognition can minimize non-specific binding of the analyte in impedance detection (Grieshaber et al., 2008). The application of the specific recognition aptamers has contributed a lot to the development of EIS biosensors. The modified aptamer immobilized on the electrodes via self-assembly act as recognition element, ferri-/ferrocyanidein ($[Fe(CN)_6]^{3+/4+}$) buffer solution was redox mediator. Upon binding target(doxorubicin) to the aptamer, electron transfer between the electrode and $[Fe(CN)_6]^{3+/4+}$ in solution was inhibited, which leads to an increase in impedance spectra (Bahner et al., 2017). Based on the similar mechanism, the DNA biosensors integrated EIS technique have been used for detecting metal ions (Hu et al., 2016), pathogens (Miranda et al., 2017) and biomolecules (Pishkar and Azadbakh, 2017; Wang et al., 2016), etc. Meanwhile, with the use of functionally modified electrodes, the DNA hybridization can be directly detected by EIS while the double strand DNA formed (Manzanares-Palenzuela et al., 2016; Wang et al., 2017).

In addition, the multi-stranded DNA conformation has been reported already in EIS biosensors. Zheng et al. developed a label-free DNA electrochemical impedance biosensor for double-strand DNA via sequence-specific recognition (Zheng et al., 2013). The TFO probe can recognize bases in the major groove of the ds-DNA and then form a triplex formation, which leads to an increased resistance of the electron-transfer between signal probe and the gold electrode. And the small change of impedance is proportional to the target concentration. Moreover, the G-rich sequence interacts with binding species to form a G-quadruplex in EIS biosensors was proposed (Meini et al., 2012). The

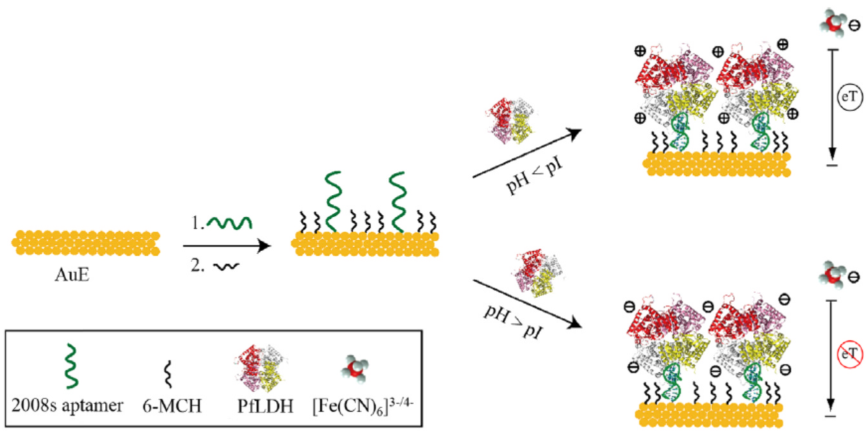


Fig. 5. Representation of stepwise aptasensor preparation and pfLDH responses in two different pH environments.

target analyte induced the aptamer to form a G-quadruplex complex, which caused a variation of the electrical properties of the sensing interface, this variation would be detected using EIS technique. As cations can stabilize G-quadruplex conformation and the hemin/G-quadruplex complex exhibits peroxidase-like activity to catalyze the oxidation reaction, this method integrated EIS has been introduced to the detection of heavy metal ions (Liu et al., 2015; Xu et al., 2015b). Based on this foundation, Liang et al. has reported a highly sensitive sensor for α-naphthol (a toxic and hazardous environmental pollutant)(Liang et al., 2013). A single-stranded G-rich DNA transformed into K^+-stabilized G-quadruplex and catalyzed H_2O_2-mediated oxidation of α-naphthol with cofactor hemin. The product 1,4-naphthoquinone precipitated on the DNA films and increased the charge transfer resistance(RCT), following a signal response in EIS.

Very recently, we developed a stepwise aptasensor utilizing plasmodium falciparum lactate dehydrogenase (PfLDH) aptamer as recognition molecule for highly sensitive malaria detection. As shown in Fig. 5, the novel aptamer, called 2008s, was immobilized on the gold electrode to recognize specifically PfLDH protein, the main biomarker for malaria detection. By simply changing the medium pH, the overall surface charge of PfLDH changed because of passing its isoelectric point (pI = 8). Thus, the redox probe $[Fe(CN)_6]^{3-/4-}$ can be attracted toward or repelled from the surface in two different pH environments, leading to an adjustable interface impedance (Miranda et al., 2017) (Fig. 5).

3.3. Electrochemiluminescence sensors

Electrochemiluminescence (ECL), also called electrogenerated chemiluminescence, which process involves the generation of reactive intermediates from stable precursors at the electrode surface and then undergoes high-energy electron-transfer reactions to form excited states that emit light, therefore the outcome is transforming electrical energy into radioactive energy (Richter, 2004). ECL means takes advantages of greater control over emission position and reaction time, that are beneficial for sensitivity and simplify operations during detection, respectively (Hu and Xu, 2010). Thus ECL has found application in DNA biosensors for many important analytes, including microRNA (Liu et al., 2014a), heavy metal ions (Huang et al., 2015)and cancer cells (Yin-Zhu et al., 2016) etc. To improve the sensitivity and obtain more accurate result, multiple signal amplification strategy has been applied in recent researches of ECL sensors. For instance, the detection of thrombin, Jie et al. has used strategies of DNAzyme assisted target recycling and hybridization chain reaction (HCR) (Jie et al., 2017), while Jin et al. has prepared a padlock probe and used hyperbranched rolling circle amplification (Jin et al., 2015). Moreover, the use of nanoparticles and quantum dots (QDs) generates a magnificently amplified ECL signal. Zhang et al. has applied boron doped graphene quantum dots (BGQDs) and glod nanoparticles(AuNPs) for detection of oncogene microRNA-20a (Zhang et al., 2016a). Liu et al. (2014b) has modified the electrode with CdTe QDs to detect ATP.

Based on the Ag^+-stabilized self-assembly triplex DNA, Xiong et al. has described a label-free ECL detection of transcription factors(TFs) with hybridization chain reaction (Xiong et al., 2016). The detection process was based on specific bond of TFs to dsDNA, leading to the dissociation of the triplex structure and releasing target DNA. In the presence of target DNA, a long chain dsDNA polymer can be formed on the gold electrode surface through hybridization chain reaction with the help of DNA-1 and DNA-2, which provides numerous intercalations of ECL indicators $Ru(phen)_3^{2+}$ into the dsDNA grooves and a significant amplified ECL signal. Besides, an "Off–On" electrochemiluminescent biosensor for ultrasensitive detection of microRNA has been perpared, whose detection process involves various DNA structures. (Zhang et al., 2015). Furthermore, using tetrahedron structured DNA(ts-DNA) to construct ECL aptasensor has also been reported (Fig. 6**A**) (Bu et al., 2013). The ts-DNA contained one oligonucleotide with anti-ATP aptamer. The functionalized oligonucleotide (FO) intercalated $Ru(phen)_3^{2+}$ contained a complementary strand to the anti-ATP aptamer. After the hybridization between the anti-ATP aptamer and FO completed, $Ru(phen)_3^{2+}$ was introduced to the electrode. Thus ECL emission can be observed with tripropylamine as a coreactant. Upon ATP reacted with its aptamer, the FO dissociated and the containing $Ru(phen)_3^{2+}$ was released. The change in emission was used to quantify ATP.

Taking the advantages of good biocompatibility, fascinating electrocatalytic activity, the ECL of metal nanoclusters have been applied in our research. We have used triplex DNA as synthesis template for the site-specific, homogeneous and highly stable silver nanoclusters (AgNCs) fabrication. Through rational design of DNA sequence, AgNCs were obtained in the predefined position of CG.C+ sites of triplex DNA. The electron-transfer (ET) between negatively charged $Ag_n^{\bullet-}$ and $SO_4^{\bullet-}$ radicals produced by electroreduction of $S_2O_8^{2-}$ resulted in an excited state (Ag_n*). This excited state emitted light in the aqueous solution to produce an ECL signal at a low potential (Fig. 6**B**). Then, we utilized the enhanced catalytic reaction and a robust interaction between the triplex-AgNCs and biothiols to develop a label-free ECL biosensor. And the ECL counts were corresponding to the thiol concentration with a liner relationship, ranging from 0.5 to 50 μM (Feng et al., 2017). The novel triplex DNA conformation supplies special base binding composition and the microenvironments for metal nanoclusters stability and fluorescence property.

3.4. Field-effect transistor sensors

Field-effect transistor(FET) is a type of transistor that consist of a gate electrode and a thin semiconducting layer that separates source and drain electrodes by a distance (channel length) (Zaumseil and

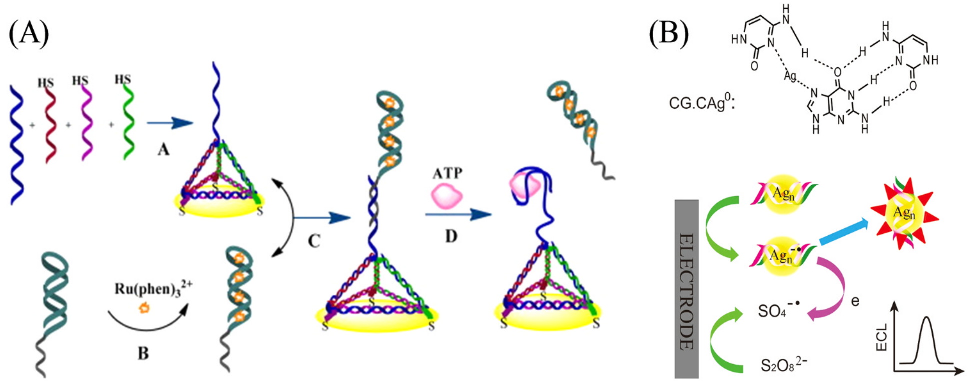


Fig. 6. Schematic representation of (A)an aptasensor based on tetrahedron structured DNA and ATP aptamer bioconjugation; (B) the ECL of silver nanoclusters based on the template of triplex DNA for biothiols detection.

Sirringhaus, 2007). As FET controls the channel conductivity between the source electrode and drain electrode via electric field, the direct measurement of conductance change induced by binding on the gate surface corresponds to the concentration of the target analyte and then can be transduced into an electrical signal. Thus FET based biosensors have proven to be of paramount importance in detecting diverse biomolecular species with the advantages of high sensitivity, target selectivity, fast and label-free detection (Grieshaber et al., 2008; Kaisti, 2017).

Recent advances in the microfabrication techniques have accelerated the development of novel bioelectronic devices, including silicon nanowires (Li et al., 2014), carbon nanotubes (Xuan et al., 2017), and graphene-based (Forsyth et al., 2017) FET devices for DNA biosensor applications. A graphene FET biosensor has been applied for microRNA detection with the graphene oxide(R-GO) drop-casted onto the sensing channel of FET as the conducting material and AuNPs decorated on the R-GO surface, the neutral PNA probe was immobilized through the covalent binding. Then the presence of target miRNAs caused n-doping to the devices due to the interaction between graphene and electro-rich nucleobases in miRNA. Thus the miRNA detection can be measured through PNA-miRNA hybridization by FET electrical measurements with a silver wire reference electrode (Cai et al., 2015).

In addition to the nucleic acid detection, FET DNA biosensors have been applied for metal ions detection. In one carbon nanotube-based FET, 1-pyrenebutanoic acid, succinimidyl ester, stacking on CNT surface via non-covalent hydrophobic and π–π interactions, was used for immobilizing aptamers. Recognition of K^+ ions induced the aptamer to fold into G-quadruplex structure, which increased the charge density close to the CNT surface. Finally this effect resulted in an output current variations (Zheng et al., 2016). Based on the G-quadruplex structure-switching mechanism and altering charge density, a graphene field-effect transistor for detection of Pb^{2+} has been also prepared (Li et al., 2016).

Furthermore, we and our colleagues have recently investigated a graphene FET(GFET) and operated the GFET in an ambipolar mode near its neutrality point that can markedly reduce the 1/f noise in graphene as potent DNA sensors. Using pyrene-linked peptide nucleic acid molecules to functionalize the surface of graphene, and Tween 20 could minimize non-specific binding and rule out possible false non-specific positives. The signal response of the pPNA functionalized graphene has demonstrated in the presence of ssDNA when operated near its neutrality point with a limit of detection as low as 2 pM (Fu et al., 2017).

4. DNA polymorphism in fluorescent sensors

Fluorescence detection demonstrates an immediate response and real time detection without any separation events. With development of advanced instrumentation, the detection of single molecule fluorescence is possible. Fluorescence detection has high sensitivity and the consumption of samples in fluorescent sensors is minimal (Suzuki and Yokoyama, 2015). Due to the most important advantage of intracellular detection, fluorescence-based biosensors have attracted considerable efforts in its development and application during the past several decades. A summary table containing some typical fluorescent biosensors were listed to shown the state-of-art performances (Table 2).

Natural state DNAs are usually non-fluorescent and fluorescent DNA biosensors always employ external fluorophore (Liu et al., 2009). In the presence of target molecules, the fluorescence intensity of fluorophore would be influenced and the change amount can be an indicator to the concentration of sensing molecule. With the application of the labeled probe, a various fluorescent DNA biosensors have been constructed. An aptamer modified with carboxyfluorescein (FAM) was used to hybridize its complementary strand which was labeled with a quenching group, so that the hybridization of the two strands resulted in the fluorescence of FAM quenched. Upon the addition of target, the formation of target/

Table 2
DNA conformational polymorphism in fluorescent biosensors.

DNA design	Roles in sensor	Target	LOD	Range	Recovery	Complexity	Ref.
ssDNA	Recognition/signal probe	Hg^{2+}	2.6 nM	5–200 nM	Yes	Yes	(Cui et al., 2015)
Duplex	Recognition/signal probe	ATP	65 nM	0.1–10 mM	Yes	Yes	(Yao et al., 2017)
Triplex	Recognition probe	cocaine	0.1 nM	1–500 nM	Yes	Yes	(Zhang et al., 2016b)
Triplex	Recognition/signal probe	thrombin	261 fM	1 p.M. to 100 nM	Yes	Yes	(Li et al., 2015)
Triplex	Recognition	HIV-1	65 p.M.	100 p.M. to 200 nM	Yes	Yes	(Zhu et al., 2017)
Quadruplex (G4)	Recognition/signal probe	Pb^{2+}	96 p.M.	0–0.05 nM	Yes	Yes	(Ravikumar et al., 2018)
		Hg^{2+}	356 p.M.	0–0.05 nM.			
Quadruplex (G4)	Recognition	Pb^{2+}	2.2 nM	2.4–11.5 nM	Yes	Yes	(Sun et al., 2017)
Quadruplex (G4)	Recognition/signal probe	tetracycline	0.029 μg/mL	0.05–100 μg/mL	Yes	Yes	(Sun et al., 2018)
Quadruplex (G4)	Recognition/signal probe	DNA	40 p.M.	0.05–25 nM	Yes	Yes	(Liu et al., 2017)
Aptamers	Recognition	Aflatoxin B_1	1.6 ng/mL	5–100 ng/mL	Yes	Yes	(Lu et al., 2017)

aptamer complex was induced and the fluorescence of FAM recovered (Lu et al., 2017). Li et al. has developed a biosensing platform based on triplex DNA formation and polymerase chain reaction (PCR) technology (Li et al., 2015). The probes contained aptamer sequence for thrombin. Upon addition of thrombin, two probes hybridized to each other and then PCR amplification was carried out. The double-stranded PCR product can sequence-specific recognize molecular beacon to form a triplex structure, thus an increased fluorescence intensity can be observed. Since some fluorescent dyes can specifically bind to G-quadruplex, the related researches have been already carried out. A typical fluorescent dye, N-methyl mesoporphyrin IX (NMM) has a weak fluorescence itself, but it exhibits a significant fluorescence in the presence of G-quadruplexs. The presence of target opened the hairpin structure and the G-quadruplex-forming sequences can fold into G-quadruplex. Through the strand displacement mechanism and repeated cycles, massive active G-quadruplex formed. Finally, NMM associated with these active G-quadruplex and exhibited significantly enhanced fluorescent signal for sensitive monitoring of the target DNA (Liu et al., 2017). Based on this detection mechanism of G-quadruplex, tetracycline detection with thioflavin T and thiazole orange were reported, respectively, as well as heavy metal ions. Furthermore, a (Xu et al., 2017).

In addition to the diverse external fluorophores modification, the introduction of novel nanomaterials to fluorescent biosensors has been common. Among that, graphene-based nanomaterials represent a wide range application (Liu et al., 2014c; Zheng and Wu, 2017). Due to the adsorption of DNA with the appropriate affinity and the ability to quench all types of fluorophores with high efficiency, graphene-based nanomaterials can act as a unique platform for fluorescence sensing (Zhang et al., 2017). Carbon dots (CDs) and graphene oxide (GO) are the two newest members of the carbon materials family with excellent optical properties. The CDs-labeled oligodeoxyribonucleotide (ODN) adsorbed on GO would undergo the fluorescence quenching via fluorescence resonance energy transfer(FRET). Upon binding to target molecules(Hg^{2+}), the ODN-CDs was released away from the GO surface due to the formation of T-Hg^{2+}-T duplex. Then the fluorescence of CDs recovered and the intensity indicated target concentration (Cui et al., 2015). This platform can be used for the detection of specific sequences. The labeled ss-DNA adsorbed on GO recognized the complementary strand and formed double-stranded structure, which released the label from inhibited state and recovered the fluorescence (Ryoo et al., 2013). Moreover, Luo et al. has applied the different conformation of DNA and their varying affinities to GO for detection of pH values (Luo et al., 2016). Two labeled probes contained a certain content of TAT under acidic conditions, the probes would fold into triplex DNA structures, which would not be absorbed on GO and retained a strong fluorescence. By contrast, under alkaline conditions the probes contained a single stranded tail would be absorbed on the GO with substantially quenched fluorescence. Zhang et al. has employed GO and exonuclease III-assisted signal amplification to detect cocaine (Zhang et al., 2016b). The presence of cocaine induced a triplex complex and the affinity between FAM-labeled mononucleotide and GO is negligible. The cleaved FAM-labeled mononucleotides are not adsorbed on the surface of GO, so a strong fluorescence signal enhancement is observed as the cocaine triggers enzymatic digestion. Furthermore, the GO platforms based G-quadruplex to detect the heavy metal ions have also been proposed (Sun et al., 2017; Ravikumar et al., 2018).

5. Conclusions and future perspectives

In this review article, we have briefly summarized the rich DNA conformational polymorphism in biosensing applications, mainly with the electrochemical and fluorescent techniques. By carefully considering the different functions of DNA strand in sensor design, DNA structures are carefully discussed according to their special roles, like recognition receptor, linking staple/scaffold, as well as the signal motif and sensor scaffold.

Notably, the field of biosensor is blooming very quickly and incredible developments have been proposed in past years, including the successful commercialized biosensors, glucose sensors and lateral flow pregnancy test kits. Although the continuous advancement of DNA biosensors has received extensive attention, most of their development has still been in the stage of laboratory research. Some challenges for the development of biosensors, such as lower detection limit, poor reproducibility and being susceptible to interference, are urgent to resolve, especially for further point-of-care test or clinical applications. The biosensors with very small amounts of analyte or ultrasensitive detection can provide new opportunities for determining a series of new analytes, especially the disease biomarkers and rare pathogens. With the applications of DNA conformational polymorphism with nanoparticles or biological enzymes during the fabrication of biosensors, a greater signal amplification with the femtomolar detection can be realized. Another major focus of biosensor in the future involves the development of single-molecule sensing, which is not just beneficial for ultrasensitive detection but overcome false positive response on sensing interface. And since the functional DNAs, such as aptamer, hold the high affinity to different targets, an ensuring bright future is also expected by use of DNA in single molecule detection.

To finish, the DNAs polymorphism and their novel functions in different biosensor construction hold great promises to construct rapid, stable, high-throughput and miniaturized high-sensitivity DNA biosensor for real biological samples in the near future.

CRediT authorship contribution statement

Ziheng Hu: Writing - original draft. **Zhiguang Suo:** Writing - original draft. **Wenxia Liu:** Writing - review & editing. **Biying Zhao:** Writing - review & editing. **Feifei Xing:** Writing - review & editing. **Yuan Zhang:** Conceptualization, Project administration, Supervision, Writing - review & editing. **Lingyan Feng:** Conceptualization, Project administration, Supervision, Writing - review & editing.

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Declaration of interests

None.

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