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REVIEW ARTICLE

# Progress of new label-free techniques for biosensors: a review

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**Abstract**

The detection techniques used in biosensors can be broadly classified into label-based and label-free. Label-based detection relies on the specific properties of labels for detecting a particular target. In contrast, label-free detection is suitable for the target molecules that are not labeled or the screening of analytes which are not easy to tag. Also, more types of label-free biosensors have emerged with developments in biotechnology. The latest developed techniques in label-free biosensors, such as field-effect transistors-based biosensors including carbon nanotube field-effect transistor biosensors, graphene field-effect transistor biosensors and silicon nanowire field-effect transistor biosensors, magnetoelastic biosensors, optical-based biosensors, surface stress-based biosensors and other type of biosensors based on the nanotechnology are discussed. The sensing principles, configurations, sensing performance, applications, advantages and restriction of different label-free based biosensors are considered and discussed in this review. Most concepts included in this survey could certainly be applied to the development of this kind of biosensor in the future.

**Keywords**

Biosensor, field-effect transistors, label-free, magnetoelastic, nanocomposite, optical, surface stress

**History**

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## Introduction

Progress in biosensors has mainly been achieved by improvement of detection techniques. The detection techniques used in biosensors can be broadly classified into label-free techniques and label-based techniques. Label-based techniques use ''tags'' or ''labels'' to detect a particular analyte in a background of other materials. Fluorescence (Harz et al., 2011; Li et al., 2008; Ma et al., 2014; Toseland & Webb, 2010; Xu et al., 2014), chemiluminescence (Akshath et al., 2012; Ma et al., 2012; Wang et al., 2013a; Wu et al., 2013; Yu et al., 2010, 2011) and radioactive (Gibson et al., 2011; Qi et al., 2011; Shlyapnikov et al., 2010) are three popular label-based techniques for detecting a particular target in biosensors. Fluorescence can be thought of as the short-time category of luminescence. The fluorescence biosensor's principle is that the target molecules with labelled reagent, such as antigens with fluorophore are loaded on the surface immobilized the probe molecules, such as antibodies. They will bind to probes, and then the bound targets can be detected. The labeling of biomolecules with fluorescent or other similar tags for detection can result in sample losses during the labeling and purification process and occasional loss of functionality. Furthermore, the disadvantage of fluorescence is that most fluorophores are bleached quickly upon exposure to light and are very sensitive to environment conditions such as the solution's pH value (Sang, 2010). Indirect labeling is more complicated and time consuming, while fluorescence tags in direct labeling may be less stable and more disruptive to the labeled proteins as compared to small molecule tags in indirect labeling. However, fluorescence is generally preferred and the most widely used detection method for reasons of sensitivity, stability and availability of fluorescent scanners tailored for microarray use (Macbeath & Schreiber, 2000). Fluorescence is still in use for most purposes. Chemiluminescence (CL) is the phenomenon of light emission as a result of a chemical reaction, which promises high sensitivity with simple instruments and without any light source. It is an attractive detection method in μ-TAS (Huang et al., 2001; Masahiko et al., 2000; Xu et al., 2000). Many flow sensors based on CL reaction have great sensitivity in environmental, biomedical and chemical analysis (Li & Zhang, 2000; Li et al., 2001; Ramos et al., 2001; Zhou et al., 2002). The limited feature resolution, due to signal bleeding and limited dynamic range, is the reported drawback (Schweitzer et al., 2003). In addition, sensing with CL can be performed only once, unlike fluorescence-based methods which can be archived for future imaging. For radioactivity-based detection, the labels are radioisotopes. Techniques using radioactive labels offer robust and reproducible protocols in applications that require ultimate sensitivity and/or resolution. However, it is difficult to automate hand liquid for radioactivity due to the need for safe handling

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and disposal of radioactivity. It is also generally limited to manual, low-throughput applications. Enzymatic tags (Bai et al., 2008; Liu et al., 2012; Martin, 2004) are another common label-based techniques to enhance sensitivity. Some applications of these biosensors are in clinical sample testing and cell analysis. However, several obstacles currently hamper the enzymatic tags based technique. One of the bottlenecks is enzyme activity loss. It is a challenge to immobilize enough native enzyme (Xie et al., 2009) onto a solid substrate and a platform to improve sensitivity, and the basement membrane should be fabricated as thin as possible to shorten the response time and prolong the lifetime of the biosensors.

Label-free technique is another one increasing awareness of novel techniques that do not require labeling of ligand or the receptor, and may allow any complex to be screened with minimal assay development (Fang, 2010; Citartan et al., 2013; Liu et al., 2014; Musayev et al., 2014; Wang et al., 2013b). Label-free assays can screen for biologically active molecular interactions and cellular responses, give detailed information on the selectivity, affinity and in many cases, also the binding kinetics and thermodynamics. The label-free detection field as a whole has been undergoing great progress in recent years.

Depending on different kinds of transducers, label-free biosensors are mostly divided into optical and non-optical based. The traditional non-optical based label-free screening platforms contain acoustic waves (Kang et al., 2011; Länge et al., 2008; Ballantine et al., (1997), electrochemistry (Choi, 2004; Denuault, 2009; Grieshaber et al., 2008; Yang, 2012) and micro-calorimetry (Lawrence et al., 2014; Uelivon et al., 2009; Wang et al., 2012). Biosensors exploited, based on surface plasmon resonance (SPR; Knobel & Cleland, 2003; Lopatynskyi et al., 2014; Novotny & Hecht, 2006; Nylander et al., 1982), have continued to dominate the field of commercially available label-free optical technologies. The actual situation today is changing very quickly. In the last 5 years, more types of optical label-free biosensors have emerged with a much better performance than SPR depending on the figures of merit evaluated, such as optical waveguide-based biosensors including optical slot-waveguide (Goddard et al., 1994, 2002; Yuan et al., 2013), optical ring and disk resonator based biosensors (Gaathon et al., 2006; Goral et al., 2011; Grist et al., 2013; White & Fan, 2008), interferometer-based biosensors (Blanco et al., 2006; Heideman et al., 1993), bio-photonic sensing cells (BICELLs)-based biosensors (Álvaro et al., 2013; Sanza et al., 2011) and porous material for optical biosensing (Cunin et al., 2002; Gaur et al., 2013; Hiraoui et al., 2012; Rendina et al., 2007). They all have a wide range of disciplines in the life sciences, including apoptosis, bacteriology, virology, molecular engineering, cell biology, cell adhesion, signal transduction, immune regulation and enzyme mechanisms.

Nowadays, the tendency of label-free techniques has been in the advances of newer signal transducer detection schemes. Most of these schemes profited from developments in nanotechnology. With the progress of the nanotechnology-base transducer, label-free biosensors enabled high-throughput, high sensitivity, low sample consumption, low damage to the analytes and automatic control. This review mainly focuses on recent developments in the field of the new label-free techniques, for example, field-effect transistors (FETs), magnetoelastic biosensors, optical-based biosensors, surface stress-based biosensors and other types of biosensors based on nanotechnology. Basic aspects of new label-free based biosensors with their relevant configurations, properties and application are summarized. We hope that this review will be helpful to understand the importance of label-free techniques in developing the next generation of biosensor devices. Furthermore, since these label-free techniques can be fabricated to micro-scale systems or label-free systems, they have immense potential to satisfy the demand for better quality sensors and have been investigated extensively in recent years. Most concepts in this survey concluded that they could certainly be applied to the development of this kind of biosensor.

## Field-effect transistor-based biosensors

Field-effect transistors (FETs) are suitable candidates for designated sensors, due to their ability to directly translate the interaction with analytes taking place on the FET surface into a readable signal. Consequently, the analytes need not to be labeled, and we classify this technique as the label-free technique for biosensors. From the electrochemical point of view, FET-based biosensors are a three-electrode system, including source, drain and gate electrodes. The work principle is that the electrical conductance of a sensing component between the source and the drain is sensitive to its environment and varies significantly with surface adsorption of various chemicals and biomolecules.

Nowadays, a diversity of FET-based biosensors can be employed for specific interactions of biomolecules, such as enzymatic reaction, DNA hybridization and antibody–antigen reactions. We tried to classify these biosensors into enzyme-based FETs (ENFETs) (Kharitonov et al., 2000), cell-based FETs (Duan et al., 2012) and immunodetection-based FETs (ImmunoFETs; Hideshima et al., 2011). ENFETs which combine ion-sensitive field-effect transistors (ISFETs) with enzymes, are based on biocatalytic reactions affecting the charge at the gate surface, and produce an electronic signal dependent on the enzyme substrate concentration. Various enzymes are studied in the ENFETs, such as glucose oxidase (Liu et al., 2008), urease (Sekiguchi et al., 2000), penicillinase (Gorohkov et al., 1996), horseradish peroxidase (Varma, 2002), tyrosinase (Anh et al., 2002), etc. Cell-based FETs are exploited in the detection of cells metabolism and the analysis interaction of drugs and cells. FETs can also record electric potentials inside cells. Duan et al. (2012) has reported a new approach in which a $SiO_2$ nanotube is synthetically integrated on top of a nanoscale FET. The nanotube can penetrate the cell membrane, bringing the cell cytosol in contact with the FET, which is then able to record the intracellular transmembrane potential.

ImmunoFETs are the most frequently used biosensors. It is expected to provide immediate and important information regarding initial therapy by detecting the charged antigens related to serious diseases using immobilized antibody-modified FETs. However, ImmunoFET biosensing devices for use in the medical field have not been put into full-scale practice until now because there are two challenges. The first

potential impediment is the fact that ImmunoFET sensors have difficulty detecting macromolecules in physiological solutions without pretreatment. The second is to overcome the inherent screening of the Debye length (Kulkarni & Zhong, 2012). Therefore, it is critical to increase the sensitivity of FET detection through controlling the Debye length based on the height of the adsorbed receptor. In fact, it has to structure the antibody-modified surface so that it can withstand the electric application throughout the FET measurements to improve reproducibility.

In recent years, many types of nano-materials have been intensely selected as the promising candidates of FET-biosensors. One-dimensional semiconducting nanomaterials configured with FETs offer opportunities for real-time and label-free sensing applications, such as silicon nanowires and carbon nanotubes (referred to as carbon nanotube field-effect transistors (CNT-FETs; Iijima, 1991; Kim et al., 2007; Wang, 2005), and silicon nanowire field-effect transistor (SiNW-FETs; Gao et al., 2011; Zhang et al., 2010a). They are also amenable to large-scale and high-density integration. Two-dimensional semiconducting nanomaterials also have attracted great attention as they can be made an ideal biosensor with high selectivity and sensitivity, such as graphene field-effect transistor (GFET; Cheng et al., 2010; Novoselov et al., 2005, 2007).

## Carbon nanotube field-effect transistor biosensors

We know that CNTs have a high aspect ratio and outstanding electrical characteristics. Many works have been devoted to the fundamental understanding of their properties in a wide range of applications since the report of CNTs in 1991 (Iijima, 1991). CNTs are divided into single-walled carbon nanotubes (SWNT) and multi-walled carbon nanotubes (MWNT). Semiconducting SWNTs, which are one-dimensional nanostructures with all the carbon atoms on the surface, have many highly desirable and distinctive device properties and have played a central role in the operation of SWNT-based field-effect transistors (SWNT-FETs) (Kim et al., 2007; Wang, 2005; Yotprayoonsak et al., 2014). Dekker's group reported SWNT-FET firstly in 1998 (Tans et al., 1998). SWNT-FET devices are composed of individual SWNTs or random networks of SWNTs placed between a source (S) and a drain (D) electrode on a $SiO_2$/Si substrate. For this type of structure, the Si layer can act as back gate, which is separated by an insulating layer of $SiO_2$. The work function of SWNTs is higher than that of most metals, so the contact barrier between SWNTs and metals is usually a Schottky barrier (SB). The conductance of SWNTs in devices can be modulated by applying a potential to the gate electrodes with a constant D–S bias voltage ($V_{DS}$).

Researchers found that the electrical conductance of a semiconducting SWNT is sensitive to its environment and varies significantly with surface adsorption of various chemicals and biomolecules (Charlier et al., 2007). This makes SWNT-FETs very promising candidates for label-free biosensing. The SWNT-FETs can be made by SWNT networks or individual semi-conducting SWNTs. SWNT-FET-based biosensors have been reported to detect various biological species such as DNA (Dong et al., 2008; Kim et al., 2012; Martínez et al., 2009), living cells (Huang et al., 2009b; Sudibya et al., 2009) and single-molecule (Goldsmith et al., 2007, 2008).

SWNT-FET sensors, which measure DNA hybridization, hold great potential for wide scale genetic testing, clinical diagnostic and fast detection of biological warfare agents. Label-free electrical detection of DNA hybridization utilizing SWNT FET-based biosensors suggests a new generation of DNA chips that can give direct electrical readouts. Dong et al. (2008) reported that the detection sensitivity of SNFETs for DNA can be further improved to *ca*. 100 fM using a ''nanoparticle enhancement'' approach, in which the target DNAs are hybridized with probe DNAs on the device, and reporter DNAs labeled with Au nanoparticles (AuNPs) flank a segment of the target DNA sequence. With detection limits in the femtomolar range, SNFET-based biosensors and immunosensors may be adapted to detection of a variety of biomarkers for applications ranging from molecular diagnostics to *in vitro* diagnostics. A new approach to ensure specific adsorption of DNA to the nanotubes was developed. Tseng and coworkers carried out electronic detection of the DNA hybridization by using a large array of CNTFETs (Martínez et al., 2009). The method uses a synthetic polymer that is well adsorbed onto the walls of CNT and carries activated succinimidyl ester groups used to fix the $NH_2$-ssDNA probes. This method of anchoring the probe DNA can prevent the non-specific adsorption of DNA molecules onto the CNTFET that can occur by virtue of aggregation on the sidewalls of the contact electrodes. The mechanism of the CNTFETs' electrical response is modified significantly by the utilization of the polymer.

In the CNT network, FET-based DNA sensors, the modulation of Schottky barriers by DNA hybridization, has been known to play a crucial role in detecting target DNA. A simple but efficient way to enhance the sensitivity of the Schottky barrier-based sensors has been reported. Kim et al. (2012) developed a floating electrode-based biosensor for the detection of DNA molecules with controllable responses. Probe DNA was adsorbed only on the surface of the floating electrodes, source and drain electrodes were covered by photoresist to block leakage currents (Figure 1a). The energy-band diagram shows the formation of Schottky barriers at the contact regions between CNTs and metal electrodes. These Schottky barriers determine the conductance of the device. Figure 1b shows the schematic diagram of the target DNA sensing experiment. When a target DNA solution was injected, the target DNA molecules were hybridized with their complementary probe DNA molecules on the floating electrodes (upside). During the hybridization process, the work function of the floating electrodes was decreased, and the Schottky barrier height was increased.

The dynamic detection of the release of biomolecules from living cells in real time is important both in fundamental studies and during the evaluation of drugs for the treatment of secretion-related diseases. To this goal, Huang et al. (2009b) utilized a SWNT network to directly interface with living neuroglial astrocytes and, without labels, detect the triggered release of ATP from these cells. The detection scheme shows high temporal resolution. Further research was conducted by Sudibya et al. (2009) to improve the biocompatible

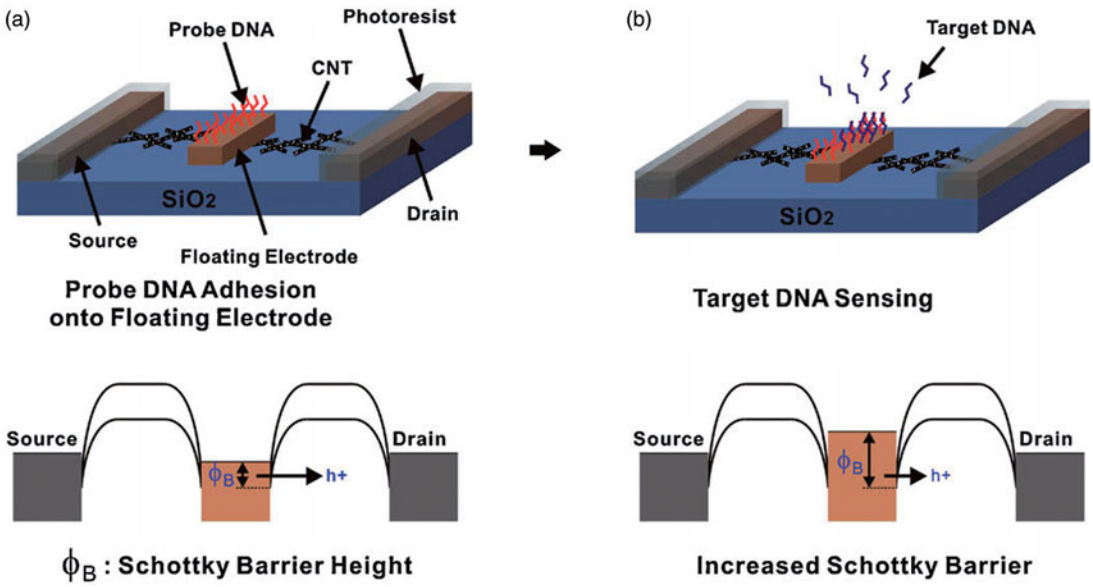
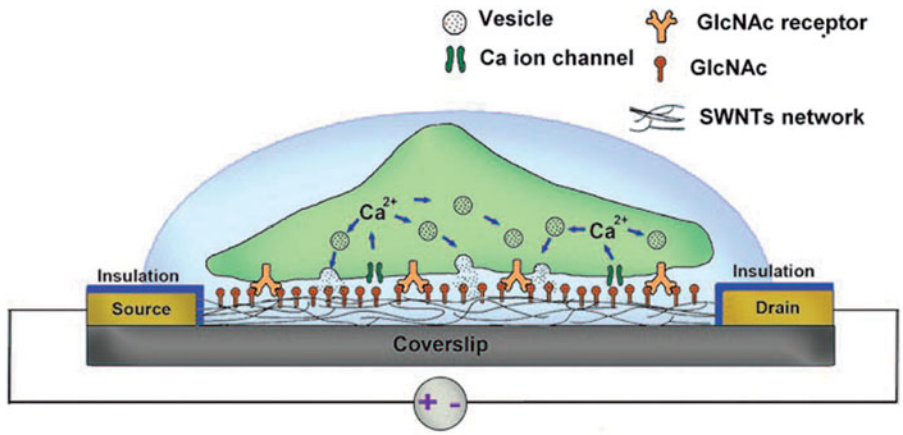



Figure 1. Sensing mechanism of floating electrode-based CNT-FET sensors.

Figure 2. Triggered exocytosis and SWNT-net detection.




interactions between SWNTs and living cells without sacrificing SWNT functionalities (Figure 2). The SWNT network was first surface-functionalized via $\pi$–$\pi$ interactions with bioactive sugars (*N*-acetyl-D-glucosamine) to allow PC12 cells to adhere and grow on the SWNT-net substrate. This nanotube approach provided real-time and non-invasive measurements from living cells with high sensitivity, high temporal resolution, high throughput and ease of detection.

Although great progress has been achieved in the field of CNT-based FET biosensors, most of the work so far has been focused on individual devices. To realize the practical applications of these promising analytic devices, future investigations should emphasize the development of arrays of CNT sensors. Several shortcomings should be encountered in the fabrication and applications of CNT-FETs. First, in the fabrication of CNT-FETs, the mixtures of semiconducting and metallic CNTs still hamper future developments in nanoelectronics, and controlling the diameter of carbon nanotubes remains a critical issue, as the electrical characteristics of carbon nanotubes strongly depend on their diameter and metal work function (Avouris & Chen, 2006). Second, the determining factors for the sensing mechanisms of a CNT-FET are complex and were reported to involve field-effects (Gruner, 2006), electron transfer (Wang et al., 2010), Schottky barriers (Heinze et al., 2002), etc.

## Silicon nanowire field-effect transistor biosensors

Silicon nanowire (SiNW) sensors are typical FET-based devices. The typical structure of SiNW biosensors for the detection of biomolecules is illustrated in Figure 3 (Zhang & Ning, 2012). The SiNW connected between the source and the drain in the semiconductor channel serves as the sensing component of the device. A Si dioxide layer locating under SiNW plays the role of the back gate, while the gate electrode modulates the channel conductance. In general, SiNWs-based FET biosensors exhibit some advantages. First, the dopant type and concentration of SiNWs can be well controlled, enabling a tunable sensitivity for the detection of various chemical and biological species. Second, naturally formed silicon oxide on the surface can effectively passivate surface dangling bonds. The selectivity for particular analytes can be improved easily because the oxide surfaces can be further modified with receptors via well-known silanol chemistry for

achieving specific surface functionalization. Finally, SiNWs in the nanosize regime might exhibit quantum confinement effects for diameters below 5 nm. The dependence of their quantized conductance on molecular adsorption could possibly be used for highly sensitive molecular detection (Ramgir et al., 2010).

There are two approaches (electrostatic adsorption and covalent binding) have been mainly adopted for use in SiNW biosensors to attach the probe on the surface. Electrostatic adsorption uses the attractive force responsible for adsorbing ionic solute on an oppositely adsorbent. The covalent binding method is based on the binding of the probe molecule on the SiNW surface by covalent bonds. The biological receptors were anchored to the surface of the semiconductor channel by chemical modification to recognize the target analytes through their high specificity and strong binding affinity in the buffer environment. The target–receptor interaction then varied the surface potential of the semi-conductor channel and modulated the channel conductance, and the signal was eventually collected by a detection system. Due to the large surface-to-volume ratio, tunable electrical properties and biocompatibility, the SiNWs have been proven to be ultrasensitive and selective sensors for direct and label-free detection.

Recently, many SiNW-FET devices have been developed to protein–protein detection (Lin et al., 2009; Tian et al., 2011), protein–DNA interactions (Zhang et al., 2010b, 2011a), DNA hybridization, early cancer detection (Chen et al., 2011), peptide–small molecule interaction (Wang et al., 2005), and biomarker detection (Patolsky et al., 2004). Biosensors based on silicon nanowire (Si-NW) promise highly sensitive dynamic label-free electrical detection of various biological molecules. Among several efforts being made to improve detection sensitivity, Zhang et al. (2010c) achieved direct electrical detection limit of DNA down to 10 fM by the oxide-etched SiNW devices. The surface of the SiNWs was functionalized with a densely packed organic monolayer via hydrosilylation, subsequently immobilized with peptide nucleic acid (PNA) capable of recognizing the label-free complementary target DNA. They also developed a SiNW-FET biosensor incorporated with the RT-PCR technique (Zhang et al., 2010b), based on peptide nucleic acid (PNA)–DNA hybridization and electrical detection for highly sensitive and rapid detection of Dengue virus. A cross-sectional view of the SiNW sensor is schematically illustrated in Figure 4. For highly sensitive dynamic label-free electrical detection of various biological molecules, Kulkarni et al. (2012) reported that the use of fabricated SiNW array device for label-free detection of 2D double crossover biotinylated lattice (DXB) with protein streptavidin (SA; Kulkarni et al., 2012). Figure 5 illustrates the sensing principle of the Si-NWs array biosensor: Si-NW array surface was firstly pre-treated by delivering physiological buffer used as electrolyte solution for the following bio-sensing application. Second, 0.5 µl of DXB solution at 400 nM was injected onto the surface of the Si-NWs array, acting as the bio-affinitive sensing interface. A 0.5 µl of SA solution (400 nM) was introduced on the DNA functionalized Si-NWs array surface in sequence. The formation of an electrical field at the Si-NW surface provides enough sensitivity for the detection of the binding interaction between biotin-SA.

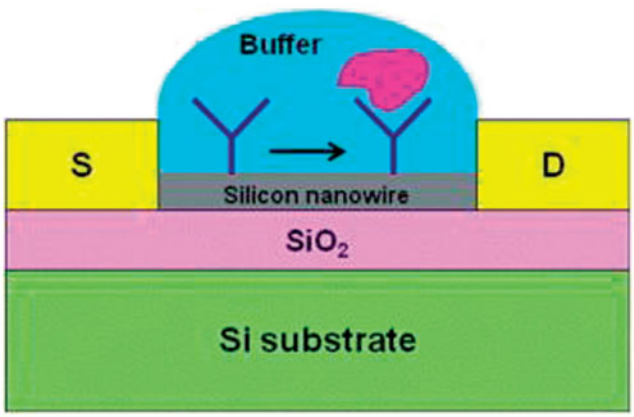



Figure 3. The illustration of a SiNW-FET biosensor with a cross-sectional view.

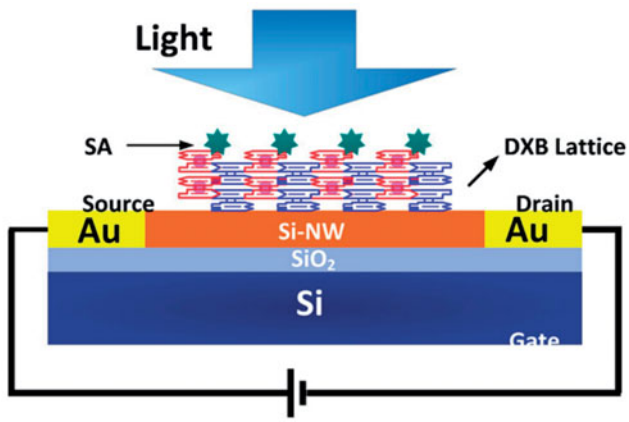
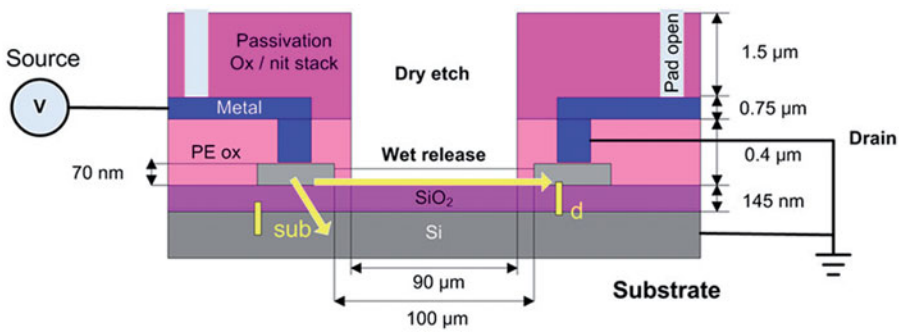



Figure 5. Experimental setup with the sensing scheme of bioanalytes.

Figure 4. Schematic diagram of a cross-sectional view of the SiNW sensor with electrical connection illustrated.



The sensitivity of the SiNW-FET sensor is affected by many factors such as SiNW size, Debye screening, surface chemistry, charge layer distance from SiNW surface. Stern et al. (2007) investigate the influence of different buffer ionic strengths on detection sensitivity, a p-type SiNW-FET biosensor was used to study biotin–streptavidin binding. The results demonstrated the importance of selecting a buffer with an appropriate Debye length to ensure proper NW-FET sensing. Careful control of the solution Debye length ensures that specific binding of macromolecules contributes to the sensor response. Gao et al. (2012) presented an analytical result for triangle cross-section wire for predicting the sensitivity of nanowire surface-charge sensors. Based on the sensing experiments, the authors confirmed that the back-gated SiNW-FET sensor had the highest percentage current response in the subthreshold regime and the sensor performance could be optimized in low buffer ionic strength and at a moderate probe concentration. The optimized SiNW-FET nanosensor reveals ultrahigh sensitivity for rapid and reliable detection of target DNA with a detection limit of 0.1 fM and high specificity for single-nucleotide polymorphism discrimination.

In order to obtain the better characteristics of SiNW for biosensors, we also studied the fabrication of silicon nanostructures based on metal-assisted chemical etching (Zhang et al., 2014). We presented a facile method to fabricate one-dimensional Si nanostructures based on Ag-induced selective etching of silicon wafers. To obtain evenly distributed SiNWs (Figure 6), the fabrication parameters have been optimized (Figure 7). As a result, a maximum of average growth rate of 0.15 μm/min could be reached. The concentration and temperature could influence the growth rates, and the concentration is the primary influencing factor. We believe that the method presented in our work is simple and low cost, which might not only be useful for nano-electronics and optoelectronics but also have potential applications in the fields of biology.

The progresses on SiNW biosensors will be an exciting issue from both science and technology perspectives. Notwithstanding the restriction, we believe that SiNW-FETs will play a significant role in the development of biomedical sensors in the future. In the long run, we envision that the demand of this nanobiosensing technique will be focused on how to advance this novel sensory gadget at a commercial level. For example, a convenient purpose would be minimizing the size of a SiNW-FET device to an easily carried electronic sensor which will benefit people requiring immediate diagnosis. Moreover, studies on the compatibility between SiNW-FET sensors and human body, e.g. for disease diagnosis or blood testing, should be an important topic for future biomedical applications.

The SiNW and carbon nanotube can be classified as one dimensional nanomaterials. Interconnection of these one-dimensional nanomaterials with other parts or components is crucial for nanodevices to realize electrical contacts and mechanical fixings. Interconnection has gradually been paid great attention since it is as significant as nanomaterials properties, and determines nanodevices performance in some cases. We have published a paper about recent progress on techniques that are commonly used for one-dimensional interconnection formation (Ji et al., 2013).

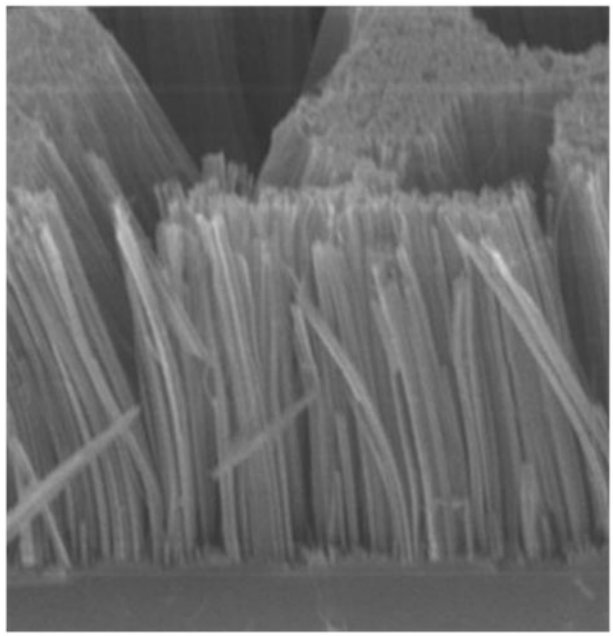


Figure 6. SEM image of silicon nanowires.

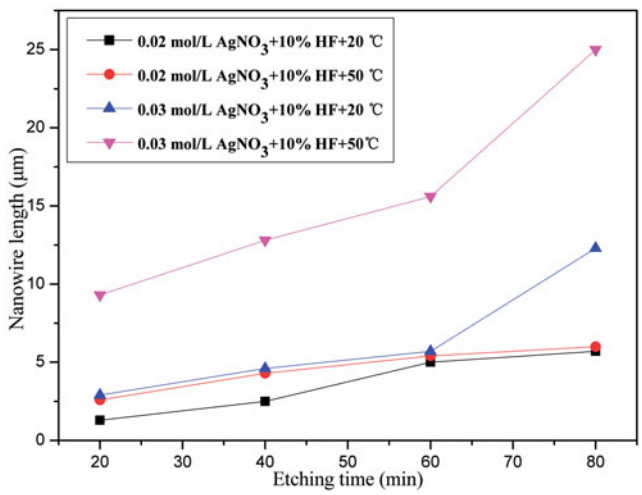



Figure 7. Si nanowires length versus etching time, obtained with samples prepared under different reaction conditions.

## Graphene field-effect transistor biosensors

Graphene is attracting tremendous attention in nano-electronics due to its excellent physical and electronic properties (Koo et al., 2014; Novoselov et al., 2005, 2007). With its high carrier mobility, high saturation velocity and large current density, graphene field-effect transistor (GFET) has been proposed for sensitive and label-free detection of chemical and biological species (Cheng et al., 2010). Single-layer graphene has extremely high carrier mobility (>20 000 $cm^2$/Vs at room temperature) with large carrier concentrations (~$10^{12}$ $cm^{-2}$; Standley et al., 2012). In a GFET, the grapheme film acts as the semiconducting channel between the source and drain metal electrodes. When the

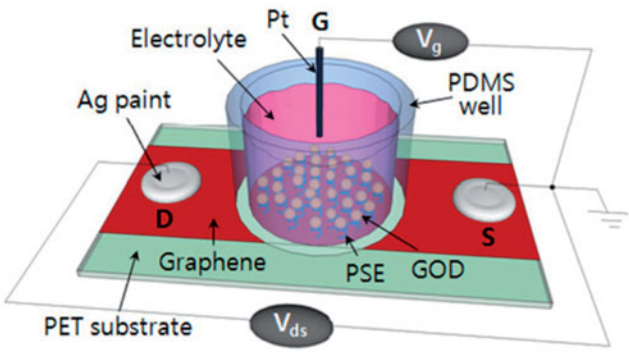



Figure 8. The solution gated CVD grapheme-based FET sensor.

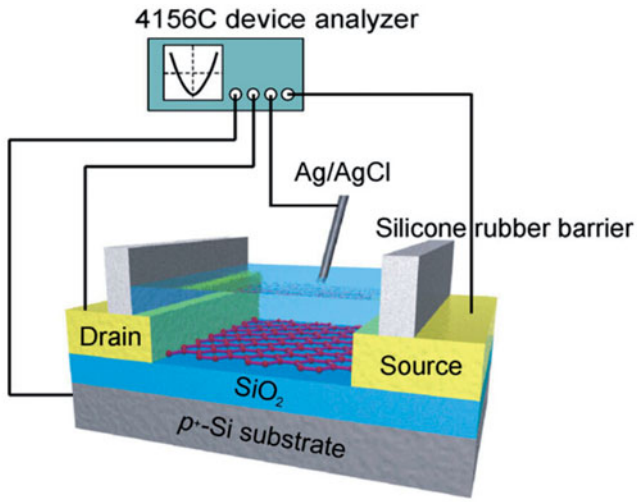



Figure 9. Schematic illustration of experimental setup with G-FETs.

charged biological molecules bind on the surface of the graphene film, there is a measureable resistance change. According to this detection principle, the GFET device is able to act as a real-time biosensor for the detection of biological molecules (Huang et al., 2010; Ohno et al., 2009, 2010a).

The first GFET-based electrical biosensors were demonstrated by Mohanty & Berry (2008), who made graphene transistors from chemically modified graphenes (CMGs), such as grapheme oxides (GOs) or graphene amines (GAs) obtained by treating GOs with nitrogenous plasmas or ethylenediamine. Sensors using graphene or GOs have been developed for the electrochemical detection of glucose. Kwak et al. (2012) fabricated a flexible glucose sensor using the CVD-grown graphene-based FET as shown in Figure 8. PET was selected as a flexible FET substrate and a graphene monolayer film as a channel, source and drain electrodes were prepared by using conductive silver paint and epoxy resin at the two opposite ends of the graphene film on the PET substrate. The polydimethylsiloxine (PDMS) well was attached on top of the graphene channel to maintain the same active area. The GOD functionalized graphene that uses PSE as a linker was exploited to detect glucose. The authors experimentally proved that the FET sensor could detect glucose levels in the range of 3.3–10.9 mM, which mostly covers the reference range of medical examination or screen test for diabetes diagnostics. To achieve real-time biomolecular sensing, Huang et al. (2010) demonstrate that one field-effect transistor fabricated by large-sized CVD-grown graphene films. The CVD-grown graphene film-base FET functionalized with specific redox mediators can detect glucose or glutamate molecules by the conductance changes of the graphene transistors. This study postulates the promising potential of graphene in nanoelectronic biosensing as the label-free technique.

Some strategies have been presented to improve the detection sensitivity. Ohno et al. (2010b) carried out highly sensitive solution pH sensing and monitoring of the charge-type dependence of protein adsorptions on the surface of graphene using single-layer GFETs, as shown in Figure 9. The authors claim in this article that the lowest detection limit (signal/noise = 3) of the change in solution pH value is 0.025 and the GFETs could be electrically distinguished between positive and negative charged proteins in a buffer solution, indicating the high potential of GFETs for applications in chemical and biological sensors. Mohanty & Berry (2008) demonstrated a graphene-based single-bacterium resolution biodevice and DNA transistor: interfacing graphene derivatives with nanoscale and microscale biocomponents. The bacteria biodevice is highly sensitive with a single - bacterium attachment generating ~1400 charge carriers in a p-type chemically modified graphene. Single-stranded DNA tethered on graphene hybridizes with its complementary DNA strand to reversibly increase the hole density by $5.61 \times 10^{12}$ $cm^{-2}$. Mohanty & Berry (2008) said that the device sensitivity can be controlled by manipulating surface groups.

Doping as one of the popular methods to manipulate the properties of nanomaterials has received extensive application in deriving different types of graphene derivates that can be utilized as energy conversion and storage components (Hou et al., 2011), biosensors (Artiles et al., 2011), high-performance FET devices (Wei et al., 2009) and others (Shin et al., 2010), while the understanding of the resonance properties of dopant graphene is still lacking in literature. We studied the resonance properties of N-doped grapheme, reactive empirical bond order potential and the Tersoff potential based on the large-scale molecular dynamics simulation (Zhan et al., 2013). The studied samples were established according to previous experiments with the N atom's percentage ranging from 0.43% to 2.98%, including three types of N dopant locations, i.e. graphitic N, pyrrolic N and pyridinic N. We found that different percentages of N-dopant exerted different influences on the resonance properties of the graphene, while the amount of N-dopant is not the only factor that determines its impact. For all the considered cases, a relative large percentage of N-dopant (2.98% graphitic N-dopant) is observed to introduce a significant influence on the profile of the external energy, and thus lead to an extremely low Q-factor comparing with that of pristine graphene. The most striking finding is that the natural frequency of the defective graphene with N-dopant appears uniformly larger than that of the pristine defective graphene. While for perfect graphene, the N-dopant shows less influence to its natural frequency. The study will enrich the current understanding of the influence of dopants on graphene, which will eventually shed light on the design of different molecules-doped graphene sheet.

By considering the performance of graphene FET-based biosensors and their exceptional properties, it can be concluded that graphene-based sensors may have few advantages over CNTs and other materials. For example, graphene-based devices are easier to fabricate compared to CNTs and transferable to different substrates due to their 2D structure. Graphene is free from any catalytic metallic impurity when prepared under exfoliation process. It also has the capability to detect both negative and positive charged biospecies due to its bipolar nature. Graphene-based FET devices are expected to show low levels of thermal and electrical noise due to its high conductivity and crystal structure as well being able to reduce the noise level by fabricating suspended devices. The properties of the graphene device can be tuned by controlling the number of layers. The maximum sensitivity can be achieved by making it either metallic or semiconducting. Furthermore, high mechanical properties of graphene make it a suitable material for the fabrication of future flexible FET-based biosensor devices. Although graphene-based biosensors present excellent performance in biomolecular detection, the sensor performance should be further improved to meet demanding requirements in terms of sensitivity, selectivity and stability. The sensor fabrication method should also be suitable for large-scale manufacturing critical for future product/technology commercialization.

## Magnetoelastic biosensors

A magnetoelastic (ME) biosensor as one type of new label-free detection technique has been developed in recent years. Briefly, the ME resonator platform is made of an ME strip as the sensing element and an immobilized biomolecular recognition element (antibody, phage, enzymes, etc.) or molecular self-assembled monolayers (SAMs) as the receptor for specific target agents (bacteria, spores, viruses, etc.). The operating principle is based on the phenomenon of magnetoelasticity. When the sensor platform is subjected to a time-varying external magnetic field produced by an exciting coil, it undergoes a corresponding oscillating shape change in dimensions, i.e. it elongates or contracts along the direction of an applied external magnetic field (Engdah, 2000; Gibbs, 2000), effectively converting the applied magnetic energy into mechanical vibration. When the frequency of the applied field is the same as the characteristic frequency of the ME platform, the oscillation of the ME resonator resonance will result in an emission of a magnetic signal. This, in turn, causes a change in the current passing through a pickup coil, and thus the vibration can be remotely detected. The basic structure of the detection system for ME biosensors is presented in Figure 10 (Shen et al., 2009). This type of biosensors is sensitive to the mass change of the ME element. The relationship can be approximated as described in Equation (1) (Wohltjen et al., 1997).

$$\frac{\Delta f}{\Delta m} \approx -\frac{f_0}{2M} \tag{1}$$

where $\Delta f$, $\Delta m$ and $M$ represent the resonant frequency change, mass change and the mass of the ME strip, respectively.

Matglas is one of the commercially available ME materials. This material has much potential for sensor applications due to its high magnetoelastic coupling coefficient (up to 0.98) and high magnetostriction (up to 12 ppm), which allows for highly efficient energy conversion between magnetic energy and elastic energy and the signal from the material to be observed easily (Randy et al., 2005). In addition, a great deal of research has been carried out to discover more magnetoelastic materials suitable for use as the sensitive element of magnetoelastic sensors. Terfenol-D has a very high magnetostriction coefficient (nearly 1000 ppm; Gibson et al., 2011) and is therefore widely used in actuators (Sang, 2010) and sensors (Moser et al., 1993; Schweitzer et al., 2003). However, Terfenol-D is brittle, making it difficult to use in micro and nano-sensors (Liu et al., 2012). FeGa-based biosensors have also been studied, and, unlike Terfenol-D, FeGa alloys (Galfenol) have been found to be ductile and are easily machined (Bai et al., 2008). Therefore, it can be used to replace Terfenol-D in some devices (Gibson et al., 2011). Furthermore, Galfenol has a large magnetostriction coefficient (110–300ppm; Qi et al., 2011)), nearly 10 times greater than Metglas2826. Based on the theory, simulation and experiment, we have studied Metglas2826 and $Fe_{83}Ga_{17}$, as

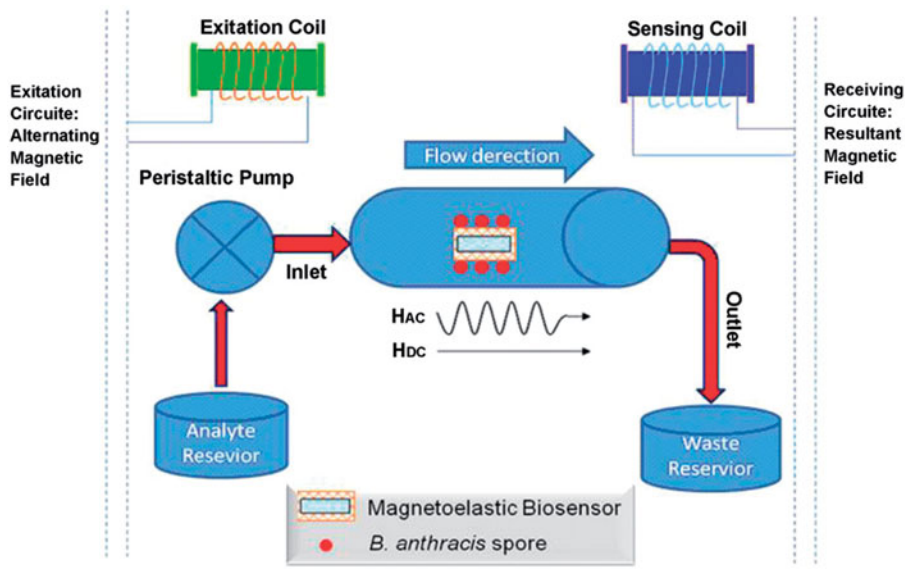



Figure 10. Schematic of the magnetoelastic biosensor detection system.

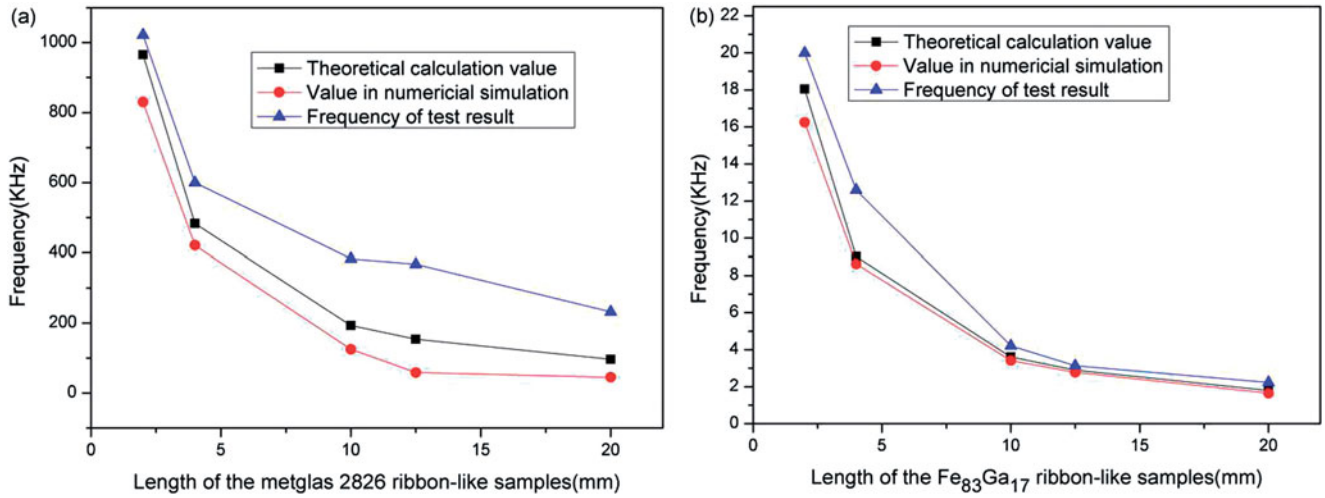



Figure 11. Frequency comparison between the theoretical calculation, simulation and experiment.

shown in Figure 11. The frequency response becomes smaller with the length increase of the samples for both Metglas2826 and $Fe_{83}Ga_{17}$. It is also revealed that the smaller length, the more obviously frequency variation. The experimental frequency values are generally consistent with those from both the theoretical calculations and the simulation results, thus the frequency response test system as constructed is correct and can be used for further experimental testing.

ME biosensors can be employed in enzyme detection, protein detection, immune reaction, and so on. Recently, free-standing, phage-based ME biosensors have been investigated as a novel wireless biosensor system for real-time pathogen detection by many researchers. The ME biosensors have been successfully shown to detect various pathogens, such as *Salmonella* (Huang et al., 2009b; Lakshmanan et al., 2007; Li et al., 2010), *Bacillus anthracis* spores (Shen et al., 2009) and *E. coli* (Lina et al., 2010). Li et al. (2010) gave the results of an investigation to directly detect *Salmonella typhimurium* on fresh tomato surfaces using filamentous E2 phage-based ME biosensors. Shen et al. (2009) presented a ME sensor coated with JRB7 phage for the real-time *in vitro* detection of *Bacillus anthracis* spores (Shen et al., 2009). It was demonstrated both experimentally and theoretically that the frequency versus mass sensitivity of the sensor is high for millimeter and micrometer sized sensors and that it increases significantly as the sensor length decreases. We have been working on designing and building our own portable prototype of ME biosensor for medical or food security inspection (Patent: 201310579839.0, China). The foil detector, made by Matglas 2826, was tested based on the prototype built by us, as shown in Figure 12. The change of the resonance frequency under different conditions, only foil detector, after functionalization and adsorption of human saliva, can be detected. It decreases with the absorption of functionalized material and human saliva on the foil detectors, which is consistent with the theory. Furthermore, the test results from the prototype are consistence with the data from the analyzer. It has potential usage in medicine.

ME sensing technology-based biosensors are easy to operate and suitable for using as disposable sensor development, which have wireless and remote characteristics. They

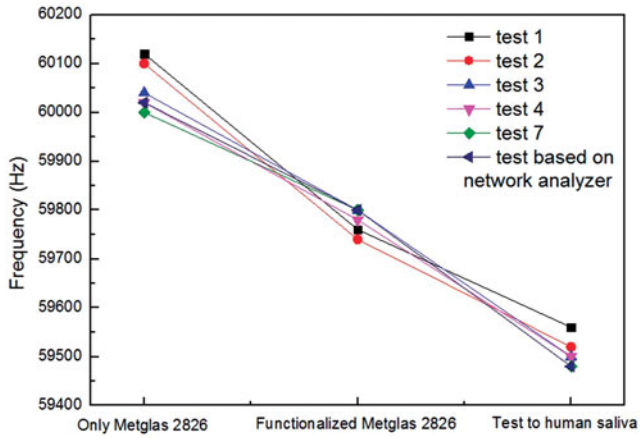



Figure 12. The test results of the magnetoelastic papers under different conditions.

can be used in some special environments where a direct probe or an electrical contact with the sensing element is not feasible. By putting the ME sensor in an airtight container, we can monitor the microbial metabolism process online, as well as review the efficacy of antibiotic and other drugs. Therefore, ME biosensors provide an effective research and real-time *in vivo* analysis for food inspection and clinical medicine. We promise that ME sensing technology will have vast potential for future development as a new analysis technique. To improve the performances of ME biosensor, new generation of MB materials with better properties should be developed. The MB materials must be inexpensive for the extensive application.

## Optical-based biosensors

### Biophotonic biosensors

Biophotonics is the science of generating and harnessing light to image, detect and manipulate biological materials. It is an exciting frontier that involves a fusion of photonics and biology. In this technology, scattering and penetrating light are frequently used to detect and image biological systems at molecular, cellular and organismal levels, which is the common operating principle. The light generated by

metabolic processes in living organisms also provides a good optical means to reflect the structure and function of living cells and organisms, which leads to a special aspect of biophotonics.

The current lead technology for label-free screening is based on the optical properties of the gold plasmon either on a continuous surface, SPR, or as a nanoparticle localized particle plasmon. An advantage of gold nanoparticle structures over continuous gold surface platforms for biosensing applications is the potential to tailor the optical properties of the nanoparticle for each specific assay (Olkhov et al., 2012). Single nanoparticles have been suggested as possible biosensors, and enhancement sensitivity to the biological processes has been achieved by control of the geometry such as nanopin optical resonators.

A gold nanoparticles-based biophotonic array functionalized with antigen proteins has been used to determine the concentrations of the respective antibodies in solution (Olkhov & Shaw, 2010). The four-protein functionalized biophotonic microarray using nanoparticle light scattering centers was successful in determining the absolute concentration of antibodies in solution as a label-free screening technology. A schematic of the array reader, including the injection systems, is shown in Figure 13. Its detection limit is typically 250 ng/ml potentially in whole serum with an accuracy of 15% for a 16-spot assay with an 8-min kinetic response measurement. Olkhov et al. (2012) enabled to screen antibodies in whole blood using label-free nanoparticle biophotonic array platform. They have demonstrated that the near-field illumination of gold nanoparticles viewed through the total-internal reflection element allows analysis of the specific response of allergen anti-bodies in whole blood samples. This technology has potential application in blood testing.

In recent years, novel biophotonic techniques for manipulation and characterization of drug delivery nanosystems in cancer therapy have been discussed, such as optical tweezers (Neuman & Nagy, 2008). Optical tweezers are non-invasive tools which are developed using a laser beam for manipulation of matter in micro- and nano-world. Figure 14 illustrates graphically the unraveling of a double strand of a DNA molecule using optical tweezers. DNA was tethered between two polystyrene microspheres. One DNA end was fixed to a cover glass surface and the other end was captured and held stable in an optical trap, formed by focusing tightly a laser beam with an objective lens (Spyratou et al., 2012). This is a promising tool for biomedical applications in the revolutionary field of genetics, biology, chemistry, medicine and biomechanics. Another biophotonic technique is biophotonic sensing cells (BICELLs), which can be referred as the micro-/nano-photonic structures immobilized bioreceptors on its surface with the capability of recognizing the molecular binding by optical transduction. The classical device based on the sensing principle of BICELLs consists of a periodic lattice of micro–nano pillars built on a silicon or glass substrate with, or without, an interferometric layer chosen among $SiO_2$ for Si as substrate or indium tin oxide (ITO) for glass as substrate. The biosensing capability was experimentally proved through gestrinone/anti-gestrinone and BSA/anti-BSA pairs under different optical configurations (Álvaro et al., 2013; Holgado et al., 2007, 2010; Sanza et al., 2011)

Biophotonics can deal with photons and biological interaction matter. It offers great hope for the early detection of diseases and for new modalities of light-guided and light-activated therapies. It also provides powerful tools for studying molecular events, such as gene expression, protein–protein interaction, spatial and temporal distribution of the molecules of biological interest and many chemico-physical processes in living cells and living organisms.

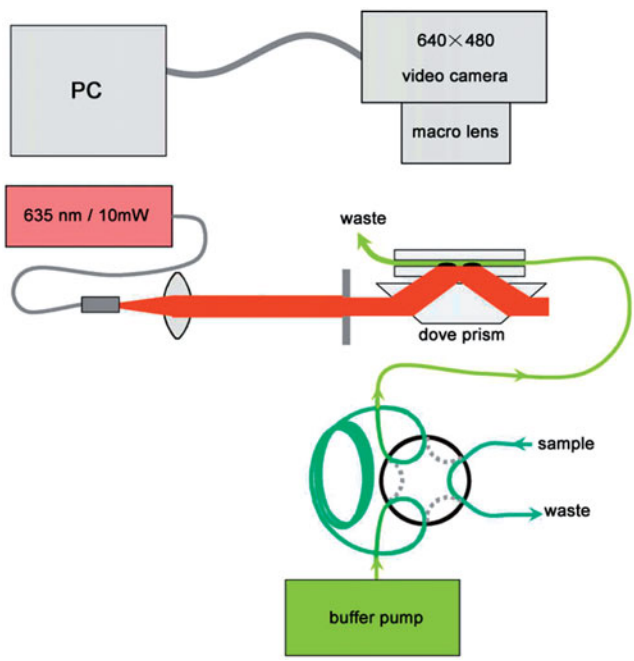



Figure 13. Schematic of the sensor array reader.

## Other optical-based biosensors

Other various optical structures, such as optical waveguide based biosensors (Skivesen et al., 2005, 2007; Sørensen et al., 2006), optical ring and disk resonator based biosensors (Schweinsberg et al., 2007; Armani et al., 2007; Boyd & Heebner, 2001), interferometer-based biosensors (Barrios et al., 2009; Fan et al., 2008; Daghestani & Day, 2010; Robert et al., 2001) have been investigated for sensitive label-free detection. Besides conventional strip and rib waveguides, optical slot-waveguides are also commonly used in biochemical sensors (Carlos et al., 2009; Dell & Passaro, 2007; Francesco et al., 2007). For interferometer-based biosensors, it includes Mach–Zehnder interferometer (Hsu & Huang, 2005; Prieto et al., 2003), Young's interferometer (Brandenburg, 1997; Swann et al., 2004), Hartman interferometer (Schneider et al., 1997, 2000), Backscattering interferometry (Varma et al., 2004; Zhao et al., 2006).

With the development of biotechnology, there is a new research progress on optical waveguide based biosensors (Kim et al., 2014), optical ring and disk resonator-based biosensors (Chrostowski et al., 2012), interferometer-based biosensors (Ben Salem et al., 2014; Hong et al., 2009) in the last 5 years. Additional types of optical label-free biosensors have emerged, such as porous material based optical biosensing. The surface areas of porous materials are

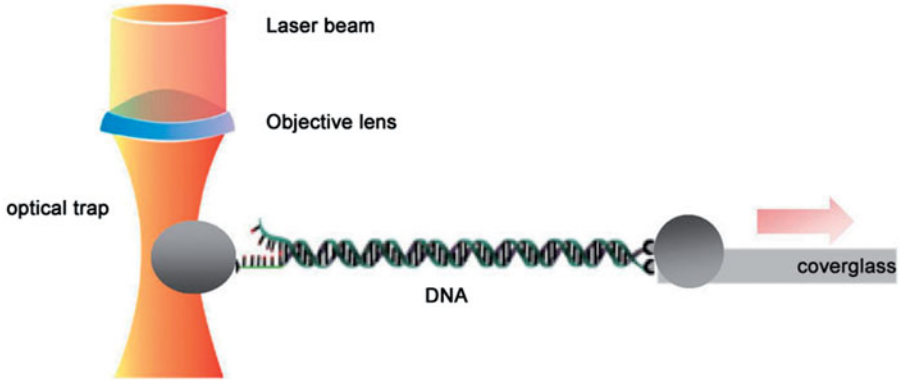



Figure 14. Schematic image of the unraveling of a double-stranded DNA molecule using optical tweezers.

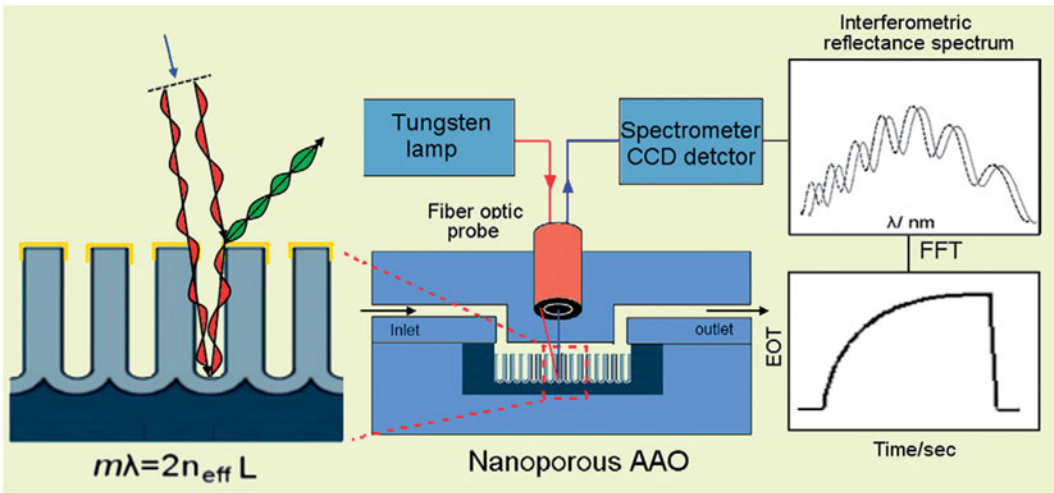



Figure 15. Schematic of the RIfS microchip detection system: comprising an AAO nanopore as sensing platform integrated into a microfluidic chip, fiber optic probe connected to a light source and CCD detector.

considerably larger than those of planar biosensors which results in higher sensitivities and consequently lower detection limits (López-Romero et al., 2010). The commonly used porous materials are porous silicon (PSi) or porous alumina (AAO). The simplest devices are the reflectometric sensors that consist of a few microns thickness interferometer porous layer among the large variety of optical biosensors based on porous materials (Figure 15). The analytes bind to the corresponding bioreceptors previously immobilized on the pore walls, which results in a change in the refractive index and is then detected as a corresponding shift in the interference pattern (Lin et al., 1997). Both porous silicon and porous alumina have been used this approach for biosensor devices based on the reflectometric interference spectroscopy (RIfS) method (Kumeria et al., 2012; Orosco et al., 2009; Tsang et al., 2012). Porous material-based multilayer structure optical biosensors is another alternative which exhibit high reflectivity in a well-defined wavelength range such as Bragg mirrors (Rendina et al., 2007) or rugate filters (Chapron et al., 2007; Cunin et al., 2002). These usually exhibit higher sensitivities due to the enhancement of the light-matter interaction produced by the multiple reflections of light within the multilayer (Ouyang et al., 2006). In addition, planar waveguides, made in porous materials, have also been proposed (Rong et al., 2008). They consist of a thin waveguiding layer of medium porosity material on top of a highly porous layer substrate whose refractive index is lower than the waveguiding layer.

These optical-based biosensors allow the detection of a huge diversity of bioanalytes by measuring the variation of refractive index induced by molecular binding. However, there are some common noises coming from the temperature fluctuations, which can result in a thermo-optic effect (i.e. temperature-dependent RI changes) and a thermo-mechanic effect (e.g. thermal expansion) in both sensor substrate and buffer solution. Some methods, such as the thermoelectric cooler to stabilize temperature, can be used to reduce the thermally induced noise. The second method is to balance the thermo-optic and thermo-mechanic effects. Of course, the reference channel can be employed as a reference channel, which is also built into the same sensor or placed on a different sensor nearby, to reduce so-called common-mode noise, such as temperature related noise. The sensor performance can be improved significantly through these methods.

## Surface stress-based biosensors

Surface stress-based biosensors, as one new technology of micro-scale and label-free system, have been investigated extensively in recent years. This type of sensor uses a balance of free energy change and offers a universal platform for chemical and biological sensing (Satyanarayana, 2005).

This type of biosensors has many advantages over other sensors, such as short response time (less than milliseconds) and a typical sensitivity at nanogram, picoliter, femtojoule and attomolar level. Surface stress-based biosensors also could be made into paralleled array, enabling multiple sensing simultaneously. Furthermore, as one type of label-free sensors, it simplifies sample preparation and testing procedures compared to methods that involve labeling, e.g. fluorescent and others (Sang & Witte, 2010). This technology has been discussed in our paper ''surface stress-based biosensors'' (Sang et al., 2014). Readers can refer to the corresponding reference. Herein, we do not discuss the technology in detail.

## Other type of nanotechnology for biosensors

In a sense, the development of biosensors pursues high sensitivity, good biocompatibility and stability, multifunction, miniaturization and integration. It is worth emphasizing that new sensing mechanisms of biosensors make contributions to improve the sensitivity and accuracy of biosensors. With the application of new composite materials, nanocomposites consisting of metal nanoparticles-doped polymer matrices, especially free-standing nanoparticles–polymer films (Hussain et al., 2013; Mallick et al., 2006; Porel et al., 2005a) and nanowire-polymer film (Choi et al., 2013; Rodd & Agarwal, 2011), have attracted enormous interests in the field of biosensors (Chen et al., 2006; Sulak et al., 2006; Xian et al., 2006).

In some reports, the optical and electronic properties of nanoparticles–polymer films can be tuned due to the size change of the metal particles (Mason, 2005; Ruffini et al., 2006, 2008) or the molecular weight and/or structure of the organic component (Baek et al., 2008; Cong & Pan, 2008; Fernandes et al., 2010). The film conductivity from *n*-alkylthiol-stabilized gold nanoparticles (AuNPs) decays exponentially with the length of the ligands' alkyl chain (Brust et al., 1998; Joseph et al., 2003; Wuelfing et al., 2000). Similar results were also reported by Brust and co-workers (Brust et al., 1998) and others (Joseph et al., 2003). The resistivity of such Au nanoparticle/alkanedithiol films strongly increased with increasing length of the dithiol linkers. In general, the charge transport in films can be described as an activated tunneling process, which has higher sensitivity. More metal nanoparticles, such as Ag nanoparticles (Rezaei et al., 2014; Ruffino & Grimaldi, 2014), Pd nanoparticles (Brancewicz et al., 2014) were also studied to form nanoparticles–polymer films.

Furthermore, several alternatives about nanowire–polymer films have been pursued to achieve novel sensors. For example, polymer comprised of carbon nanotubes (CNTs; Yamada et al., 2011; Yin et al., 2011; Zhang et al., 2011b), zinc oxide nanowires (Xiao et al., 2011; Zhou et al., 2008) or grapheme (Eswaraiah et al., 2011; Kumar & Guo, 2012; Li et al., 2012), used to develop for new sensors due to their outstanding properties. Among them, carbon nanotubes composites of various polymers have also been researched (Bauhofer & Kovacs, 2009; McLachlan et al., 2005; Yu et al., 2011). The tubular structures allow the formation of a more efficient electron-conducting network in CNT-based composite. Also, the piezoresistivity of CNTs make them a suitable candidate for biosensors. Recently, Amjadi et al. (2014) researched a sandwich-structured AgNWs-PDMS nanocomposite. The new type of structure has high sensitivity, stretchability and stability with simple and low cost of fabrication process. In addition, silver nanowires (AgNWs) have been widely used in flexible electronics due to their excellent electrical, optical and mechanical properties (Krantz et al., 2013). They have been demonstrated in transparent and flexible devices (Ho et al., 2013; Lee et al., 2012; Liu & Yu, 2011; Xu & Zhu, 2012).

These nanoparticles/nanowire–polymer composites have various potential applications such as personal health monitoring (Liu & Choi, 2009; Lourussi et al., 2005) structural health monitoring (Kang et al., 2006; Zhang et al., 2011a) and human motion capturing for entertainment systems (Lu et al., 2012; Rautaray et al., 2011; Xiao et al., 2011). The current major applications focus on the highly stretchable and sensitive strain sensors required in biomechanics, physiology and kinesiology. The high sensitive composite films also have potential application in the surface stress biosensors. The surface stress resulting from the interaction between analytes and the sensitive element fabricated by the composite films can be detected electrically. Now we are engaged in the fabrication and experimental application of AuNPs-PDMS composite thin membrane surface stress biosensor (Patent: 201410144773.7, China). Of course, more and better biosensors would be exploited with the improvement of these composites and the development of the biotechnology.

## Summary and outlook

Label-free measurements represent an alternative and complementary approach to traditional label-based assays. In contrast to label-based detection, label-free monitoring is expected to become more important due to several well-known advantages mainly related to analytical quality, easy operation, cost-effectiveness and the target molecules are not labeled or altered, in some cases, on real-time. Of particular interest, several new label-free techniques based biosensors have been developed recently besides the traditional label-free techniques. In this article, different types of label-free techniques for biosensor applications have been reviewed. FETs have recently drawn tremendous attention as a promising tool in biosensor design due to their ultrasensitivity, selectivity, label-free and real-time detection capabilities. Carbon nanostructures including carbon nanotubes and graphene are central materials for novel sensor architectures due to their structure and excellent electric properties. These carbon nanostructure-based FET sensors show a promising future as analysis tools due to their ultrahigh sensitivity and potential for miniaturization. CNTs have been used as active materials, but a major drawback is the difficulty in the separation of metallic nanotubes from semiconducting ones. The more consistent electronic structure of graphene generally makes it more suitable than CNTs for use in such devices. GFET devices are a promising candidate to replace silicon-based semiconductor devices in integrated circuits due to their high-carrier mobility and ability to maintain good performance low temperature.

With the emergence of magnetostrictive materials, ME biosensors become a hot research. No physical connections between the sensor and the detection systems are required and nor any internal power required, it belongs to the passive wireless sensor. The wireless nature of the magnetoelastic biosensor makes it a powerful candidate for *in situ* and *in vivo* analysis. In contrast, optical technology is more mature. Besides the biophotonic technique-based biosensors, there are more types of optical label-free biosensors, for example, optical waveguide-based biosensors, optical ring and disk resonator based biosensors, interferometer-based biosensors, porous material based optical biosensor. These optical-based biosensors have potential applications on the early detection of diseases, new modalities of light-guided and light-activated therapies, studying molecular events, and so on. Thus, we expect that the label-free optical imaging to be a valuable addition to biology. Surface stress-based biosensors provide a promising platform that combines biological/chemical selectivity and high sensitivity and offers the possibility to realize biosensing applications. Furthermore, novel biosensors based on the new material have been exploiting with the development of material and biotechnology.

In conclusion, label-free biosensors are focused at high sensitivity and stability in the future. More study should be conducted to research the effect of different sensing structure on the sensitivity and limit of detection (LOD). Other techniques or improvements may be developed to make biosensors superior, for example, more portable, more miniaturized and more successful commercialization. As the utilization of such biosensors grows, the demand for novel and more effective methods for their preparation will certainly increase.

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## Declaration of interest

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