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Review Article

Advances in biosensors: Principle, architecture and applications☆

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ABSTRACT

The ability to detect pathogenic and physiologically relevant molecules in the body with high sensitivity and specificity offers a powerful opportunity in the early diagnosis and treatment of diseases. Early detection and diagnosis can be used to greatly reduce the cost of patient care associated with the advanced stages of many diseases. However, despite their widespread clinical use, these techniques have a number of potential limitations. For example, a number of diagnostic devices have slow response times and are burdensome to patients. Furthermore, these assays are expensive and cost the health care industry billions of dollars every year. Therefore, there is a need to develop more efficient and reliable sensing and detection technologies. A biosensor is commonly defined as an analytical device that uses a biological recognition system to target molecules or macromolecules. Biosensors can be coupled to a physiochemical transducer that converts this recognition into a detectable output signal. Typically biosensors are comprised of three components: (1) the detector, which identifies the stimulus; (2) the transducer, which converts this stimulus to a useful output; and (3) the signal processing system, which involves amplification and display of the output in an appropriate format. The goal of this combination is to utilize the high sensitivity and selectivity of biological sensing for analytical purposes in various fields of research and technology. We review here some of the main advances in this field over the past few years, explore the application prospects, and discuss the issues, approaches, and challenges, with the aim of stimulating a broader interest in developing biosensors and improving their applications in medical diagnosis.

Introduction

Over the past decade, many important technological advances have provided us with the tools and materials needed to construct biosensor devices. Since the first invention of the Clark Oxygen Electrode sensor, there have been many improvements in the sensitivity, selectivity, and multiplexing capacity of the modern biosensor. Before the various types of biosensor technologies and application are discussed, it is first important to understand and define "biosensor". According to IUPAC recommendations 1999, a biosensor is *an independently*

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integrated receptor transducer device, which is capable of providing selective quantitative or semi-quantitative analytical information using a biological recognition element (Thevenot et al., 1999). Essentially it is an analytical device, which incorporates a biological or biological derived recognition element to detect a specific bio-analyte integrated with a transducer to convert a biological signal into an electrical signal (Lowe, 2007). The purpose of a biosensor is to provide rapid, real-time, accurate and reliable information about the analyte of interrogation. Ideally, it is a device that is capable of responding continuously, reversibly, and does not perturb the sample. Biosensors have been envisioned to play a significant analytical role in medicine, agriculture, food safety, homeland security, bioprocessing, environmental and industrial monitoring (Luong et al., 2008). A biosensor consists of three main elements, a bioreceptor, a transducer and a signal processing system (David et al., 2008). A biological recognition element or bioreceptor generally consists of an immobilized biocomponent that is able to detect the specific target analyte (Kahn and Plaxco, 2010). These biocomponents are mainly composed of antibodies, nucleic acids, enzyme, cell and etc. The transducer on the other hand is a converter. The reaction between the analyte and bioreceptor bring about chemical changes such as the production of a new chemical, release of heat, flow of electrons and changes in pH or mass. The biochemical signal is converted into an electrical signal by the transducer. Eventually, the electrical signal is amplified and sent to a microelectronics and data processor. A measurable signal is produced, such as a digital display, a print-out or an optical change. Fig. 1 shows a schematic diagram of the typical components in a biosensor. There is a need for a simple, rapid and reagentless method for specific determination, both qualitative and quantitative, of various compounds in various applications (Shantilatha et al., 2003). Hence, it is paramount to have fast and accurate chemical intelligence which is particularly conspicuous in human health care.

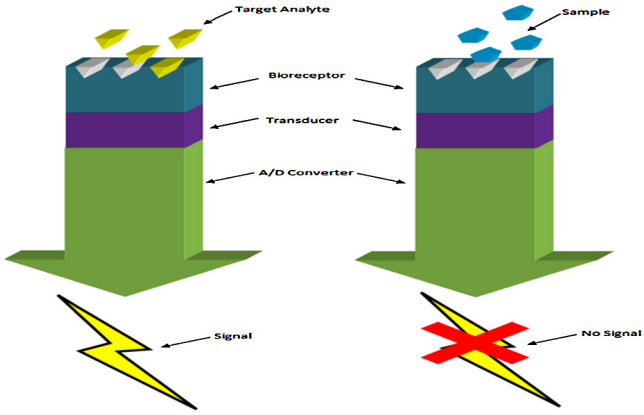

Fig. 1 – Biosensor operation.

Classification of biosensor

Biosensors can be classified either by the type of biological signalling mechanism they utilize or by the type of signal transduction they employ. Fig. 2 shows the different categories of biosensor.

Based on biological signal

The bioreceptor or biological recognition element is the significant distinguishing feature of a biosensor. The bioreceptor compromises the recognition system of a sensor towards the target analyte. Essentially it is crucial for a bioreceptor to be selective and sensitive towards the specific target analyte to prevent interference by another substance from the sample matrix (Lowe, 2007). Generally biosensors can be classified by the type of biological signalling mechanism they utilize. The biological signalling used by biosensors can be divided into five major mechanisms (Fig. 3). Here, we will discuss each of these mechanisms in detail and their application.

Enzyme based sensor

Enzyme based biosensors were the earliest biosensors, introduced by Clark and Lyons in 1962 – an amperometric enzyme electrode for a glucose sensor which used a "soluble" enzyme electrode (Shantilatha et al., 2003). Since the first

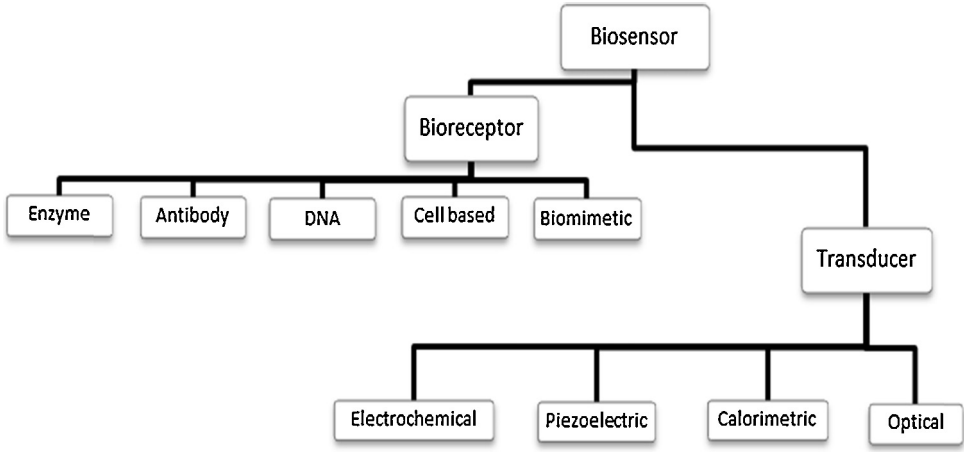

Fig. 2 – Different categories of biosensor.

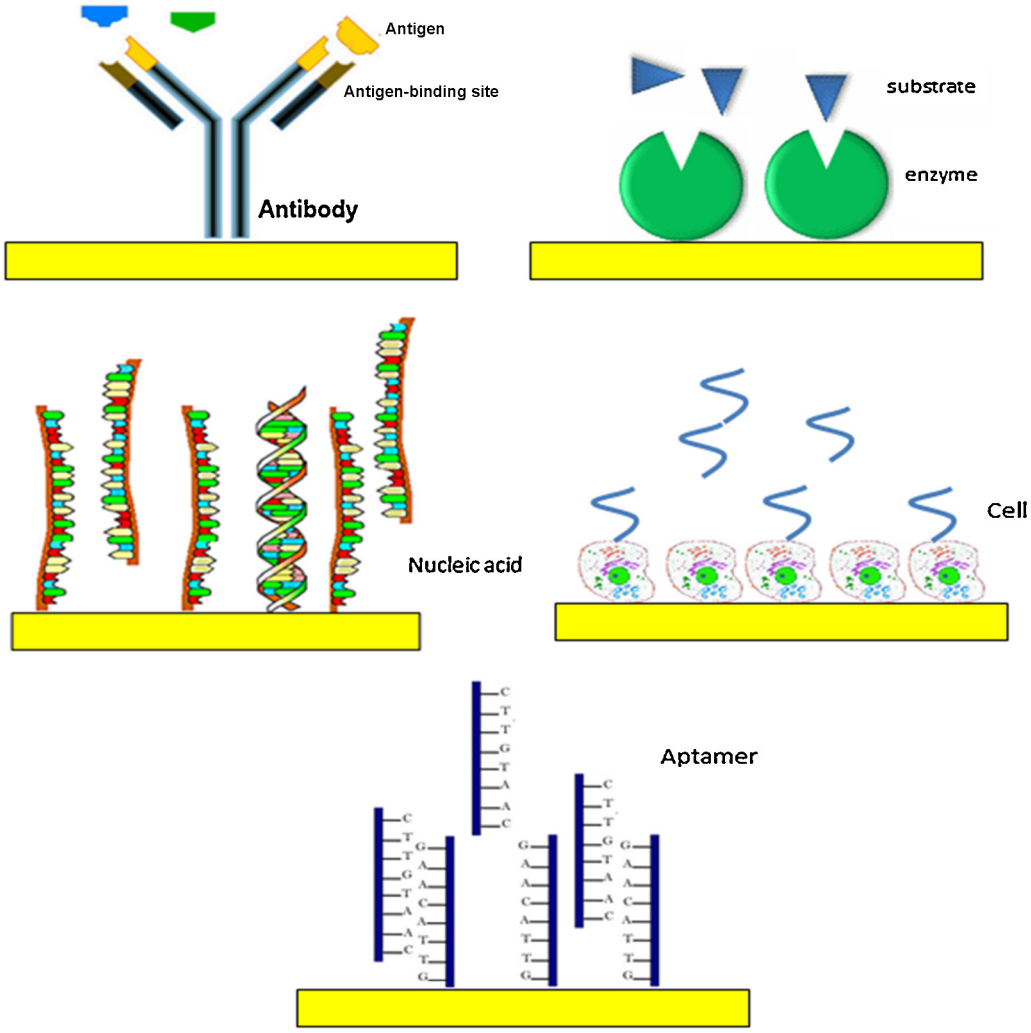

Fig. 3 – Methods of biosensing with various biological signal mechanism: (a) antibody/antigen; (b) enzyme catalyze; (c) nucleic acid; (d) cell-based; (e) biomimetic.

biosensor, enzyme based biosensors have faced a massive growth in usage for various applications up to the present. Enzymes are very efficient biocatalysts, which have the ability to specifically recognize their substrates and to catalyze their transformation. These unique properties make the enzymes powerful tools to develop analytical devices (Leca-Bouvier and Blum, 2010). Enzyme-based biosensors associate intimately a biocatalyst-containing a sensing layer with a transducer. The working principal is based on catalytic action and binding capabilities for specific detection (David et al., 2008). They are made of an enzyme as bioreceptor which detects the targeted analyte from a sample matrix. The lock and key and induced fit hypothesis can apply to explain the mechanism of the enzyme action which is highly specific for this type of biosensor. This specific catalytic reaction of the enzyme provides these types of biosensor with the ability to detect much lower limits than with normal binding techniques. This high specificity of enzyme–substrate interactions and the usually high turnover rates of biocatalysts are the origin of sensitive and specific enzyme-based biosensor devices (Leca-Bouvier and Blum, 2010). Ideally enzyme catalytic action can be influenced by several factors such as the concentration of the substrate, temperature, presence of a competitive and non-competitive inhibitor and pH (Cass, 2007). Essentially the Michaelis–Menten equation can be used to further explain the detection limit of the enzyme based biosensor (Parkinson and Pejcic, 2005). Glucose oxidase (GOD) and horseradish peroxidase (HRP) are the most widely used enzyme based biosensors reported in literature. However, some recent studies have shown that enzyme based biosensors can be used to detect cholesterol, food safety and environmental monitoring, heavy metals and also pesticides (Amine et al., 2006; Ju and Kandimalla, 2008; Zapp et al., 2011; Nomngongo et al., 2012; Soldatkin et al., 2012). Moreover, recent studies have reported the used of enzyme catalytic implication incorporating a nucleic acid biosensor for DNA detection (He et al., 2011; Lin et al., 2011).

Immunosensors

An antibodies based biosensor was applied for the first time to detection in the 1950s, opening the doors to the possibility of immuno-diagnosis (Donahue and Albitar, 2010). Since then,

there have been vigourous efforts made to develop an immunosensor which is composed of an antigen/antibody as bioreceptor as a tool for clinical diagnostics (Conroy et al., 2009; Orazio, 2011). An antibody is "Y" shaped immunoglobin (Ig) that is made up of two heavy chains (H) and two light chains (L). However some human antibodies form a dimeric or pentameric structure by utilizing disulphide bonds and an extra protein called the joining or J-chain (Wood, 2006; Pohanka, 2009). Each chain has a constant and variable part. The variable part is specific to the antigen that is bound with a corresponding antigen which is highly specific and selective (Conroy et al., 2009; Donahue and Albitar, 2010). Hence, an immunosensor which is composed of an antigen as bioreceptor utilizes the ability of the antibody to bind with the corresponding antigen which is highly specific, stable, and versatile. The specificity of an antibody towards the binding side of its antigen is a function of its amino acids (Fowler et al., 2008). These days, there are two type of detection method which are frequently used in immunosensor; optical and electrochemical. However the optical detection transduction method has suffered from poor sensitivity when coupled with a radioimmunoassay, the short half-life of radioactive agents, concerns of health hazards, and disposal problems. Electrochemical detection overcomes problems associated with other modes of detection of immunoassays and immunosensors. In contrast, electrochemical immunoassays and immunosensors enable fast, simple, and economical detection that is free of these problems (Fowler et al., 2008). However, recent advances in science and technology have created an optical transduction method which is a new path towards a highly sophisticated automated instrument. Hence, the optical and electrochemical detection methods are gaining mutual importance in the development of the immunosensor (Shankaran et al., 2007; Bhatta et al., 2010b). According to Ramírez et al. (2009), immunosensors have been envisioned to play an important role in the improvement of public health by providing applications for which rapid detection, high sensitivity, and specificity are important, in areas such as clinical chemistry, food quality, and environmental monitoring. The development of an immunosensor for bacteria and pathogen detection has gained a great deal of attention due to its application in the point of care measurement (POC) (Skottrup et al., 2008; Barton et al., 2009; Braiek et al., 2012; Holford et al., 2012). Some recent studies show that the immunosensor is widely explored for its use in the detection of cancer/tumours. Since the traditional diagnostics method is poor in sensitivity, selectivity and time consuming, the immunosensor are become promising tools for detection of the early stages of cancer (Ushaa et al., 2011).

DNA/nucleic acid sensor

The use of a nucleic acids sequence for a specific diagnostics application was developed in the early 1953 and is still growing widely (Liu et al., 2012a). The highly specific affinity binding's reaction between two single strand DNA (ssDNA) chains to form double stranded DNA (dsDNA) is utilized in the nucleic acids based biosensor which appoints the nucleic acids as the biological recognition element. This method has promoted the development of DNA based sensor from the traditional method such as coupling of electrophoretic separations and radio iso-tropic which are high cost, hazardous, time consuming etc. (Parkinson and Pejcic, 2005). This biosensor working principal is based on recognition of the complementary strand of ssDNA to form a stable hydrogen bond between two nucleic acids to become dsDNA. In order to achieve this, an immobilized ssDNA is used as a probe in a bioreceptor in which the base sequence is complementary to the target of interest. Exposure of the target to the probe which results in hybridization of complementary ssDNA to form dsDNA will result in the production of a biochemical reaction that allows the transducer to amplify the signal into an electrical one. Subsequently, literature shows that the presence of some linker such as thiol or biotin is needed in the effort to immobilize the ssDNA onto the sensing surface (Cagnin et al., 2009; Lazerges et al., 2012). An important property of DNA is that the nucleic acid ligands can be denatured to reverse binding and regenerated by controlling the buffer ion concentration (Parkinson and Pejcic, 2005). The nucleic acid biological recognition layer which incorporates with the transducer is easily synthesizable, highly specific and reusable after thermal melting of the DNA duplex (Teles and Fonseca, 2008). In addition, this biosensor possesses a remarkable specificity to provide analytical tools that can measure the presence of a single molecule species in a complex mixture (Brett, 2005). The DNA based biosensor has potential application in clinical diagnostics for virus and disease detection (Lui et al., 2009; Chua et al., 2011; Thuy et al., 2012). Moreover, Yeh et al. (2012) recently has reported an optical biochip for bacteria detection based on DNA hybridization with a detection limit of 8.25 ng/ml. The development of an electrochemical DNA biosensor has received a great deal of attention lately and this has largely been driven by the need to developed rapid response, high sensitivity, good selectivity and experimental convenience (Liu et al., 2012a).

Cell based sensor

Cell based sensors are a type of biosensor, which use the living cell as the biospecific sensing element and are based on the ability of the living cell to detect the intracellular and extracellular microenvironment condition, and the physiological parameter and produces a response through the interaction between stimulus and cell (Wang and Liu, 2010). Microorganisms such as bacteria and fungi can be used as biosensors to detect specific molecules or the overall "state" of the surrounding environment (Acha et al., 2010). Furthermore, proteins that are present in cells can also be used as bioreceptors for the detection of a specific analyte (Acha et al., 2010). Essentially, the living cell based biosensor is a unique biosensor in contrast to other types of biosensor that contain materials extracted from living things. These types of biosensor have a number of pros and cons. The detection limit of this biosensor is mainly determined by the natural environmental conditions in which the cell can stay alive for a long period in order to control the physical and chemical parameters of the environment. However the major limitations of the cell based biosensor are the stability of the cell, which depends on various conditions such as sterilization, lifetime, biocompatibility and etc. Another issue that governs the success of cell based sensors depends primarily on selectivity, in which the cell based sensor has poor selectivity

of microbial sensor due to the multireceptor behaviour of the intact cells (Belkin and Gu, 2010). Despite these pitfalls the cell based biosensor is still favoured by researchers due to the advantages over the enzyme based biosensor. The cell based biosensors are less sensitive to inhibition by solutes and are more tolerant of suboptimal pH and temperature values than the enzyme based biosensor, though they must not exceed a narrow range because of the possibility of cell death. A longer lifetime can be expected than with the enzymatic sensors and they are much cheaper because the active cells do not need to be isolated (Struss et al., 2010). The literature indicates that cell based sensors have become emerging tools for medical diagnostics (i.e., such as disease detection), environmental analysis, food quality control, chemical–pharmaceutical industry and drugs detection (Veiseh et al., 2007; Banerjee and Bhunia, 2009, 2010; Wang et al., 2010a; Bohrn et al., 2012; Liu et al., 2012b; Melamed et al., 2012). Similarly, Shinde et al. (2012) conclude that the cell based biosensor is envisioned to be an emerging frontier in the area of nano-diagnotics due to their attractive characteristics.

Biomimetic sensor

A biomimetic biosensor is an artificial or synthetic sensor that mimics the function of a natural biosensor. These can include aptasensors, where aptasensors use aptamers as the biocomponent (David et al., 2008). Aptamers were reported for the first time in the early 1990s and described as artificial nucleic acid ligands. Aptamers were thus chemically related to nucleic acid probes, but behaved more like antibodies and showed surprising versatility compared to other bio-recognition components (Brys et al., 2007; Schneider et al., 2010). Aptamers are synthetic strands of nucleic acid that can be designed to recognize amino acids, oligosaccharides, peptides, and proteins. An aptamer has a few advantages over antibody based biosensors such as high binding efficiency, avoiding the use of animals and smaller and less complex. However, a common challenge facing the aptasensors is that they have the properties of nucleic acids such as structural pleomorphic and chemical simplicity which reduce the assay efficiency and also increase its production cost. Subsequently, some effort has been directed towards characterization and optimization of the aptamer to overcome this limitation. Aptamer properties such as their high specificity, small size, modification and immobilization versatility, regenerability or conformational change induced by the target binding have been successfully exploited to optimize a variety of bio-sensing formats (Schneider et al., 2010). The aptamer based biosensor has been widely used in various ways. Recently sufficient progress has been made in biomimetics sensor and aptasensor for clinical application (Vallet-Regí and Arcos, 2008). This includes clinical diagnostics to detect pathogen, virus and infectious disease (Strehlitz et al., 2008; Torres-Chavolla and Alocilja, 2009; Wang et al., 2012; Weng et al., 2012).

Based on transduction

Biosensors are normally categorized according to the transduction method they employ (Fig. 4). The transducer is a component of the biosensor which has an important role in the signal detection process. Hence the transducer can be defined as a device that converts a wide range of physical, chemical or biological effects into an electrical signal with high sensitivity and minimum disturbance to the measurand (Lowe, 2007). There are a number of transducer methods which have developed over the last decade, and recent literature reviews have highlighted the most common methods that are available (Fig. 4). This group can be further divided into two general categories; labelled and label free types, the latter gaining more prominence recently (Parkinson and Pejcic, 2005).

Electrochemical biosensor

The electrochemical sensor in which an electrode is used as the transduction element, represents an important subclass of sensors. According to a IUPAC recommendation in 1999, an electrochemical biosensor is a self-contained integrated device, which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element (biochemical receptor) which is kept in direct spatial contact with an electrochemical transduction element (Thevenot et al., 1999, 2001). Electrochemical biosensors measure the current produced from oxidation and reduction reactions. The current produced can be correlated to either the concentration of the electroactive species present or its rate of production/consumption. The resulting electrical signal is related to the recognition process by target and analyte, and is proportional to the analyte concentration. A review by Wang et al. (2008) has revealed that electrochemical immunosensors are gradually increasing in popularity in clinical analysis and this is partly due to improved sensor design. Similarly, Belluzo et al. (2008) have revealed that the electrochemical immunosensor is a promising alternative compared to existing laboratory methods. Wang (2006) has reported the use of an electrochemical-based device for point-of-care cancer diagnostics which has brought the electrochemical biosensor to new levels in clinical diagnostics. Subsequently, all reports have revealed that the electrochemical biosensor has advantages such as speed, simplicity, low cost, high sensitivity, and relatively simple instrumentation (Grieshaber et al., 2008; Mono et al., 2012). Electrochemical biosensors fall into one of four categories: amperometric, potentiometric, impedance and conductometric, depending upon the nature of the electrochemical changes detected during a biorecognition event.

Amperometric

Amperometric sensors are based on the measurement of current as a function of time resulting from the oxidation and reduction of an electroactive species in a biochemical reaction that mainly depends on the concentration of an analyte with a fixed potential. There are three types of electrode that are usually employed in a amperometric sensor; the working electrode which is usually made of gold (Au), carbon (c), or platinum (Pt); a reference electrode usually silver or silver chloride (Ag/AgCl) which has a fixed potential that controls the potential of the working electrode and the third electrode which is called the counter or auxiliary which is included sometimes to help measure the current flow (Wang, 1996;

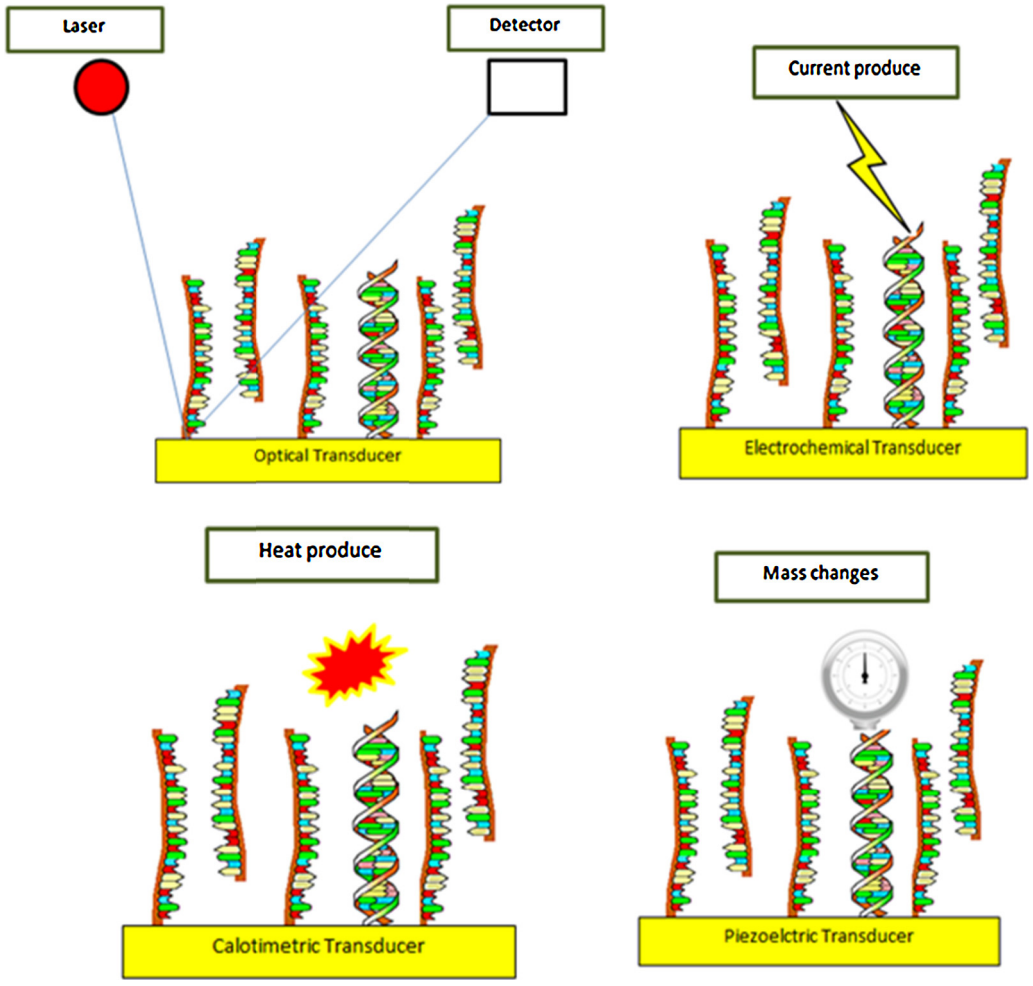

Fig. 4 – Methods of biosensing with various transducer mechanisms: (a) optical; (b) electrochemical; (c) calorimetric – thermal; (d) piezoelectric – mass sensitive.

Wang et al., 2008). As the certain molecules are oxidized or reduced (redox reactions) at inert metal electrodes, electrons are transferred from the analyte to the working electrode or to the analyte from the electrode (Banica, 2012). The direction of flow of electrons depends upon the properties of the analyte which can be controlled by the electric potential applied to the working electrode. If the working electrode is driven to a positive potential an oxidation reaction occurs, and the current flow depends on the concentration of the electroactive species (analyte) diffusing to the surface of the working electrode. Similarly, if the working electrode is driven to a negative potential then a reduction reaction occurs (Parkinson and Pejcic, 2005). A third electrode called the counter electrode is often used to help measure the current flow. There are three generations of biosensor: the first generation biosensor where the normal product of the reaction diffuses to the transducer and causes the electrical response; the second generation biosensor which involves specific ''mediators'' between the reaction and the transducer in order to generate improved response, and third generation biosensor where the reaction itself causes the response and no product or mediator diffusion is directly involved (Saxena and Malhotra, 2003; Wang et al., 2008). The amperometric transduction can be integrated with enzymes, nucleic acids and an immunosensor biological recognition element for various applications such as glucose detection, disease, environmental monitoring and etc. (Ivnitski et al., 1998, 2003; Amine et al., 2006; Wang, 2006; Wang et al., 2008; Fang et al., 2011). However, there are limitations to the use of this biosensor where the presence of electroactive interference in the sample matrix can cause the transducer to generate a false current reading (Rogers and Mascini, 1999). There been various methods identified to overcome this limitation such as diluting the sample, coating the electrode with various polymer, changing the medium of analyte, adding amediator etc. (Jelen et al., 2002; Belluzo et al., 2008; Shinde et al., 2012).

Potentiometric

Potentiometric biosensors rely on the use of an ion-selective electrode and ion-sensitive field effect transistor for obtaining the analytical information. In such sensors, the biological recognition element converts the recognition process into a potential signal to provide an analytical signal. Potentiometric transduction was first reported in the year 1969 where the enzyme based sensor was used for urea detection (Schelfer and Schubert, 1992; Saxena and Malhotra, 2003). It consists of

two electrodes: an indicator electrode to develop a variable potential from the recognition process and a reference electrode (usually Ag/AgCl) which is required to provide a constant half-cell potential. The working principle of the potentiometric transduction depends on the potential difference between the indicator electrode and reference electrode which accumulate during the recognition process in an electrochemical cell when a zero or negligible amount of current flows through the electrode. The electrical potential difference or electromotive force (EMF) between two electrodes is measured using a high impedance voltmeter. The working electrode is made of a permselective ion-conductive membrane which is sometimes called an ion-selective electrode (ISE). The measurement of potential response of a potentiometric device is governed by the Nernst equation in which the logarithm of the concentration of the substance being measured is proportional to the potential difference (Grieshaber et al., 2008; Wang et al., 2008). According to Bakker and Pretsch (2006) recent progress has enabled the development and application of potentiometric sensors with limits of detection (LODs) in the range 10^{-8}–10^{-11} M. These LODs relate to total sample concentrations and are defined according to a definition unique to potentiometric sensors. The ISEs have the largest number of applications in clinical chemistry, particularly the determination of the biologically relevant electrolytes in physiological fluids, and billions of measurements are performed each year all over the world (Makarychev-Mikhailov et al., 2008). This comes as no surprise considering that the potentiometric transduction mechanism is very attractive for the operation of biosensors due to its selectivity, simplicity, rapidity, low cost and maintenance free measurement. However, the device is still less sensitive and often slower than its amperometric counterpart (Makarychev-Mikhailov et al., 2008). The field effect transistor has been used for the fabrication of the integrated biosensor and there are many devices derived from this principle, such as the ion-selective field effect transistor (ISFET), the electrolyte-insulator semiconductor (EIS), and the light addressable potentiometric sensors (LAPS), CHEMFET, BioFET and ENFET (Saxena and Malhotra, 2003). Essentially, the LAPS device is an example of optical/electrochemical hybrid technique which consists of n-type silicon doped with phosphorus and an insulating layer that takes advantage of the photovoltaic effect in the presence of a light source as a light emitting diode (LED), which flashes rapidly (Pohanka and Skládal, 2008). A review by Koncki (2007) has discussed the application of the potentiometric based biosensor in biomedical analysis. The author concludes that the bioaffinity-based biosensor using potentiometric transduction is not reliable. However, LAPS devices have proved to be highly successful for immunoassay and overcome the previous problem of lower sensitivity encountered by potentiometric transduction (Wang et al., 2010b; Jia et al., 2012). Recently, Jia et al. (2012) has developed a graphene oxide modified light addressable potentiometric sensor for ssDNA with a detection limit (LOC) of 1 pM to 10 nM.

Conductometric

In this method the analytical information is obtained by measuring electrolyte conductivity, which varies with the changes in the concentration of the ionic species. In other words, conductometric based transduction provides information about the ability of an electrolyte solution to conduct an electric current between electrodes. The conductometric device is made of two electrodes which are separated by a certain distance or by a medium such as nanowire, etc. Most of the work that is reported in the literature on the conductometric sensor associates it with enzymes where the ionic strength, and thus the conductivity, of a solution between two electrodes changes as a result of an enzymatic reaction. The AC supply is used to apply across the electrode for conductivity measurement. Thus, the ionic composition changes and provides a conductance which is measured using an Ohmmeter. However, some recent studies have shown the conductometric transduction employed in micro/nano electronic devices such as FET to directly monitor the changes in conductance of an electrode as a result of the hybridization of DNA, complementary antibody–antigen pair, etc. (Arya et al., 2007; Hnaiein et al., 2008; Tang et al., 2011). The major advantages of the conductometric device are that no reference electrode is required, it is inexpensive, and there is the possibility of miniaturization and direct electrical response (Grieshaber et al., 2008; Lee et al., 2012). Unfortunately, the conductometric transduction measurement is an additive property, hence less sensitive compared to the other electrochemical methods and strongly dependent on the response to buffer capacity (Wang, 1996). A review by Arora et al. (2011) revealed that conductometric based transducers have been used for detection of food borne pathogens. However, recent literature has shown that conductometric based transduction has received a great deal of attention and overcome the previous power sensitivity problem. Subsequently, some research has been directed towards the improvement of performance and sensitivity (Kannan et al., 2012).

Electrical impedance spectroscopy

The electrical impedance spectroscopy (EIS) based transduction method is not a commonly used method of electrochemical detection; however, this method has only recently become a popular tool for bioreceptor transduction. This method is known to be similar to other electrochemical detection devices but with a conductivity detection that scans the detection volume with an electrical frequency sweep in the range of 10 kHz and 10 MHz (McGuinness and Verdonk, 2009). Essentially, impedance spectroscopy has major advantages over lower concentration detection methods. A recent study shows that EIS based transduction has been employed in tumour growth detection in 100–600 fg/ml with a sensitivity/detection limit of 100 fg/ml (Onur and Kemal, 2011). The EIS type measurement is suitable for real time monitoring since it is able to provide a label free or reagentless detection (Parkinson and Pejcic, 2005; Pejcic et al., 2006). In EIS measurement, the sample is placed on the sensing device such as nanogap, and a controlled alternating voltage is applied to the electrode, and the current flows through the sample are monitored. The electrical impedance resulting from the sample is calculated as the ratio of voltage over current. The resulting electrical impedance measurement has both a magnitude and a phase: a complex number. For any time-varying voltage applied, the resulting current can be in phase with the applied voltage (resistive behaviour), or out of

phase with it (capacitive behaviour). The EIS consists of a 3 electrode system, a potentiostat and a frequency response analyser (FRA). The three electrode are: the working electrode, that provides the measurement of current, the counter electrode that provides current to the cell and the reference electrode for voltage measurement. The potentiostat functions as a high input impedance provider in order to maintain the voltage across the electrode (Barsoukov and Macdonald, 2005). Essentially, the FRA is incorporated to supply an excitation waveform and to provide a very convenient, high precision, wide band method of measuring the impedance (Barsoukov and Macdonald, 2005). A recent review by Yang and Bashir (2008) has discussed the progress and application of the impedance biosensor for foodborne pathogenic bacteria detection. Impedance spectroscopy has been widely used by many research groups to detect cancer/tumour cells, viruses, bacteria and pathogens (Bayoudh et al., 2008; Diouani et al., 2008; Kukol et al., 2008; Hong et al., 2012; Ohno et al., 2012; Thi et al., 2012). This biosensor could become a powerful tool for clinical diagnostics in the imminent future (Pejcic and Marco, 2006).

Optical based biosensor

Over the past decades, the optical biosensor had made rapid advances and has been applied in a number of important areas including food safety, security, life science, environmental monitoring and medicine (Tsoka et al., 1998; Védrine et al., 2003; Johansson et al., 2008; Bhatta et al., 2010a, 2012; Md Muslim et al., 2012). In medicine, the optical transducer has been established in both routine medical diagnostic and for medical research applications (Caygill et al., 2010). The word ''optrode'' is a combination of the words ''optical'' and ''electrode'' and is sometimes used to define optic based devices (Biran et al., 2008). This method of transduction has been employed in many classes of biosensor due to the many different types of spectroscopy such as absorption, fluorescence, phosphorescence, Raman, SERS, refraction and dispersion spectroscopy (Abdulhalim et al., 2007). These transduction methods are capable of measuring different properties of the target/analyte. The optical based biosensor is able to provide label free, real time and parallel detection (Francia et al., 2005; Fan et al., 2008; Bhatta et al., 2010b). The surface plasmon resonance or fluorescence which is integrated with optical fibre is the most popular method available for optical based biosensing (Caygill et al., 2010). It appears that sensors based on the optical fibre principle are gaining research interest and are being employed in biosensor studies.

Surface plasmon resonance

Surface plasmon resonance (SPR) biosensors use surface plasmon waves (electromagnetic wave) to detect changes when the target analyte interacts with a biorecognition element on the sensor. In principle, when the SPR biosensor is exposed to any changes, it will induce changes in the refractive index which is used to measure or observe the reaction. The SPR transducer is incorporated into a biomolecule/biorecognition element which recognizes, and is able to interact with a specific analyte (Mol and Fischer, 2010). Hence when a target analyte interacts with the immobilized biomolecule on the sensor surface, it produces a change in the refractive index at the sensor surface (Mol and Fischer, 2010). This, change produces a variation in the propagation constant of the surface plasmon wave and the variation is measured to produce a reading. A spectrophotometer is used to measure the absorption spectrum of the sample. Various biorecognition elements have been incorporated with SPR biosensors such as protein, antibody–antigen, nucleic acids and enzymes (Endo et al., 2005; Mannelli et al., 2006; Nguyen et al., 2007; Nakamura et al., 2008; Park et al., 2009). An important feature of the SPR biosensor is that it is able to provide label-free sensing without radioactive and fluorescence which makes it highly attractive for real time monitoring (Endo et al., 2008; Fan et al., 2008). In addition, SPR based transduction can be used for an interaction without exhibiting any special properties of fluorescence or characteristic absorption and scattering bands (Homola et al., 2008). However, some reports suggest that this method has suffered from lack of specificity due to non-specific interaction with the biorecognition element which is wrongly correlated by the biosensor (Homola et al., 2008). The SPR based transductions are not suitable for studying small analytes. Because the SPR measures the mass of material binding to the sensor surface, very small analytes ($M_r < 1000$) give very small responses (Merwe, 2001). The recent improvements in the signal to noise ratio have made it possible to measure binding of such small analytes (Merwe, 2001). SPR biosensors can effectively detect binding by molecules as small as about 2 kDa, but smaller molecules generate insufficient changes in bound mass and so cannot be directly measured adequately (Mitchell and Wu, 2010). To date, SPR has been widely used in fundamental biological studies, health science research, drug discovery, clinical diagnosis and environmental and agriculture monitoring (Shankaran et al., 2007). Several articles have appeared in the literature reviewing the application of the SPR based biosensor in pathogen and disease detection (Skottrup et al., 2008; Caygill et al., 2010). Recently, Springer et al. (2010) have demonstrated that the SPR based biosensor is able to detect short sequences of nucleic acids (20 bases) characteristic for *Escherichia coli* down to femtomole level in 4 min.

Chemiluminescence

Chemiluminescence can be described as a method using energy from a chemical reaction which produces an emission of light usually described as luminescence (Li, 2008). Essentially, when a chemical reaction occurs, the atom or molecule relaxes from its excited state to its ground state which then produces luminescence as a side product of the reaction. Hence, chemiluminescence can be used to detect specific biochemical reactions and this property has led to the development of the chemiluminescence based biosensor. In the chemiluminescence biosensor, the reaction between the analyte and the immobilized biomolecule which has been marked with chemiluminescence species will end in generating light as result of biochemical reaction. This emitted light can be detected using a Photo Multiplier Tube (PMT). A review by Dodeigne et al. (2000) and Zhang et al. (2005) has shown that chemiluminescence is an emerging tool for diagnostics with extremely high sensitivity along with simple instrumentation, fast dynamic response properties, and a wide calibration range, and has been widely applied and embraced for

immunosensing and nucleic acid hybridization (Atias et al., 2009; Ding et al., 2008; Holford et al., 2012; Guo et al., 2013). Similarly, a number of papers have shown chemiluminescence applications in use in clinical, pharmaceutical, environmental and food analysis (Kricka, 2003; Gámiz-Gracia et al., 2009; Lara et al., 2010; Liu et al., 2010). These methods have also been incorporated with immunosensor and optical fibre for the detection of the dengue virus in humans (Atias et al., 2009). More importantly, it was revealed that this type of transduction has a detection limit of 5.5×10^{-13} M (Ding et al., 2008). However, chemiluminescence transduction has a few drawbacks, such as a low quantitative accuracy due to short lifetime and is not suitable for real time monitoring (Parkinson and Pejcic, 2005; Zhang et al., 2005; Mathews et al., 2009).

Fluorescence

The term luminescence as described above is the product of atoms or molecules which relax from their excited state to their ground state. The various types of luminescence differ from the source of energy to obtain the excited state. This energy can be supplied by electromagnetic radiation (photoluminescence also termed as fluorescence or phosphorescence), by heat (pyroluminescence), by frictional forces (triboluminescence), by electron impact (cathodoluminescence) or by crystallization (crystalloluminescence) (Dodeigne et al., 2000). Fluorescence requires an external light source (short-wavelength light) to initiate the electronic transitions in an atom or molecule which then produces luminescence (a longer wavelength light). Eventually, the fluorescence based biosensor is incorporated with fluorochrome molecules which are used to produce light during the biorecognition event (Daly and McGrath, 2003). Since most of the biological sensing element and most analyte does not possess intrinsic spectral properties, the biorecognition event is transduced to an optical signal by coupling fluorescence in optically responsive reagents to the sensing elements (Biran et al., 2008). For example, nucleic acid or antibodies are used to tag with flourochrome and convert the hybridization interaction between two complementary DNA stands into an optical signal (Ramanathan et al., 2005; Berdat et al., 2006; Schultz et al., 2008). In fact, fluorescence technology has been widely applied and embraced for immunochemical sensing in the medical field (Hong and Kang, 2006; Moghissi et al., 2008). Fluorescence based biosensing has been optimized widely in environmental monitoring, as reported by Védrine et al., 2003. Nonetheless a recent article has been appeared on the use of the flourescene marking DNA biochip for analysis of DNA-carcinogen adducts (Grubor et al., 2004). The major drawbacks of fluorescence technology are the additional complexity required of time-resolved instrumentation, in either the time or frequency domains or both, and the fact that it is not suitable for real time monitoring (Abdulhalim et al., 2007; Thompson, 2008).

Optical fibre

Optical fibre, sometimes called optrodes, has received considerable interest for development as a biosensor particularly in lower detection limit (LOC) sensing applications. Optrodes based optical fibre biosensors are composed of few major components: a light source, a biorecognition element which is immobilized, an optical fibre which is used to transmit light and act as the substrate, and a detector (e.g., spectrophotometer) where the output light signals the measurement. Hence, when the target analyte interacts with the biorecognition elements at the surface of the fibre, a biochemical reaction takes place resulting in changes in the optical properties. These changes can be collated to the analyte concentration. The light source is transmitted through the fibre optic, where the biorecognition event takes place. The same or different fibre is used to guide the output light to the detector. The current trends of bio-sensing using optical fibre are gaining researcher interest due to its major advantages which are: a miniaturized high performance sensor, small fibre optical sensors, high sensitivity, fast responses, high selectivity, and low detection limits (Lee et al., 2009; Zhang et al., 2011). Optical fibre based biosensors also have several advantages over electrochemical and other biosensing because of their higher sensitivity, safety, freedom from electromagnetic interference (because no reference electrode is needed) and because they are suitable for real time monitoring (Biran et al., 2008). In addition this type of transduction is reagentless and flexible and therefore suitable for remote sensing, and single molecule detection (Biran et al., 2008). However, there are several drawbacks such as the poor stability of biorecognition elements and sensitivity to ambient light (Biran et al., 2008). Most of the work that is reported in the literature on optical fibre biosensor applications has employed the optic fibre with other optical methods (Atias et al., 2009; Huang et al., 2009; Jang et al., 2009; Cecchini et al., 2012). Furthermore, these methods have been used for the detection of various biomolecules such as antigen and nucleic acid (Brogan and Walt, 2005; Leung et al., 2007; Amin et al., 2012). Optical fibre biosensing is versatile and is being widely being used for pathogen and virus detection (Atias et al., 2009; Huang et al., 2009; Caygill et al., 2010). Leung et al. (2008) have reported label free detection of DNA hybridization for pathogen detection using a fibre optic biosensor.

Piezoelectric based biosensor

Piezoelectricity can be explained as a linear interaction between the mechanical and electrical systems in a non-centric crystal or similar structure which was first discovered by the Curie brothers in 1880 (Katzir, 2006; Tichý et al., 2010). Essentially, the piezoelectric based biosensor works on the principal that an oscillating crystal resonates at a natural resonance frequency (Steinem and Janshoff, 2007; Tichý et al., 2010). The fundamental elements in a biosensor are the transducer and biorecognition elements. Hence, in the piezoelectric biosensor the transducer is made of piezoelectric material (e.g., quartz) and the biosensing material is coated with the piezoelectric material which vibrates at a natural frequency. The frequency is controlled by an external electrical signal which produces a certain value of current, and when the target analyte is exposed to the sensing material the attachment/reaction will cause a frequency shift which will produce changes in the current reading that can be collated to the mass of the analyte of interest. There are two main types of piezoelectric sensors: bulk wave (BW) and surface acoustic wave (SAW). However, the literature shows

that piezoelectric sensors are not receiving much attention and are considered inferior compared to electrochemical and optical based biosensing.

Bulk wave (BW) and surface acoustic wave (SAW)

The bulk wave, quartz crystal microbalance and surface acoustic wave transducer is fundamentally based on the piezoelectric effect. The unique properties of piezoelectric material are utilized in this type of sensing. Quartz is the most commonly used material since it is cheap, can be processed to yield a single crystal and can withstand chemical, thermal and mechanical stress; however, it is reported that lithium niobate and lithium tantalate can also be used (Tichý et al., 2010). A recent review has shown that this method is very appealing when integrated with microelectromechanical systems (MEMS) for biosensing applications (Nicu et al., 2005). In addition the review states that this type of transduction is suitable for sensitive, portable and real time biosensing (Nicu et al., 2005). Piezoelectric transducers have been widely applied and embraced for immunosensing applications (Vaughan and Guilbault, 2007; Serra et al., 2008; Tothill, 2009). Some reports suggest that the piezoelectric transducer is suitable for DNA and protein detection with a detection limit of 1 ng/cm^2 (Nirschl et al., 2009). Several articles have appeared in the literature reporting the use of a piezoelectric sensor in various applications such as cholera toxin diagnostic detection, hepatitis B, hepatitis C and food borne pathogen detection (Skládal et al., 2004; Chen et al., 2008, 2010; Yao et al., 2008; Serra et al., 2008). More importantly, it has been revealed that the piezoelectric method is very sensitive, in that a detection limit of 8.6 pg/l has been obtained for hepatitis B virus DNA and 25 ng/ml for cholera toxin detection (Yao et al., 2008; Chen et al., 2010). The advantages of using this type of transduction are real time monitoring, label free detection and simplicity of use (Dell'Atti et al., 2006; Chen et al., 2010). However, there are some drawbacks needing to be overcome such as lack of specificity and sensitivity as well as excessive interference (Glynn and O'Connor, 2010). In addition, this type of transducer method has format and calibration problems (Leca-Bouvier and Blum, 2010). Kim et al. (2011) have recently reviewed the principle and application of the nano diagnostic for the nanobiosensor. The review also concluded that the application range of the quartz crystal has been gradually expanded, and that new measuring techniques that use the quartz crystal as a transducer for chemical sensors and biosensors have also been developed (Kim et al., 2011).

Calorimetric based biosensor

The first enzyme based biosensors introduce by Clark and Lyons in 1962 have inspired and attracted researcher interest in the development of calorimetric based transduction. In fact, almost all chemical and biological reactions involve exchange of heat (Xie et al., 1999). Thus, the general idea of generation and absorption of heat resulting in all biochemical reaction has contributed to the birth of the calorimetric based biosensing device. Initially, calorimetric transduction was employed for the enzyme based sensor, and has subsequently been applied in cell and immunosensor (Xie et al., 1999; Ahmad et al., 2010). The calorimetric principle involves the measurement of the changes in temperature in the reaction between the biorecognition element and a suitable analyte. This change in temperature can be correlated to the amount of reactants consumed or products formed (Xie et al., 1999). A review by Yakovleva et al. (2013) notes that the enzyme thermistor (ET), among all the various concepts of thermal detection, has been researched widely for various applications. The major advantages of this type of thermal detection are the stability, increased sensitivity and the possibility of miniaturation (Ahmad et al., 2010). In addition the calorimetric based biosensor can be easily miniaturized and integrated with microfluidic for increased sensitivity (Zhang and Tadigadapa, 2004). In the calorimetric device, the heat change is measured using either a thermistor (usually metal oxide) or thermopile (usually ceramic semiconductor). A review by Cooper (2003) has shown that this method is very appealing for label free screening of biomolecule interaction. Some recent studies have shown that this technique is capable of rapidly detecting DNA hybridization (Watterson et al., 2002; Buurma and Haq, 2008; Paul et al., 2010; Xi et al., 2010). Recently, the calorimetric method also has been used in the food industry and in environmental monitoring (Kirchner et al., 2012; Maskow et al., 2012).

Conclusion and outlook

The past decade has seen great advancements in the field of the biosensor and along many fronts. This dynamic tool has been applied in many areas of life: science research, health care, the environment, food and military applications. Biosensor technology has received heightened interest over the past decade, since it is a promising candidate for lower detection limits with rapid analysis time at relatively low cost. However, reviews show that there are many studies that have been undertaken using indirect measurement with simple clean buffer solutions instead of direct measurement for in situ real-sample monitoring which is more vital. Technological advances have provided us with the tools and materials needed to construct a biochip which can be integrated with a microfluidic system, probe, sampler, detector, amplifier and logic circuitry. This biochip is a promising candidate for label free, reagentless, real time monitoring, miniaturization and low cost application. For medical application, this cost advantage would allow the development of extremely low cost, disposable biochips that can be used for in-home medical diagnostics of diseases without the necessity of sending samples to a laboratory for analysis which is time consuming.

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