

Recent Advances in Potential Applications of Biosensors

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ABSTRACT: Biosensors are electronic devices that are sensitive to convert bio-recognition processes into measurable signals through a physicochemical process. They are highly sensitive, usually very selective and their development can be done easier, inexpensively and integrated in other devices. The biosensors can be classified based on the type of transducers into three categories, namely electronic (electrical or electrochemical) biosensors, optical biosensors (fluorescent, surface plasmon resonance, or Raman) and piezoelectric (quartz crystal microbalance) biosensors. According to the nature of biological recognition, there are several types of biosensors such as cellulose and cellulose-based composite, enzyme-based biosensors (EBB), immunological biosensors (IB), DNA-biosensors (DNA-B), microbial biosensors (MB) and graphene based biosensors (GBB). For the EBBs, three generations have launched between 1962 and 2003, namely glucose oxidase (GOD) enzyme, modified GOD- enzyme, and reconstructed GOD enzyme. The IBs are a new and cheap version of enzyme-linked immunosorbent assay (ELISA) with higher sensitivity and operation convenience. They can be classified into two types, namely a capture antibody that is immobilized at the electrode capturing specific target antigen and a capture antigen that is immobilized at the electrode capturing specific antibody. Different techniques have been developed to improve DNA hybridization detection including optical, acoustic and electronic devices. Among these methods, the fluorescent detection has preferred as genosensors in the few past decades. The MBs are analytical devices that integrate microorganism(s) with a transducer to measure a generated signal that is correlated to the analytes concentration.

KEYWORDS: Biosensors, Enzyme-based biosensors, DNA biosensors, Microbial biosensor, Cellulose derivatives-based biosensors.

INTRODUCTION

In order to minimize the diseases attacked crops during growth, harvest and postharvest steps to maximize productivity and ensure agricultural sustainability, advanced disease detection and prevention in crops are imperative [1]. Bioelectronics can be made by integrating biological materials with electronic elements for monitoring biochemical and biotechnological processes [2]. Biosensors are attracting more attentions as practical and highly sensitive tools in pathogen detection, molecular diagnostics, environmental monitoring and food safety control as well as in defense purposes. Electrochemical biosensors are promising due to low-cost, operation convenience and miniaturized devices [3].

The biosensors are defined as analytical devices incorporating a biological material (e.g. tissue, microorganisms, organelles, cell receptors, enzymes (Figure 1), antibodies (Figure 2), nucleic acids, natural products etc.), a biologically derived material (e.g. recombinant antibodies, engineered proteins, aptamers) or a biomimic (e.g. synthetic receptors, biomimetic catalysts, combinatorial ligands, imprinted polymers) intimately associated with or integrated within a physicochemical transducer or transducing microsystem, which may be optical, electrochemical, thermometric, piezoelectric, magnetic or micromechanical [4,5]. The blood glucose measurement for the management of diabetes comprises approximately 85% of the world market for biosensors [6].

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There are three main advantages of using biosensors in diagnosis purposes [3]:

1. Biosensors are highly sensitive due to biomolecules often possess high affinity toward their targets, for example, antibodies captures antigens with a dissociation constant at the nanomolar scale, and DNA-DNA interactions are even stronger than antigen-antibody.
2. Biological recognition is usually very selective often leads to selective biosensors. For instance, the attraction between enzyme and substrate can be described as lock and key.
3. The development of modern electronic transducers can be done easier, inexpensively and integrated in other devices.

According to the nature of biological recognition, there are several types of biosensors such as: 1) enzyme-based biosensors, 2) immunological biosensors, 3) DNA biosensors and microbial biosensors. In addition, the biosensors can be classified based upon the type of transducers into three categories: 1) electronic (electrical or electrochemical) biosensors ([7,8], 2) optical biosensors (fluorescent, surface plasmon resonance, or Raman) biosensors ([9,10,11] and 3) piezoelectric (quartz crystal microbalance) biosensors [12,13].

Electrochemical sensing

Advantages of electronic detection include: 1) highly sensitive, rapid screening and inexpensive [14]; 2) many electroactive labels such as metallocenes are stable and environmentally insensitive comparing to fluorophores that often have photo-bleaching problems; 3) possibility of doing multi-color-labeling by suitable molecular design [15], 4) expansion of the silicon industry has paved the road to mass-production of integrated circuits which renders electronic detection especially compatible with microarray-based technologies and 5) the great achievements in accurate controlling of surface properties reinforced the bioelectronic applications [16,17,18].

Electrochemical techniques are useful for biological sensing, where electrodes serve as either electron donors or electron acceptors. More studies indicated that heterogeneous electron transfer between electrodes and surface-confined redox molecules can be obtained analogous to donor-acceptor pairs in homogeneous solutions ([19,20,21]. This means that small distance changes of surface-confined redox molecules might produce large variations in heterogeneous electron-transfer rates that can be converted into electrochemical signals. For instance, an electrochemical sensing strategy was reported by Benson *et al.* [22] to exploits ligand-mediated hinge-bending motions in proteins. In this strategy, a gold electrode was first coated with self-assembled monolayer (SAM), which provides a versatile platform for site-specific immobilization of proteins. The maltose-binding protein (MBP) was then tethered to the gold electrode surface with a specific orientation in which the ruthenium (Ru) redox reporter group is fixed at a certain distance above the electrode. When the ligand maltose binds to the active site, it induces a hinge-bending motion of MBP that moves the Ru (II) reporter away from the electrode. This maltose-binding induced distance change induces concentration-dependent decrease of electrochemical signals useful to electronically detecting maltose.

Several cellulose-based biomaterials were designed during the last three decades for many types of sensors such as gas sensor, humidity sensor, UV sensor, strain sensor as well as capacitive sensor were introduced ([23]. These cellulose derivatives can be designed and finely-tuned to insert desired properties ([2]. Cellulose acetate, cellulose acetate propionate, cellulose formate, cellulose nitrate, cellulose sulphated, hydroxypropyl cellulose, carboxymethyl cellulose are examples of cellulose derivatives that can be included in biosensors [2] due to their excellent biocompatibility that make them suitable for immobilization of biological compounds[24,25].

Enzyme-based biosensors (EBB)

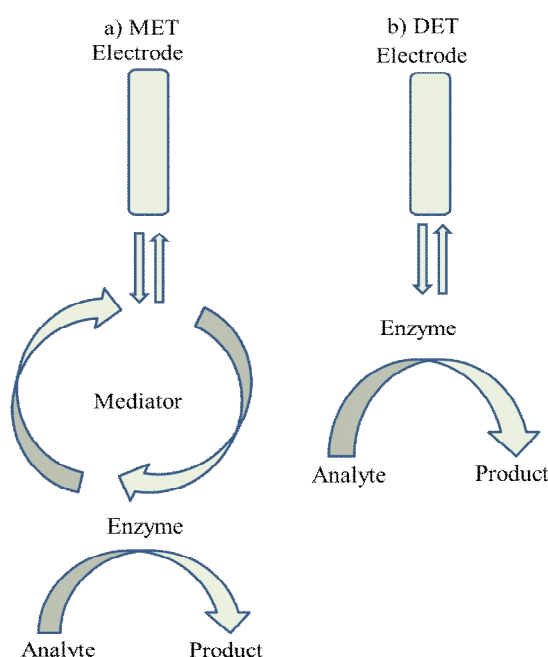


Figure 1. Schematic representative of enzymatic biosensor based on (a) mediated electron transfer (MET) and (b) direct electron transfer (DET).

Three EBB-generations have launched between 1962 and 2003 [3] using the following systems:

a) Glucose oxidase (GOD) enzyme such as Clark's biosensor in which the oxidized form of GOD reacts with glucose, if present, and produces gluconic acid and reduced GOD. This oxidation of glucose also consumes oxygen in solution since dissolved oxygen reacts with reduce GOD forming H_2O_2 and oxidized GOD, and lowers oxygen pressure. As a result, the electrode can sense the glucose by electrochemically sensing oxygen with a Clark oxygen electrode.

b) Modified GOD- enzyme by substitution of the natural oxygen in the enzyme by artificial redox molecules as ferrocene, thionine, methylene blue, methyl viologen which act as redox mediators and exchange electrons between electrodes and enzymes improving the sensor performance in view of sensitivity and signal-to-noise ratio. Initially, when the above-mentioned mediators dissolved in solution, they withdraw electrons from electrodes and then these electrons are shuttled to the redox center of enzymes, or vice versa. Subsequently, immobilized mediators were proposed in order to develop reagentless biosensors for H_2O_2 [26]. They first modified gold electrodes with L-cysteine, and then multilayers of horseradish peroxidase (HRP) was linked to the amine group of cysteine by using glutaraldehyde, thionine was further linked to the enzyme by the same chemical linking. As a result, both the enzyme and the mediator were immobilized at the gold electrode, which could sensitively detect hydrogen peroxide in the test solution without further addition of reagents. An obvious advantage of this biosensor configuration is that mediator is fixed at the electrode surface, thus obviating the problem arising due to the diffusion. It was reported an alternative approach involving the use of redox polymers [27,28]. They first prepared a polymer doped with osmium (Os^{2+}) complex that serves as a molecular wire and exchanges electrons between the electrode and the enzyme. Therefore, they co-immobilized the Os^{2+} polymer and glucose oxidase on carbon electrode which produces sensitive response to

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the presence of glucose. By using these redox polymers, they were able to make nearly 100% immobilized enzyme molecules electroactive leading to glucose detection with very high sensitivity.

The commercialization of the second-generation enzyme-based biosensor revealed a MediSense biosensor and other recent amperometric biosensors consists of disposable, screen-printed carbon electrodes coated with GOD and mediators (test strips). Upon applying a droplet of blood on the test strip, the sensor begins to work and records amperometric response, which is converted to a digit displayed on LCD, representative of glucose concentration.

c) Reconstructed GOD enzyme

The first prepared apo-GOD done by Xiao *et al.* [29] was free of the flavin adenine dinucleotide (FAD) cofactor. Subsequently, they functionalized a 1.4-nm gold nanoparticle with FAD and insert it into the apo-GOD by reconstruction. Such a reconstructed enzyme was linked to gold electrodes by using a dithiol monolayer. They showed that electron transfer turnover of this artificial enzyme is as high as 5000 s^{-1} , approximately 8-fold higher than the natural enzyme (700 s^{-1}). In this system, gold nanoparticle acts as an electron relay for electrical wiring of the redox center of the enzyme. This type of biosensor is free of any mediator and highly sensitive to glucose detection. More recently, a modified version of this sensor by using single wall carbon nanotubes (SWNTs) instead of gold nanoparticles and realized similarly high efficiency was reported by [30].

Immunological biosensors (IBs)

The IBs are a new and cheap version of enzyme-linked immunosorbent assay (ELISA) with higher sensitivity and operation convenience. There are two types of the Ibs: 1) a capture antibody is immobilized at the electrode, which captures specific target antigen. Signal transduction is realized via a secondary antibody tagged with redox molecules or enzymes and 2) an antigen is immobilized at the electrode, which detects a specific antibody [3].

Dai *et al.* [31] reported a developed amperometric immunological biosensor for carcinoembryonic antigen (CEA). Co-immobilized thionine and HRP-labeled CEA antibody were crosslinked with glutaraldehyde on a glassy carbon electrode. The catalysit-HRP reduces the H_2O_2 in solution coupling it into the electrode reaction of thionine leading to a catalyzed signal. Capturing CEA partially blocked the redox center of HRP revealing to attenuation of amperometric signals.

Introducing the single wall carbon nanotubes (SWCNTs) to improve the performance of immunological biosensors was reported by Yu *et al.* [32]. The use of SWCNT significantly improved the detection sensitivity due to the enhancement of electron transfer reactivity of HRP encapsulated in SWCNT.

DNA biosensors

DNA hybridization detection has been attracting more attention of scientific researchers due to fast growing interest of chip-based clinical diagnosis [27] Accordingly, different techniques have been developed including optical [9,10,11], acoustic [12,13,33], and electronic devices [33,30,8]. Among these methods, the fluorescent detection has preferred as genosensors in the few past decades [34,35,27]. In addition, electrochemical techniques have proven successful in simple chemical metal ions [36,37,38].

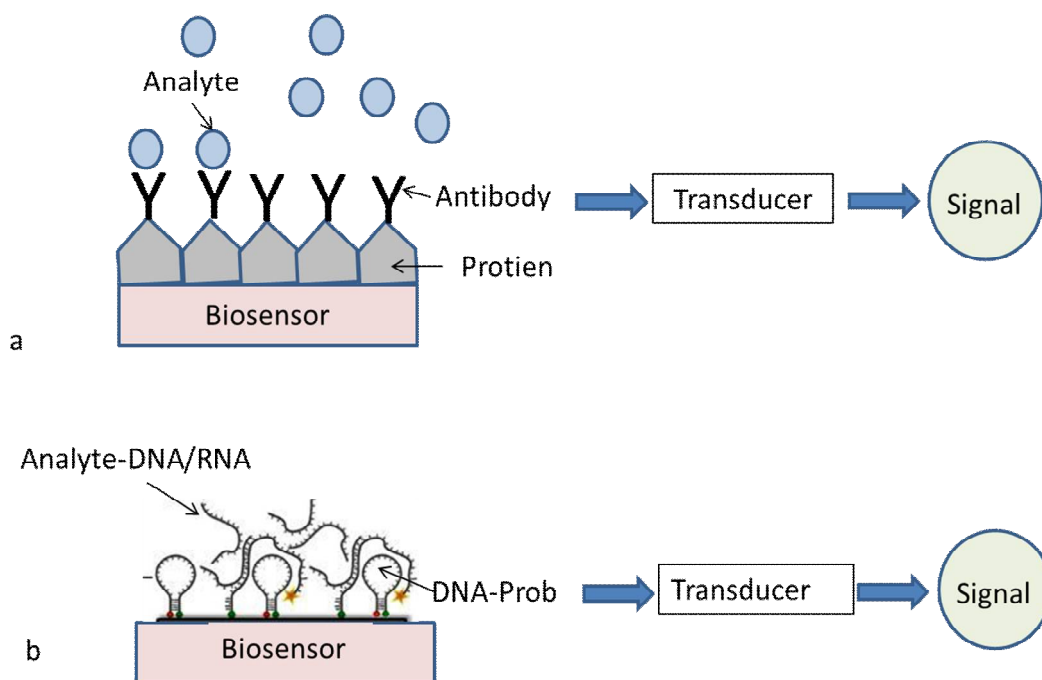


Figure 2. Biosensing for analyte detection: a) The specific combination of analyte and immobilized antibody and b) DNA/RNA probe for inducing a measurable physicochemical change.

DNA double helix was suggested to be a medium for long-range electron transfer (ET) via its base stacking [30,4]. Well-oriented DNA films at gold electrode allows long-range electron transfer and that such ET is extremely sensitive to base stacking perturbations such as mismatches [40,41]. They observed that electroactive intercalators such as methylene blue (MB) could be efficiently reduced at an electrode modified with fully matched DNA duplex. However, the presence of just a single mismatch converts the wire-like ET medium to an insulator, which completely disrupts ET between the MB and the electrode. Such a difference can be measured via cyclic voltammetric or coulometric assays, which forms the basis of a rapid DNA mutation screening sensor [33,42]. Furthermore, it was reported that the sensitivity of this approach could be improved by electrocatalysis. Addition of ferricyanide in solution repetitively pulls electrons from electrochemically reducing the MB concentration which amplifies electron flow through the DNA double helix [33]. This allows detection of ~108 DNA molecules with a 30- μm electrode. In addition, they also constructed DNA-based sensor to detect DNA binding proteins [43]. Certain DNA-binding proteins or enzymes interfere with DNA base pair stacking converting DNA double helix from efficient ET wires to insulators. Furthermore, a sensitive way to electrically assay a variety of DNA-binding proteins was developed.

Sequence-selective DNA target detections based on electroactive hybridization indicators, which provide electronic signals as well as discrimination between double and single stranded DNA was proposed by Millan and Mikkelsen [44]. In an attempt to reduce high background arisen from the minor binding of hybridization indicators to ssDNA, sandwich type-detections have suggested [45,46,17]. Besides an immobilized DNA probe, a DNA strand, possessing an electroactive label, has introduced to act as the signaling molecule. Similarly, Park *et al.* [8] have developed an array-based electrical DNA detection using nanoparticle probes with high sensitivity and selectivity. In addition, Thorp [47] developed a technology based on the relatively high oxidation activity of guanine and its facilitation by exogenous redox catalysts. This method is highly sensitive in detection of PCR products however relatively poor in discrimination of hybridization events.

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However, it is still more important to develop an all-in-one (ie, reagentless) sensor that directly signals upon target capturing. DNA or RNA aptamers provide a viable means to this end. Aptamers are well-structured DNA or RNA which, as well as natural enzymes, possess high affinity and selectivity to specific targets whereas demonstrate superior robustness to fragile enzymes [48,40]. A simple structured hairpin-like DNA with an electroactive label (electronic DNA hairpin) as building blocks was applied by Fan *et al.* [7] to detect hybridization events. This design has been an extremely interesting aptamer that forms the basis of fluorescent molecular beacons for homogeneous hybridization detection. The DNA sequence has been designed such that this beacon is in the close state in the absence of targets while will be turned on when it meets its specific gene target. The existence of the stem-loop structure in the design provides an on/off switch as well as a stringency to discriminate single mismatch in DNA hybridization. For the electronic DNA hairpin, a thiolated terminus provides a sticky end to the gold surface while a ferrocene tag at the other end transduces electronic signals. The initial hairpin localizes the ferrocene proximal to the electrode surface, thus allowing interfacial electron transfer. After hybridization, the formation of the linear duplex structure disrupts the hairpin and forces apart the ferrocene and the electrode. This significant distance change (up to a few nm) effectively blocked the interfacial electron transfer leading to diminution of corresponding electrochemical current signals. Such a design help for integrating the capturing part (probe sequence) and the signaling part (electroactive species) within a single surface-confined hairpin structure. Accordingly, this design is effectively reagentless and provides the basis to construct a portable, continuous DNA analyzer useful in medical and military applications [50,47].

Microbial biosensor (MB)

The MBs are analytical devices that integrate microorganism(s) with a transducer to measure a generated signal that is correlated to the analytes concentration. These types of biosensors are applicable for environmental, food, and biomedical applications [51].

Bacteriophage is a promising pathogen-detectors due to its high sensitivity, selectivity, low cost and higher thermostability[52,53,54].

It is well known that bacteriophage is a virus, composed of protein capsid encapsulating a DNA or RNA genome. It infects the bacteria replicates itself within the bacteria and finally lyses the bacterial host to propagate. Accordingly, bacteriophage has been used in phage therapy to cure bacterial infections [55] for human and plant diseases control [1]. Upon the interaction between the bacteriophage and the target analyte, the impedance of charge transfer reactions at the interface changes can be used as a signal for detection. Furthermore, bacteriophages have used successfully in controlling potatoes and tomatoes pathogens such as *Dickeyasolan*[56,57].

Graphene based biosensors (GBB)

Graphene has been attracting interests in the electrochemical biosensors field due to its intrinsic properties (electronic, optical, and mechanical properties) associated with its planar structure. Its large surface area and excellent electrical conductivity permit it to act as an electron wire between the redox centers of an enzyme or protein and an electrode's surface. In addition, rapid transfer of electron leads to accurate and selective detection of biomolecules [58]. Many smart biosensing strategies has been creating for applications in clinical diagnosis and food safety [59].

Graphene based enzymatic and non-enzymatic electrodes can efficiently detect glucose, cytochrome-c, nicotinamide adenine dinucleotide (NADH), hemoglobin, horseradish peroxidase enzyme (HRP), and cholesterol, hydrogen peroxide. Furthermore, the high sensitivity of graphene in detecting different gaseous species make it suitable in detection of hydrogen, carbon monoxide, ammonia, chlorine, nitrogen dioxide, oxygen, and dinitrotoluene.

Quantum dots based Biosensors(QDBB)

The QDBBs have been used for disease detection [60] using fluorescence resonance energy transfer (FRET) mechanism [61]. Many QD-FRET-based sensors have been developed for phytodisease detection such as the witches' broom disease of lime caused by *CandidatusPhytoplasmaaurantifolia* and Rhizomania, which is the most destructive disease for sugar beet caused by *beet necrotic yellow vein virus (Polymyxabetae)* as indicated by Safarpouret *al.* [62].

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II. CONCLUSION

- According to the type of transducers, biosensors are classified into three categories, namely electronic, optical and piezoelectric biosensors.
- According to the nature of biological recognition, biosensors are classified into cellulose and cellulose-based composite, enzyme-based biosensors, immunological biosensors, DNA-biosensors, microbial biosensors and graphene based biosensors.
- For the enzyme-based biosensors, three generations have launched between 1962 and 2003, namely glucose oxidase (GOD) enzyme, modified GOD- enzyme, and Reconstructed GOD enzyme.
- The immunological biosensors are based on enzyme-linked immunosorbent assay with higher sensitivity and are classified into capture antibody and capture antigen.
- DNA hybridization detection was improved as optical, acoustic and electronic devices.
- The microbial biosensors are analytical devices that integrate microorganisms with a transducer to measure a generated signal that is correlated to the analytes concentration.
- Electrochemical techniques are useful for biological sensing, where electrodes serve as either electron donors or electron acceptors.
- Several cellulose-based biosensors were designed such as gas sensor, humidity sensor, UV sensor, strain sensor as well as capacitive sensor.

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