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Review Article

AN OVERVIEW ON BIOSENSORS

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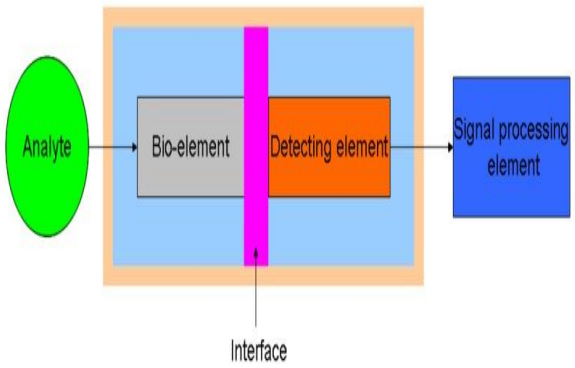
ABSTRACT

Biological and biochemical process have a very important role on medicine, biology and biotechnology. However, it is very difficult to convert directly biological data to electrical signal, the detection of toxins, and advanced diagnostics recent advances in biofabrication may allow sensors to achieve the high spatial sensitivity required, and bring us closer to achieving devices with these capabilities. Biosensors and devices that are designed to detect a specific biological analyte by essentially converting a biological entity (i.e, protein, DNA, RNA) into an electrical signal that can be detected and analyzed. The use of biosensors in cancer detection and monitoring holds vast potential. Biosensors can be designed to detect emerging cancer biomarkers and to determine drug effectiveness at various target sites. Biosensor technology has the potential to provide fast and accurate detection, reliable imaging of cancer cells, and monitoring of angiogenesis and cancer metastasis, and the ability to determine the effectiveness of anticancer chemotherapy agents. This review will briefly summarize the biosensing devices which as well as some future applications of biosensor technology identifying methods and the biosensor technology available today.

WHAT IS BIOSENSOR?

"An analytical device which incorporates a biologically active element with an appropriate physical transducer to generate a measurable signal proportional to the concentration of chemical species in any type of sample"

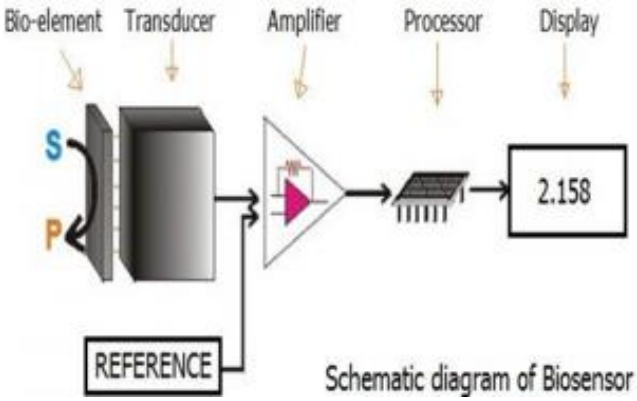


INTRODUCTION

Biosensors started with the introduction of first generation glucose oxidase (GOx) biosensor in 1962 by Clark and Lyons. The International Union of Pure and Applied Chemistry (IUPAC) defines a biosensor as "a device that uses biochemical reactions mediated by isolated enzymes, organelles or whole cells to detect the effects of chemical compounds by electrical, thermal or optical signals" biosensor consists of basic elements, biological recognition element, signal transduction unit and signal processing unit (figure 1). Antibodies, receptor proteins, nucleic acids, enzymes, cell and organelles can act as biological recognition element of biosensor whose function is to detect the signal environment through some biochemical reactions. Transducer converts the particular biochemical reaction into electrical signal which further processed by the signal processing unit Since then, biosensors have been intensively studied and extensively utilized in various applications, ranging from public health and environmental monitoring to home land security and food safety .Biosensors can be categorized according to the basic principles of signal transduction and bio recognition elements.

In general scheme of a biosensor , the bio recognition element responds to the target compound and the transducer converts the biological response to a detectable signal, which can be measured electrochemically, optically, acoustically, mechanically ,calorimetrically, or electronically, and then correlated with the analyte concentration. Biological elements include enzymes, antibodies, micro-organisms, biological tissue, and organelles. When the binding of the sensing element and the analyte is the detected event, the instrument is described as affinity sensor when the interaction between the biological element and the analyte is accompanied or followed by a chemical change in which the concentration of one of the substrates or products is measured the instruments is described as metabolism sensor. Finally, when the signal is produced after binding the analyte without chemically changing it but by converting an auxiliary substrate, the biosensor is called catalytic sensor. The method of transduction depends on the type of physicochemical change resulting from the sensing event. Often, an important ancillary part of biosensor is a member the covers the biological sensing element and has a main functions of selective permeation and diffusion control of analyte, protection against mechanical stresses, and support for the biological element.

WORKING OF BIOSENSOR

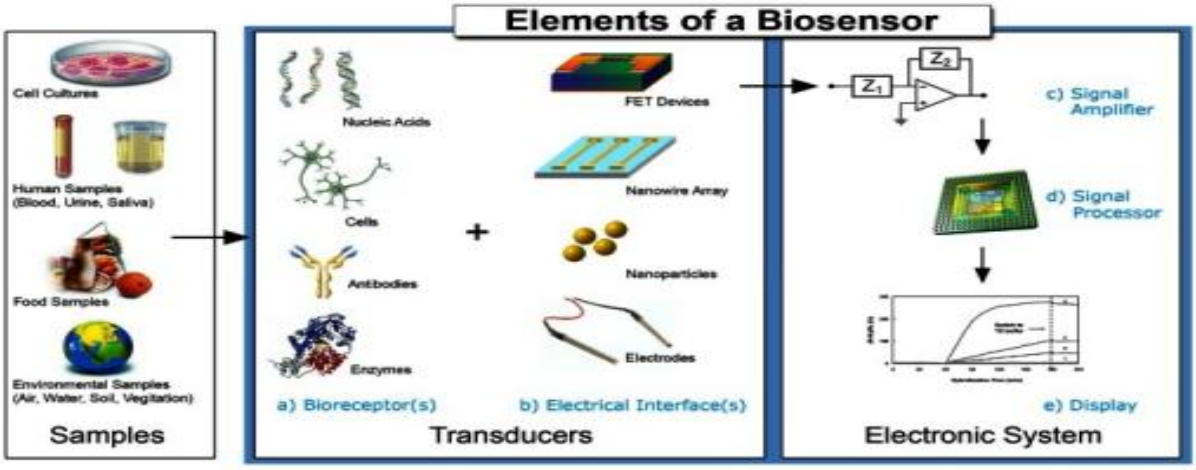


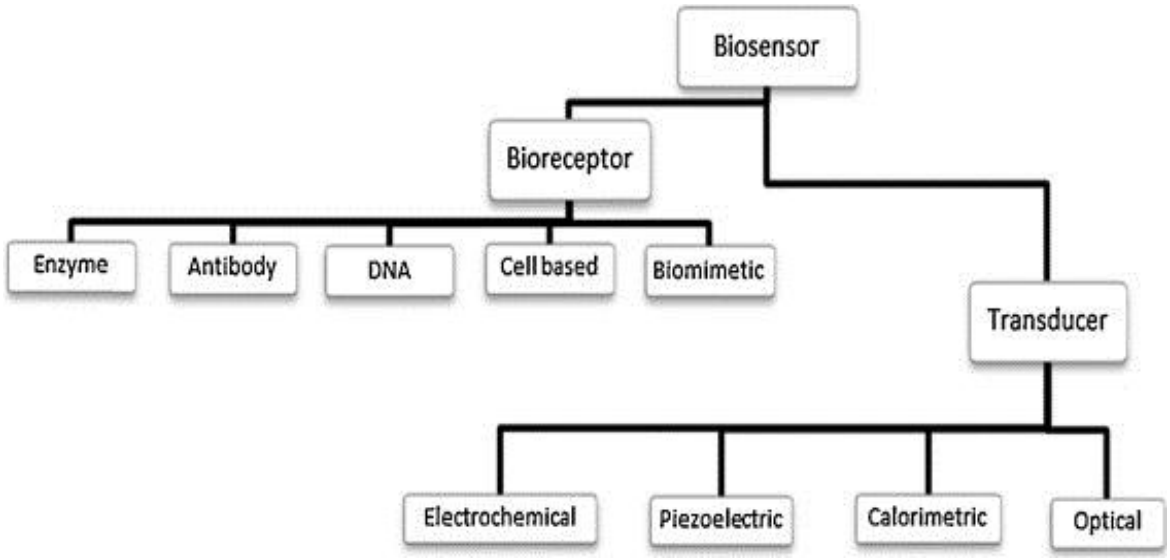
ELEMENTS OF BIOSENSOR

Biosensing elements are a set of biological entity, those are capable of carrying out specific group reactions or can bind with particular group of compounds, to yield a detectable signal that is read and transformed by the transducers. Commonly used biosensing elements are of two type's namely catalytic type and affinity type. The catalytic sensor include enzymes, microbes, organelles, cells, or tissues. The affinity type sensors are antibiotics, receptors, and nucleic acids. Enzymes like glucose oxidase (GOx), horseradish peroxide, and alkaline phosphates have been widely used in many biosensor studies.

CLASSIFICATION OF BIOSENSOR

Biosensor can be classified either by the type of biological signaling mechanism they utilize or by the type of signal transduction they employ.





BASED ON BIOLOGICAL SIGNIAL

The bio receptor or biological element is the significant distinguishing feature of a 15 biosensor the bio receptor comprises the recognition system of sensor towards the target 16 analyte. Essentially it is crucial for a bio receptor to be selective towards the 17 specific target analyte to prevent the interference by other substance from sample matrix 18 generally biosensors can be classified by the type of biological signaling mechanism they utilize the biological signaling used by biosensors can be divided in to 20 major mechanisms here, we will discuss each of mechanism in detail and their application

Enzyme based biosensor

Enzyme based biosensor are the earliest biosensor among all the other biosensor, these biosensors are first introduced by Clark and Lyons 1962 an amperometric enzyme electrode for glucose sensor which use 'soluble' enzyme electrode. Since the first biosensor, enzyme based biosensor has a massive growth in the usage of various application till 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 enzyme-based biosensors associate intimately a biocatalyst containing sensing layer with a transducer. enzymes like glucose oxidase Enzymes. Enzymes like glucose oxidase (GOx), horseradish peroxidase, and alkaline phosphatase have been widely used in many biosensor studies. The enzyme based biosensors utilize the principle of enzyme catalytic reactions accompanied by consumption or generation of detectable compounds like O2, CO2, H2O2, NH3, and H+ or by activation or inhibition of the enzyme activity by the analyte that can be easily detected by the transducers. These biocatalysts can be directly immobilized on the transducers by gel entrapment technology, covalent bonding, or physical adsorption. Enzyme based biosensors have been extensively studied because of their medical applicability, commercial availability, and ease of enzyme isolation and purification from different sources. The major advantage of using enzymes as biorecognition element is their aptness for modification of active sites by genetic engineering and thus modifying their substrate specificity to detect a wide range of analytes. Besides, the catalytic action of enzymes remains unaltered till the end of the reaction; the sensors can be used continuously. The limitations of these enzyme based biosensors are due to the limited enzyme stability and dependency of their activities on factors like pH, ionic strength, chemical inhibition, and temperature. Though de novo designing modifies the enzyme substrate specificity, at the same time it jeopardizes its kinetic property and reaction rate. Recent articles have updated various new strategies for making use of enzyme stabilization in enzyme based biosensors. Carbon nanotubes (CNTs) due to their excellent electroconductivity and tensile strength are very much suitable to act as a scaffold for

enzyme and forming a jumbled meshwork limits their usefulness in this technology. However, new approaches of integrating the CNT surfaces with biopolymers or using dissolved CNTs in a mixed solution of cyclodextrin and its prepolymers can maintain the bioactivity of the immobilized enzymes on it for a longer time. Such chemical modification can be utilized for fabricating more stable chemically modified electrode surfaces. Further modifications of CNTs have been successfully achieved in improved sensitivity by tailoring the thickness of scaffolds , covalent immobilization of organophosphorus hydrolase (OPH) enzymes , or covalent modification of glucose oxidase (GOx) on carboxy-functionalized grapheme sheets or graphemechitosan nanocomposite films.

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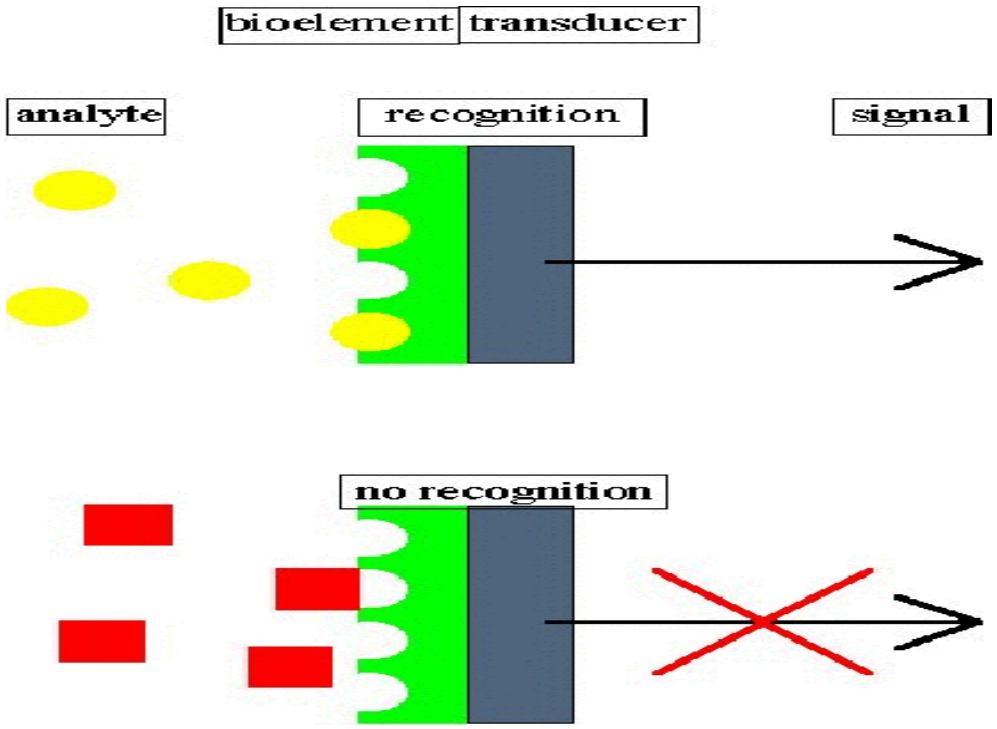
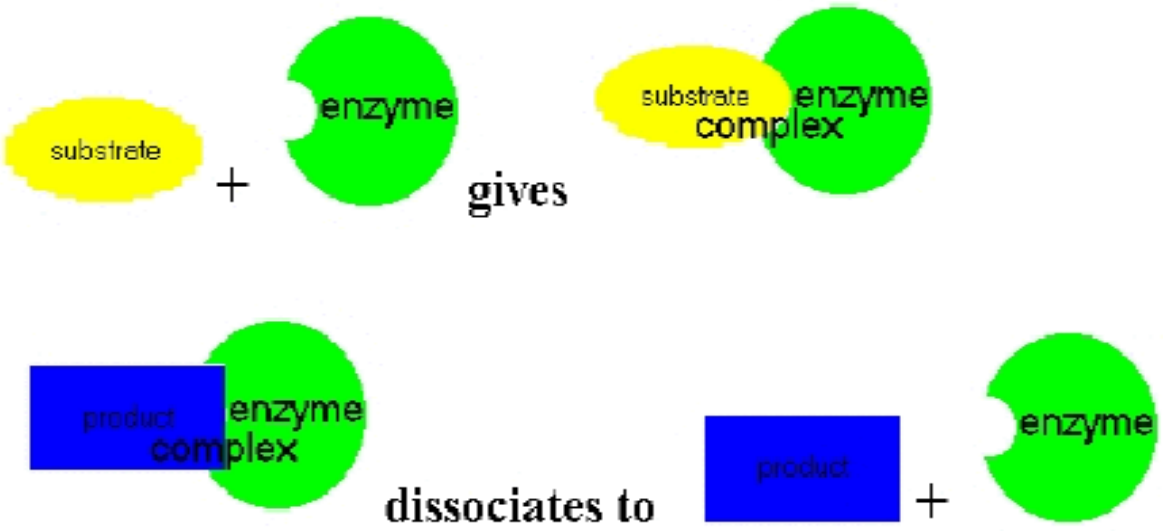


Besides CNTs, sol gels/hydrogels have been extensively used for providing an excellent conducive base for enzyme immobilization in constructing the third-generation enzyme based biosensors. These matrices are fabricated using metal oxide preparations such as silica-encapsulated OPH and gold nanoparticles (AuNPs) embedded with horseradish peroxidase (HRP) or GOx that immensely increase the sensitivity of detection range of blood glucose by the biosensor in a linear range of 0.1 to 10 mM. The immobilization of enzymes and their alignment on electrode surfaces can be modified by constructing apoenzymes that need a specific cofactor to function. Apoenzymes can be reconstituted and linked to cofactor functionalized nanostructures on the electron conducive area. Apo-GOx coupled to AuNPs integrated with cofactor flavin adenine dinucleotide (FAD) shows an enhanced electrical conductivity on the electrode surfaceimmobilization and enhance electron transfer to the electrodes . The tendency of CNTs deposition along the electrode surface.



Working Principle of Enzymes

Antibodies

The antibody is a critical part of immunosensors. These immunosensors utilize the principle of highly selective antigen-antibody reaction. The antibodies are immobilized on the surface of matrix in an array format and linked to the transducers covalently through amide, esters, or thiol. The antibodies interact with the analyte, allowing modification at the functional groups attached to transducer surface for detection and quantification. They are more specific and faster as compared to other traditional immunoassays like ELISA test. These are widely used for infectious disease diagnosis [37]. There are also some limitations such that antigen-antibody complex formed is irreversible and so a single array can be used only once. Antigen-antibody interaction also depends on the strength of affinity and the orientation of the antibody when it is immobilized on the surface

DNA/Nucleic acid sensor

Nucleic Acids. DNA is an appropriate candidate for biosensing because of its specific ability of base pairing with complementary sequence. Nucleic acid biosensors (NABs) employ short synthetic single-stranded oligonucleotide probe that is immobilized on the transducer to detect the DNA/RNA in the sample .These probes can be reused because the hybridization between probes to the sample can be denatured to reverse binding and then regenerated. But the limitation lies in the sample DNA quantity because, for accuracy of the result, the sample DNA content has to be multiplied to readable quantity by polymerase chain reaction (PCR) which is again time consuming. Researchers are working on developing biosensing elements to identify the natural DNA/RNA from the organism and in human blood with a view towards a successful application for point-ofcare testing of metabolic disorders (diabetes, cardiovascular diseases), infectious diseases (tuberculosis, hepatitis, dengue, cholera, and salmonellosis), cancer, and genetic diseases. At present, microRNA (miRNA) based biosensors act as an ultrasensitive tool to detect cancer associated miRNAs in serum sample

Cell based sensor

Cells have the ability to modify as per the surrounding environment for which they are subjected to be used as biosensing component. Adhesiveness to surface is another characteristic advantage that makes it a suitable candidate for immobilization on the matrix surface and attachment of receptors on cell membrane. They are often used in monitoring treatment effects of drugs, toxin levels, level of different stress factors, and organic derivatives. Tissues are advantageous over cells and organelles because of high content of enzymes, cofactors, higher activity, and stability. But they lack specificity because of presence of unwanted enzymes which leads to ambiguous catalytic reactions . Single-cell analysis of neuronal cells during neuronal regeneration can be achieved by quantitative measurement of cellular transmitter released by the cells trapped in a closed microchip close to a band of microelectrodes. Cell based microfluidic technology is most suitable for cell migration

assay and invasion assay applicable in drug screening. It can quantify the migrating cells in response to chemotactic gradient across a physical barrier. Breast cancer cell detection at single-cell resolution was achieved using high density electrochemical impedance biosensor array for tumor cell detection

A biomimetic biosensor

an artificial or synthetic sensor that mimics the function of a 22 natural biosensor. These can include aptasensors, where aptasensors use aptamers as the 23 biocomponent . Aptamers were reported for the first time in the early 24 1990s where described as artificial nucleic acid ligands. Aptamers were thus chemically 25 related to nucleic acid probes, but behaved more like antibody and showing surprising 26 versatility compared to other bio-recognition components . Aptamer are synthetic strands of nucleic acid that can be designed to recognize amino 28 acids, oligosaccharides, peptides, and proteins. An aptamer has few advantages over antibody 29 based biosensor such as high binding efficiency, avoiding the use of animal (i.e reduced 30 ethical problem), smaller and less complex, and etc. However, common challenge facing 31 aptasensor is that they inherent the properties of nucleic acids such as structural pleomorphic 32 and chemical simplicity which reduced the assay efficiency and also increase its production 33 cost. Subsequently, some effort has been directed towards characterization and optimization 10 1 of aptamer to overcome this limitation. Aptamer properties such as their high specificity, 2 small size, modification and immobilization versatility, regenerability or conformational 3 change induced by the target binding have been successfully exploited to optimize a variety of 4 bio-sensing formats . Aptamer based biosensor has been widely used in 5 various application. Recently sufficient progress has been made in biomimetics sensor and 6 aptasensor for clinical application (Vallet-Regi and Arcos 2008). This including clinical 7 diagnostics to detect pathogen, virus and infectious disease

Resonant Biosensors

In this type of biosensor, an acoustic wave transducer is coupled with an antibody (bio-element). When the analyte molecule (or antigen) gets attached to the membrane, the mass of the membrane changes. The resulting change in the mass subsequently changes the resonant frequency of the transducer. This frequency change is then measured.

Optical-detection Biosensors

The output transduced signal that is measured is light for this type of biosensor. The biosensor can be made based on optical diffraction or electrochemiluminescence. In optical diffraction based devices, a silicon wafer is coated with a protein via covalent bonds. The wafer is exposed to UV light through a photo-mask and the antibodies become inactive in the exposed regions. When the diced wafer chips are incubated in an analyte, antigen-antibody bindings are formed in the active regions, thus creating a diffraction grating. This grating produces a diffraction signal when illuminated with a light source such as laser. The resulting signal can be measured or can be further amplified before measuring for improved sensitivity.

Thermal-detection Biosensors

This type of biosensor is exploiting one of the fundamental properties of biological reactions, namely absorption or production of heat, which in turn changes the temperature of the medium in which the reaction takes place. They are constructed by combining immobilized enzyme molecules with temperature sensors. When the analyte comes in contact with the enzyme, the heat reaction of the enzyme is measured and is calibrated against the analyte concentration. The total heat produced or absorbed is proportional to the molar enthalpy and the total number of molecules in the reaction. The measurement of the temperature is typically accomplished via a thermistor, and such devices are known as enzyme thermistors. Their high sensitivity to thermal changes makes thermistors ideal for such applications. Unlike other transducers, thermal biosensors do not need frequent recalibration and are insensitive to the optical and electrochemical properties of the sample. Common applications of this type of biosensor include the detection of pesticides and pathogenic bacteria. 3.4 Ion-Sensitive Biosensors These are semiconductor FETs having an ion-sensitive surface. The surface electrical potential changes when the ions and the semiconductor interact. This change in the potential can be subsequently measured. The Ion Sensitive Field Effect Transistor (ISFET) can be constructed by covering the sensor electrode with a polymer layer. This polymer layer is selectively permeable to 4 analyte ions. The ions diffuse through the polymer layer and in turn cause a

change in the FET surface potential. This type of biosensor is also called an ENFET (Enzyme Field Effect Transistor) and is primarily used for pH detection.

Electrochemical Biosensors

Bioelectroanalysis with electrochemical biosensors is a new area in rapid development within electroanalysis. In biosensor development studies, suitable bioreceptor molecule, suitable immobilization method and transducer should be selected firstly Bioelectroanalytical sensors permit the analysis of species with great Specificity, very rapid, sensitive, highly selective and cheap cost in principle. They can be used in clinical analysis, in on-line control processes for industry or environment, or even in vivo studies [6]. The difference between biosensor and physical or chemical sensors is that its recognition element is biological. The investigated bioelectrochemical reaction would generate a measurable current (amperometric detection), a measurable potential or charge accumulation (potentiometric detection) or measurable conductivity change of a medium (conductometric detection) between electrodes. When the current is measured at a constant potential this is referred to as amperometry. If an electrical current is measured while controlled variations of the potential is being applied, this is named as voltammetry. Potentiometric, amperometric and conductometric measurement techniques forms the kinds of electrochemical biosensors. Potentiometric sensors have an organic membrane or surface that is sensitive to an analyte. The reaction between them generates a potential (emf) proportional to the logarithm of the electrochemically active material concentration. This potential is compared with the reference electrode potential. Enzyme immobilized electrodes reacts with substrate and products are detected by electrodes. Amperometric sensors measure the current change resulted by chemical reaction of electroactive materials while a constant potential is being applied. The change of the current is related to the concentration of the species in solution. Generally biological compounds (glucose, urea, cholesterol, etc.) are not electroactive, so the combination of reactions to produce an electroactive element is needed. This electroactive element leads a change of current intensity. This change is proportional to the concentration of analyte. Conductometric biosensors can measure the change of the electrical conductivity of cell solution. Most reactions involve a change in the composition of solution. Thus conductometric biosensors can detect any reactive change occuring in a solution. Electrochemical biosensors have advantages that they can sense materials without damaging the system. The use of biosensors for industrial and environmental analysis is very important. The control of food manufacturing processes, evaluation of food quality, and control of fermentation processes and for monitoring of organic pollutants are some of the applications of biosensors. The present popularity of analytical biosensors is due to their specific detection, simple use and low cost. For example an electrochemical biosensor can be used to detect Salmonella and E. coli O157:H7 in less than 90 min. Electrochemical biosensor studies are performed with electrochemical cells.

Electrochemical biosensors are mainly used for the detection of hybridized DNA, DNA-binding drugs, glucose concentration, etc. The underlying principle for this class of biosensors is that many chemical reactions produce or consume ions or electrons which in turn cause some change in the electrical properties of the solution which can be sensed out and used as measuring parameter. Electrochemical biosensors can be classified based on the measuring electrical parameters as:

(1) Conductometric,
(2) Amperometric and
(3) Potentiometric.

A comparative discussion of these three types of electrochemical biosensors is given in Table

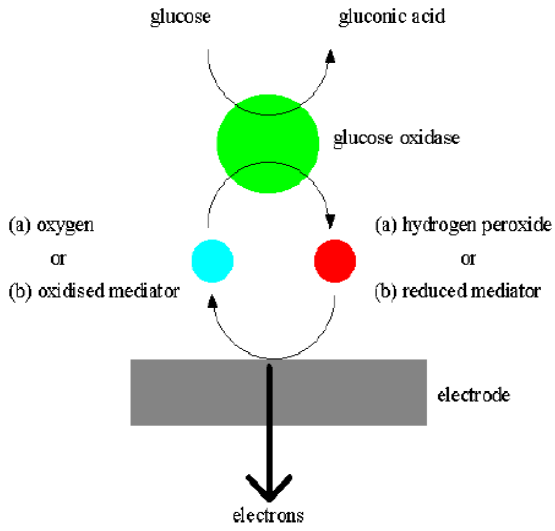
1 Conductimetric The measured parameter is the electrical conductance / resistance of the solution. When electrochemical reactions produce ions or electrons, the overall conductivity or resistivity of the solution changes. This change is measured and calibrated to a proper scale. Conductance measurements have relatively low sensitivity. The electric field is generated using a sinusoidal voltage (AC) which helps in minimizing undesirable effects such as Faradaic processes, double layer charging and concentration polarization.

2 Amperometric This high sensitivity biosensor can detect electroactive species present in biological test samples. Since the biological test samples may not be intrinsically electro-active, enzymes are needed to catalyze the production of radio-active species. In this case, the measured parameter is current.

3 Potentiometric In this type of sensor the measured parameter is oxidation or reduction potential of an electrochemical reaction. The working principle relies on the fact that when a ramp voltage is applied to an electrode in solution, a current flow occurs because of electrochemical reactions. The voltage at which these reactions occur indicates a particular reaction and particular species.

4. Glucose Biosensors

The most commercially successful biosensors are amperometric glucose biosensors. These biosensors have been made available in the market in various shapes and forms such as glucose pens, glucose displays, etc. The first historic experiment that served as the origin of glucose biosensors was carried out by Leland C. Clark. He used platinum (Pt) electrodes to detect oxygen. The enzyme glucose oxidase (GOD) was placed very close to the surface of platinum by physically trapping it against the electrodes with a piece of dialysis membrane. The enzyme activity changes depending on the 5 surrounding oxygen concentration. shows the reaction catalyzed by GOD. Glucose reacts with glucose oxidase (GOD) to form gluconic acid while producing two electrons and two protons, thus reducing GOD. The reduced GOD, surrounding oxygen, electrons and protons (produced above) react to form hydrogen peroxide and oxidized GOD (the original form). This GOD can again react with more glucose. The higher the glucose content, more oxygen is consumed. On the other hand, lower glucose content results in more hydrogen peroxide. Hence, either the consumption of oxygen or the production of hydrogen peroxide can be detected by the help of platinum electrodes and this can serve as a measure for glucose concentration. Disposable amperometric biosensors for the detection of glucose are also available. The typical configuration is a button-shaped biosensor consisting of the following layers: metallic substrate, graphite layer, isolating layer, mediator modified membrane, immobilized enzyme membrane (GOD), and a cellulose acetate membrane. This biosensor uses graphite electrodes instead of platinum electrodes (as originally used by Clark). The isolating layer is placed on the graphite electrodes which can filter out certain interfering substances (ascorbic acid, uric acid) while allowing the passage of hydrogen peroxide and oxygen. The mediator modified membrane helps in keeping the GOD membrane attached to the graphite electrode when the electrochemical reaction takes place at a specific applied potential. The cellulose acetate outer layer placed over the GOD membrane also provides a barrier for interfering substances. The amperometric reading of the biosensor (current versus glucose concentration) shows that the relationship is linear up to a specific glucose concentration. In other words current increases linearly with glucose concentration, hence it can be used for detection. The current and future applications of glucose biosensors are very broad due to their immediate use in diabetic self-monitoring of capillary blood glucose. These types of monitoring devices comprise one of the largest markets for biosensors today and their existence has dramatically improved the quality of life of diabetics



CONCLUSION

The past decade has seen great advancements in the field of biosensor along many fronts. This dynamic tool has been applied in many area of life science research, health care, environmental, food and military application. Biosensor technology has received heightened interest over the past decade, since it is a promising candidate for lower detection limit with rapid analysis time at relatively low cost. However, the review shows that there is a lot of studies have been undertaken using indirect measurement with simple clean buffer solution instead 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 biochip which integrated with 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 will allow the development of extremely low cost, disposable biochips that can be used for in-home medical diagnostics of diseases without the need of sending samples to a laboratory for analysis which time consuming. Hence biosensors offer an exciting alternative to traditional methods, allowing rapid "real-time" and multiple analyses for detection, diagnosis and estimation of any sample. For medical applications nanobiosensors, integrated biosensors and biochips will reduce the cost and time thereby increasing the efficiency of the tests. Also disposable biochips offer an added advantage of in-home medical diagnostics of diseases without the need of sending samples to a laboratory for analysis. In the past 40 years various biosensors have been researched and developed encompassing a wide range of applications but the number of commercially available biosensors is limited. Nevertheless, biosensor technology presents an opportunity for the development of robust, low cost, specific detection and analyses. Future prospects of biosensor technology, with special emphasis on the development of sensing elements and transducers are under current research.

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