Journal of Biotechnology and Biomaterials

Bhanot, J Biotechnol Biomater 2022, 12:10

Review Article **Open Access**

Biosensors: Status and Perspectives

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Abstract

Biosensor technology is a comparatively new and revolutionary technology. In recent times there has been an increase in the demand for the development of low cost, rapid and simple devices which can give results in the real time and biosensors have the potential to fulfil all these requirements. Biosensors have two main components, one is the biological recognition element where the instrument detects the analyte molecule, and the other is the transducing system that converts biological reaction into electrical signal which is the output of biosensor. Depending on the type of bio recognition element and the type of transducer employed, various types of biosensors can be developed like electrochemical, optical, piezoelectric biosensors. Amalgamation of nanotechnology in this field has led to the development of better, more accurate miniature versions of biosensors. Biosensors have a wide range of applications, and can be used in the medical field for disease diagnosis, drug discovery, in environmental monitoring of pollutants, identification of pathogens or contaminants in the food, fermentation and beverage industries, in agriculture and in the defense sector, etc.

Keywords: Biosensors; Transducer; Surface plasmon resonance

Introduction

Biosensors are the analytical devices that can turn a biological response into an electrical signal, allowing the identification of biological or chemical substances. The signal it generates contains all the information required to understand the process under examination. The biological reaction occurs in close proximity to the transducer to make sure that the majority of the biological reaction is detected. Whole cells, enzymes, nucleic acids, or antibodies can act as the bio recognition elements and are combined with the transducer element. These biosensor devices provide very rapid, more specific and selective results [1-5].

Biosensors can be used in a variety of applications ranging from handheld medical diagnostic devices to devices that can monitor environmental pollutants in the field or detection of pathogens in the food industry [6].

Literature Review

Biosensors are preferred over conventional analytical techniques like immunoassays, biochemical assays or physical instruments like spectrophotometer, PCR etc. for the detection and estimation of certain analytes, due to the following reasons (Figure 1):

- The biological sensing element occupies a small space and is extremely sensitive, allowing for the examination of even very small quantities of molecules.
- The immobilized biological material in a biosensor is close to the transducer, allowing the biochemical signal to be promptly translated into an electrical signal.
- The biological molecules which are usually expensive can be reused in a biosensor due to the immobilization technique.
- Biosensors can be customized to meet specific requirements and can be either extremely specific or broad spectrum.

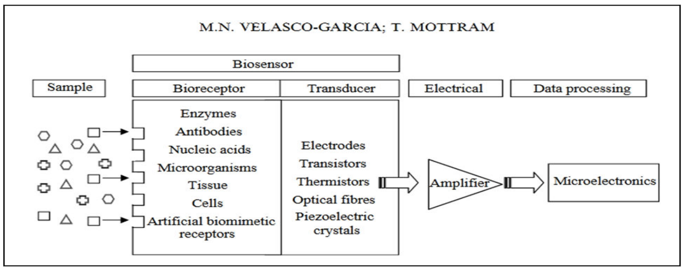

Figure 1: Principle and operation of a biosensor.

Principle: A biosensor is made up of two parts: A biological component that detects the presence and concentration of a material and a transducer device. The sample is permitted to pass through a membrane allowing for selection while interfering molecules are kept outside the barrier. After that, the sample interacts with the biological sensor to produce a signal which could be an electric current/charge, heat, gas or an appropriate chemical. After passing through another membrane, the product reaches the transducer, which turns the biochemical signal to an electrical signal that may be amplified and read on a digital monitor or recorded on recorders. This enables for the determination of a substrate's concentration without the need for processing, avoiding sample consumption [7-10].

History: The first "real" biosensor for measuring dissolved oxygen in blood was invented by Leland C Clark, Jr. in 1956. He is renowned

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Received: 27-Jun-2022, Manuscript No. JBTBM-22-67750; **Editor assigned:** 30-Jun-2022, PreQC No. JBTBM-22-67750; **Reviewed:** 14-Jul-2022, QC No. JBTBM-22-67750; **Revised:** 26-Aug-2022, Manuscript No. JBTBM-22-67750; **Published:** 02-Sep-2022, DOI: 10.4172/2155-952X.1000299

Citation: Bhanot Y (2022) Biosensors: Status and Perspectives. J Biotechnol Biomater 12: 299.

as the "Father of Biosensors" and his oxygen electrode, the "Clark electrode" bears his name. Leland Clark, in 1962 coated and immobilized the enzyme "glucose oxidase" in a gel on the oxygen electrode (amperometric biosensor) to measure blood glucose [11-13].

Yellow spring instruments in 1975 developed the primary commercial biosensor. Around 1976, the first microbial biosensor was developed. And in 1977, Karl Cammann coined the term "biosensor". In the 1980's, "whole cell biosensors" were also created, which utilize whole microbial cells or organelles. Surface plasmon resonance technique was developed in the year 1983 by Liedberg. And in 1992, handheld biosensors were developed by i; STAT.

Immobilization of bio-receptor: The immobilization of the bioreceptor close to the transducer is a crucial aspect of biosensor manufacturing. The target molecule, the matrix, and the coupling mechanism are all important components in immobilizing a molecule. During immobilization, two major factors have to be considered: operating stability and long-term use [14-17].

Physical adsorption, entrapment, covalent bonding or cross-linking is the methods that can be used to immobilize the target. Physical adsorption uses a combination of van der Waals and hydrophobic forces, hydrogen bonding, and ionic interactions to bind bioreceptor to the surface of the transducer. Chemical attachment commonly involves covalent bonding to the transducer surface by appropriate chemicals.

The immobilization allows the expensive biological molecule to be used again and again and also helps in maintaining close proximity between the transducer and the biological material for proper functioning of biosensors.

Characteristics of an ideal biosensor:

- The capacity of a sensor to respond only to the target analyte is known as selectivity. The desired trait is a lack of reaction to other interfering substances.
- The sensitivity of a sensor is its responsiveness to a change in analyte concentration per unit change.
- The sensor's response time is the amount of time it takes to provide responses.
- The change in its baseline or sensitivity over a set length of time is referred to as stability.
- The concentration range over which the sensor's sensitivity is good is called range.
- The detection limit of an analyte is the lowest concentration at which it produces a quantifiable response.
- The sensor's lifetime is the amount of time it can be used before its performance deteriorates significantly.

Key components of a biosensor: Bio-receptor, transducers, electronics and displays are the major components of a biosensor (Figure 2).

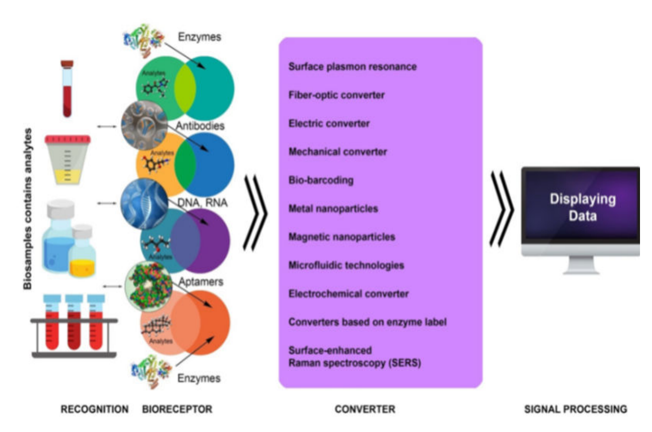

Figure 2: Schematic diagram of a biosensor.

Bioreceptor: A bioreceptor is a molecule that uniquely recognizes the analytes. Bioreceptor can be a biological molecule like whole cells, DNA (Deoxyribonucleic Acid), RNA (Ribonucleic Acid), enzymes and antibodies [18].

Transducer: A transducer is a component that transfers one type of energy into another. In a biosensor, the transducer's role is to convert the bio-recognition action into a measurable signal. This process of energy conversion is known as signalization number of analytes bioreceptor interactions is usually proportionate to the amount of optical or electrical signals produced by most transducers.

Electronics: This portion of a biosensor is responsible for processing and displaying the signal that has been transduced. It is made up of a complicated electrical circuitry that conducts signal conditioning operations such as amplification and digital signal transformation. The biosensor's display device quantifies the processed signals [19].

Display: Display refers to the screen through which the user can interpret the outcome or result of the bio sensing reaction. It usually displays some numbers, values or curves according to the needs of the user. It consists of both hardware and software which helps the user to better understand the biosensor result.

Nanotechnology in biosensors: Nanotechnology has advanced tremendously in recent years and so is their application in biosensors. Gold nanoparticles, carbon nanotubes, magnetic nanoparticles and quantum dots are among the nanomaterials being researched for biosensor applications. These nanomaterials can improve the sensitivity and specificity of detection in biosensors. They can help in the efficient identification of small molecules, DNA, RNA, proteins, pesticides, glucose [20].

Types of biosensors

Biosensors are often classified according to the type of transducer or bioreceptor employed. The main categories of biosensors based on the transducer used include electrochemical, piezoelectric, calorimetric and optical biosensors. The biosensor categories based on bio recognition elements include enzymatic, cell based, antibody based, microbial, DNA biosensors, etc. These biosensors are commonly used for various purposes like in medical diagnostics, environmental monitoring, and food industries. Some of the main types of biosensors are:

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Electrochemical biosensors: Electrochemical biosensors are the biosensors in which charge is transferred from the working electrode to the reference electrode. Chemical reactions between immobilized bioreceptor and the target analyte generate or utilize ions or electrons altering the solution's electrical properties. Electrochemical biosensors appear to be better suitable for field monitoring applications and miniaturization for implantable biosensor manufacturing. Because of their great sensitivity, simplicity and low cost electrochemical transducers are the most frequently used transducers in the biosensors. Amperometric and potentiometric transducers are the most popular electrochemical transducers.

- These biosensors are based on the principle of oxidation or reduction of electroactive biological species which leads to the generation of current. Therefore, in these types of biosensors current generated is measured which is directly proportional to the concentration of the analyte. These biosensors usually contain 3 electrode cells. Between a working electrode and a reference electrode, a constant voltage is maintained during amperometric measurement. Clark's oxygen electrode is an example of an amperometric biosensor. The inexpensive cost and usage of disposable electrodes are the key advantages of this transducer.
- Under zero flow of current, the voltage between two electrodes is measured by potentiometric transducers. A linear logarithmic relationship exists between the charge generated at the electrode and the activity of the ion of interest. It is a non-destructive approach because the analyte is not consumed in this instrument. Field Effect Transistors (FETs) is one type of potentiometric transducer that is widely used in biosensors.

Calorimetric/thermometric biosensors: Calorimetric transducers are capable of sensing the heat of a biological reaction. The analyte concentration is proportional to the heat of the reaction. The heat of reaction is detected when the analyte comes into contact with the bioreceptor. Because all biological reactions are exothermic, micro fabricated thin-film thermophiles can be employed to create biosensors that are unaffected by the sample's chemical characteristics. These biosensors are in the initial stages of development and will definitely improve in the future. A good example of calorimetric biosensor is the cholesterol biosensor which makes use of enzyme cholesterol oxidase (53 kJ/mol).

Piezoelectric (Mass-Sensitive) biosensors: The basis of piezoelectric transducers is the coupling of bioreceptor with piezoelectric elements, which is typically a quartz crystal covered in gold electrodes. Quartz crystals, for example, have no center of symmetry and emit an electrical signal when mechanically pressured. A crystal oscillates at a specific frequency that can be influenced by its surroundings. When a crystal is coated with a substance, the actual frequency is determined by the crystal's mass as well as the coating. The mass of the analyte adsorbed onto the crystal surface may be calculated using the resonance frequency, which can be measured with excellent precision. The capacity to detect binding events in real time, providing for the examination of affinity interactions in terms of their kinetics, is one of this biosensor's major benefits, as is the inexpensive cost of the requisite apparatus. The requirement of calibrating the crystal and the possibility of variability while covering the surface with antigen or antibody are the limitations of this transduction approach.

Optical biosensors: Optical sensors direct light to the sensing film using optical fibers or planar waveguides chemiluminescence, light absorbance, fluorescence, surface plasmon resonance, phosphorescence, photo thermal approaches, light polarization and rotation, and total internal reflectance are some of the techniques used by optical transducers to check for the presence of specific analyte. This approach can be used to evaluate both catalytic and affinity reactions. Between two mediums of differing densities, the refractive index of the surface changes and as a result of the interactions, the fluorescence or absorbance changes. For example, the refractive index of the medium in contact with a metal layer alters when antibodies bind to that layer. When antigen binds to antibodies that have previously been bound on this layer, the refractive index changes even more. Fluorescence/absorbance is used to assess changes in refractive index as a result of reactions. These optical biosensors are non-electrical devices that provide significant safety benefits in physiological applications. Furthermore, optical fiber probes provide a greater degree of mechanical flexibility while maintaining a small size and a low cost, disposable design. Although optical biosensors are desirable for directly monitoring an outsized number of samples, miniaturization for introduction into the bloodstream is incredibly challenging. To detect changes in signal, most optical transduction methods still require the use of a spectrophotometer (Figure 3).

Surface plasmon resonance:

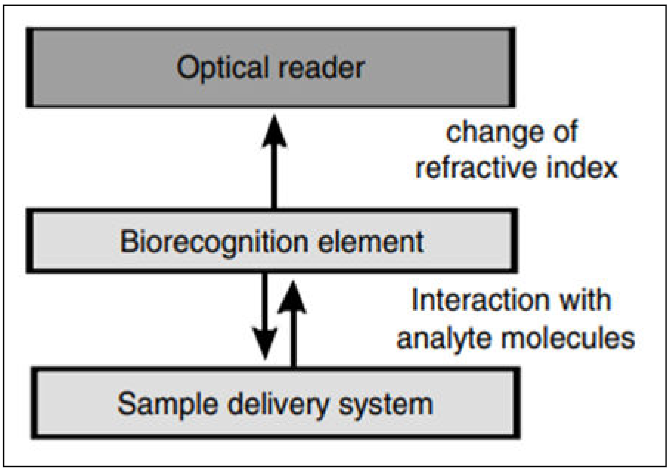

Figure 3: Principal components of SPR affinity biosensor.

Surface Plasmon Resonance (SPR) biosensors are based on optical biosensor technology. They track the changes in surface optical properties. A biological molecule that is specific to the analyte molecule is immobilized at the sensor's metal surface. Then the analyte molecule present in the sample solution binds to the bio recognition element. This leads to change in the solvent's refractive index near the surface of the sensor, which is detected and measured by the optical reader. These biosensors are mainly used to measure the biomolecular interactions in real time. When molecules attach to the surface, the refractive index near the surface changes, affecting the angle of minimum reflected intensity.

Real time analysis of binding reactions is possible with these biosensors and that too with no need of labelling. As a result, many macromolecules like lipids, proteins, etc., as well as macromolecules like cells or viral particles, etc. can all be studied using SPR biosensors.

Enzymatic biosensors: Enzymatic biosensors are the ones that make use of enzymes as the biological recognition element coupled to a suitable transducer. The enzymes should be capable of catalyzing a certain biological reaction and be stable under the biosensor's usual working conditions in order to function. The main enzymes used in these biosensors are oxidoreductases and hydrolases. Enzymes were widely used for the development of the first generation of biosensors due to their high specificity and selectivity and commercial availability. Immobilization of enzymes on transducers has helped in maintaining the enzymatic activity for longer periods as the same enzyme can be used again and again. They find wide applications in the food industry as they help in detecting toxic compounds in the food like pesticides, heavy metals, etc.

Immunosensors: Immunosensors are the biosensors that are based on the interactions between antigens and antibodies and the immunochemical response is linked to the transducer. Antibodies are most often immobilized in the immunosensors and are used as the biological recognition molecule integrated with a suitable transducer. They easily recognize and bind to the specific antigen leading to the generation of signal that is later read and displayed by the biosensor device. Antibodies are essential components of immunosensors because they provide sensitivity and specificity.

Analytes containing a protein mixture can also be immobilized in an array format on an antibody coated support surface. A biotin labeled antibody is used in conjunction with an enhanced chemiluminescence or fluorescence detection system to identify the protein in analytes. The precise amount of protein can be quantified. Only one immunoassay can be performed due to the nearly irreversible nature of the antibody-antigen complex. Immunosensors are also being used to build point of care devices. They can help in the early detection of cancer.

DNA biosensors: DNA biosensors are based on nucleic acid recognition mechanisms and play a significant role in environmental, clinical and food analysis. Single stranded DNA probes can be immobilized on different electrodes and hybridization between DNA probes and complementary DNA strands can be measured using electroactive indicators. Hybridization is frequently detected using changes in current signal generated by a redox indicator (that recognizes dsDNA) or other hybridization related changes in electrochemical methods. They are constantly being developed to diagnose genetic and infectious disorders in a quick, easy, and cost-effective manner.

DNA biosensors are improving with advancement in technology. One such example is the development of PNA (Peptide Nucleic Acid) in which a pseudo peptide chain is present instead of the regular sugar phosphate backbone. This PNA chain can be immobilized onto the surface of any transducer thereby making DNA biosensors highly selective and specific.

The DNA based biosensor also serves as a supplement to the research of biomolecular interactions of compounds with double stranded DNA. They can also be used to test and examine the effects of health hazardous compounds and oxidizing substances on ds DNA. The complementary coupling between the specific single stranded DNA (ssDNA) sequences (target) within the analyte, that also contains non-complementary ssDNA strands, and the specific single stranded DNA sequences (probe) immobilized onto the solid support (the transducer) is the basis of operation of a DNA hybridization biosensor.

Cell based biosensors: Cell Based Biosensors (CBBs) are the biosensors which are based on using whole cells that have been genetically modified and are used for detecting the analytes with high sensitivity and specificity. These are also cost-effective and can give result in real-time. The cell based biosensor can detect biochemical effects directly *via* living cells and convert these effects into digital electrical signals *via* sensors or transducers and is one of the most durable biosensors. CBBs may constantly detect biomolecules and communicate this information by coupling natural transcriptional responses to production of colorimetric, fluorescent or bioluminescent reporter genes.

These cell based biosensors may incorporate mammalian cells, or microbial cells like that of bacteria, algae or fungi. Biosensors embedded in mammalian cells have the unusual benefit of responding in a way that can reveal information about an analyte's physiological effect. The limited specificity of whole cell biosensors compared to pure enzyme biosensors is a drawback. This is primarily owing to unfavorable side reactions catalyzed by other enzymes within a cell.

The most extensively used whole cell biosensor is the microbial biosensor, which measures different variables such as growth inhibition, enzyme inhibition, and cell viability to report carcinogenicity and toxicity using genetically modified microbes.

Microbial biosensors: Microbial biosensors are composed of natural or genetically engineered microorganisms integrated with a suitable transducer that give signals upon detection of analytes or other external stimuli. Advancement in synthetic biology has resulted in the production of better microbial biosensors as it has helped in genetically modifying the microorganisms. Microorganisms have a lot of advantages over other biological entities like, they are abundantly present in the environment, easily adapt to unfavorable conditions, can metabolize or degrade many toxic compounds and most importantly can be easily modified genetically through recombinant DNA technology.

The most important components of microbial biosensors are the sensing elements and the reporter. Most of the microbial biosensors make use of bacteria and are designed in such a way that the analyte induces the promoter of the reporter gene, leading to the expression of the gene and produces some output signal in the form of fluorescence or light. The best example of the reporter gene is the “lux” gene, found in lux operon in the bioluminescent bacterium *Vibrio fischeri* which are found in marine environments. These genes code for luciferase that is responsible for producing light.

Escherichia coli, *Pseudomonas putida*, *Staphylococcus aureus* are some of the bacteria that are genetically engineered to be used as biosensors.

Microbial biosensors are widely used in the environmental field, like measuring the BOD value of wastewater. They also have applications in biomedicine; they help in identification of certain important biomarkers of diseases, thereby helping in diagnosing and treating the disease. They are also used in food and fermentation industries for detection of pathogens or other contaminants in food.

Discussion

Applications

Biosensors can find its application in various fields like medicine (in diagnostics etc.), in environmental monitoring, food and fermentation industries, agriculture, plant biology sector, in defense sector and in various biotechnological researches, etc. Biosensors are getting integrated with smartphones for point of care monitoring of health. The application of biosensors in these various fields can make life easier and will improve quality living.

Environmental monitoring: Due to the increase in population and advancement in technology, environmental pollution is increasing day by day. Biosensor is a very convenient and significant tool that can be widely used for environmental monitoring. They are most commonly used to detect and identify contaminants in the environment.

They detect and measure toxic chemicals, pesticides, heavy metals, pathogenic microorganisms, hazardous industrial chemicals, etc. Biosensors can be employed in land, air or water and can also be used to determine the Biological Oxygen Demand (BOD) in the wastewater.

Herbicides can be detected using an electrochemical biosensor made with silicon micro processing technology that analyses the photosynthetic and metabolic processes of algae.

Genetically engineered microbial biosensors are widely employed to detect pollutants and that too with high accuracy. In one study, the plasmid containing TOL operon was combined with the gene for firefly luciferase and introduced into *E coli*. This modified organism was studied for its ability to detect benzene compounds in the environment. This modified organism was studied for its ability to detect benzene compounds in the environment.

Genetically modified microbes and cell based biosensors are well suited for the detection of Volatile Organic Compounds (VOC), which is an important environmental pollutant.

Pseudomonas putida is a natural bacterium that helps in the identification and detection of lead and benzene. Algae (e.g. Spirulina subsalsa) are also used in the cell based biosensors for pesticides, insecticides, and heavy metal detection.

Thiobacillus ferrooxidans is a bacterium that has the ability to oxidize Fe (II) in the presence of sulfate. Therefore, this microbe-based biosensor can be used to detect sulfate in rainwater.

Some industries deliberately pollute water streams with hazardous chemicals that make the water unfit for consumption. Biosensors can detect these chemicals, e.g. they can detect surfactants, phenols, PCBs (Polychlorinated Biphenyls), heavy metals, etc. Cyanide is one of the most toxic chemicals found in the polluted river water that causes harm to many living organisms. Therefore, biosensors are beneficial as they can rapidly detect cyanide and other contaminants e.g. biosensor based on cyanide induced inhibition of respiration of yeast (*Saccharomyces cerevisiae*).

Whole cell biosensors have been developed to detect heavy metal ions, for example, genetically modified luminescent bacteria like *Vibrio fischeri* based biosensors. DNA biosensors can also be utilized to monitor the pollutants in the sample. Massive research is being carried out in Europe for developing biosensors to monitor environmental pollution.

Biosensors in medical field: Biosensors have one of the most important and best applications in the medical field. They are widely used in biomedical, pharmaceutical and health care sectors. Infectious disease screening, prophylaxis, chronic disease therapy, detection of pathogenic microorganisms, cardiovascular disease diagnosis, cancer diagnosis, drug discovery and patient health surveillance are all applications of biosensors and hence biosensors can help in improving the healthcare system. Biosensors are extremely useful in the medical field since they may aid in the rapid detection of a variety of diseases, as well as in the treatment planning. One of the most prevalent applications of biosensors in medicine is the detection of biomolecules that are either disease indicators or therapeutic targets. Nowadays simple devices are being developed that incorporate biosensors that can be used even at homes to monitor one's own health. Point of care devices are being developed that can monitor one's own health at any place and at any time. Biosensors are proved to be very good point of care devices and can help in the diagnosis and monitoring of various diseases.

Glucose biosensors: Glucose biosensors are the most used and sold biosensors throughout the world. The glucose biosensor is critical in the diagnosis and treatment of diabetes. Diabetes mellitus is chronic and one of the most prevalent diseases in the modern world. It is caused due to the defective insulin production by beta cells of pancreas, leading to high glucose levels in the blood. Therefore, diabetes can be diagnosed by monitoring the blood glucose levels with the help of biosensors.

Clark developed the first electrochemical based glucose biosensor and since then, many biosensors have been developed.

Glucose oxidase is a key enzyme that acts as a bioreceptor molecule and is widely used in many commercial glucose biosensors. This enzyme catalyzes the oxidation of glucose; it converts glucose into gluconic acid and hydrogen peroxide using oxygen as an electron acceptor. Flavin Adenine Dinucleotide (FAD^+) acts as a redox cofactor. FAD^+ acts as an electron acceptor and thus, gets reduced to FADH-2 and upon further reaction with oxygen, FAD^+ is regenerated. Using a Clark oxygen electrode, glucose oxidase may be immobilized close to an electrode and the depletion of oxygen can be measured. It is clear from this reaction scheme that glucose can also be measured by this method. Since the enzymatic activity produces hydrogen peroxide, it must be oxidized. This is proportional to the amount of glucose in the blood.

Nonenzymatic glucose biosensors are widely used and are based on glucose electrochemistry (oxidation/reduction). For glucose monitoring, electrochemical approaches, particularly amperometric ones, have been frequently used. Because of their strong electro catalytic activity, high sensitivity and good selectivity to the electro-oxidation of glucose, a variety of metal materials, such as noble metals (e.g. Au and Pt) and their composites, have been widely used as electrode materials in nonenzymatic glucose sensing.

COVID-19 diagnosis: Coronaviruses are a group of RNA viruses that cause respiratory disorders in humans and animals. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) has caused a pandemic that started in 2019 and has resulted in the death of thousands and infected millions of people around the world. Virus is spreading at an alarmingly high rate and more and more people are contracting the virus. There is shortage in the testing facilities and this leads to asymptomatic people to pass on the virus to other non-infected people. Also, people need to go to the hospitals for testing which makes hospitals very crowded and a high risk zone for other patients. Hence, there is an urgent need to develop a faster diagnostic test so that infection rate can be reduced.

Biomarkers specific for COVID-19 that are used for the diagnosis, includes RNA, antigens, antibodies, cytokines. The most common test for the diagnosis of COVID-19 is the RT-PCR test. In this test, RNA is extracted from the sample and is first converted into cDNA. This cDNA is then amplified with the help of a PCR machine. This test is not sufficient in the time of pandemic as it is time consuming and experts are required to perform it.

For viral RNA detection, lateral flow technology can also be used as a simple bio sensing technique that can be combined with nucleic acid testing methods. For SARS-CoV-2a CRISPR/CAS-9 (Clustered Regularly Interspaced Short Palindromic Repeats) based biosensor with a lateral flow assay was developed recently that gives the result in roughly 10 minutes.

Biosensors have shown very promising results as they can give results in real time and the test can be conducted even at home (point of care devices) and there is no need to go to the hospital. Hence, the risk of spreading the virus is also reduced.

The presence of Reactive Oxygen Species (ROS) in sputum was employed as a biomarker in the creation of a real-time electrochemical biosensor for the diagnosis of COVID-19.

Biosensors for food and fermentation industry: There is an increasing risk of contamination of food due to the presence of microbial pathogens which may cause serious health problems to people. Therefore, there is a burning pressure for worldwide food safety improvements. Unfortunately, detecting and identifying these harmful microorganisms in a timely, appropriate, and effective manner is very difficult. The food sample is usually sent to a laboratory, where pathogens are detected using culture techniques. However, because of advancements in biosensor technology, real time, portable pathogen detection with increased sensitivity is now possible.

Biosensor devices have the capability to detect and identify the pathogens in the food sample on site in the food industry, thus saving a lot of time. Some bacteria like *Escherichia coli*, *Listeria monocytogenes, Salmonella, Staphylococcus* and *Campylobacter* species are very commonly found in food products and are known to cause foodborne diseases in humans. One of the most common diseases is salmonellosis, caused by *Salmonella*. They are the major cause of food poisoning. Another harmful pathogen is *Escherichia coli* that commonly cause diarrhoea and other gastrointestinal problems. Immunosensors are usually used for their detection. Fungi are also known to cause spoilage in food. Biosensors can rapidly detect these pathogens. These pathogens are carefully removed from food by the food industries.

Biosensors can play a vital role in improving the quality of food and beverages. They may aid in the detection of artificial sweeteners which are undesirable in food and may cause diseases like diabetes or some cardiovascular disease.

Biosensors are proved to be very beneficial in the fermentation industries. They can monitor the fermentation conditions in the bioreactors and help in improving its efficacy. Biosensors can be used to determine the fermentation conditions indirectly by checking for the presence of products, enzymes, biomass, antibodies or by-products. They also have the ability to identify biochemical molecules like ethanol, glucose, lactate, etc. Glucose biosensors, which have wide applications in the medical field can also, be used in the fermentation industry for monitoring the saccharification process. Biosensors provide additional benefits for “online” monitoring of fermentation processes. As this can save a lot of time and money and helps in the optimization of the process quickly.

Biosensors for agriculture: In agriculture, biosensors have the potential to be immensely beneficial. They might be useful in detecting pollutants, pesticides, herbicides, chemical fertilizers and harmful pathogens in the agricultural field. They may also help in the animal breeding sector, screening of veterinary drug residues, diagnosis of animal diseases, etc.

Pesticide detection: Pesticides are used for the inhibition of growth of pests on or near the crops. But pesticides are very harmful for the environment and cause pollution in water, soil and air. They also have detrimental effects on the health of humans and animals. Many cases related to the death of animals and even humans due to pesticide poisoning are reported every year.

Pesticides are known to contain toxic compounds like carbamate or organophosphorus. These compounds inhibit Acetylcholinesterase (AChE), an enzyme that is responsible for the termination of acetylcholine (a neurotransmitter) action. Biosensors are developed which can help in the determination of these toxic compounds in the pesticides. Biosensors make use of Cholinesterases (ChE) as biological recognition elements along with amperometric, potentiometric or optical transducers.

The underlying concept behind biosensors in the agriculture field is based on the relationship between pesticide toxicity and a decrease in the activity of the specific biomarker. Biosensors are very sensitive devices which can detect even trace amounts of toxic materials in crops.

Disease detection: There are many microorganisms that target crops and cause diseases in them. Funguses are microorganisms that cause a lot of diseases in the crops. Some fungi like *Aspergillus niger* produce aflatoxin which may cause severe disease in humans if ingested. Biosensors are being developed that can help in the detection and quantification of aflatoxin in the crops like maize, peanuts, etc. Rapid detection of such toxins and pathogens can save many people from contracting serious diseases like respiratory infections, liver damage and from various other diseases.

Wastewater treatment: Wastewater management is one of the biggest concerns in the present time. Amid the water shortage in the whole world, water cannot be wasted. Hence, there is an urgent need to treat the wastewater coming from households or industries. One of the most important tasks in wastewater treatment is the detection of contaminants in water. Biological Oxygen Demand (BOD) is a good measure to check for the pollutants in the wastewater. Biosensors are designed to suit the needs of easy, rapid, automatic and continuous determination of a wide range of biochemical markers in monitoring, which is critical in the wastewater treatment process.

The Biological Oxygen Demand (BOD) of wastewater can be measured using microbial based biosensors. The quantity of organic matter in the wastewater is measured by the BOD value. Usually, BOD tests take at least 5 days but with the help of biosensors, the result can be obtained within a few minutes. Therefore, BOD values for both treated and untreated sewage wastewater can be determined with the help of biosensors. Nisshin electric, a Japanese company, developed the first commercial BOD sensor in 1983 and a lot of biosensors have been developed since then. One example of such a BOD biosensor based on microbes includes soil bacterium *Pseudomonas putida* which is capable of detecting very low levels of BOD in river water. Disposable BOD biosensors have also been developed and more study is being conducted in this area.

Biosensors in defense: Many biological agents, mainly microbial pathogens have posed a great threat to the safety of people. Microbial cultures which are usually kept in labs can be misused by some criminals and this can lead to mass killing of people that is known as bioterrorism. These biological weapons can be as lethal as nuclear weapons. When biological agents are used for terrorism, criminals may go undiscovered since signs and symptoms of the disease may take hours to days to appear. Biosensors can be extremely useful in identifying the bio warfare agents that can be viruses, bacteria, and toxins in the real time. This can greatly help the military or forces at the time of attack.

The most lethal or dangerous biological weapons that can be used intentionally are Bacillus anthracis, Yersinia pestis, etc. These agents are usually used to infect a large population.

Portable biosensors can be particularly valuable in military and defence organizations for detecting poisonous gases and chemical warfare weapons like mustard gas.

Future perspectives: Biosensors are not very popular and are still in the initial developmental stage. Not many biosensors are approved for commercialization. Biosensors need to be used in real world samples and enough data should be collected to support the research, before commercialization. There should be a transfer of knowledge from universities to industries. This means that biosensors should be created with the market's needs in mind. This will lead to the development of a better product which will have a better market value.

Biosensor technology is better than the conventional techniques as it can provide more specific, sensitive and rapid results. Because of their small size, biosensors have a lot of potential for equipment miniaturization.

Wearable biosensors have shown some advantages, like the detection of biomarkers to monitor health. Hence, a lot of research is going on in this field. Microfluidic system combined with wearable biosensors allows for the easy and non-invasive sample collection.

Although biosensor technology appears to be very promising, their transition from the lab to the marketplace has been really gradual. They have great potential but a lot of improvement is also required. Biosensor is a multidisciplinary field that requires more study in the fields of biology, physics, electronics, material science, etc. Biosensor market will definitely see a huge jump in the near future and will become a multi-billion dollars industry very soon.

Conclusion

In future, there would be no requirement to visit the hospitals and stand in a queue for medical diagnostic tests. Instead, most of the tests could be performed at home and the result would become available in real time. As a result, diseases could be treated more effectively because early detection is possible. COVID-19 pandemic has also shown the need for rapid detection of pathogens to prevent or manage outbreaks. Therefore, the requirement of biosensors will increase in the medical field.

Biosensors for environmental monitoring will become most important, as there would be an urgent need to detect the pollutants and reduce or eliminate them quickly.

Their demand in the food and fermentation industries is also increasing. Their role in the defense sector is becoming more important as the threat of bioterrorism is increasing.

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