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Biosensors: Technological Advancement and their Potential Applications

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Abstract

Biosensors are analytical devices and a hybrid form of physical and chemical sensing technique that convert a biological response into an electrical signal proportional to the concentration of a specific analytes. In its technical aspect, biosensing is a phenomenon that withholds set techniques for the production of an accessible detection signal of interaction between biological molecules and another molecule or analyte of interest. Such molecular device that enables sensing of these molecular interactions is called biosensors. IUPAC provide recognition to this type of sensors only some seventeen years prior to today. In principle, biosensors are receptor-transducer based tool which could be used for interpreting the biophysical or biochemical property of the medium. The presence of biological/organic recognition element which enables the detection of particular biological molecules in the medium distinguishes biosensors apart from other types of sensors. The first biosensor device was invented in order to measure blood glucose level in biological samples. This strategy involved electrochemical detection of oxygen or hydrogen peroxide by using immobilized glucose oxidase electrode. Since then, amazing progress has been made both in technology and applications of biosensors with innovative approaches involving electrochemistry, nanotechnology to bioelectronics.

Keywords: Biosensors • Biorecognition • Transducers • Application of biosensors

Introduction

In its technical manner, the biosensor composed of two parts i.e., receptor and transducer. Receptor capture the physical/chemical stimulus and transmutes this information in the form of electrical energy while transducer performs the function of transducing this energy into measurable analytical signal which can further be analyzed and presented in an electronic form [1]. In the utilization of biosensor technology biorecognition element such as enzyme, antigen, antibody or nucleic acid mediates selective biocatalysis or specific binding of analyte and the specificity of measured system depends on it [2]. Biorecognition elements are tightly bound onto physico-chemical transducer by physical or chemical immobilization methods. In genera there are five groups of transducers such as: electrochemical, optical, mass-based, thermal and magnetic biosensor. Improving technologies allow development of novel, advanced and new designed transducers. Biosensors have several practical applications in areas like biochemical, medical, environmental, food, industrial, biosecurity or pharmaceutical analysis and personal diagnostics) which are based on connection of biological element or molecule with biological activity toward measured analyte onto surface of the used transducer [3]. Therefore this paper presents the technological advancement, construction methods, types and application of biosensor [4].

Literature Review

Components of biosensors

The components of biosensors are broadly categorized in to two such as, analytical devices consisting of biological molecule (biorecognition element) and physico-chemical transducer providing measurable signal working as a physical sensor [5]. Biorecognition element mediates selective biocatalysis or specific binding of analyte. Enzyme, antigen, antibody or nucleic acid usually belongs to one of recognition element and the specificity of measured system depends on it [6].

Biorecognition elements: Biorecognition elements can be divided into two categories such as:

- Biocatalytical receptors like enzymes, whole cells, cell organelles, tissues and whole microorganism

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- Bioaffinity receptors like (antibodies, cell receptors or nucleic acids).

Biocatalytical receptors are usually connected with electrochemical, optical or thermometric transducers and transform biological reaction into a measurable physical value such as current, potential, fluorescence or spectral absorbance (Table 1) [7].

Table 1. Measurable physical values of biorecognition elements.

Biorecognition elements	
Biocatalytical receptors	Bioaffinity receptors
Measurable physical values	
Current	Simple construction
Potential	Highly sensitive
Fluorescence	Availability
Spectral absorbance	Satisfactory limits of detection

In Biosensor construction, enzymes are commonly used biorecognition elements for their simple construction, high sensitivity, availability, satisfactory limits of detection and affordability [8]. For instance glucose oxidase based glucose biosensors belong to the one of the mostly used enzymatic biosensors and it was also used in the first biosensor construction [9].

Antibodies have structure of immunoglobulins that consists two polypeptidic heavy and two polypeptidic light chains linked by disulfide bonds [10]. Based on heavy chains differences there are five groups of antibodies; IgG, IgM, IgA, IgD and IgE. Antibodies have been used as biorecognition elements due to their broad spectrum of application such as, high specificity, sensitivity, selectivity and strong antigen-antibody interactions [11,12]. The biosensors having embedded antibody or working on antibody-antigen interaction are called immunosensors [13]. Polyclonal or recombinant antibodies that are secreted by multiple plasma cells, monoclonal antibodies secreted by single clonal lineage and recombinant antibodies produced during recombinant engineering by gene manipulation are usually used in clinical practice and diagnosis [14,15]. The monoclonal antibodies that produced by fusing an immortal myeloma cells with spleen cells have high specificity of antibody-antigen binding, homogeneity and production in large quantities [16].

Antibody-antigen complex cannot generate proper signal for optical and electrochemical transduction [17,18]. Therefore, antigens or antibodies can be labeled by enzymes, fluorescent or electrochemical compounds, radionuclides or avidin-biotin complex. On the other hand, use of mass-based transducers converting mechanical deformation and voltage to measure mass or viscoelastic effects enables direct detection of arising bound without necessity of labeling [19,20]. The selectivity of measured system is determined by two identical very specific antigen binding sites on the molecule of immunoglobuline [21,22].

Deoxyribonucleic acid (DNA) used as a biorecognition element, by integrating pre-synthesized probe on transducer surface or by immobilizing each base of DNA on transducer surface individually [23]. DNA sensors (also called genosensors) are based on specific nucleic acid-analyte binding process like hybridization between targeting DNA and complementary probe and signal from hybridization is measured [24].

Transducers: Transducers vary according to their construction, principle and possibility and frequency of their application. Electrochemical transducers have major role in diagnostic, optical transducers have important influence on research, but thermal, magnetic and mass-based transducers have not gained great clinical impact and nowadays they are used rarely [25,26]. The electrochemical transducers are determined by monitoring of electric potential or electric current changes caused by electron or ions altering during biochemical reaction of biorecognition element (mostly enzyme) with analyte [27,28].

The enzyme transforms substrate to electroactive product creating measurable signal for electrochemical transducer [29,30]. Amperometric transducers are based on measuring of current corresponding with amount of electroactive substance produced during chemical reaction in solution. Constant potential is set on electrode so the measured current response to concentration of determined substance [31]. Potentiometric biosensors involves measuring of potential changes between two electrodes (at near zero current) corresponding with amount of determined substance. Potentiometry is suitable for measuring of very low concentration of analyte due to logarithmic device response on analyte concentration [32]. The benefits of electrochemical transducers includes: low cost, high sensitivity and measuring turbid samples. Electrochemical biosensors have a multiple discipliner applications in biotechnology, food industry, health care, medicine or environmental monitoring because they are high sensitive and selective electroanalytical device [33].

Immobilization techniques of biorecognition elements to transducers

There are two types of immobilization techniques in general: Physical and chemical immobilization. Choosing of a suitable immobilization technique the most important steps for sensor preparation because the possibility of biorecognition element inactivation caused by selecting inappropriate immobilization method is very high [34]. Selection of appropriate method depends on nature of the chosen biorecognition element, used transducer, physico-chemical conditions and properties of analyte [35].

Physical immobilization techniques: Physical immobilization is based on binding of biological molecules (most often enzymes) to transducer surface without creation of any chemical bonds. Physical immobilization technique includes: physical entrapment, Electro polymerization, microencapsulation, physical adsorption and sol-gel techniques (Entrapping biomolecule into memberan) [36,37].

Physical entrapment: Physical entrapment is a method based on embodying biorecognition elements in three-dimensional matrices and it consisted of polydimethylsiloxane, a photopolymer, gelatin, alginate, cellulose acetate phthalate, modified polypropylene and polyacrylamide membranes or a carbon paste can be named as examples of entrapping matrices [38,39].

Electro polymerization: Electropolymerization is immobilization of biorecognition element mostly enzyme on electrode surface under applied current or potential in aqueous solution containing both biomolecule and monomer molecule (such as aniline, pyrrole or thiophene). Conducting polymerized film with precise spatial resolution over surfaces where the bioelement is entrapped inside is created [40,41].

Physical adsorption: Physical adsorption is based on attaching of biorecognition element to the outside of inert material by van der Waals forces. This method provides several advantages such as simplicity, great variety of materials and it does not require chemical modification of biological components. Despite that the clinical application may be limited by the possibility of biomolecule activity loss [42,43].

Microencapsulation: Microencapsulation is based on low temperature forming of solid glass-like transparent film *via* hydrolysis and condensation of precursor alkoxide where bioelements are encapsulated. Extraordinariness of sol-gel membrane lies in its thermal and chemical stability, simplicity of preparation and possibility of large amount of biomolecule entrapment [44-49].

Entrapping of biomolecule into membrane: Entrapping of biomolecule into membrane is based on hydrophilic and hydrophobic polymers attachment with biorecognition elements. Soluble photo sensitive pre-polymer with crosslinking properties is polymerized under light exposition to form insoluble matrix [50]. For entrapping imobilization alginate (the brown algae) is the most commonly used material due to its biocompatibility with bounded biorecognition element, non-toxicity and its sufficient accessibility for electrons, but other materials (such as gelatin, cellulose acetate phthalate, polypropylene, polyacrylamide) are also frequently used as the entrapping membranes [51]. These substance connecting the entrapped biorecognition element to surface of transducer. It is usually used with electrochemical transducer [52].

Chemical immobilization: Chemical immobilization is based on creation of chemical bonds between functional group of biorecognition element (side chains unnecessary for its catalytic activity) and surface of the used transducer [53]. Chemical bonds that formed on activated transducer surface carrying out by chemical reagents (such as glutaraldehyde or carbodiimide) or they are created directly because of pre-activated membrane applied on transducer surface. Covalent binding and covalent cross-linking belongs to the chemical immobilization techniques. There are two types of chemical immobilizations such as covalent binding and cross-linking [54,55].

Covalent binding: Is a process where biorecognition element receives firm bond to either surface or inner cavity of membrane [56]. It is the most widely used type of enzyme immobilization technique. The binding process is based on reaction between functional protein groups (usually side chain of amino acids) of biorecognition element and reactive groups of transducer/membrane matrix surface. Covalent binding provides increased lifetime stability and strong and effective bonding and it includes chemical adsorption (also called chemisorptions) and activation of carboxylic or amino groups [57,58].

Cross-linking: Is an immobilization process based on covalent binding between biorecognition elements or between biorecognition element and functionally inert protein (for example bovine serum albumin). It leads to formation of three dimensional aggregates bonded *via* multifunctional linker molecule such as glutaraldehyde, glyoxal and hexamethylendiamine to the transducer surface [59]. Process of cross linking requires optimal conditions such as pH, temperature and ionic strength to allow shorter response time, stronger attachment and higher catalytic activity of enzymes. Despite many advantages poor stability and partial denaturation of protein structure may limit application of cross linking immobilization [61-65].

Methodology

Types of biosensors

Based on their components (biorecognition elements and transducers) biosensor devices can be categorized as electrochemical, optical/visual, polymers, silica and glass, nanomaterials, genetically encoded biosensors and microbial biosensors [66].

Electrochemical biosensors: Electrochemical biosensors are typically prepared by modifying the surface of metal and carbon electrodes using biomaterials, such as enzyme, antibody or DNA. Biosensor's output signal is usually generated upon specific binding or catalytic reactions of biomaterials on the surface of electrode. The need for the discovery of electrochemical sensors became extremely desirable for clinical diagnosis of diseases in early detection [67]. For development of non-enzymatic biosensors synthetic materials have be used in place of proteins. Electrochemical biosensors are used to assess the levels of antioxidants and reactive oxygen species in physiological systems. Major application in this line is the detection of uric acid as primary end product of body fluid purine metabolism, which provide diagnostic tool for various clinical abnormalities or diseases [68].

Even though, electrochemical-based measurement of uric acid oxidation for glucose quantification seems ideal, the resemblance of uric acid in terms of oxidation with ascorbic acid poses major experimental hurdle to develop highly sensitive electrochemical biosensor. To overcome this, scientists have developed amperometric detection-based biosensor which possesses the ability to measure both reduction and oxidation potentials [69-71].

According to the report of electrochemical biosensors have been successfully used for hormone measurements. Another potential area of technology development in biosensors relies on targeting nucleic acids. This provides ideal electrochemical biosensors for miRNA detection based on label-free detection involving guanine oxidation subsequent to the hybrid formation involving the miRNA [72]. Environmental monitoring is another important aspect wherein biosensor technology is required for rapid identification of pesticidal residues to prevent health hazards. Even though traditional methods, such as high-performance liquid chromatography, capillary electrophoresis and mass spectrometry, are effective for the analysis of pesticides in the environment, they have drawbacks like complexity, time-consuming procedures, requirement of high-end instruments and operational capabilities [73,74].

Certain enzyme-based electrochemical biosensors were developed to understand the physiological impact of pesticides in the environment, food safety and quality control. For this purpose, Acetylcholinesterase (AChE) inhibition-based biosensors were developed. To cope up with the demand, the biosensor underwent revolution with rapid advances in fabrication and use of nanomaterials or quartz or silica. The selection of receptors for biosensor development needs to place special emphasis for the use of different transduction techniques and fast screening strategies for applications of biosensor in food and environmental safety [75].

Optical/visual biosensors: More recently, hydrogels, used as DNA-based sensor, are emerging materials for immobilization usage with fiber-optic chemistry. Compared to other materials, immobilization in hydrogels occurs in three dimensions (3D) which allows high loading capacity of sensing molecules [76]. Hydrophilic cross-linked hydrogels (polyacrylamide) polymers are used for different forms of immobilization ranging from thin films to nanoparticles. Hydrogels have several advantages like entrapment, controlled release, analyte enhancement and DNA protection beside being a simple substrate for DNA immobilization. These features are unique to hydrogels compared to other materials which offer biomolecular immobilization. Furthermore, good optical transparency of hydrogels provides convenient strategy for visual detection [77]. Detailed methods for immobilizing DNA biosensors in monolithic polyacrylamide gels and gel microparticles are often considered as technical advancement in the field of biosensor technology. Single molecule detection has also been developed using electrochemical oxidation of hydrazine for DNA detection [78].

Nanomaterials-based biosensors: Biosensor development involves several nanomaterials such as; gold, silver, silicon and copper nanoparticles, carbon-based materials like (graphite, grapheme and carbon nanotubes) because of their great sensitivity and specificity [79]. Among the metallic nanoparticles, gold nanoparticles have great potential use because of their stability against oxidation and almost have no toxicity, while other nanoparticles like silver can oxidize and have toxic manifestation [80].

Nanomaterials are considered as critical components in bio-analytical devices that enhancing the sensitivity and detection limits for single molecule detection [81]. For instance platinum-based nanoparticles for electrochemical amplification with single label response for the detection of low concentration of DNA. Similarly, semiconductor quantum dots and iron oxide nanocrystals having optical as well as magnetic properties that can be effectively linked to tumor targeting ligands [82]. The ligands have high affinity and specificity to tumor can be applied to understand the tumor microenvironment for therapeutics and also for the delivery of nano-medicine. Now a days biosensors are made from materials like silica, quartz or crystal and glass due to their unique properties [83].

Silica and glass biosensors: Due to their biocompatibility, abundance, electronic, optical and mechanical properties; silicon nanomaterials have greater potential for technological advances in biosensor applications among other materials Silica based biosensor offers wide range of applications ranging from bioimaging, biosensing and cancer therapy. Silicon nanowires in combinations with gold nanoparticles provide hybrids which are used as novel silicon-based nano-reagents for effective cancer therapies [84]. Covalent attachment of thiol-modified DNA oligomers on silica or glass provides DNA films for better usage in UV spectroscopy and hybridization methods. Considering the unique features of silica or quartz or glass materials, a variety of new biosensors were developed with high-end technology for the improvement of bioinstrumentation to biomedicine technology yet cost-effectiveness and biosafety requires attention [85].

Genetically encoded or synthetic fluorescent biosensors: Understanding the biological process including various molecular pathways inside the cell needs to use tagged biosensor that developed by using genetically encoded or synthetic fluorescence. The fluorescent biosensor so-called fluorescent-tagged antibodies and was first developed to image fixed cells [86]. Now a day, fluorescent biosensors employed in analyzing of motor proteins using single molecule detection with specific analyte concentration. The creation of green fluorescent protein and other fluorescent proteins gave several advantages in terms of optical probe design and efficiency.

Until the past decade, genetically encoded biosensors targeting molecules related to energy production, reactive oxygen species and cAMP provided better understanding of mitochondrial physiology until last decade [87]. Forster Resonance Energy Transfer (FRET)-based biosensors have been developed for visualizing cGMP, cAMP and Ca^{2+} in cells. Several of these sensors work efficiently in primary culture and live-cell *in vivo* imaging. Considering the advent of *in vivo* imaging with small molecule biosensors, a better understanding of cellular activity and many other molecules ranging from DNA, RNA and miRNA have been identified. Now the transformation in this field requires whole genome approach using better optical based genetic biosensors.

Microbial biosensors: More recent trend in environmental monitoring and bioremediation is to utilize state-of-the-art innovative technologies based on genetic/protein engineering and synthetic biology to program microorganisms with specific signal outputs, sensitivity and selectivity. From the wider applications of live cell having enzyme activity degradation of xenobiotic compounds an exemplar of its role in bioremediation. Similarly, microbial fuel-based biosensors have been developed with aim to monitor biochemical oxygen demand and toxicity in the environment [88].

Bacteria have the potential of breaking the organic substrate and generating electricity for fermentation. Basically, the microbial biosensor technology involves use of a bio-electrochemical device that controls the power of microbial respiration to convert organic substrates directly into electrical energy. In spite of these, there are some drawbacks in microbial biosensors due to low power density in terms of production and operating costs [89]. Efforts are being made to enhance the performance and cutting down the costs with new systemic approaches, wherein technologies have provided a platform to develop self-powered engineered microbial biosensors [90].

Another area of microbial biosensors potential applications is in pesticidal and heavy metal detection. This is primarily due to the advantage of developing whole cell biosensors with selective and sensitive applications related to the detection of heavy metal and pesticidal toxicity. Furthermore, the higher eukaryotic microbes can have wider sensitivity to several toxic molecules and have importace to higher animals [91].

Interestingly, the applications of microbial biosensors are diverse ranging from environmental monitoring to energy production. Innovative strategies will provide novel biosensors with high sensitivity than selectivity from microbial origin from eukaryotes to engineered prokaryotes. In future, these microbial biosensors will have wider applications in monitoring environmental metal pollution and sustainable energy production [92].

Application of biosensors

The most recent application of biosensor includes: biomedicine, food, environmental and defense fields. Biosensors have been widely used in different scientific disciplines due to their outstanding results. Medically, biosensors can be used for accurate and precise detection of tumors, pathogens, elevated blood glucose levels in diabetic patients, to study and analyze the chemical processes going on in the cells. The long term incorporation of any specific substance into the host cells could also be achieved through these biosensors. In case of food industry, biosensors could be linked to the detection of gasses released from spoiled food, detection of food contamination or for checking and minimizing the growth of bacteria or fungus in fresh food.

From environmental point of view, these biosensors could be enhanced to detect pollution in air and presence of any pathogens, heavy metals etc. In military defense the biosensors can be employed to detect the bioterrorist attacks like the intentional use of the biological entities like *Bacillus anthracis*, Ebola, hepatitis C viruses etc. [93].

Biomedical applications: Biomedical application of biosensor includes: measuring of blood glucose level, genetic diagnostics and DNA encoding, tissue/cell engineering and the measuring of H_2O_2 amount. There are few successes that have achieved with few potential molecules for novel therapeutic, antimicrobial and drug delivery. Invention on this line leads to discovery of electrochemical biosensors as analytical devices for pathogen detection of avian influenza virus in the complex matrices. More recent report revealed potential applications of affinity-based biosensors in sport medicine and doping control analysis [94].

Measuring of blood glucose level: The demand for use of glucose sensing technologies has grown due to the enhancing number of diabetics patients every year. The enzymes that are effectively utilized at large scale for glucose detection are glucose oxidases (G-ox) and glucose dehydrogenases. A case reported by Binesh and co-workers evidently presents that facile and single stepped methodology for the preparation of graphene-(G-ox) biocomposite, displayed excellent sensitivity of 1.85 μAmM-1cm-2 over the glucose concentration range of 0.1-27 mM [95].

Diagnose of infectious diseases: Biosensors are being used in the medical field to diagnose infectious diseases. A novel newly invented biosensor based on Hafnium Oxide (HfO_2), has been used for early stage detection of human Interleukin (IL)-10. The interaction between recombinant human IL-10 and corresponding monoclonal antibody is studied for early cytokine detection after device implantation [96]. Fluorescence patterns and electromechanical impedance spectroscopy characterize the interaction between the antibody-antigen and bio-recognition of the protein is achieved by fluorescence pattern. Chen and co-workers applied HfO_2 as a greatly sensitive bio field effect transistor. Hafnium oxide biosensor has been used for antibody deposition with detection of a human antigen by electrochemical impedance spectroscopy [97].

Also there are biosensor techniques like immunoaffinity column assay, fluorometric and enzyme-linked immunosorbent for detection of cardiovascular diseases (heart failure) that suffering one million people and biggest situation faced today. The ultra-sensitive sensor based over nuclease mediated highly targeted recycling of DNAzyme for the electrochemical detection of oral cancer from the saliva secretions. With this sensor, they quantified up to the 0.02 fM of the targeted DNA and detected gene mutation up to the single basepair mismatch. Along with the operation and maintenance conveniences and low engineering cost make this biosensor a promising candidate for oral cancer detection at the commercial level. An altered graphene electrode which possesses the ability to chemically bind with ssDNA and generate Volta-metric signal for its counter analogue DNA for detection [98].

Measuring H_2O_2 content: In humans the H_2O_2 content is a direct indicative of the oxidative stress of cell or hypoxic conditions of tissues. To know or to measure the amount of hydrogen peroxide (H_2O_2) various analytic techniques like titration, electrochemistry and photo catalysis could be utilized. The instability of hydrogen peroxide in any biological system makes it highly injurious and cytotoxic for humans, plants, animals as well as bacteria. In the field of tissue engineering, and the electrochemical methods are commonly used for H_2O_2 quantification in nature and poses several difficulties (poor detection, low sensitivity, less portability and applicability issues on the organic system) to the user. Enzyme based bio sensing technique which is the recent finding have quite high stability and accuracy. Immobilization techniques used for this specific application includes: quantum dots, polymers and nanostructures [99].

Application in food industry: Biosensor applications in food industry can categorized in to two main groups: Detection of food borne pathogens and detection of chemical contaminants. Microorganisms responsible of large economic losses in the food industry due to productivity loss, medical costs and food product recalls, including: Bacteria (*Salmonella*, *Listeria monocytogenes*, *Campylobacter* and *Escherichia coli*) and fungi (*Botrytis* sp., *Aspergillus*, *Colletotrichum* and many other fungal species) [100].

Chemical contaminants outline biosensor applications in the determination of contaminant residues including pesticides, fertilizers, heavy metals, food additives and antibiotics [101]. In order to ensure the safety of processed foodstuffs, specific methods have been adopted by the food industries to sort out the problems leading to food spoilage and detection and destruction of such chemicals or biological agents that are responsible for the spread of some serious health related problems [102].

Biosensors are being targeted to be specific, highly sensitive and quickly responsive and used to determine the chemical activities that lead to the food spoilage. All processed or unprocessed food products can be tested by on spot visualization at the binging and to make final decisions other quality testing attributes like touch, taste and smell can later be utilized [103]. The enzyme substrate interaction or antibody-antigen complex that can be easily detected is the fundamental determinant factors of biosensors. The common types of biosensor employed in food industry are enzyme-based biosensors and immunosensors. Food industries have use biosensors for timely detection and monitoring of food born pathogens and chemical contaminants that causes food spoilage in food industry [104].

Food born pathogens detection: The microbes that involved in food spoilage mainly includes bacteria and fungi that lead to the spread of serious health hazards [105].

Bacterial monitoring: Common food spoiling bacterial species that cause health problem are: *E. coli* strain 0157:H7, *Listeria monocytogenes*, *campylobacter* and *salmonella*. These bacteria are common problems faced by the food industries as they reduce the consumer demands of the food [106].

Salmonella are rod-shaped Gram-negative bacteria naturally found in the gastrointestinal tract of warm blooded animals and humans. They cause food poisoning that leading to excessive loss of water and salts from the body and might be fatal under severe cases. Food industries had been striving to get rid of the cause of food poisoning by timely detection and removal of this bacterium [107]. For monitoring *Salmonella*, piezoelectric biosensors are commonly used that can detect monoclonal antigen-antibody complex quickly and easily but are poor detectors of polyclonal antibody complexes, which is its main drawback and needs to be addressed for upgradations [108].

Listeria monocytogenes, Gram positive, flagellate microaerophilic coccobacillus, can cause listeriosis associated to the consumption of fresh and processed foods such as meats shellfish, unpasteurized milk and vegetables. Fibre-optic biosensors have been used to monitor the presence of low level of L [109]. *monocytogenes* cells. Fiber-opitic device based on the measurement of fluorescent light generated by a wave when there is a change in resonance. The biosensor uses monoclonal fluorescent antibodies that generateexcitation of atoms and wave production when bound to the pathogen. The biosensor is made of a polystyrene support that immobilizes the antibodies; obtained by inducing the immune response of rabbits after inoculating with *Listeria monocytogenes* for three months [110].

Along with fibre-optic biosensors, Surface Plasmon Resonance (SPR) biosensors have been satisfactory for *L monocytogenes* detection. The genus *Campylobacter*, are Gram negative, microaerophiles, comma-shaped bacteria cause of gastroenteritis, in children. They are common causative agent for food spoilage worldwide [111]. Optical Surface Plasmon Resonance SPR can also be used for quick detection of *campylobacter*. *Escherichia coli* strain (0157:H7), may cause inflammation in the small intestine, causing severe diarrhea (including bleeding) and kidney damage. Amperometric biosensors based on enzymatic system had been successfully used for the detection of *E. coli* 0157:H7 [112].

Fungal pathogens detection: Fungi are also the common cause of food spoilage and causing severe health related problems that may prove to be life threatening in most cases. Fungi that cause food contamination are commonly *botrytis* species, *aspergillus*, *colletotrichum* and many other fungal species. Due to the remarkable specificity, reduced costs and easy and quick monitoring through biosensors, fungal mycotoxins can be also detected using optical SPR biosensors [113].

Biosensors for determination of chemical contaminants: Chemical contaminant that causes food spoilage includes pesticides, fertilizers, heavy metals, food additives and antibiotics [114].

Biosensors used for the detection of contaminant residues and pesticides: The presence of pesticide residues and

and metabolites in food, water and soil currently represents one of the major issues [115]. Analytical methods for the determination of organophosphate pesticides and N-methyl carbamates are complex or not existent for some compounds. High Performance Liquid Chromatography (HPLC) is an appropriate technique for the determination of organophosphate pesticides and N-methyl carbamates since it preserves pesticide stability. However, to set the adequate sensitivity for the method, several pretreatment steps are required, adding time and cost [116].

The use of most common enzymatic biosensors for the detection of pesticides, fertilizers and heavy metals discussed. Enzymes like cholinesterase (AChE), Organophosphorus Hydrolase (OPH) and urease are used in the design of electrochemical biosensors for pesticides detection. Biosensors devices, based on OPH and cholinesterase inhibition, have been widely used for the detection of carbamates and Organophosphate compounds (OP) [117]. During the use of OPH in a biosensor for the detection of paraoxon and parathion, the transducer structure of the sensor chip consists of a pH sensitive Electrolyte-Insulator-Semiconductor (EIS) structure that reacts to pH changes caused by the OPH catalyzed hydrolysis of the organophosphate compounds. Immobilized cells of *Flavobacterium* species have been used for the detection of methyl parathion. *Flavobacterium* species have the enzyme organophosphorus hydrolase, which hydrolyzes the methyl parathion into detectable product p-nitrophenol [118].

Biosensors used for the detection of heavy metals: Eating foods containing residues of heavy metals cause several health problems like: cardiovascular and respiratory problems, infertility, irritations, inhibition of some hormonal activities, malfunction of the principal organs and death [119]. Devices have been designed to determine the concentration of heavy metals such as arsenic, cadmium, mercury and lead, in water and soil samples. These devices contain genetically modified microorganisms and enzymes such as urease, cholinesterase, glucose oxidase, alkaline phosphatase, ascorbate oxidase and peroxidase [120].

Conduct metric biosensors use immobilized *Chlorella vulgaris* microalgae as bio receptors. Immobilized algae inside bovine serum albumin membranes have made a network structure with glutaraldehyde vapors deposited on interdigitated conduct metric electrodes and local conductivity variations caused by algae alkaline phosphatase and acetylcholinesterase activities could be detected [121].

In addition, it is possible to know the presence of cadmium through detection of the inhibition of the urease enzyme by using fiber optics biosensor that can sense down to 0.1 g/l of cadmium in milk. The biosensor can be made from whole cells of *bacillus badius* with phenol red as an indicator co-immobilized onto circular plastic discs with sol-gel approach and fiber optic transducer system. Urea is added to the plastic disc to detect the inhibition of enzymatic reactions [122].

Biosensors as indicators of product acceptability: Food quality involves nutritional and organoleptic characteristics such as freshness, appearance, taste and texture. The food sensory basis is essential for the industry. During storage, compounds that provide aroma and abnormal flavors or may be harmful to consumer may be synthesized, indicating in most cases microbial growth and insufficient food safety. The ethanol and methanol that have been used as indicators of food freshness and quality of alcoholic beverages are determined by conventional methods: colorimetric, refractometric, chromatographic and spectrophotometric. However, some of these techniques require expensive equipments and longtime [123].

Use of biosensor to determine freshness and quality of food overcomes these drawbacks. Biosensors that use whole cells or enzymes have been used for the detection of alcohol. Biosensor with immobilized enzymes: Alcohol oxidase, alcohol peroxidase and a chromogen, have used to detect injuries caused by low O_2 in lettuce, cauliflower, broccoli and cabbage lightly processed and packed in a modified atmosphere. This biosensor could also be used to monitor ethanol during the storage of apples in a controlled atmosphere, the decay in potato tubers [124].

Similar research has been done to detect organic acids and sugars as indicators of fruit and vegetables maturity. By co-immobilization of alcohol oxidase and glucose oxidase on the same electrode an amperometric biosensor have been developed for the determination of glucose and ethanol. Measurements are based on current reduction potential of tetrathiafulvalene (at 0.1 V *vs*. Ag/AgCl) by using a cyclic voltammetry method and correlations between decreases in biosensor responses and glucose oxidase or alcohol oxidase activity were monitored [125].

Multiple compounds giving unpleasant flavors and aromas in foods can be potentially detected by biosensors. Varelas and his co-workers developed a biosensor system based on a bioelectric recognition assay for detection of 2, 4, 6-trichloroanisole, a compound that causing considerable losses to the wine industry. Biosensors technology for substance detection significantly reduces analysis time and improves specificity, reliability and test sensitivity [126].

Environmental applications of biosensors: The main classes of bioreceptor elements that are applied in environmental analysis are whole cells of microorganisms, enzymes, antibodies and DNA. Additionally, in most of the biosensors described in the literature for environmental applications electrochemical transducers are used. For environmental applications, the main advantages of biosensors over conventional analytical techniques are portability, miniaturization, work on-site and the ability to measure pollutants in complex matrices with minimal sample preparation. The major pollutant that can be successively detected and removed using biosensors includes heavy metals, polychlorinated biphenyls, pesticides, Biochemical Oxygen Demand (BOD) and nitrogenous compounds [127].

Biosensors for heavy metals detection and monitoring: Heavy metals pose maximum threat to health of humans and their hyper-accumulation leads to various inappropriate health conditions, as they cannot be easily biodegraded. The metal contaminants most commonly observed in the environment are: Lead, chromium, zinc, mercury, cadmium and copper [128].

Several types of biosensors have provided great success in detection and monitoring of the toxic levels of heavy metals that would lead to injurious health conditions. Bacteria-based cell biosensors require the use of genes that resist certain types of heavy metals like copper, mercury, tin cobalt etc. However, their action is dependent on heavy metals interaction with their cytoplasm, dependence of these sensors is based on the conjugation of some luminescent proteins like luciferin, with those genes that resist heavy metals [129].

Enzyme-based biosensors have also provided promising results. Fibre-optic biosensors have been used for the detection of the toxic levels of various heavy metals like lead, cadmium, mercury, copper nickel, cobalt etc. These biosensors work by inhibition of these heavy metals by metal ions on various kinds of enzymes, these inhibitions are then monitored by using different types of biosensors with HIGH specificity. Amperometric biosensors were used for the successful detection of inhibition of mercury ions (Hg^{+2}) by urease enzyme action. Inhibition of cobalt, nickel, mercury, gold and lead with same urease enzyme lead to the monitoring of the toxic levels using fibre optic sensors [130].

Biosensor for Polychlorinated Biphenyls (PCBs) detection: Polychlorinated biphenyls are non-biodegradable agents used in various types of herbicides and insecticides that though prove to be good for pest control but also lead to the accumulation of these PCBs in the soil which are then taken up by the crops and in turn they enter human body and causes serious health problems, most of the times related to cancers. Biosensors have been most promising in the past years in precise detection of these organic compounds in foods and soils, using immunological biosensors that monitors antigen-antibody interaction using piezoelectric transducers [131].

Biochemical Oxygen Demand (BOD): It is the amount of molecular oxygen (O_2) required by microorganisms to thrive in waste water and is mostly required during break down of organic compounds. This leads to the increased environmental pollution in water sources. Nisshin Denki Electric Co. Ltd. developed the first commercial biosensor for BOD level monitoring a biosensor in 1983. A system for measuring BOD from cells of recombinant *Escherichia coli* with *vibrio fisheri* genes lux AE. An optical biosensor for parallel multi-sample determination of biochemical oxygen demand in wastewater samples has been developed. The biosensor monitors the dissolved oxygen concentration in artificial wastewater through an oxygen sensing film immobilized on the bottom of glass sample vials [132].

Biosensors for pesticides detection: As defined by the Environment Protection Agency (EPA), pesticides is any substance or mixture of substances intended for preventing, destroying, repelling or lessening the damage of any pest. Pesticides are the most abundant, present in water, atmosphere, soil, plants and food. Organophosphates that used as insecticides (pesticides) affects the soil fertility, damage many beneficial insects and microbes in soil and leads to the loss of biodiversity. For their detection, another type of Nano technological sensors have been used recently to measure toxic levels of these pesticides in soils and in water. Enzymatic biosensors have been modified by allowing them to be immobilized. The common example is of acetylcholinesterase (enzyme) sensors which work by inhibiting acetylcholinesterase activity in order to detect organophosphates, where acetylcholinesterase activity is constantly monitored [133].

Biosensors for nitrogen compounds and microbial detection: The increasing levels of nitrate found in groundwater and surface water are of concern because they can harm the aquatic environment. In line with this, the regulations for treatment of urban wastewater to decrease pollution from (nitrates, sewage treatment works of industrial and domestic have been implemented. There are commercial biosensors that have been successfully used to monitor dioxins, nitrates, *E. coli* and dioxin-like compounds. Microbes-based biosensors can also be employed for monitoring airborne contaminants and also pathogens. Phage-sensors can be used for detecting air-borne pathogenic microbes [134].

Biosensors in defense: The warfare strategies using toxins are evident, use of toxins for assassination purposes against individual enemies and the armies, such as the fall of Kaffa (14^{th} century) and the French-Indian war. Advances in science through the 19th century allowed more severe and extensive use of Chemical and Biological Toxins (CBTs) as weapons during World Wars I and II. Episodes of anthrax attacks in the United States and the Sarin attacks in Japan and recently in Syria are some of the tragic events happened in the past that have caused intense fear among civilians. In response to the destructiveness and the fear associated with such conceivable attacks or accidents, global efforts have focused on developing biosensor technologies to detect environmental CBTs. Development in biosensors for the detection of biological warfare agents ranging from bacteria, virus and toxins is often attempted using various devices of biosensors such as: electrochemical, nucleic acid, optical and piezo electric, have huge applications in military defense and security [135].

Discussion

There are several biosensors applied in the field of defense now a day. The label-free cell-based electric impedance biosensor technology shows good correlation with standard label-based cytogenetic assays and is very rapid. Optical biosensors that characterize changes in the refractive index (resonant waveguide grafting; RWG and surface Plasmon resonance; SPR and scattering of incident light (Raman spectroscopy; RS) have shown great success as label-free cell-based optical sensor technologies. Biosensor and immunosensor technologies based on SPR and RWG have been used extensively for the rapid detection of CBT [136].

Advanced biosensors detect the general response of cells when exposed to toxins (changes in refractive index, impedance etc.). Bio reporter technology is well established to detect the cellular stress response to known/unknown toxins. There is a report that indicates possibility of monitoring RAD54 and HSP70 stress markers level in eukaryotic microbes exposed to environmental toxins using bio reporter. Yeast, *Saccharomyces cerevisiae* is the modeleukaryotic organism, which is used over bacteria and animal cells to develop a portable biosensor. Several yeast bio reporter assays for monitoring environmental toxins are internationally validated, such as green screen and bio luminiscent yeast estrogencity screen. Raman Spectroscopy (RS) is the optical biosensor technique that gives a chemical fingerprint of an analyte (chemical/biological) including cells and organisms and can be used *in vitro* as well as *in vivo*. The RS cell-based biosensor for rapid detection, identification and monitoring the levels of chemical and biological warfare agents in live Cells have reported [137].

Conclusion

Biosensor that composed biorecognition element and transducers is a rapidly growing field encompassing various fields like medicine, agriculture, food industry, environmental science and defense. Nowadays various types of biosensors have devised, such as electrochemical, optical, genetic encoded, microbial and Nano material based which will have immense applications. Biosensors application in medical field is highly advanced especially in the area of medical diagnostics. In the food industry quality control is a major thrust area, the need for fast methods to monitor the quality of food like freshness, flavors and aromas is urgent. In agriculture and environmental science: Pesticides, fertilizers and heavy metals residues can be quickly detected in small quantities with biosensors, facilitating *in situ* implementation in pre-and post-harvest processes. Conventional methods are expensive, time consuming and labour intensive. Development of efficient sensors will not only speed up the process but will be also cost effective. The advances in detection techniques have allowed the fabrication of rapid and user-friendly advanced biosensor devices imperative for chemical and biological defense. Advanced biosensors enable the label-free and cell-based detection of toxins and the response of the cell and organism to toxins. Biosensor is an interdisciplinary field involving many areas; research in genetic engineering, material science, microfabrication and nanofabrication will enhance the development of suitable sample preparation steps, such as immobilization, extraction and concentration. Future sensors developments must focus on provide multi-analyte detection combined with signal transmitters for remote sensing and modify these bio sensing elements to enhance them to the extent that would be able to detect even most dangerous diseases like the viral diseases (HIV, EBOLA, Crimean-Congo Virus, Rabies etc.) and can also be employed for bioremediation of pollutants.

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