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Review Paper

Biosensors Technological Advancement and Their Biomedical, Agricultural, Environmental and Food Industrial Applications: A Review

Tariku Abena [1,]*

1) *Microbial Biotechnology Research Program, National Agricultural Biotechnology Research Center (NABRC), Ethiopian institute of Agricultural Research, Ethiopia*

*) *Corresponding Author: tarikuabena8@gmail.com*

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***Abstract*—The biosensors are devices that receive the biological message and convert it into a sensible electrical signal. The biosensing involves a combination of biological entities like DNA, RNA, and proteins/enzymes to the electrochemical transducers. Biosensors comprise a biorecognition element (enzyme, antigen, antibody or nucleic) that mediates selective biocatalysis or specific binding of analyte and transducers that able to measure the signal. There are several types of biosensors being employed today, such as optical, surface plasmon resonance, enzymes, DNA, Phage, and microbial biosensors. Now days biosensor technologies have been employed in biomedicine, food safety standards, defense and environmental monitoring. Detection of the lower or higher limits of glucose in the body, microbial invasion in the body and food, heavy metal detection in soil, water and airborne microbes, pesticides in water and soil and various harmful chemicals produced by body, can be easily and timely monitored with high precision using the different types of biosensors. Biosensors can overcome all the limitation of the traditional methods of chemical and microbiological analyses by offering rapid, non-destructive and affordable methods for quality control. Thus, this review paper highlights biosensor and its components, types of biosensors and its application in different disciplines.**

Keywords*—Bio-recognition element, Biosensor, Immobilization, Transducers

I. Introduction

The biosensors are analytical devices and a hybrid form of physical and chemical sensing technique that converts 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 of 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 the sensing of these molecular interactions is called biosensors. In principle, the 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 [129].

Clark and Lyons 1962 [19] were discovered the first biosensor technology for measure the amount of glucose in biological samples by electrochemical detection of oxygen or hydrogen peroxide using immobilized glucose oxidase electrode [125]. Since then, biosensor advanced both in technology and applications with innovative approaches involving electrochemistry, nanotechnology to Bioelectronics [125].

The sensor is composed of two parts, i.e., receptor and transducer. Receptor receives the physical/chemical stimulus and transmits this information in the form of electrical energy while the transducer performs the function of transducing this energy into a valuable analytical signal which can further be analyzed and presented in an electronic form [36]. In the utilization of biosensor technology, bio recognition elements include immobilized enzymes, antigens, antibodies and DNA/RNA [30]. Biorecognition element is tightly bound onto the physical-chemical transducer by physical or chemical immobilization methods. In general there are five groups of transducers such as: electrochemical, optical, mass-based, thermal and magnetic biosensor [73, 69]. Improving technologies allow the development of novel, advanced and new designed transducers [113].

Biosensors have several practical applications in areas including 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 [44, 83]. Therefore, this review presents the technological advancement, construction methods, types and application of biosensor.

II. Components of Biosensors

The components of biosensors are broadly categorized into two such as, analytical devices consisting of biological molecule (biorecognition element) and physico-chemical transducer providing measurable signal working as a physical sensor [88]. Biorecognition element mediates selective biocatalysis or specific binding of analyte. Enzyme, antigen, antibody or nucleic acid usually belongs to one of recognition elements and the specificity of measured system depends on it [30].

A. Biorecognition Elements

The biorecognition elements can be divided into two categories such as: (a) biocatalytical receptors like enzymes, whole cells, cell organelles, tissues and whole microorganism and (b) bioaffinity receptors like (antibodies, cell receptors or nucleic acids) [73, 42]. Enzymes are very common biorecognition elements mostly for their simple and well-known construction, high sensitivity, availability, satisfactory limits of detection and affordability. 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 [73 42, 113]. Antibodies have structure of immunoglobulins that consists two polypeptidic heavy and two polypeptidic light chains linked by disulfide bonds. Based on heavy chains differences there are five groups of antibodies: IgG, IgM, IgA, IgD and IgE [20]. 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 [69]. The biosensors having embedded antibody or working on antibody-antigen interaction are called immunosensors [127]. Polyclonal or recombinant antibodies that 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 [20]. 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. Antigens or antibodies can be labeled by enzymes, fluorescent or electrochemical compounds, radionuclides, or avidin-biotin complex because of inability of antibody-antigen complex to generate proper signal for optical and electrochemical transduction [33].

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. The selectivity of measured system is determined by two identical very specific antigen binding sites on the molecule of immunoglobuline [82]. Deoxyribonucleic acid (DNA) contains two antiparallel complementary polynucleotide strands consisted of purine and pyrimidine nucleotides linked by hydrogen bonds [28] used as a biorecognition element is integrated on transducer surface as whole pre-synthesized probe (sequence of polynucleotide chain containing tens of nucleotides) or each base is immobilized on transducer surface individually [98]. 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 [28, 99].

B. Tranducers

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 use rarely. The electrochemical transducers are based on 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, 59]. The enzyme transforms substrate to electroactive product creating measurable signal for electrochemical transducer [87]. 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 [123]. The potentiometric transducer that measures the change between two electrodes is suitable for detecting of very low concentration or presented mass of analyte due to logarithmic device response on analyte concentration [123]. The benefits of electrochemical transducers includes: Low cost, high sensitivity and measuring turbid samples [59, 77]. 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 [25].

III. Immobilization Techniques for Biosensors Preparation

There are two types of immobilization techniques in general: physical and chemical immobilization. Selection of a suitable immobilization technique is one of crucial steps of sensor preparation because the possibility of biorecognition element inactivation caused by choosing inappropriate immobilization method is very high and Selection of more appropriate method depends on nature of the chosen biorecognition element, used transducer, physico-chemical conditions and properties of analyte [92, 18].

A. 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, microencapsulation, adsorption and sol-gel techniques [3, 114, 122]. 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 [114, 122].

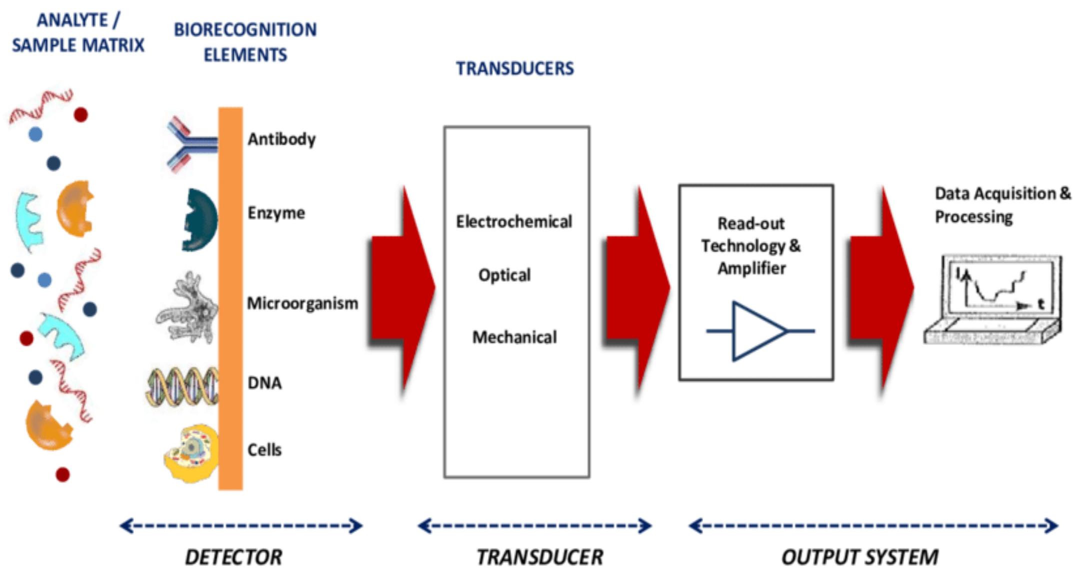

Fig. 1. schematic diagram of Biosensor adapted from [76].

i. Electropolymerization

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 [21, 22].

ii. Physical adsorption

Physical adsorption technique involves attachment of bio recognition element to the inert material by van der Waals forces, hydrophobic interaction as well as by hydrogen bonds [75]. This method has a lot of advantages such as the 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 [73, 7].

iii. Microencapsulation

It 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 [92].

iv. Entrapping of biomolecule into membrane

It is based on physical, either hydrophilic or hydrophobic binding of a biomolecule on inert membranes that provide close contact between biomaterials and the transducer. Types of membranes used include cellulose acetate, polycarbonate, collagen, and Teflon [49, 41]. Carbon paste consists of graphite powder and pasting liquid and it makes up ideal substance connecting the entrapped biorecognition element to surface of transducer. It is usually used with electrochemical transducer [114].

B. *Chemical Immobilization Techniques*

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. Chemical bonds are mostly forming 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 [98, 18]. There are two types of chemical immobilizations such as: Covalent binding and cross-linking.

i. Covalent binding

Covalent binding is a process where biorecognition element receives firm bond to either surface or inner cavity of membrane. It is the most widely used type of enzyme immobilization technique [1, 91]. 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 [18] 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 [1].

ii. Cross-linking

It 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 [92, 91]. 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 [91]. Despite many advantages poor stability and partial denaturation of protein structure may limit application of cross linking immobilization [92, 98].

IV. Types of Biosensors

Biosensor devices can be categorized as electrochemical, optical/ visual, polymers, silica and glass, nanomaterials, genetically encoded biosensors and microbial biosensors [50].

A. *Electrochemical Biosensors*

Electrochemical biosensors are analytical devices prepared by modifying the surface of metal and carbon electrodes using biomaterials and that transduce biochemical interactions (enzyme-substrate reaction and antigen-antibody) to detectable electrical signals [131]. The electrochemical sensors became extremely desirable for early detection of diseases [38]. Electrochemical biosensors are employed to detect the amount of antioxidants and reactive oxygen species in physiological systems [125, 74]. 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 [31]. Even though electrochemical sensor based measurement of uric acid oxidation for glucose quantification seems ideal, similarity of uric acid oxidation with that of ascorbic acid poses major experimental hurdle to develop highly sensitive electrochemical biosensor [125]. In response of this problem, scientists have developed amperometric detection-based biosensor which has the ability to measure both reduction and oxidation potentials [31]. Electrochemical biosensors have been utilized for hormone detection [125]. Another potential area of technology development in biosensors is that it can be developed from nucleic acids that used for miRNA detection [40, 125].

Environmental monitoring is another important aspect wherein biosensor technology is required for rapid identification of pesticidal residues to prevent health hazards [68, 124]. Even though traditional methodsIncluding: 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 [124, 125]. Some enzymatic biosensors were utilized to understand the physiological effect of pesticides in the environment, food safety, and quality control [90, 125]. For example, acetylcholinesterase (AChE) inhibition-based biosensors were developed [90]. It is important to place special emphasis for selection of receptors for biosensor development, the use of different transduction techniques and fast screening strategies for applications of biosensor in food, and environmental safety [125].

B. *Optical/Visual Biosensors*

An optical biosensor is a compact analytical device containing a biorecognition elemens (enzymes, antibodies, antigens, receptors, nucleic acids, whole cells and tissues) integrated with an optical transducer system [26]. The most commonly used optical biosensors include: surface plasmon resonance (SPR)-based biosensors (SPR imaging and localized SPR) , evanescent wave fluorescence and bioluminescent optical fibre biosensors, as well as interferometric, ellipsometric and reflectometric interference spectroscopy and surface-enhanced Raman scattering biosensors [26]. Optical biosensors is advantageous than that of traditional analytical techniques since it is highly sensitive, specific and cost effective [105]. Optical biosensors have been utilized in clinical diagnostics, drug discovery, food process control, and environmental monitoring [15]. Optical biosensor also utilized for ethanol determination in fermented beverage samples [57]. Recently, CRISPR-Cas12a powered visual biosensor with a smartphone readout developed for for ultrasensitive and selective detection of SARS-CoV-2 [70].

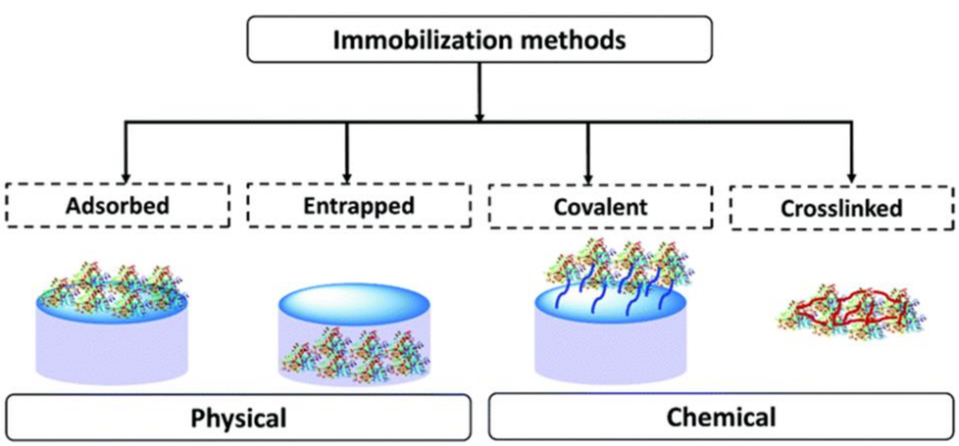

Fig. 2. The genera schematic representation of immobilization techniques used for biosensor development, [46].

TABLE I. LIST OF SOME POTENTIAL BIOSENSORS WITH PRINCIPLE AND APPLICATIONS

Sl. No.	Type	Principle	Applications	Ref
1.	Glucose oxidase electrode based biosensor	Electrochemistry using glucose oxidation	Analysis of glucose in biological sample	[19]
3.	Uric acid biosensor	Electrochemistry	For detection of clinical abnormalities or diseases	[52]
4.	Acetylcholinesterase inhibition-based biosensors	Electrochemistry	Understanding pesticidal impact	[90]
7.	Hydrogel (polyacrylamide)- based biosensor	Optical/visual biosensor	for the detection of biological warfare agents (BWAs)	[52]
8.	Silicon biosensor	Optical/visual/fluorescence	Bioimaging, biosensing and cancer therapy	[85,102].
10.	Nanomaterials-based biosensors	Electrochemical or optical/ visual/fluorescence	For multifaceted applications including biomedicine, for example diagnostic tools	[53, 58, 97]
11.	Genetically encoded or fluorescence- tagged biosensor	Fluorescence	For understanding biological process including (monitoring kinase activity, for protein–DNA interaction analyses, eal-time assays of motor proteins).	[80,55,132]
12.	Microbial fuel cell- based biosensors	Optical	To monitor biochemical oxygen demand and toxicity in the environment and heavy metal and pesticidal toxicity	[39,108]

Adapted with slight modification of the review paper published by Vigneshvar and coworkers [125].

C. *Nanomaterials-based biosensors*

The nanomaterials involved in the development of biosensor includes: gold and silver nanoparticles, quantum dots, mesoporous silica nanoparticles, carbon nanomaterials, and hybrid nanocomposites [133, 97]. They are used either as carriers for immobilizing biorecognition elements, or as labels for signal generation, transduction and amplification [133]. The nanomaterials-based detection technology showed advancement over the conventional methods in selectivity and sensitivity and its physical, chemical, electrical and optical properties makes it suitable for the application in biosensors [9]. The Nanomaterials Like semiconductor quantum dots and iron oxide nanocrystals have been applied to understand the tumor microenvironment for therapeutics and also for the delivery of nano-medicine [79, 47]. Recently, rapid and unamplified nanosensing technology has been developed for detection of SARS-CoV-2 RNA in human throat swab specimens [63].

D. *Genetically Encoded Biosensors*

Understanding the biological process and different metabolic pathways inside the cell needs to use tagged biosensor that developed by using genetically encoded or synthetic fluorescence [125]. Genetically encoded sensors are engineered fluorescent proteins that have been developed for ions metabolites, redox potential, biophysical processes [95]. The invention of genetically encodable green fluorescent protein has made remarkable progress in terms of optical probe design and efficiency [80]. Förster resonance energy transfer (FRET)-based biosensors have been developed for visualizing cGMP, cAMP, and Ca2+ in cells [112]. Now adays, various genetically encoded biosensors have been developed to sense aromatic monomers, including phenolic compounds obtained through direct lignin depolymerisation and other potential intermediates relevant to biomass valorization [2]. According to Lin and coworkers [66] genetically encoded fluorescent biosensors used to investigate kinase signaling in cancer cells and tumor tissue sections and enabled visualization of biological processes and events directly in situ. 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 [48]. Now the transformation in this field requires whole genome approach using better optical based genetic biosensors.

E. *Microbial biosensors*

Microbial biosensor is an analytical device which developed by immobilization of microorganism(s) onto physical transducer to generate a measurable signal proportional to the concentration of analytes [107, 144]. Microbial biosensors have been applied in numerous fields including medicine, environmental monitoring, defense, food processing and safety [24, 61]. Microbial biosensors have been integrated with many recently developed micro/nanotechnologies and applied to a wide range of detection purposes [64]. In future, these microbial biosensors will have wider applications in monitoring environmental metal pollution and sustainable energy production [108, 125].

V. APPLICATION OF BIOSENSORS

The most recent application of biosensor includes: agriculture, biomedicine, food, environmental and defense fields.

A. Biomedical Applications

Biomedical application of biosensor includes: measuring of blood glucose level, genetic diagnostics and DNA encoding, tissue/cell engineering and measuring the H2O2 amount. Little success is also achieved with few potential molecules for novel therapeutic, antimicrobial, and drug delivery. Invention on this line leads to discovery of electrochemical biosensors as reliable analytical devices for pathogen detection of avian influenza virus in the complex matrices [37]. More recent report revealed potential applications of affinity-based biosensors in sportmedicine and doping control analysis [72].

i. 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 [34, 138].

ii. Diagnose of infectious diseases

Biosensors are being used in the medical field to diagnose infectious diseases. A novel biosensor based on hafnium oxide (HfO2), has been used for early stage detection of human interleukin (IL)-10 [60]. Interaction between recombinant human IL-10 with corresponding monoclonal antibody is studied for early cytokine detection after device implantation. 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 HfO2 as a greatly sensitive bio-field-effect transistor [14]. HfO2 biosensor has been functionalized for antibody deposition with detection of a human antigen by electrochemical impedance spectroscopy.

The biggest dilemma faced today is of heart failure with about one million people suffering from it. Techniques for detection of cardiovascular diseases include immunoaffinity column assay, fluorometric, and enzyme-linked immunosor-bent assay [81, 12]. Chen and co-workers synthesized 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 [13]. Yang and coworkers devised an altered graphene electrode which possesses the ability to chemically bind with ssDNA and generate Voltametric signal for its counter analogue DNA for detection [10].

iii. 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 H_2O_2, various analytic techniques like titration, electrochemistry and photocatalysis could be utilized [93]. The instability of hydrogen peroxide in any biological system makes it highly injurious and cytotoxic for humans, plants, animals as well as bacteria [130]. In the field of tissue engineering, generally employed methods for H_2O_2 quantification are mostly electrochemical in nature and poses several difficulties (poor detection, low sensitivity, less portability and applicability issues on the organic system) to the user [42]. Enzyme based biosensing technique which is the recent finding have quite high stability and accuracy [103, 136].

B. 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. To ensure the safety of processed foodstuffs, specific methods have been developed by the food industries to detect and identify chemicals or biological agents that cause food spoilage and responsible for the spread of some serious health related problems ([135]. Biosensors being target specific, highly sensitive and quickly responsive and used to determine the chemical activities that lead to the food spoilage. The enzyme substrate interaction or antibody-antigen complex that can be easily detected is the fundamental determinant factors of biosensors [110]. The common types of biosensor employed in food industry are enzyme-based biosensors and immunosensors [4].

i. Food borne pathogens detection

The microbes that involved in food spoilage mainly include bacteria and fungi that lead to the spread of serious health hazards.

a. 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. Food industries had been striving to avoid the problem relate to food poisoning, by timely detection and removal of this bacterium. For this different type of biosensors like Piezoelectric biosensors for detection of monitoring *Salmonella* monoclonal antigen-antibody interaction quickly and easily, Fibre-optic biosensors to monitor the presence of *Listeria monocytogenes* [335, 96]. Amperometric biosensors based on enzymatic system had been successfully used for the detection of *E. coli* 0157:H7 [109].

b. Fungal pathogens detection

Fungal pathogens are the common food deteriorating microorganisms that cause severe health problems. The common food contaminating fungi includes: Botrytis sp., Aspergillus, Colletotrichum and many other fungal species. Due to the remarkable specificity, reduced costs and easy and quick monitoring through biosensors and there are reports that fungal mycotoxins can be detected using optical SPR biosensors [62, 134].

ii. Biosensors for determination of chemical contaminants

Chemical contaminant that causes food spoilage including pesticides, fertilizers, heavy metals, food additives and antibiotics.

a. Biosensors for contaminant residues and pesticides detection

The presence of pesticide residues and metabolites in food, water and soil currently represents one of the major issues [78]. Due to the limitations in conventional methodologies, the development of biosensors for direct and indirect pesticide detection is of particular interest. The enzymatic biosensors like cholinesterase (AChE, BChE), organophosphorus-hydrolase (OPH), and urease are used for the detection of pesticides, fertilizers, and heavy metals [101]. Analytical devices, based on OPH and cholinesterase inhibition, have been widely used for the detection of carbamates [139] and organophosphate compounds (OP) [84]. Immobilized cells of Flavobacterium sp have been used for the detection of methyl parathion. Whole cells of Flavobacterium sp. Flavobacterium sp. have the enzyme organophosphorus hydrolase, which hydrolyzes the methyl parathion into detectable product p-nitrophenol [54]. Immunosensors have great potential for monitoring herbicides in drinking water, the detection of polychlorinated terphenyls and atrazine [89].

b. 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. 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 incorporate genetically modified microorganisms and enzymes such as urease, cholinesterase, glucose oxidase, alkaline phosphatase, ascorbate oxidase and peroxidase [115]. Immobilized algae inside bovine serum albumin membranes have made a network structure with glutaraldehyde vapors deposited on interdigitated conductometric electrodes and local conductivity variations caused by algae alkaline phosphatase and acetylcholinesterase activities could be detected [17]. 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 made from whole cells of Bacillus badius with phenol red as an indicator that can sense down to 0.1 g/l of cadmium in milk.

c. 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 [119]. During storage, compounds that provide aroma and abnormal flavors indicating in most cases microbial growth and insufficient food safety [101].

Biosensors that use whole cells or enzymes have been used for the detection of alcohol [120]. Biosensor with immobilized enzymes: alcohol oxidase, alcohol peroxidase and a chromogen, have been used detect injuries caused by low O2 in lettuce, cauliflower, broccoli and cabbage lightly processed and packed in a modified atmosphere [106]. This biosensor could also be used to monitor ethanol during the storage of apples in a controlled atmosphere, the decay in potato tubers (Castillo et al., 2003). Similar research has been done to detect organic acids and sugars as indicators of fruit and vegetables maturity [5]. The co-immobilized biosensor containing alcohol oxidase and glucose oxidase have been used to determine glucose and ethanol [6]. Measurements are based on monitoring decrease in current on reduction potential of tetrathiafulvalene (at 0.1V 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.

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 [121]. Biosensors technology for substance detection significantly reduces analysis time, and improves specificity, reliability and test sensitivity. These properties allow for real time decision making during food processing. A listing of biosensors used to evaluate food composition is presented by Serna et al. [101].

C. *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 the most of the biosensors described in the literature for environmental applications electrochemical transducers are used [111]. For environmental applications, the main advantages offered by biosensors over conventional analytical techniques are the possibility of 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.

i. Heavy metals detection and monitoring

Heavy metals are non-degradable compounds that affect humans' health and their hyper-accumulation leads to various inappropriate health conditions [23]. The metal contaminants most commonly observed in the environment are: lead, chromium, zinc, mercury, cadmium and copper [67]. There are various types of biosensors have been utilized in measring and monitoring toxic heavy metals.

Bacteria-based cell biosensors require the use of genes that resist certain types of heavy metals like copper, mercury, tin cobalt etc. [94]. The bacterial cell biosensors interact with heavy metals by their cytoplasm that is based on the conjugation of some luminescent proteins like luciferin, with those genes that resist heavy metals [23].

Enzyme-based biosensors have also provided promising results in that regard have been used for the detection of the toxic levels of different heavy metals. These biosensors work by inhibition by metal ions on various kinds of enzymes, these inhibitions are then monitored by using different types of biosensors with HIGH specificity. For example, Amperometric biosensors were used for the detection of inhibition of mercury ions (Hg^{+2}) by urease enzyme (Dominguez–Renedo 2009). Inhibition of cobalt, nickel, mercury, gold and lead with same urease enzyme lead to the monitoring of the toxic levels using fibre optic sensors [56].

ii. Biochemical oxygen demand (BOD)

The BOD is the amount of molecular oxygen (O_2) that consumed by microorganisms during break down of organic compounds in waste water [138]. Nakamura and Karube (Kuswandi 2003) developed 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 [29]. The biosensor monitors the dissolved oxygen concentration in artificial wastewater through an oxygen sensing film immobilized on the bottom of glass sample vials.

iii. Biosensors for pesticides detection

As defined by the EPA, pesticides are any substance or mixture of substances intended for preventing, destroying, repelling, or lessening the damage of any pest [8]. Pesticides are the most abundant, present in water, atmosphere, soil, plants, and food. The organophosphates that used as insecticides (pesticides) causes different negative impacts like changing soil fertility, damaging beneficial insects and microbes in soil and loss of biodiversity. To measure toxic levels of these pesticides in soils and in water nanotechnological sensors have been developed. The nanotechnology helped to develope enzymatic biosensors by immobilizing the enzymes on different macro-molecules. The common example of enzyme biosensor that has been used as detectors of organophosphates is acetylcholinesterase sensors which work by inhibiting acetylcholinesterase activity [138].

D. Biosensors in defense

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 [104]. Episodes of anthrax attacks in the United States (1984 and 2001) and the Sarin attacks in Japan (1995), and in Syria (2013) (The New York Times, Dec. 28, 2013) 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 includes bacteria, virus, and toxins is often attempted using various devices of biosensors such as: electrochemical, nucleic acid, optical and piezo electric, which will have immense applications in military and health as well as defense and security. 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 [51; 65]. Optical biosensors that characterize changes in the refractive index (resonant waveguide grafting; RWG and surface Plasmon resonance; SPR) [32] 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 [32].

VI. Conclusion

Biosensor that composed biorecognition element and transdusers is a rapidly growing field encompassing various fields like medicine, agriculture, food industry, environmental science and defense. Now adays 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 biosensing 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 and COVID-19) and can also be employed for bioremediation of pollutants.

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