ISSN No:-2456-2165

Biosensors: Techniques and Applications- A Review

[1,2] Ibrahim Haruna Omeiza*, [1]Oluwafemi Adebayo Oyewole, [2]Orji Sylvester Oko,
[2]Egga Anita,[2]Dauda Adekunle K., [2]Adebayo Anne-Marie Tope, [2]Adedoyin Temitope O.
[1]Department of Microbiology, School of Life Sciences, Federal University of Technology, Minna, Nigeria.
[2] National Agency for Science and Engineering Infrastructure, Abuja Nigeria.

Abstract:- Processes of biological and biochemical mechanisms are significant players in a host of scientific fields, and it is important to promptly monitor the parameters involved in these processes. The conversion of biological data into an electrical signal has proven difficult in the times past, necessitating the need for technological devices for the analysis of these data and signals with real-time ease and precision. The analytical device that aids the conversion of a response from biological and/or biochemical interactions into an electrical signal is referred to as a biosensor; described often as a system made up of three-element including a bio-receptor, a transducing element and a signal-processing unit. Biosensors work through the incorporation of a biological or bio-recognition element to determine a specific analyte embeded with a transducer that is able to convert the biological signal into an electrical signal, for onward interpretation by the end-user. They are classified either by the type of biological signalling mechanism, or the type of signal transduction mechanism employed. Biosensors have the ability to measure molecules that are non-polar and do not respond to most measurement devices. They are easy and efficient to use, ultra-sensitive, with high specificity, and can be controlled rapidly and continuously. However, biosensors are impeded by heat sterilization, causing the denaturation of the biological material, and they can also be extremely expensive. In a variety of scientific areas of research and development such as monitoring of environmental impacts and pollution, medical diagnosis and clinical medicine, industrial processes, agriculture and food safety, defence and security, biosensors have found huge application.

Keywords:- *Biosensor, Bio-Receptor, Analyte, Non-Polar, Transducer.*

I. INTRODUCTION

The study bio-molecular exchange in systems, observation of cellular activity, and the determination of analytes specifically from bodily fluids, manufacturing processes, or samples from the environment hold huge significance to researches in the fields of life sciences, pharmaceuticals, medical diagnosis, and quality assurance and safety (Cunningham, 2009). The processes of bio-sensing has in times of recent shown to be a significant emerging technological innovation in various scientific areas of research endeavour, from monitoring of environmental impacts and protection of the environment, military security and defense, to applications in biomedicine (Bora *et al.,* 2013; Rocchitta *et al.,* 2016). Processes of interactions between the biological and biochemical components have a very critical part to play in these fields, and the prompt monitor and regulation of these different factors involved is of utmost significance to the array of applications available in these fields. The conversion of biological data into meaningful electrical signal in the times past has been herculean, and this has necessitated the desire to have efficient devices for rapid and precise analyses of biological data (Koyun *et al.,* 2012; Bora *et al.,* 2013).

The analytical device that aids the conversion of a biological response in the form of a data into an electrical signal is referred to as a biosensor (Kumar and Rani, 2013). This term is generally applied to encompass sensor devices used for the analyses of substance concentration and other factors that are of biological interest, even in cases where a biological system is not directly utilized. The biosensors work through the use of a transducing element to incorporate a sensing material of biological composition with a detector system (Malhotra *et al.,* 2017). They are of high portability, cost-friendly devices employed for the rapid detection of interesting analytes such as proteins and pathogens (Goode *et al.,* 2015).

Dr, Leland C. Clark, who was well known as the father of biosensors, first established the idea of the use of a biological sensing element to monitor and detect different analytes. In 1960, he came up with the ‘enzyme electrode’ to quantify the glucose concentration in a sample by using immobilized glucose oxidase (GOD) enzyme directly on an amphoteric oxygen electrode surface semi-permeable dialysis membrane (Nayak *et al*, 2009; Koyun *et al*, 2012). This great achievement opened up ways for the development of a wide range of sensors for the detection and measurement of compounds which are of biological interest using different enzymes. For example, application of urease for detection of urea, and also the use of NAD^+, glutamate dehydrogenase and lactate dehydrogenase for the detection of Nicotinamide Adenosine Dehydrogenase (NADH) using (Nayak *et al.,* 2009).

The International Union of Pure and Applied Chemistry, IUPAC aptly gave the definition of a biosensor as a “device that is able to utilize specific biochemical reactions mediated by isolated enzymes, immune-systems, tissues, organelles or whole cells to measure or determine chemical compounds usually by electrical, thermal or optical signals” (Nayak *et al,* 2009). Biosensors are self-sufficient integrated devices with the ability to provide highly specific analytical information that maybe semi-quantitative by making use of a bio-recognition element or a biochemical receptor, spatially connected directly with a transducing element. This should not be mistaken for a bioanalytical system or a bioprobe; the bio-analytical system requires additional steps during processing, such as reagents addition, while the bioprobe is not reuseable after every measurement of the analytes concentration (Koyun *et al.*, 2012).

The transducer is used by the biosensor for the coupling of a biological sensing element with the detector system (Malhotra *et al.*, 2017). This is closely connected to the recognition element aided by a supporting material. The bio-recognition element itself is made up of two affinity-pairing partners (such as antigen/antibody or enzyme/substrate), one of which is immobilised. One major function of the transducer is the contact detect between the attracted-pairing partners by converting biological data into electrical signals, and gathered for further transformation and interpretation (Mungroo and Neethirajan, 2014).

Biosensors generally are a self-sufficient integral tool primarily consisting of three (3) components; a biological recognition element, a transducer, and a signal processor, that provide highly precise and accurate, quantitative and analytical information (Su *et al.*, 2011). Figures 1 and 2 present the diagrammatic representation of these details.

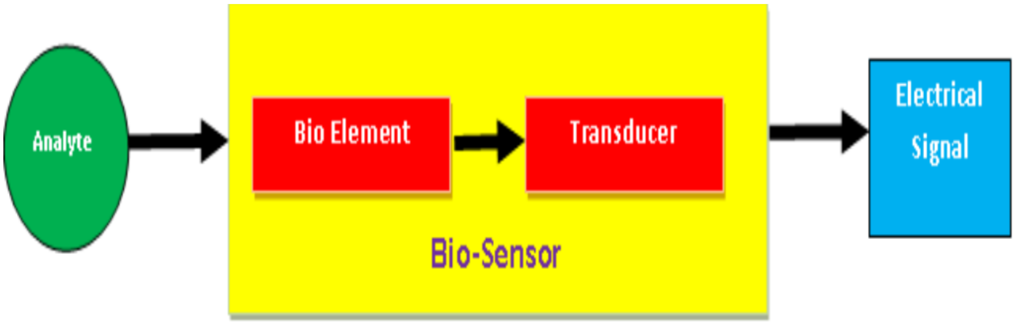

Figure 1: Elements of a biosensor. Source: Gopinath *et al.* (2015)

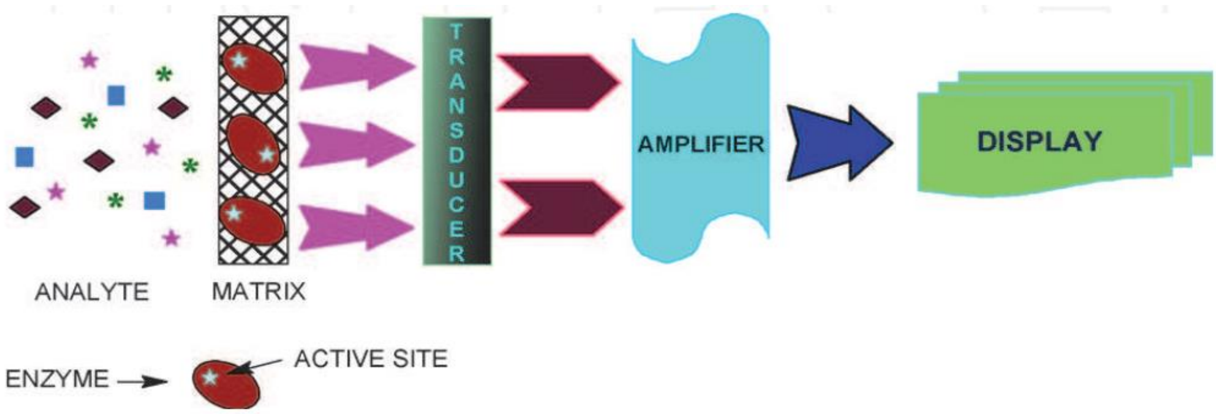

Figure 2: Schematic of a biosensor. Source: Gouvêa (2011).

II. TECHNIQUES IN BIOSENSOR

The difficulty mostly encountered in the detection of analytes of biological origin directly by using their physical characteristics such as mass, size, electrical impedance, or dielectric permittivity has caused researches in biological sciences to always rely on some form of "label" attachment to one or more of the molecules/viruses/cells being examined (Cunningham, 2009). The most crucial aspect of the biosensor process is the combination of the appropriate biological and electronic parts to produce a significant and applicable signal during analysis. The isolation and stability of the biological component in the course of analysis is as critically essential so as to ensure specific immobilization or binding of only the molecule of interest on the transducer or electronic component, and with the biological component being used outside of its natural environment, its stability is crucial and important for the success of the biosensor (Malhotra *et al.*, 2017).

Generally, there are two (2) major components of the biosensors; a bio-recognition element and a signal conversion unit called the transducer. In addition, they include an interface of input/output referred to as the electronic component used for the instruments interaction. The component that supplies the primary signal is the biological recognition element (ligand), which binds to the analyte of interest. The bio-recognition molecule is immobilised over a signal transducer to produce a reagent-less device for analysis (Kumar and Rani, 2013). The biological recognition element which includes enzymes, antibodies, DNA sequences or even whole microorganisms

ISSN No:-2456-2165

affords the biosensor to be selective, allowing it to selectively pick a molecule of interest from a matrix of many other molecules for action (Rasooly & Herold, 2006; Kumar and Rani, 2013). The transducer determines the extent of the bio-recognition process and gives response to the primary signal derived from the recognition element and then converts it to a form that can be further amplified, stored, manipulated, displayed, and analysed, which can be output to the end user by an alarm system (Rasooly & Herold, 2006; Kumar and Rani, 2013) as depicted in figure 3:

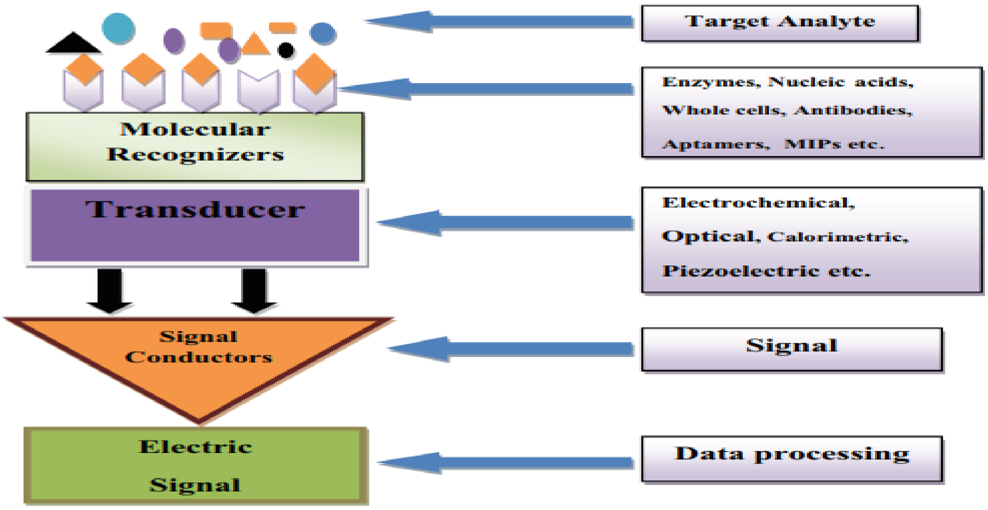

Figure 3: Basic techniques of a biosensor. Source: Verma and Bhardwaj (2015).

The techniques employed in biosensors are dependent on label-based and label-free detection; the label-based is largely dependent upon the specific qualities of the label compounds to target detection, while the label-free technique detects molecules that are unlabelled or difficult to tag (Sang *et al.*, 2015; Vigneshvar *et al.*, 2016). Direct-detection otherwise referred to as label-free biosensors are quite simpler and quicker, and typically yields a higher detection limit than the indirect-detection or label-based systems (Rasooly and Herold, 2006). The design of the label is in such a way that it has easy measurement using its colour or its photon generating capability at a particular wavelength, and additionally it acts as a substitute which indirectly signals the presence of the analyte to which it has been attached (Cunningham, 2009), as illustrated in Figure 4 below:

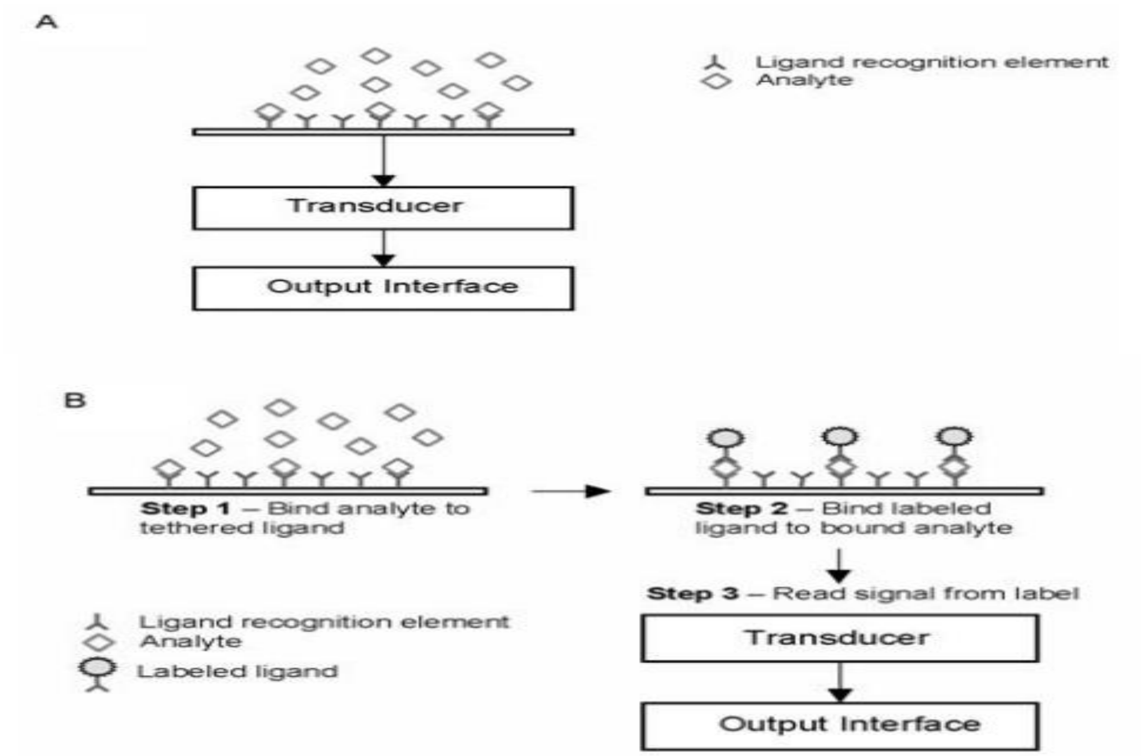

Figure 4: Generic schematic of biosensors: (A). Label-free. (B) Label-based. Source: Rasooly and Herold (2006).

Working of a Biosensor

The biological material of analytical consideration, usually in the form of a specific enzyme, DNA probe, antibody, microorganism or organelles, is conventionally immobilized using methods such as entrapment (which is either physical or membrane), binding (which could be non-covalent or covalent). The analytes, usually comprising of enzyme substrates, complementary DNA, antigen, binds to the biological material to form a bound analyte which eventually produces the measurable electronic response (Koyun *et al.*, 2012; Malhotra *et al.*, 2017).

In the design of a biosensor, great attention must be paid to both the target analyte and complexity of the medium in which the analyte will be determined (Rocchitta *et al.*, 2016). Specific detection in bio-sensing however, requires monitoring closely the exchange between a molecule and its receptor, thus enabling the biosensors to specifically transduce molecular recognition processes into electrical, mechanical or optical signals (Baaske *et al.*, 2014).

Basically, the biosensor as a device is analytical and works primarily by the incorporation of the biological or bio-recognition elements to determine a specific analyte integrated with a transducing element, to aid the conversion of a biological signal into an electrical signal, then forwarded to the end-user(s) for interpretation (Perumal and Hashim, 2014). The transducer can convert the product linked changes into electrical signals for onward amplification and measurement (Malhotra *et al.*, 2017). The interaction between the analyte and the bio-receptor produce chemical changes such as the production of a new chemical, heat release, electron flow, and in some cases changes in the pH or mass. The biochemical signal is transformed into an electrical signal by the transducing element, followed by the amplification of the electrical signal and relayed to a microelectronics and data processor. A measurable signal is then generated, such as a digital display, a print-out or an optical change (Perumal and Hashim, 2014). The working or measurement flow of a biosensor is presented in the figures 5 and 6 below:

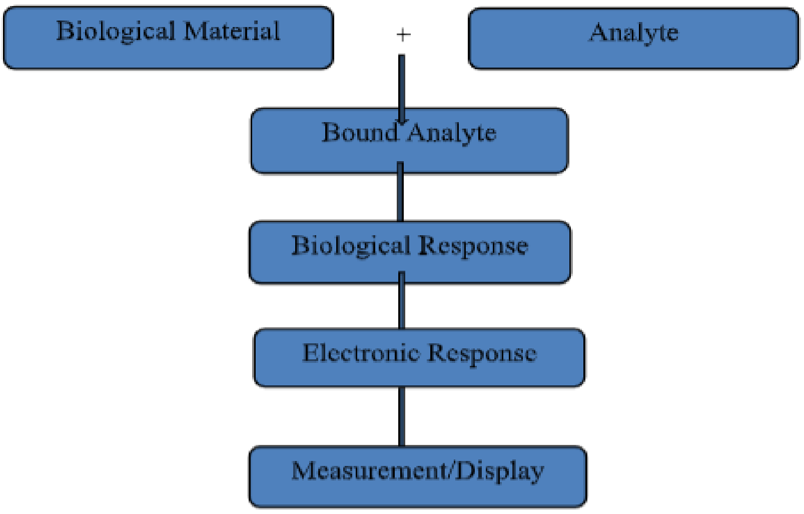

Figure 5: Working of a biosensor. Source: Malhotra *et al* (2017).

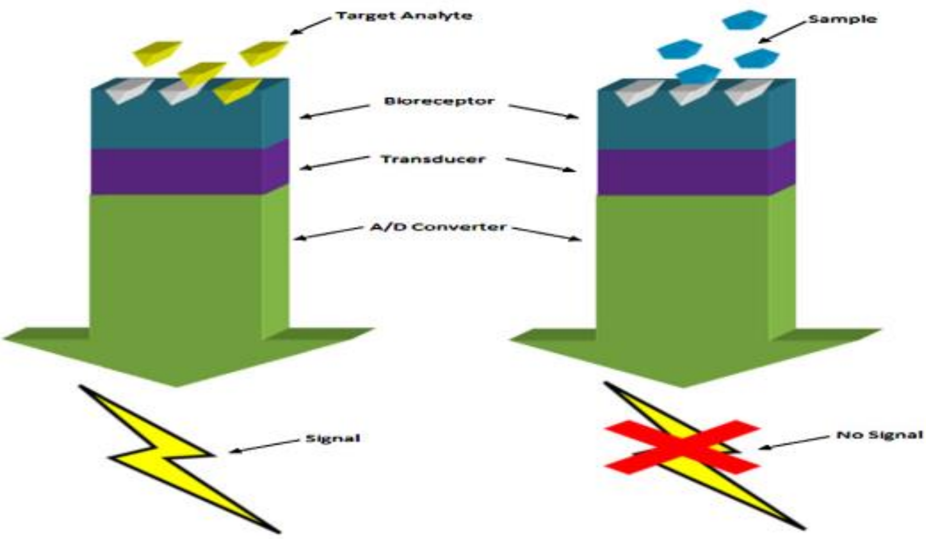

Figure 6: Diagrammatic presentation of the workings of biosensor.
Source: Perumal and Hashim (2014).

Types of Biosensors

Classification of biosensors may be in two categories which include the type of biological signalling method they utilize or by the signal transduction process they employ (Goode *et al.,* 2014; Perumal and Hashim, 2014). Biological materials or components constitute the biological element, and the type of physicochemical change resulting from the sensing process determines the mode of transduction.

Primarily, biosensors classifications on the basis of transducing element are mass based (for example piezoelectric and magno-electric) biosensors, electrochemical (for example potentiometric, amperometric, impedimetric and conductometric) biosensors, and the optical types of biosensors (for example surface plasmon resonance and fibre optics) (Malhotra *et al.,* 2017) as represented in figure 7 below:

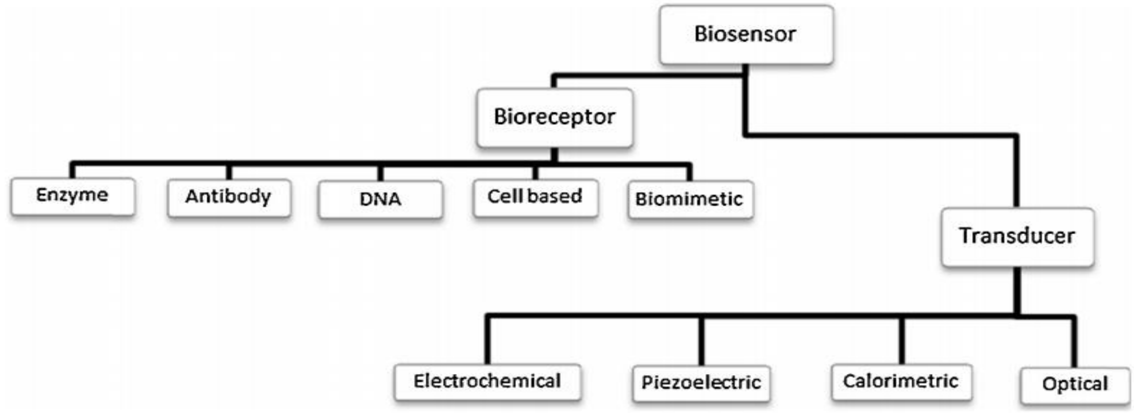

Figure 7: Classification of biosensors based on their bio-recognition element and transducer element. Source: Perumal and Hashim (2014).

Based on biological signalling mechanism

Biosensors can be categorized on the basis of the type of mechanism for biological signalling they employ, with the bio-recognition element or bioreceptor being an important distinguishing feature of a biosensor. Essentially it is of significant advantage for a bio-receptor to be of high selectivity and sensitivity towards the specific target analyte so as to prevent unnecessary interference by any other substance from the sample matrix (Perumal and Hashim, 2014). Based on this narrative, biosensors can be further divided into five major mechanisms as enzyme based sensors, immunosensors (antibody), cell based sensors, DNA/Nucleic Acid based sensors, and biomimetic (aptamers) sensors.

Based on transduction methods

Biosensors are also classified based on their employed mode of transduction; with the critical role of the transducer component in the signal detection process of the biosensor to efficiently convert data from biochemical interactions into an electrical signal (Perumal and Hashim, 2014). A number of transducing mechanisms have been developed by researchers over the last decade, and some recent literature reviews have highlighted the most common available methods to include electrochemical transducer biosensor, piezoelectric transducer mechanism biosensor, calorimetric and optical transducer mechanisms biosensors (Perumal and Hashim, 2014).

Advantages of Biosensor

Biosensors have several advantages that make for their vast applications in various fields of scientific endevour. The advantages include;

i. They require lesser reagent, in order words they have small fluid volume manipulation
ii. The high specificity of the biological elements employed in the system
iii. As a result of the immobilized system applied in biosensors the biological systems are re-useable
iv. They can determine nonpolar molecules that do not respond to most measurement devices
v. Their energy consumption is quite low
vi. They have high precision and portability
vii. The assay time for biosensors is relatively short, coupled with their high-throughput and multiplexing capability (Koyun *et al.,* 2012; Shruthi *et al.,* 2012).

Disadvantages of Biosensors

Biosensors have a number of factors militating against their functioning, or example, the denaturation of the biological material with heat sterilization thus resulting in the loss of activity during the immobilization on a transducing element. Thus, the biological materials stability is hugely dependent on the natural properties of the molecule that under any stress resulting from environmental impact can easily be denatured. Also, other molecules capable of membrane diffusion can readily over-excite the cells in the biosensor (Koyun *et al.,* 2012; Shruthi *et al.,* 2012).

Applications of Biosensors

The speedy growths recorded in the biosensor research industry have led to an increased great application of this technology in many different fields of scientific and human endeavours. Biosensors have a very wide range of applications that aim to improve the quality of life (Nayak *et al.*, 2009; Bhalla *et al.*, 2016).

The growing research in biosensors can provide efficient detection and measurement devices that are swift and easy-to-use, relatively cheap, sensitive and of high precision, in a variety of applications, as presented in the figure 8 below;

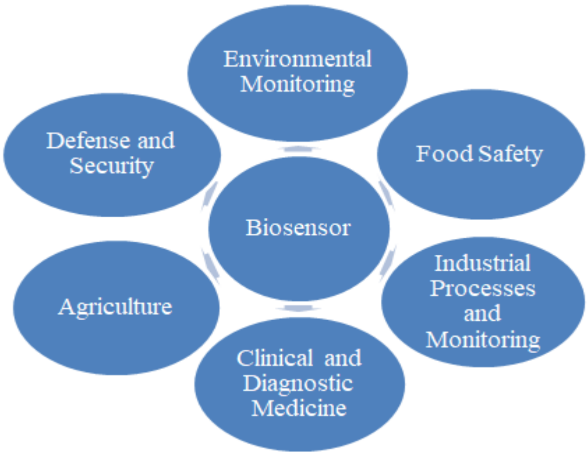

Figure 8: Areas of biosensor applications.

Clinical and Diagnostic Medicine

Biosensors have found a huge important application in the field of medical diagnostics, to detect bio-molecules that either act as pointers to diseases or drug targets. For example, electrochemical biosensors can be employed as clinical tools for the detection of protein cancer biomarkers, and are also now hugely employed in clinical biochemistry laboratories for the detection and measurement of blood glucose levels by individuals with diabetes (Malhotra *et al.*, 2017; Bhalla *et al.*, 2017). The devices are able to determine the glucose levels in the undiluted blood samples thus allowing for easy and quick self-testing and monitoring, a feat that has revolutionised the management of diabetes (Malhotra *et al.*, 2017).

Environmental Monitoring

Biosensors have also found potential use in the control and monitoring of environmental pollution. Environmental and water monitoring is one interesting area where whole cell biosensors may have substantial advantages to tackle the upsurge in the number of pollutants finding their way into the groundwater systems and eventually into drinking water. Biosensors are applied for the checking and monitoring of soil, air and water qualities. They can also be employed to pick up very small traces of organophosphates from pesticides and also to monitor the levels of wastewater toxicity, for example. (Malhotra *et al.*, 2017).

Organisms that can respond to toxic contaminants at concentrations much lesser than which humans can detect, have been utilized in biosensors to provide a quick warning of their presence. Such devices can be used to monitor the environment, trace gas detection and in facilities for water treatment (Shruthi *et al.*, 2012). Also, in some cases, bacteria species such as *Rhodococcus erythropolis* immobilised in polyacrylamide or collagen are used in biological oxygen demand (BOD) analysers, to test and determine waste water quality.

Industrial Processes and Monitoring

The application of biosensor technology in industrial bioprocesses monitoring involves the sampling of biological processes at a very large scale, such as in the fermentation of beer or wine, biodegradation and bioremediation of wastes. The standard applicable in the industry for this processes require very elaborate laboratory based procedures with highly sophisticated equipment and expertise, such as the polymerase chain reaction (PCR), fluorescence *in-situ* hybridization (FISH) and mass spectrometry, making the use of biosensors all-important (Carpenter *et al*, 2018).

In addition, along with the conventional process of industrial fermentation, cultures of bacteria and eukaryotic cells are being used for the production of a variety of novel products. Thus making the real time monitoring of these relatively complex and costly processes very important in order to minimize the production costs (Malhotra *et al.*, 2017). Biosensors have also found utilization in the food industry during the processes of quality control for example, in the measurement of carbohydrates, alcohols and acids, and are also useful in the detection of pathogens in industries that process fresh meats, poultry or fish (Mehrotra, 2016; Zeng *et al.*, 2016).

Agriculture and Food Safety

Owing to critical linkage of agriculture with the overall general health and wellbeing of humans and the ecosystem, there is the need to deploy efficient and effective technology to boost output and ensure food safety. Biosensors, in light of the above have become a significant technological tool in the agricultural sector. For example, enzyme biosensors capable of the inhibition of cholinesterases have been utilized in the detection and measurement of organophosphates and carbamates traces or rersidues from pesticides that may be present as harmful and poisonous remains on farm produce which could have adverse effects on human health (Malhotra *et al.*, 2017). In addition, they have also been employed for use in aquaculture to detect metabolites in the aftermath of fish death, to determine freshness and spoilage (Carpenter *et al*, 2018).

Biosensors are used to detect pathogens in food and food products. For example, the presence of *Escherichia coli* in vegetables is an indicator of faecal contamination. The determination of *E. coli* is carried out by measuring the variation in pH levels resulting from ammonia; a product of urease-*E. coli* antibody conjugate, using potentiometric alternating biosensing systems. Also, in assessing food quality, antibodies or immunosensors may be applied in assays to measure small molecules such as water-soluble vitamins and chemical contaminants (Mehrotra, 2016; Zeng *et al.*, 2016).

Defense and Security

Investments in military defense and security applications cannot be overemphasized, especially with the continuous evolution of conventional war to asymmetric warfare, and the proliferation of terrorism globally. Biosensors have been used to detect the chemical and biological species used in warfare in times of biological attacks. They have also been deployed to screen people, packages, and harmful substances (Carpenter *et al,* 2018). The biosensors are able to play such critical role by sensitively and selectively identifying organisms that pose even the slightest threat in virtually real time called biowarfare agents (BWAs) including bacteria (vegetative and spores form of *Bacillus anthracis, Clostridium botulinum*), viruses and toxins (Mehrotra, 2016).

III. CONCLUSION

In whatever requirement for the utilization of biosensor for biological data processing and signal detection and interpretation, it is emerging as an efficient, sensitive, high-throughput, and relatively cheap answers to an array of biotechnological applications. The inherent chemical diversity and specificity of biological molecules such as DNA, RNA, and protein, which can often outperform traditional analytics, give the biosensors the edge. And as the tools of synthetic biology continually advance to further enable the development of biosensor, they will become an integral part of the industrial, environmental, scientific, and medical industries.

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