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Biosensors: Design, Development and Applications

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Abstract

The ability to detect even the slightest physiological change in the human body with high sensitivity and accurately monitor processes that impact human nature and their surroundings has led to an immense improvement in the quality of life. Biosensors continue to play a critical role across a myriad of fields including biomedical diagnosis, monitoring of treatment and disease progression, drug discovery, food control and environmental monitoring. These novel analytical tools are small devices that use a biological recognition system to investigate or detect molecules. This chapter covers the design and development of biosensors, beginning with a brief historical overview. The working principle and important characteristics or attributes of biosensors will also be addressed. Furthermore, the basic types of biosensors and the general applications of these biosensors in various fields will be discussed.

Keywords: bio-receptor, transducer, bio-sensing, analyze

1. Introduction

The importance of monitoring vital processes and parameters in various industries has led to the discovery of small analytical devices known as biosensors. The emergence of these devices has provided solutions to various applications including drug discovery, disease diagnosis, biomedicine, food safety and processing, environmental monitoring, defence, and security [1, 2] as depicted. Biosensors are analytical devices used to investigate the presence of an analyte of interest in a sample. By definition, these are self-sufficient integrated devices that provide qualitative and semi-quantitative analytical data through the use of a biological recognition element that is coupled to a transduction element. The sole purpose of these analytical devices is to rapidly provide accurate and reliable information about an analyte of interest in real time [3–6].

Generally, biosensors are composed of three main components as depicted in **Figure 1**. These include a biological sensing element, physicochemical detector or transducer and a signal processing system [8]. Biological sensing elements are used to interact with the analyte of interest to generate a signal. Sensing elements normally include materials such as tissues, microorganisms, organelles, cell receptors, enzymes, antibodies, and nucleic acids. The signal generated through the interaction of the sensing element and the analyte of interest is then transformed to a measurable and quantifiable electrical signal via the transducer. The signal

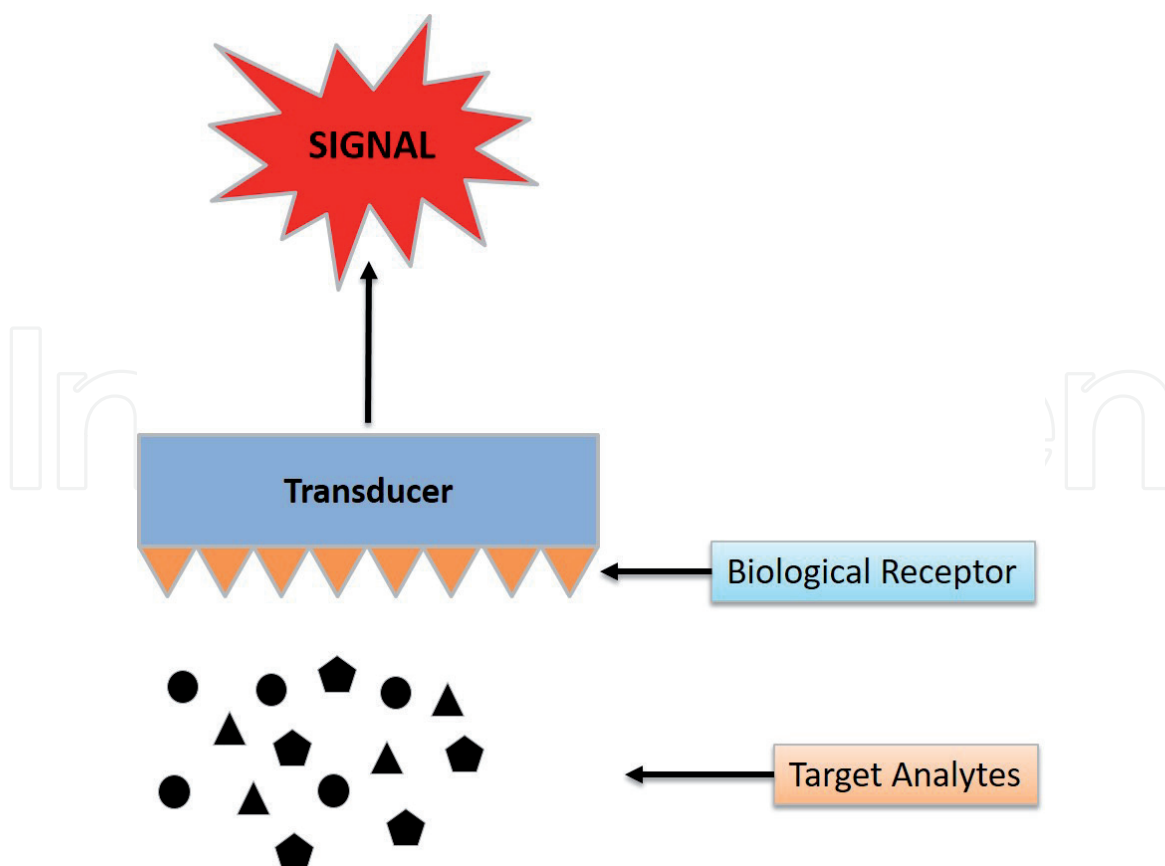


Figure 1.
Basic scheme of a biosensor. Picture adapted from Korotkaya [7] with modifications.

processing system therefore amplifies the electrical signal and conveys it to a data processor that produces a measurable signal in the form of a digital display, print out or color change [9, 10].

The concept of a biosensor is an ancient phenomenon. The first reported concept of a biosensor dates back to 1906 when Cremer [11] discovered that the concentration of an acid suspended in an aqueous solution is equivalent to the electric potential generated between sections of the solution when separated by a glass membrane. This led to the development of the concept of pH by Soren Peder Lauritz Sorensen in 1909, which was followed by the development of an electrode to measure this pH in 1922 by Hughes [12]. This paved way for the development of what is known as a “true biosensor” in 1959 by Leland C. Clark, Jr., who is affectionately known as the “father of biosensors”. Clark developed a sensor for detecting glucose in biological samples, using a glucose oxidase electrode that detects the presence of either oxygen or hydrogen peroxide. Since then, great strides have been made in developing highly sensitive and selective biosensing devices [13, 14]. The emphasis of this chapter is on the design, development and applications of biosensors. Various components that constitute a biosensor as well as the working principle of biosensors will be presented. Moreover, various types of biosensors will be highlighted and various fields where these devices are used will also be discussed.

2. Biosensor design

A successful biosensor is composed of two main components, mainly a biological receptor or sensor element and a transducer. A signal processing unit that usually contains a display or printer is normally used in conjunction to a biosensor as depicted in **Figure 2**.

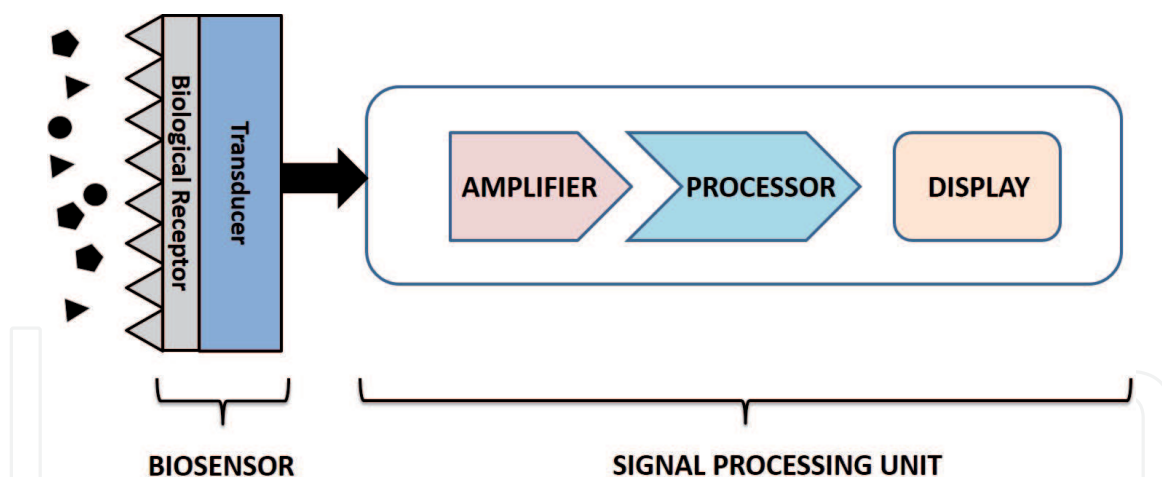


Figure 2.
 Biosensor design showing the various components necessary for generating a signal. Picture adapted from [6].

2.1 Biological receptor

This component is also known as a sensor or detector element and is responsible for sensing or detecting the presence and/or the concentration of the target analyte or substance. This is a biological component, which serves as a biochemical receptor that specifically recognizes the target analyte [15]. When the biological receptor interacts with a target analyte, it generates a signal in the form of light, heat, pH, charge or mass change [11]. This material should be highly specific, stable under storage conditions and must be immobilized. Furthermore, the biological receptor should be capable of selectively detecting the target compound or analyte in the test sample. According to Paddle [16], the biological receptor determines the sensitivity of the entire device through the generation of the physicochemical signal that is monitored by the transducer [16, 17].

This component can be a tissue, microorganism, organelle, cell receptor, enzyme, antibody or nucleic acid etc. These can be grouped into two categories, namely catalytic and non-catalytic receptors [18]. The catalytic group of biological receptors are used in devices intended for continuous monitoring of substances at millimolar or micromolar concentrations. These include enzymes, tissues and microorganisms. The non-catalytic group is used mainly in biosensor devices that measure analytes such as steroids, drugs, and toxins etc. which usually occur at very low concentrations (micro to picomolar range). These are non-reusable devices which can only be used once and discarded thereafter. Such receptors include antibodies, antigens, nucleic acids etc. [17, 19, 20].

2.2 Transducer

A transducer forms the second main component in the design of a biosensor. Generally, a transducer is a material that is capable of converting one form of energy to another [11]. In a biosensor, a transducer is responsible for converting the biochemical signal received from the biological receptor, which is a result of the interaction between the target analyte and the biological receptor, into a measurable and quantifiable signal which can be piezo-electrical, optical, electrochemical etc. The transducer detects and measures the change that occurs during biological receptor – analyte interaction [21]. An example of a transducer is a pH sensor in a glucose biosensor. An enzyme, known as glucose oxidase, is used as a biological receptor which binds glucose and converts it to gluconic acid in the presence of oxygen. The pH sensor (transducer) then detects the change in pH (due to

production of gluconic acid) and converts it into a voltage change [22, 23]. The following features are recommended when a transducer is designed; specificity to the target analyte, analyte concentration range, response time and suitability for practical applications. Ideally, a transducer should be highly specific to the analyte, give measurement at the lowest analyte concentration within the shortest time possible [24].

3. Working principle of a biosensor

As indicated in the aforementioned sections, a biosensor comprises of a biological receptor coupled with a transducer and signal processing unit, and thus operate on the basis of signal transduction. The combination of these components is designed to convert the biological response into a corresponding electrical response and ultimately a measurable output. In simpler terms, biosensors are responsible for the quantitative analysis of a molecule by relating its biological action into a measurable signal [25]. Initially, the molecule of interest in the test sample binds or interacts specifically with the biological receptor, resulting in a physiological change. This further alters the physicochemical properties of the transducer that is in close proximity to the biological receptor. This further leads to a change in the optical or electronic properties of the transducer which is further converted into an electrical signal which is detectable [26].

The signal generated by the transducer can either be a current or voltage, depending on the type of biological receptor. If the output from the transducer is in the form of a current, then this will be converted into an equivalent voltage. Also, the output voltage is usually very low and masked by a high frequency noise signal, which then requires further alterations, processing and amplification through various filters within the signal processing unit. Finally, the output generated from the signal processing unit should be comparable to the biological quantity being measured [27].

4. Important characteristics of biosensors

Owing to the nature of the applications in which biosensors are used in, several characteristics or parameters have to be met when a biosensor is designed. These characteristics define the performance and usefulness of a biosensor.

4.1 Sensitivity

This is considered as the most important characteristic of a biosensor. The sensitivity of a biosensor is defined as the relationship between the change in analyte concentration and the intensity of the signal generated from the transducer. Ideally, a biosensor should generate a signal in response to small fluctuations in the concentration of the target analyte. Depending on the application, biosensors are required to detect analytes in the ng/ml or fg/ml concentration ranges. This is usually important for medical applications and environmental monitoring purposes [28, 29].

4.2 Selectivity

This refers to the ability of the biosensor to selectively bind and respond only to the desired analyte, in the presence of other molecules or substances. When a signal

or response is generated from interactions with an analyte that is different from the target analyte such is termed a false positive result. This is common in biosensors with poor selectivity, thus failing in clinical applications. Selectivity is a very important feature especially in medical applications where the test sample or sample matrix, usually blood or urine, contains numerous molecules that are quite similar to the target analyte and compete for binding to the biological receptor [22, 30].

4.3 Stability

Stability of the biosensor is a very important characteristic especially for biosensors used for continuous monitoring. This feature determines the ability of the biosensor device to resist change in its performance over a period of time in response to interruptions arising from external factors. These can be in the form of temperature, humidity or other environmental conditions. Such interruptions have the potential to induce inaccuracies in the output signal during measurement, thereby affecting the precision and accuracy of the biosensor device [11]. This is because transducers and other electronic components that comprise the biosensor device are mostly temperature sensitive and this can greatly influence their stability. Also, temperature can affect the integrity of the biological receptor as this component tends to degrade with fluctuations in temperature [22].

4.4 Detection limit

A detection limit is defined as the lowest concentration of the target that is able to elicit a measurable signal or response. Ideally, a biosensor should have the lowest detection limit, especially if it is to be used in medical applications where the target analyte might be present at very low concentrations [22].

4.5 Reproducibility

This is also one of the most important features in biosensing, and refers to the ability of the biosensor device to produce matching output signals or results in duplicate experimental runs. The capability of the biosensor to meet this criteria relies on the transducer which is required to perform in a precise and accurate manner [11].

4.6 Response time

This property determines the time it takes for the biosensor to generate a signal or response following the interaction of the biological receptor with the target analyte [26, 27].

4.7 Range or linearity

Biosensor linearity determines the accuracy of the signal obtained, in response to a set of measurements with differing concentrations. This attribute gives insight into the resolution of the biosensor, defined as the minimal change in the target analyte concentration that will elicit a response from the biosensor. This is a very important attribute for a biosensor since most applications require a biosensor to measure a target analyte over wide concentration ranges [11, 22].

5. Considerations for biosensor design

The first step in developing a biosensing device involves investigating the target analyte and understanding how this analyte interacts with certain biological molecules. Once this has been established, the following tasks are critical:

- a. Selection of a biological receptor: the specificity and selectivity of a biosensor to the analyte of interest is dependent upon the biological receptor used. A suitable receptor with high affinity for the analyte is thus recommended. Having knowledge of the advantages and disadvantages of various biological receptors in different biosensor applications is very important in selecting a suitable receptor [10, 15, 28].
- b. Selection of a suitable immobilization method: for any biological molecule to operate reliably as a biological receptor, it requires attachment onto the surface of a transducer. This process is known as immobilization. Various methods have been used for this task and include adsorption, entrapment, covalent attachment, micro encapsulation and cross linking [31, 32].
- c. Selection of a transducer element: the transducer element greatly influences the sensitivity of the biosensor device. Employing the right transducer will result in a device with increased sensitivity while the sensitivity is more likely to be compromised by the use of an ineffective transducer [33, 34].

6. Classification of biosensors

Biosensors are classified according to their biological receptors or transducer elements. **Figure 3** displays a flowchart illustrating the different types of biosensors based on the biological receptors and transducer elements [36]. Some of the biosensors shown in the figure will be discussed further in subsequent sections.

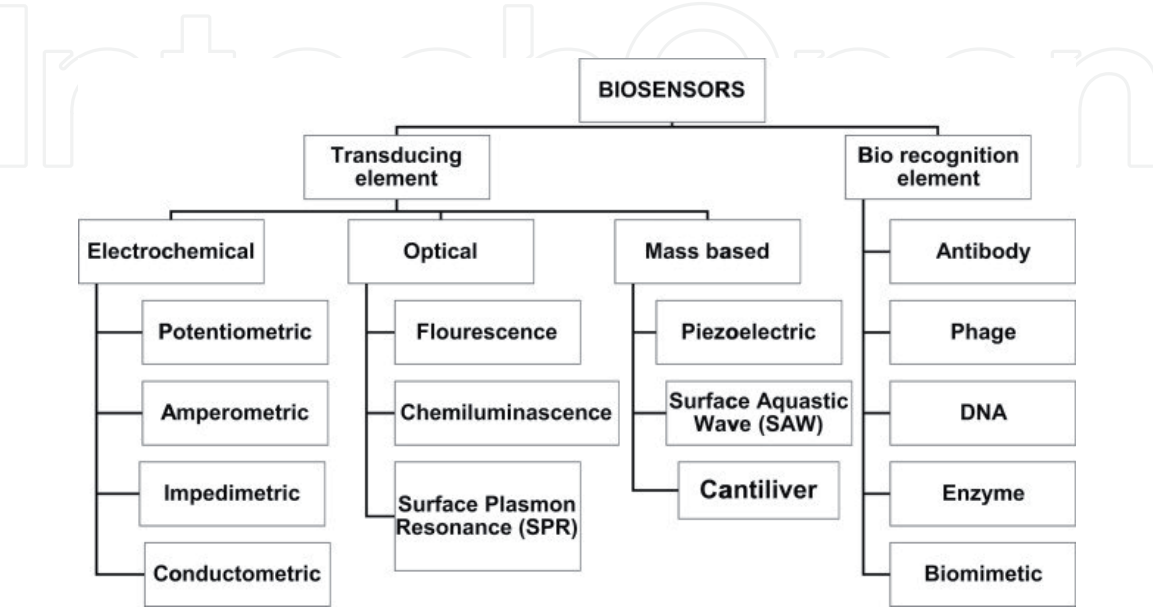


Figure 3. Flowchart showing the various types of biosensors classified based on their transducing elements and biological recognition elements [35].

6.1 Classification based on biological receptors

6.1.1 Enzyme based biosensors

These type of biosensors form the most researched and reported biosensors based on biological receptors [37, 38]. Enzyme biosensors, useful tools for monitoring rapid changes in metabolite levels in real-time, include pure enzyme preparations or biological processes. They have been derived on immobilization processes such as van der Waals forces, ionic or covalent bonding. In 1967, Updike and Hicks [39] successfully developed a working electrode for the detection of glucose levels and this is considered the first biosensor in the world. The well-known enzymatic biosensors today are glucose and urea biosensors. However, glucose biosensors are most popular among researchers and are reportedly the mostly commercialized biosensors. The glucose biosensor, which was developed by Clark, is made up of glucose oxidase immobilized within a dialysis membrane which is integrated inside oxygen electrodes. Enzymatic biosensors are known for their prolonged use and reusability due to the fact that enzymes used as biological receptors cannot be consumed. Thus, the detection limit and the lifetime of enzyme based biosensors is greatly enhanced by the stability of the enzyme [40].

6.1.2 DNA based biosensors

Another group of biosensors based on a biological receptor is DNA biosensors. The most attractive feature of biosensors is the high selectivity of biosensors for their target analytes in a matrix of chemical or biological elements. DNA biosensors, which use nucleic acids as their biological receptors, detect proteins and non-macromolecular compounds that interact with certain DNA fragments known as DNA probes or DNA primers. The interaction observed stems from the formation of stable hydrogen bonds between the double helix nucleic acid strands [41]. To develop DNA biosensors, immobilization of the probe becomes the most crucial step. The strong pairing of lined up nucleotide strands between bases in their complementary parts influences biosensors based on DNA, RNA, and peptide nucleotide acids to be the most sensitive tool [42]. Lucarelli *et al.* reported that probes, which are short oligonucleotides capable of hybridization with individual areas of the target nucleotide sequence, together with various chemical composition and conformational arrangements, were employed in the development of DNA biosensors. Extremely high sensibility and selectivity is needed to maximize the hybridization efficiency and minimize non-specific binding [43].

6.2 Biosensors based on transduction element

The most commonly applied classification of biosensors is based on the type of transduction element used in the sensor. These biosensors are grouped into three main categories, known as electrochemical biosensors, mass-based biosensors and optical-based biosensors. The working principles of each of the three biosensors are different and can thus be implemented in a variety of applications. Below is a brief description of the different types of biosensors and their working mechanisms. Some of the subclasses under the types of biosensors will also be explained.

6.2.1 Electrochemical biosensors

Electrochemical biosensors, which are the best in the detection of hybridized DNA, DNA binding drugs, glucose concentration, etc., measure the electrical

potential difference caused by an interaction between an analyte and the membrane/sensor surface. There is proportionality between the electrical potential difference and the logarithm of the electrochemically active concentration of the material. The current flowing through the system or the potential difference between the electrodes as a result of the redox reactions involving the analyte are employed for its quantification in the sample. Electrochemical biosensors have gained popularity as compared to optical biosensors in the sense that they do not suffer from the many disadvantages optical biosensors experience. They have a more stable output, high sensitivity, fast response and are not prone to interferences. Electrochemical measurements are mostly preferred for sensing applications [44–47]. Electrochemical biosensors can further be classified into various types based on the measuring electrical parameters. These include conductimetric, amperometric, potentiometric and impedimetric sensors [48].

6.2.1.1 Conductometric biosensors

Conductometric biosensors measure the electrical conductivity of the solution in the course of a biochemical reaction. When electrochemical reactions produce ions or electrons, the overall conductivity or resistivity of the solution changes. Due to poor signal-to-noise ratio, they are less commonly used in biosensing applications, particularly when the biological receptor used is an enzyme. However, these biosensors remain useful in the detection of affine interactions [49, 50].

6.2.1.2 Potentiometric biosensors

Potentiometric biosensors measure changes in pH and ion concentrations resulting from antigen/antibody interactions. Although potentiometric biosensors are the least common of all biosensors, different strategies for the development of these biosensors are found. The working principle relies on the fact that when a voltage is applied to an electrode in solution, a current flow occurs because of electrochemical reactions. The voltage at which these reactions occur indicates a particular reaction and particular analyte. Some of the known potentiometric biosensors include those used for the detection of *Neisseria meningitides*, *Brucella melitensis* and *Francisella tularensis* species [51, 52]. Similarly, Hu *et al.* included a light-addressable potentiometric sensor in a microfluidic system to monitor the metabolism of human breast cancer cells in real time [53].

6.2.1.3 Amperometric biosensors

This is perhaps the most common electrochemical detection method used in biosensors. This high sensitivity biosensor can detect electroactive species present in biological test samples [54]. Amperometric-based biosensors detect the difference in current potentials during redox reactions when antigen/antibody pairing occurs. The most common amperometric biosensors use the Clark oxygen electrode. Amperometric biosensors have been developed for the indirect detection of *E. coli* by Nakamura and co-workers [55]. Another amperometric biosensor for the detection of Salmonella Species was developed by Brookes and colleagues [56].

6.2.1.4 Impedimetric biosensors

Impedimetric-based biosensors monitor changes in impedances upon antigen/antibody interaction. Impedance, which usually employs a circuit bridge as a measurement tool, is well suited for detection of bacteria in clinical specimens,

to monitor quality and to detect specific food pathogens. Moreover, these biosensors are useful in controlling industrial microbial processes [57].

6.2.2 Mass based biosensors

Piezoelectric biosensors are a group of analytical devices working on a principle of affinity interaction recording. A piezoelectric platform or piezoelectric crystal is a sensor part working on the principle of change in oscillations due to mass bound on the piezoelectric crystal surface. Piezoelectric biosensors, which are considered as mass-based biosensors, produce an electrical signal when a mechanical force is applied. An example of piezoelectric biosensor is the quartz crystal microbalance (QCM) model. The working principle of QCM is depicted in **Figure 4**. Quartz crystal microbalance (QCM) is a very popular tool that is used extensively in the electronic industry. Currently, these tools are used as attenuators in electronic devices and they have a typically fundamental mode frequency of 1–20 MHz. Though higher frequencies provide good opportunities for a sensitive assay, QCM with high frequencies have been reported to exhibit several drawbacks such as their fragility and also the technologically demanding equipment needed for their manufacture [58]. The basic material used in the development of the QCM sensor consists of quartz crystal, which is equipped with metal electrodes. A sensitive coating material on the sensor surface is used to enable detection of the target analyte in the environment. An appropriate electronic circuit is necessary to make conversion of the measured quantity to an electrical signal [59].

6.2.3 Optical biosensor

Optical biosensors are based on the interaction of a sensing element with electromagnetic radiation. They consist of a light source, as well as numerous optical components to generate a light beam with specific characteristics and to beeline this light to a modulating agent, a modified sensing head along with a photodetector. An optical surface plasmon resonance (SPR) biosensor can detect the refractive index changes on the surface of sensor chips, label-free and in real-time. Although different optical methods such as absorption, fluorescence,

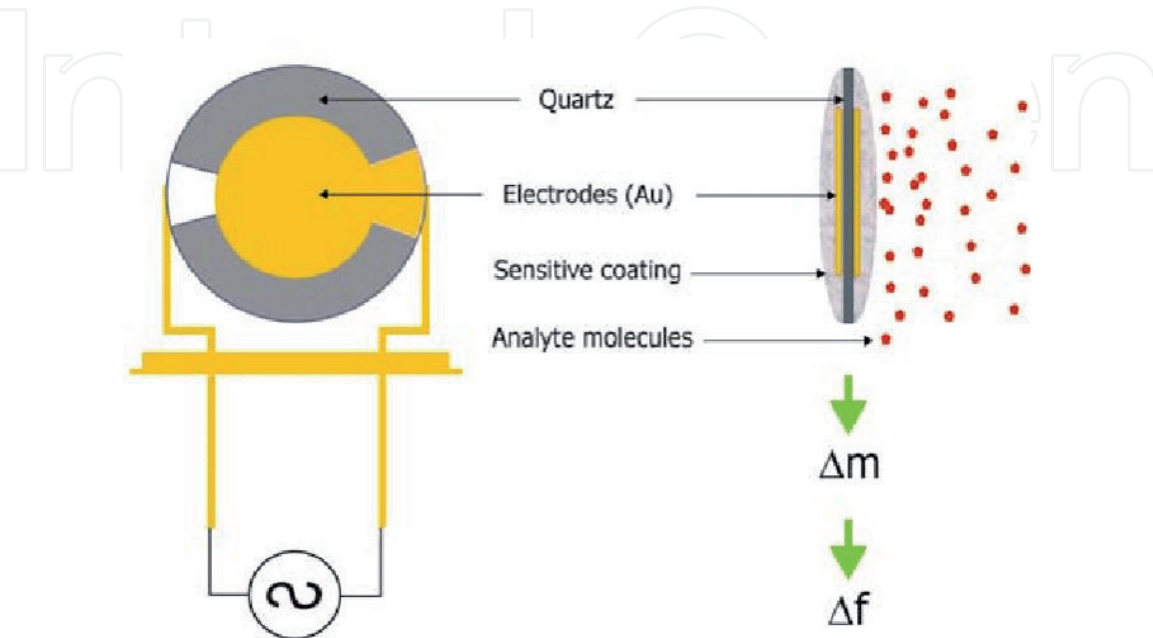


Figure 4.
Basic working principle of Quartz Crystal Microbalance (QCM) sensor [59].

luminescence, internal reflection, surface plasmon resonance, or light scattering spectroscopy utilized herein are becoming popular, fluorescence and surface plasmon resonance enabled spectroscopies still remain the most and widely researched and applied methods [60, 61].

6.2.3.1 Surface plasmon resonance based biosensors

Over the last two decades, surface plasmon resonance (SPR) based biosensors have emerged as important and useful tools due to their unique features for real-time and label-free detection of biomolecular interactions [62, 63]. SPR technology has opened a new avenue for many important applications in the field of sensing due to their attractive sensing capabilities, light weight, compactness and easy implementation [64–67]. The SPR phenomenon has been widely used in biosensing, chemical sensing and environmental sensing applications such as protein–protein hybridization [68, 69], enzyme detection [70, 71] and protein-DNA hybridization. Surface plasmon resonance (SPR), as a physical phenomenon, is not restricted only to events occurring in thin planar metal films. A broad spectrum of differently nanostructured surfaces as well as noble metal nanoparticles are frequently employed for fabrication of SPR-based assays [72–75].

However, conventional commercial SPR-based biosensors and experimental devices are often represented by instruments, which utilize Kretschmann's scheme of plasmon excitation [65]. SPR-based biosensors can be employed to characterize interactions between biomolecules immobilized onto the metal film sensor surface and their counterparts in liquid sample in real time and without labelling. Indeed, these biosensors are actively used to measure binding constants, kinetics of biomolecular interactions and to perform concentration measurements [66]. In turn, these applications make SPR-based biosensors very useful in pharmacological, biomedical, environmental and food studies.

The first practical sensing application of SPR sensors for biomolecular detection was reported by Liedberg and Nylander in 1983 [67]. Since then, SPR biosensors have experienced rapid development in the last two decades and have become a valuable platform for qualitative and quantitative measurements of biomolecular interactions with the advantages of high sensitivity, versatile target molecule selection, and real-time detection. For this reason, SPR sensors are now widely adopted for meeting the needs of biology, food quality and safety analysis, and medical diagnostics.

Over the past decade, many SPR sensors have been reported in applications such as biomolecular interaction analysis, medical diagnostics, environmental monitoring, and food safety [69, 71, 73]. Traditional SPR devices generally require expensive equipment, complicated optics, and precise alignment of the components [74, 75], features that hinder the development of a portable device. Current portable SPR devices still require a portable computer to run the instrument and are about the size of a lunch box.

7. Applications of biosensors

Conventional 'off-site' analysis requires the samples to be sent to a laboratory for testing. These methods allow the highest accuracy of quantification and the lowest detection limits, but are expensive, time consuming and require the use of highly trained personnel. Due to the above drawbacks, there has been a great interest in the technology of biosensors. There has been a phenomenal growth in the field of biosensor development in recent years with emerging applications in a wide range

of disciplines. These include environmental monitoring, disease detection, food safety, defence, drug discovery and many more as depicted in **Figure 5** below. A summary of the few and selected representatives and examples of developed applications of biosensors is given below.

7.1 Food industry

Biosensors have been used extensively in the food industry for quality control and assurance purposes. These include applications in the agricultural field during crop production and also during food processing. Quality control remains a major part of food production and is responsible for the production of healthy food with a prolonged shelf life and also complies with regulations. Biosensors have been used as on-line or at-line quality sensors that make it possible for quality sorting, automation and reduction of production cost and production time. Also, biosensors have been developed to detect particular compounds in foods. These devices detect chemicals or biological agents that contaminate food or might indicate the presence of unwanted substances in food. Moreover, biosensors have been developed for monitoring and estimating cross-contamination of surfaces and food products [77–80].

7.2 Environment

Environmental pollution has an impact on human health and can therefore compromise the quality of life. Depending on the purpose, sensitive and selective methods are needed for both quantitative and qualitative determination of target analytes. Biosensors have found widespread use in environmental monitoring for the detection of chemical agents, organic pollutants, potentially toxic elements and pathogens that might pose a health hazard. Biosensors such as immunosensors, aptasensors, genosensors and enzymatic biosensors are amongst the most preferred

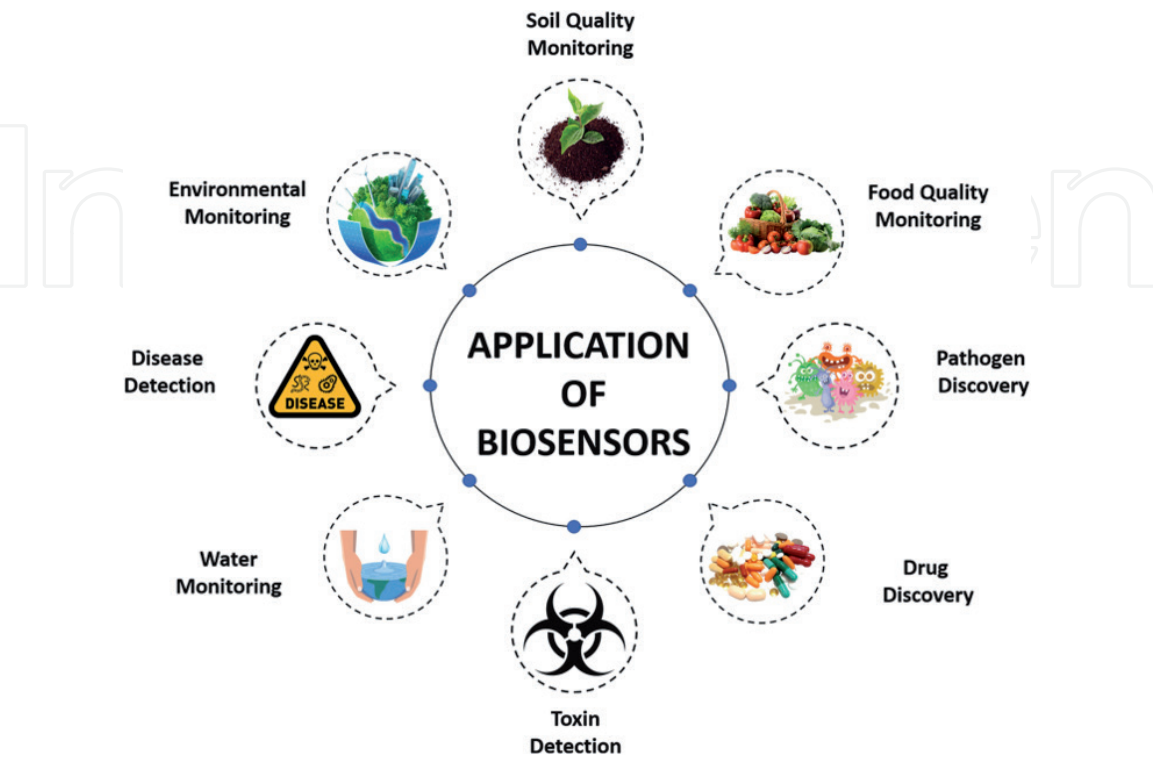


Figure 5.
Various applications where biosensors have been used. Picture adapted from [76].

for environmental monitoring. These are known to use antibodies, aptamers, nucleic acids and enzymes as biological receptors. For example, a biosensor was developed to detect pesticides such as organophosphate and carbamate and also monitor their effects on the environment. Biosensors detect pollutants by measuring colour, light, fluorescence or electric current [81–84].

7.3 Medical

Most of the biosensors reported in the past years are found to be based on the phenomena of molecular interactions which are essentially employed in various forms at different scales. In the discipline of medical science, the applications of biosensors are growing rapidly. Some of the applications that have benefited from the emergence of biosensors include cancer detection and monitoring, cardiovascular disease monitoring, and diabetes control. Cancer diagnosis and treatment are of great interest due to the widespread occurrence of the diseases, high death rate, and recurrence after treatment. In medicine, biosensors can be used to monitor blood glucose levels in diabetics, detect pathogens, and diagnose and monitor cancer progression [85]. The use of emerging biosensor technology could be instrumental in early detection of cancer for effective treatment administration [86]. By measuring levels of certain proteins expressed and/or secreted by tumor cells, biosensors can detect presence of a tumor, whether benign or cancerous, and also give information of whether treatment is effective in reducing or eliminating such cancerous cells [87, 88].

Cardiovascular diseases, which are the primary cause of death are still considered as one of the biggest dilemma the world is facing with about one million people suffering from it. The ability to detect such diseases earlier may result in the reduction of mortality cases. Some of the sensing techniques that have been used herein include immunoaffinity column assay, fluorometric assays, and enzyme-linked immunosorbent assay [89–91]. However, the above techniques are laborious, and therefore require well trained and qualified personnel and are time consuming. Therefore, biosensors are being used for the detection of cardiac markers and early diagnosis. Biosensors have been reported to offer vast advantages over conventional diagnosis assays since they are established on electrical measurements and also employ biochemical molecular recognition elements which gives a desired selectivity with a particular biomarker of interest [92, 93].

8. Conclusions

Biosensors continue to offer solutions and control of various processes across a range of applications. As technology advances, new methods that will result in the development of even better biosensors are emerging, and these seek to address all limitations associated with these devices. The development of biosensors revolves around their sensitivity, specificity, cost effectiveness and ability to detect small molecules. This is mostly determined by the right combination of a biological receptor and a transducer element, components which form the basis of a biosensor.

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Conflict of interest

Authors report no conflict of interest.

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