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A Review of Biosensors; Definition, Classification, Properties, and Applications

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Abstract

Biosensor is defined as a device that transforms the interactions between bioreceptors and analytes into a logical signal proportional to the reactants' concentration. Biosensors have different applications that aim primarily to detect diseases, medicines, food safety, the proportion of toxins in water, and other applications that ensure the safety and health of the organism. The main challenge of biosensors is represented in the difficulty of obtaining sensors with accuracy, specific sensitivity, and repeatability for each use of the patient so that they give reliable results. The rapid diversification in biosensors is due to the accuracy of the techniques and materials used in the manufacturing process and the interrelationships in scientific research between various disciplines, i.e., physics and biology, engineering and biology. This research aims to define biosensors in general, classify them and show their most important applications, with a brief description of their time development and the reason for their speared in all fields.

Keywords: Biosensor, Flavin Dinucleotide, Glucose, Redox, Organism, Food safety, Sol-gel.

مراجعة المستشعرات الحيوية: التعريف والتصنيف والخصائص والتطبيقات

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الخلاصة

تعرف المستشعرات الحيوية بأنها جهاز يحول التفاعلات بين المستقبلات الحيوية والمواد التحليلية إلى إشارة منطقية تتناسب مع تركيز المواد المتفاعلة. أجهزة الاستشعار الحيوية لها تطبيقات مختلفة تهدف في المقام الأول إلى الكشف عن الأمراض والأدوية وسلامة الغذاء ونسبة السموم في الماء والتطبيقات الأخرى التي تضمن سلامة وصحة الكائن الحي. يتمثل التحدي الرئيسي لأجهزة الاستشعار الحيوية في صعوبة الحصول على أجهزة الاستشعار بدقة وحساسية محددة وقابلية التكرار لكل استخدام من قبل المريض بحيث تعطي نتائج موثوقة. يرجع التنويع السريع في أجهزة الاستشعار الحيوية إلى دقة التقنيات والمواد المستخدمة في عملية التصنيع والعلاقات المتبادلة في البحث العلمي بين مختلف التخصصات ، مثل الفيزياء والبيولوجيا والهندسة وعلم الأحياء. يهدف هذا البحث إلى تعريف المستشعرات الحيوية بشكل عام ، ثم تصنيفها ومعرفة أهم تطبيقاتها ، مع وصف موجز لتطورها الزمني وسبب تطورها في جميع المجالات.

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1. Introduction

The human body contains small units called cells that the body depends on to perform many functions. Any deviation in the principle of cell work or activity would expose the body to a functional imbalance and thus expose it to diseases and be at risk if the cause of the defect has not been diagnosed. Therefore, biological sensors are used to measure and identify pathogens [1]. This paper's simplified approach had made to clarify the most important sensors and their functions.

2. Sensors and Biosensors

Sensors, in general, can be defined as devices that convert reactions from one form to another. It can be divided into three types. The first type is sensors based on converting the physical changes detected into electrical signals without changes occurring between the reactants. The second type is chemical sensors, which can be defined as sensors that convert chemical reactions into electrical signals, causing changes between the reactants. Sensors are named according to their type of work, for example, optical, mechanical, thermal, gas, etc. [2][3]. The third type is sensors according to the medical or biological field, and they are called biological sensors. They can be defined as sensors that transform the interactions between biological materials (enzymes, nucleic acids, whole cells, antiparticles) into a logical signal proportional to the reactants' concentration [4]. Figure1 shows the classification of sensors.

Figure 1: Classification of sensors. Reformulated from White [3].

3. Biosensor's Structure

The structure of a biosensor consists of five parts, as shown in Figure2. First, the analyte, which is the biological material to be detected. Second, the biological receptors which are biological molecules taken from biomaterial (the origin) that are used to detect certain concentrations of the same origin biological material being studied. Third, the bio-energy transducer is an electrode that converts the interactions between the analyte and the biological receptors into an electrical signal. Fourth is the electronic system, an electronic device consisting of electrical circuits such as processors and amplifiers that process the electrical signal. Fifthly, a display device, such as a computer, converts the signal into logical values to be graphically plotted on the computer screen [5-7]. Finally, a special module, called the mediator, is usually included in the composition of the biosensor. The mediator is a low molecular weight biomolecule that transfers electrons from redox reactions within the enzyme on the transducer surface. Thus, it increases the rate of electron transfer between the active site of the enzymes and the electrode surface. Oxidation and reduction media also have another advantage: the low effort of oxidation-reduction reactions to prevent the occurrence of redox and double oxidation of the interfering materials. In addition to the high chemical stability of oxidation-reduction reactions formed, low biorecognition elements allow electrons to move very long distances [8-10].

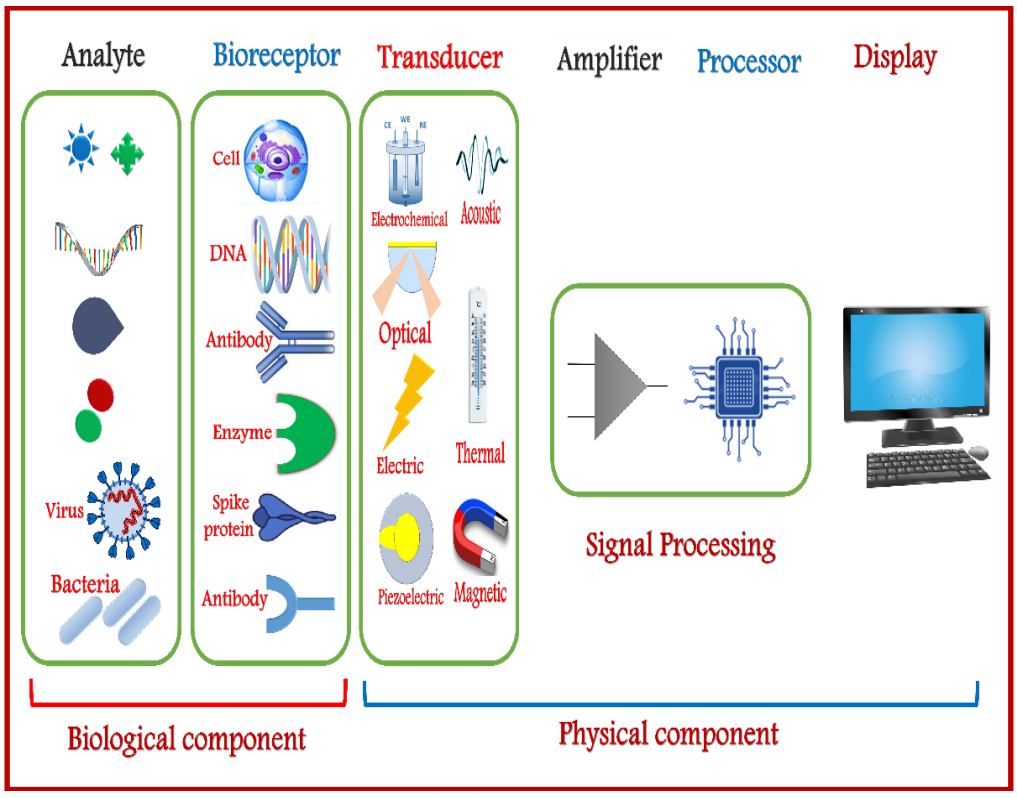

Figure 2: The biosensor's structure.

4. Timeline of the Evolution Biosensors

In this section, the chronological history of the development of biosensor systems is briefly discussed. Table 1 shows the historical evolution of biosensors.

Table 1: The development timeline of generation's biosensors [11-17].

Data	Inventor	Technology
1916	Nelson and Griffin	**First time reported immobilization of proteins: adsorption of invertase enzymes on active charcoal and aluminum hydroxide support.**
1920	Fredric and Banting	**Determine the glucose in blood and urine.**
1922	W. S. Hughes	**Determine Glass pH Electrode.**
1954	Stow and Randall	**Carbon Dioxide Electrode.**
1956	Leland. C. Clark	**Oxygen Electrode was first reported.**
1959	Rosalyn and Solomon	**Developed radioimmunoassay-based antigen-antibody to determine the hormones.**
1962	Leland. C. Clark	**Develop Glucose Electrodes.**
1963	Garry and Katz	**First, used potentiometric to detect urea**
1967	Updike and Hicks	**Invented an enzymatic amperometric biosensor using a Clark electrode to detect glucose in several biological fluids.**
1969	Guilbault and Montalvo	**First reported on an enzymatic potentiometric biosensor using ammonia electrode for urea detection.**
1970	P. Bergveld	**Discovered Ion Selective Field Effect Transistor.**
1971	A. H. Chemens	**Developed the first biosensor blood glucose meters.**
1972	P. Bergveld	**First miniaturized ISFET-based pH sensor.**
1973	Guilbault and Lubrano	**Used glucose enzyme immobilized on the platinum electrode to detect hydrogen peroxide.**
1974	Mosbach and Danielesson	**Developed enzyme biosensors based on thermal transducers (thermistors).**
1975	Suzuki	**Developed microbe-based immunosensor.**
1975	Janata	**First time fabricated immunosensor for ovalbumin.**
1975	Lubbers	**Invented PO_2/pCO_2 optical oxygen detector (optode).**
1975	J. Newman	**First time commercialized glucose biosensor by yellow spring's instruments company.**
1976	Chlemens et al.	**Invented the first bebside artificial pancreas to measure blood glucose.**
1979	Schultz	**Optical Affinity Sensor.**
1980	Peterson	**The first pH sensor was exhibited based on fiber optics for tracking in vivo blood gases.**
1981	Esther and Judith	**Design an enzymatic potentiometric biosensor by using glucose electrodes to detect glucose.**
1982	Schultz	**Invented Fiber-optic biosensor to detect glucose.**
1983	Liedberg et al.	**Discovered for the first time surface plasmon resonance (SPR) on an immunosensor.**
1983	J. Roederer and G. Bastiaans	**Developing the first microgravmetric immunosensor based on piezoelectric quartz for antigen detection.**
1984	Cass et al.	**Mediated enzyme electrode for amperometric biosensor for glucose detection.**
1987	Company	**A blood glucose biosensor named MediSense ExacTech™ was launched.**
1988	Adam and Updike	**It first used the electrical connection between the enzyme redox center and the electrode through conducting redox hydrogels.**
1990	Mun and Tamiya	**A biosensor based on SPR named Pharmacia BIACore was**

		launched.
1991	Fodor	Chip-based technologies.
1992	Company	I-STAT has released a portable blood analyzer.
1996	Company	MediSense was taken into possession by Abbott.
1996	Company	The first glucocard was launched.
1997	G. Jobst et al.	PCB-based sensor with integrated microfluidics.
1998	Company	A blood glucose biosensor named LifeScan FastTake was launched.
1999	Poncharal et al.	First demonstrated of Nanobiosensors.
2001	Company	LifeScan purchased Inverness Medical's glucose testing business.
2002	Schuhmann et al.	Used electrodeposition paints for immobilization in biosensor
2004	Company	Developed screen based for mass production of glucose sensing strips.
2018	S. Girbi et al.	Demonstrated how to measure nerve impulse conduction using a neuron-on-chip biosensor.
2021	Kulkarni et al.	Description of Al-foil-based electrode for cystine sensing.

5. Classification of Biosensors

The biological sensors can be divided into three categories, the first is according to the type of generation, the second according to the type of biological receptors, and the third according to the transducers. Figure3 shows a classification of biosensors.

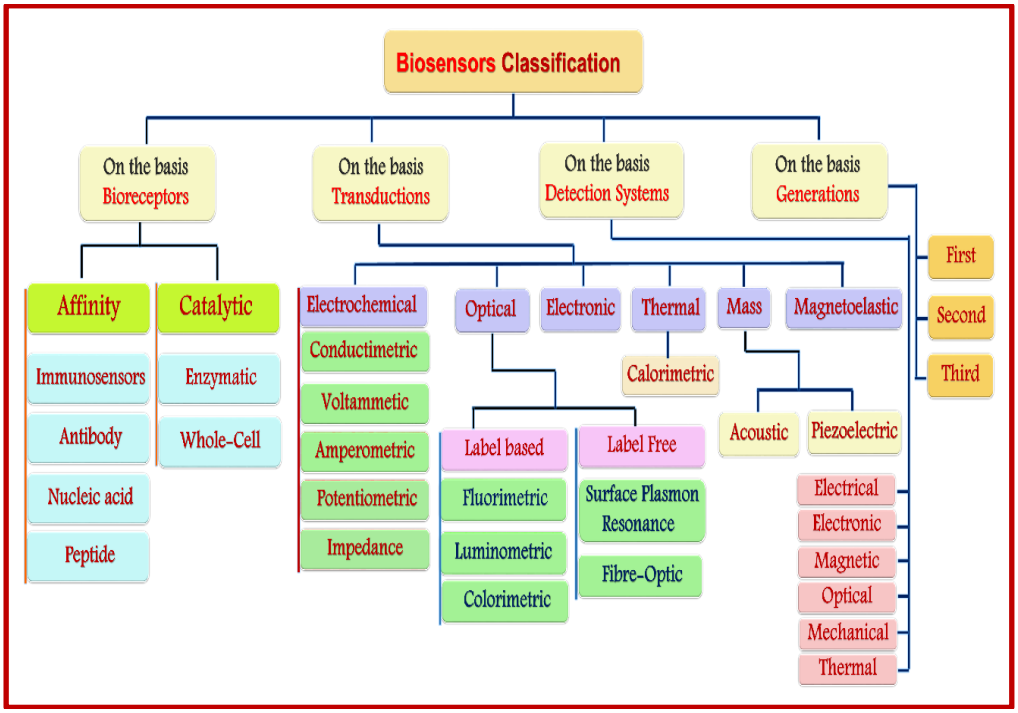

Figure 3: Classification of Biosensors.

5.1 Classifying according to the type of generation.

The biosensors are divided into three generations based on the type of bonding components between the analyte and transducers. The first generation of sensors consists of an electrode called the Clark electrode or oxygen electrode, which uses oxygen molecules to

detect hydrogen peroxide (H_2O_2) concentrations in biological materials. A thin layer of glucose oxide (GOx) is fixed to the working electrode by a semi-permeable membrane. Oxygen molecules are usually used when the enzyme lacks a means of stabilization. Glucose is detected by analyzing the oxygen molecules consumed by the catalyzed enzyme. Glucose oxide uses an organic cofactor such as Flavin Adenine Dinucleotide (FAD) in the oxidation and reduction processes. Flavin acts as an acceptor and transporter of electrons. The glucose oxide catalyst works on the oxidation of glucose to Gluconolactone and the reduction of FAD to $FADH_2$ simultaneously. Then FAD is replenished from $FADH_2$ by supplying it with dissolved oxygen to form H_2O_2. The applied voltage oxidizes the hydrogen peroxide on the electrode surface, producing an electrical signal. This type of biosensor is characterized by not containing an intermediate. One of the disadvantages of this type is the abundance of oxygen concentrations, which reduces the response of the biological sensor [18]. The second generation of sensors includes a mediator of electronic receptors (such as dyes and organic salt) that replaces oxygen to produce H_2O_2. One of the disadvantages of this generation is the small size of the medium, so the distance between the electrode and the analyte is insufficient to improve the response in the desired manner. This is because the redox centers are located inside a thick protein layer that reduces the size of the medium and increases the distance from the electron generation centers, which leads to a slow movement of electrons, thus leading to a slow response [19]. The third generation of sensors does not include a mediator but rather depends on direct contact between the surface of the electrode and the enzymes, where the transfers of electrons are direct between transducers and enzymes, which leads to a faster response time [20]. Figure4 shows the generation types of biosensors. The following equation describes the reactions of glucose.

$$Glucose + GO_X - FAD^+ \rightarrow Gluconolactone + GO_X - FADH_2 \quad (1)$$

$$GO_X - FADH_2 + O_2 \rightarrow GO_X - FAD + H_2O_2 \quad (2)$$

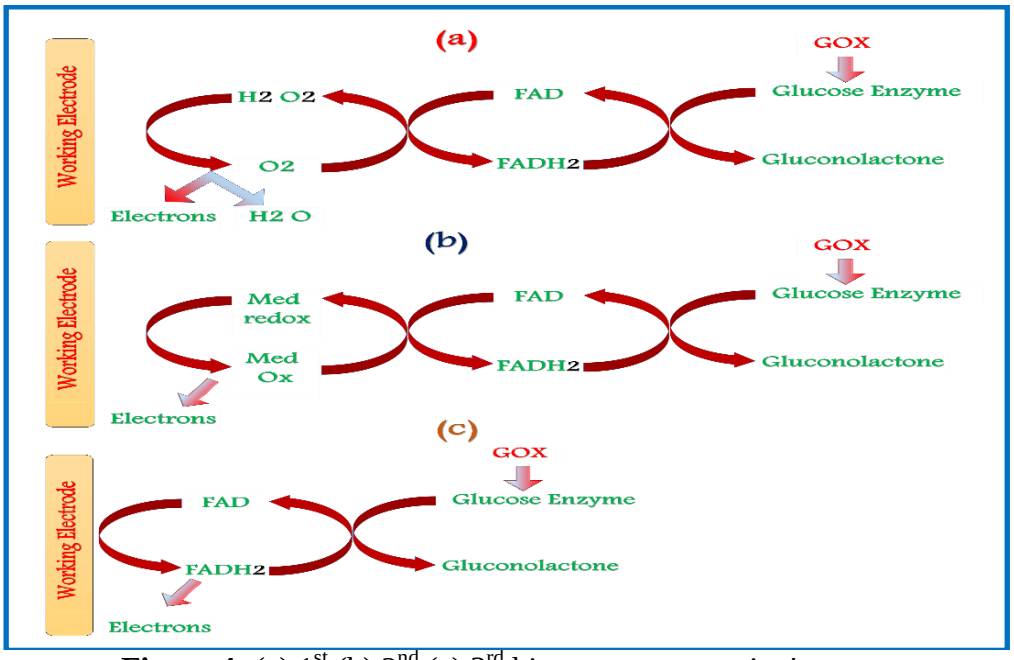

Figure 4: (a) 1st (b) 2nd (c) 3rd biosensors generation's types.

5.2 Classifying according to the type of bioreceptors or detection elements.

Bioreceptors are biological material taken from the part to be detected and fixed to the surface of the transducer. Its function is to detect and distinguish the required substance from the substances within the same liquid sample (the analyte). Bioreceptors are obtained from

natural systems like nucleic acids, antibodies, organelles, enzymes, and whole cells. Although bioreceptors are abundant, some limitations limit their use, such as their high costs, complex mechanisms, low stability, and sometimes being unsuitable. Therefore, alternative methods are used to eliminate these limitations by synthesizing bioreceptors such as Aptamers and molecularly imprinted polymers. Biological sensors are divided into two types: catalytic sensors and affinity sensors. The principle of action of the first type is based on using catalytic biomolecules (e.g., enzymes, whole cells) as a recognition element to detect the presence of target alleles through biological catalytic reactions [21]. It is characterized by the fact that there are no changes in the composition of the material when adsorption occurs on the electrode surface but instead affects a chemical change in an auxiliary substrate [22]. Whereas in the second type, the sensors use bio-affinity molecules (e.g., proteins, whole cells) as the recognition element to detect the affinity interactions between the bioreceptors and the analytes. This type is characterized by changes in the material's structure when adsorption occurs, causing physicochemical changes. [23]. Figure5 shows the bioreceptors types. Table 2 lists the advantage and disadvantages of analytes.

Enzymes: - are large complex protein molecules used in biosensors to activate chemical reactions in living organisms. The effectiveness of enzymes is affected by specific molecules, such as inhibitors that reduce enzyme activity and activators that increase enzyme activity. The molecules on which enzymes act are called substrates. The region to which enzymes bind is called the active region. The substrate is transformed into products when the enzyme interacts with the substrate. And the enzyme is released from the active region to move to another region. The link is in order if more than one substrate is present. As a result, the enzymes have high selectivity, making them more popular for biosensors [24, 25].

Antibodies: - are Y-shaped proteins generated within the lymphatic system that attack and encapsulate foreign bodies and then break them down to analyze their genetic codes so that they can be easily identified when they enter the body again. The structure of the Y antibody consists of immunoglobulin (Ig), which consists of two adjacent chains, the first is polypeptide light chains, and the second is heavy chains, both linked by disulfide bonds. Antibodies are classified into five types based on differences in the heavy chains: IgD, IgE, IgG, IgA, and IgM. Allergens that use this type of biological material are called lymphatic sensors or immunosensors [26-28].

Nucleic acid: - is the most important part of the organism that possesses basic genetic information, which can describe as large molecules of proteins with complex chains formed by regular repetition, resulting in a double strand wrapped around each other by covalent bonds. The double strand transfers the genetics of an organism, and the genetic information is stored inside deoxyribonucleic acid (DNA). The DNA strand consists of four nitrogenous bases: thymine, guanine, adenine, and cytosine. The sensor of this type is called a nucleic acid biosensor. These sensors work to identify the small parts cut from the DNA strand of the studied organism and measure the strength of antigen bonds and the intensity of their recognition of the individual nucleic acids of foreign bodies inside the body. The antigen stimulates immune cells to secrete antibodies to kill germs or viruses to protect the body. This type of sensor began to be used in early 1953 [29, 30].

Peptides: - are a series of amino acids that have gained wide fame due to their self-formation in one-, two- and three-dimensional structures with high order through non-covalent bonds (such as hydrogen bonds or Vander Waals—produced) between amino acids to form many

different proteins. Proteins enter the composition of enzymes and work to form the supports and joints of the organism's body [31, 32].

Tissue: - the tissues of plants and animals are usually used as a biological detection element with minimal preparation conditions. Although tissues contain many enzymes, they differ greatly from tissues with pure enzymes. In addition, although enzymes are widely present in nature, they are less susceptible to damage, and thus sensors of this type have a long life [33].

Whole Cells: - are micro-organisms such as bacteria and viruses. Microorganisms play a major role in the development of biosensors, and allergens of this type are called whole-cell sensors. In this type, microorganisms, such as eukaryotic cells, such as tissues of plants and animals, and nonnuclear cells, such as bacteria and viruses, are used as biological recognition elements [34, 35].

Aptamers: - are a short chain of DNA strands or messenger DNA or are molecules of peptides linked with a specific molecule. They are obtained randomly from the locations of the DNA pools. They tend to bind selectively to a specific target, such as carbohydrates, peptides, and even living cells, and take many forms, such as spiral and single-loop, so they are found in various forms. It is used in the pharmaceutical industry [36].

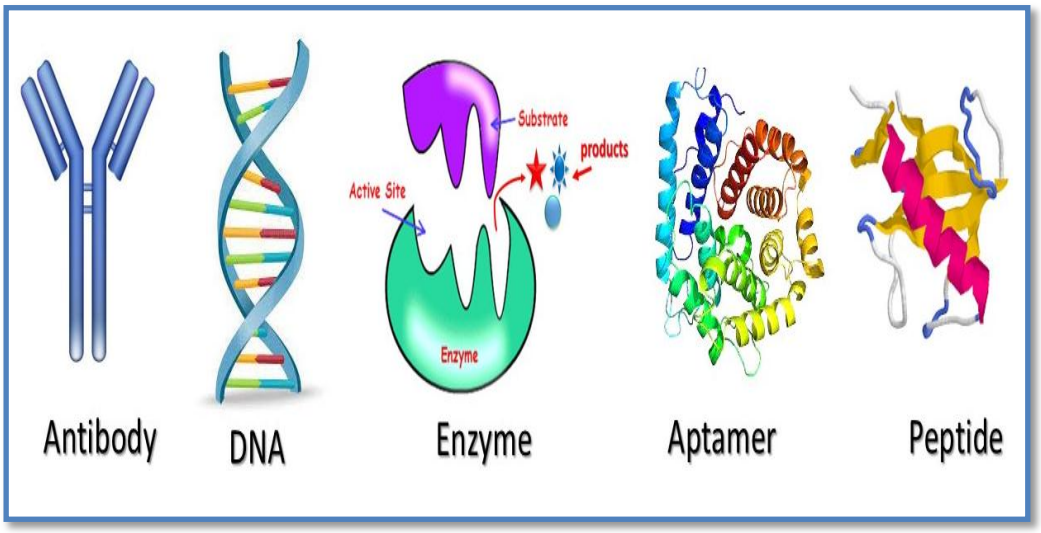

Figure 5 : Bioreceptors types.

Table 2: The advantage and disadvantages of analytes [34, 38-41].

Analyst	Advantages	Disadvantages
Enzymes	Characterized by good actives of catalytic, it can inhibit and stimulate reactions involving target analyses, good ability for binding.	Require several test steps, have less stability toward temperature and pH, increasing the interference between the endogenous enzymes.
Antibodies	Diversity allows full detection of bacteria cells and their metabolite toxins, allows for the reaction between specific biomolecules, and has the direct ability to recognize and non-invasive capability.	Characterized by difficulty distinguishing between dead and living bacteria cells, challenges in production, the inspection process takes a long time and has high production costs.
DNA	The recognition and detection process depends on sequence pairs of DNA; compared with antibodies and enzymes, the DNA may quickly regenerate and be produced.	High synthesis cost, low solubility inside aqueous media, it suffers from aggregation that is difficult to separate when purified and filtered, have less stability toward temperature and pH, which poses a challenge to the development of portable on-site biosensors.
Tissue	Tissue-based biosensors are characterized by cheaper than purified enzymes; the activity of enzymes is stabilized and maintains the enzymes in their natural environment.	Suffers from interference processes, resulting in some loss in selectivity
Whole cells	Compared with the enzymes, the whole cell has different advantages like high stability, low synthesis cost, lower purification requirements, and effective cofactor regeneration.	Its validity is limited, its operation requires certain environmental conditions, and increased interference between multiple biochemical pathways leads to the same response and, thus, wrong positive results.
Aptamers	Compared with DNA, the recognition and detection process depends on the shape, easy preparation, easy adjustment, and good stability.	Increasing the passive production capacity results when dealing with large biomolecules.

5.2 Classifying according to the type of transducers.

Transducers are an electrode that converts the interactions between the receptor or the biological identification element (immobilized on its surface) with the analyte into measurable electrical signals such as current, voltage, and impedance. The signal resulting from the interaction is proportional to the concentration of the biological substance to be detected. Three types of electrodes work together inside the electric cell. One example is the Working Electrode (WE), which is an electrode made of glassy carbon, where the material is deposited on its surface and interactions occur. The Reference Electrode (RE) is an electrode made of Ag/AgCl that works to measure the potential difference. The Counter Electrode (CE) is made of platinum that works to measure the current, the product of oxidation-reduction reactions. The function of the reference electrode is to complete the electrical circuit and keep the electrode voltage constant [41-43]. Transducers or working electrodes are classified according to their principle of operation into several types.

A) Electrochemical biosensors: - It is one of the most common biosensors due to their high selectivity, sensitivity, and detection ability. They can be defined as sensors that measure current, voltage, and impedance as a result of an electrochemical reaction occurring inside the electrochemical cell between the three electrodes. These interactions occur between the bio-receptors installed on the surface of the electrode and the solution containing the biological

substance (the analyte) to be detected. Its working principle depends on the oxidation and reduction processes between the electrodes, whether two or three electrodes [44, 45]. The bio-electrochemical sensor is divided into five types according to the electrical properties generated, including:

Conductometric biosensors: - Its working principle is based on measuring the change in electrical conductivity resulting from redox reactions of bio- and analyte receptors between the working electrode and the counter electrode. When an interaction occurs between biological receptors and analytes, such as enzymes, they may consume or produce some ions or ions that change the conductivity [46].

Potentiometric biosensors: - The principle of its work is based on measuring the change in the electric potential resulting from the charges accumulating on the surface of the working electrode when the current is zero. When biological molecules interact with the analyte, either consumption or production of charged samples occurs that selectively accumulate on the surface of the working electrode. Several electrodes are used in this type, such as ion selective electrode ion selective field effect transistors. This system consists of two electrodes, the first is the working electrode, and the second is the counter electrode [47].

Amperometric biosensors: - The principle of its work is based on measuring the change in electric current resulting from oxidation and reduction reactions when the voltage applied to the working electrode is constant compared to the reference electrode. This system consists of three electrodes [48].

Voltammetric biosensors:- The principle of its work is based on measuring the electric current produced by oxidation and reduction reactions when the voltage applied to the working electrode is not fixed, i.e., for a certain range of voltage. This system consists of three electrodes [49].

Impedance biosensors: - The principle of operation is based on measuring the electrical impedance. It results from oxidation and reduction reactions between the boundary of the working electrode and the solution when voltages are applied with a different frequency range to study and know the impedance properties (inverse conductivity) when the correlation event occurs. In other words, different frequencies are shed after the correlation event to study the ability of the material fixed on the electrode in the electrolytic solution to conduct charges between the electrodes [50, 51]. Figure 6 shows the output signal types of the electrochemical biosensor.

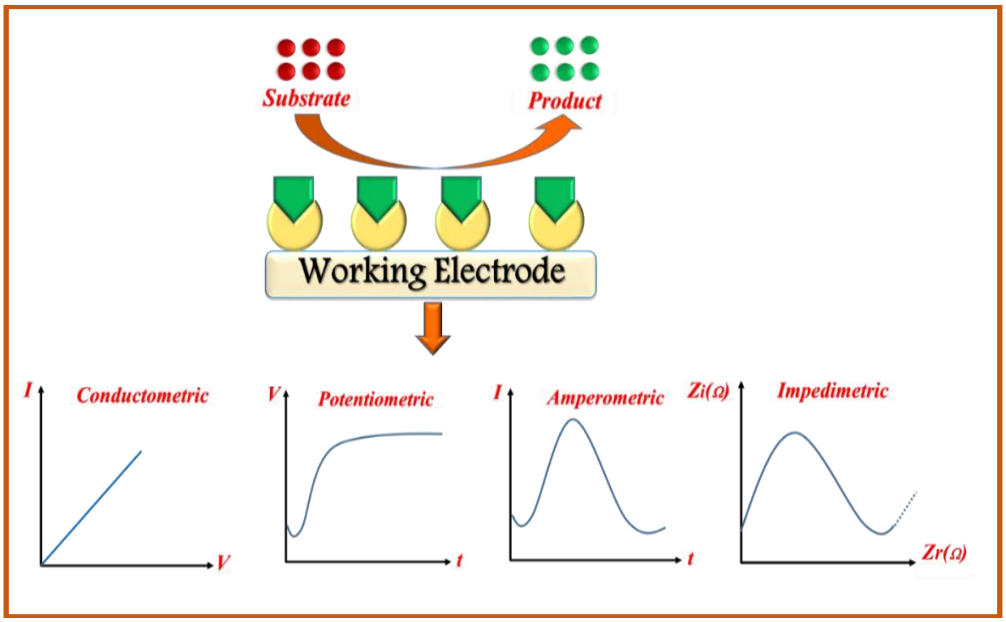

Figure 6 : Output signal types of the electrochemical biosensor.

B) Optical Biosensors: -It is a class of sensors which includes an optical transducer that detects changes in the optical properties resulting from the binding event. The signal generated by the electrode is an optical signal. This type of transducer is characterized by high sensitivity, selectivity, and rapid detection of toxins and drugs. Optical sensors are divided into two types according to the method or mechanism of detection. The first is a detection technique that includes labels attached to the bioreceptors that help produce colored or fluorescent flash signals after binding. The second is called the label-free detection process, which includes direct interaction between the analyte and the bioreceptor. The detection mechanism using labels is expensive, so this method is currently avoided. Sensors are divided into five types based on the optical output [52-54].

Fluorimetric biosensors: - are a class of optical sensors that work on the principle of fluorescence so that the bioreceptors are linked to fluorescent labels. These labels are fluorescent quantum molecules such as dyes or fluorophores, either proteins or organic molecules that absorb a specific wavelength and emit for longer distances when binding occurs between the biological receptor and the analyte [55].

Luminometric biosensors: - luminescence is a phenomenon of photon emission from an electron at a moment of relaxation from the excited to the ground state. This process is classified or named according to the source of the irritation; for example, chemical luminescence is produced by chemical reactions, and the resulting light is a property of that substance. In chemiluminescence biosensor, the bioreceptors like enzymes or proteins has been marked with chemical luminescence species to produce a signal proportional to their concentration when chemically reacted [56, 57].

Colorimetric biosensors: - are a class of optical sensors that use small and colored compounds such as dyes on the analyte. When the linking event occurs, a change in the color of the reaction occurs. This type is simple, inexpensive, and an effective technique for detecting toxic water [58].

Fiber-Optic biosensors: - It is a type of optical biosensor that is free from labels and works on optical fibers. Optical fibers transmit light to the detector based on the principle of total internal reflection of the waves. The light scattered in the fiber consists of two components,

one propagates inside the fiber's core, and the other propagates outside the fiber's core. These waves are sensitive to the medium around them. The basis of their action is that when a binding event occurs between the biological receptors and the analyte, a change in the intensity of the light arriving at the detector will occur. The biosensor structure consists of two mediums with two reflective indexes, n_1 (first medium) and n_2 (second medium). Any change in refractive index will change the shape of the wave i.e. if it was $n_1>n_2$, it would result in an evanescent wave penetrating the fiber's surface (n_2) and interacting with the biomolecules [59, 60].

SPR biosensors: - Plasmon resonance is an optical phenomenon due to electromagnetic waves interacting with electrons at the boundary between conductor and insulator. This resonance occurs when the frequency of the vibrating electrons corresponds to the incident waves and is either local in nanomaterials or nonlocal in bulk materials. From the biological point of view, this phenomenon is used to reveal the correlation event during the refractive index change. Therefore, these sensors are label-free sensors that detect changes in the refractive index. For example, when light falls on a film of gold, it will be reflected at the same angle of incidence. Bioreceptors are deposited over the thin membrane. If there is an association between the analyte and the biological receptor, the angle of the reflected light will change by a certain value, indicating that the binding event has occurred [61, 62].

C) Electronic biosensors:- sensor device whose principle of operation is similar to that of field effect transistors (FET), which consists of three regions: gate, source, and drain. Its working principle is based on measuring the electric field generated from the correlation event. When the link between the biological receptors and the analyte occurs at the gate surface, it will change the electrode properties, resulting in a change in the current between the source and the drain [63, 64].

D) Piezoelectric biosensors: - sensor device whose principle of operation is to measure the resulting change in the electrode mass (change in the density of the semiconductor charges due to the piezoelectric effect). The working electrode in this type is a slice of a gold-coated quartz crystal. The bioreceptors are immobilized on the surface of the slice. When the binding occurs, a change in the crystal frequencies gives an impression of the adsorption occurrence. Moreover, the intensity of these changes gives the concentration of the bound materials [65]. Therefore, it is concluded that the frequency is a function of mass. There are two types of piezoelectric quartz crystals: one in the form of a thin disk crystal (quartz crystal micro-balance) and the other in the form of a rectangular crystal. And both are mediated between two electrodes of gold [66].

E) Acoustic biosensors: - sensor device whose principle of operation is to measure the change in the physical properties of mechanical sound waves (mass change) as a result of a change in the properties of the working electrode surface material (such as elasticity, dielectric, and viscosity) after the occurrence of the binding event. The electrode material is usually a chemically active thin film based on the piezoelectric principle [67]. This type of sensor is divided according to the nature of the piezoelectric material that transmits the waves. The first is a surface sound wave (SAW), in which the waves travel longitudinally on the surface of the crystal. In contrast, the second is a Bulk Acoustic Wave (BAW), in which the waves travel longitudinally on the edge of the crystal face [68, 69].

F) Thermal biosensors: - biological calorimeter sensors are a type of sensor whose principle of action depends on measuring the change in emitted or absorbed temperatures due to the

binding event between enzymes. Two types of temperature gauges are used in the first biological sensor called thermostat, a transducer sensitive to the change in the resulting or extruded enthalpy determined by changing the electrical resistance properties with temperature. The resulting signal is proportional to the concentrations of reactive enzymes on the surface of the thermostat. This type of thermostat is called an enzymatic thermostat, i.e., sensitive to the heat generated by the enzymes. In contrast, the second thermopile is a series of thermocouples that work to measure the difference in temperature between two different regions. These sensors are used in wastewater contaminated with organic matter, where the heat emitted by the oxidation processes inside the polluted water is measured [70- 72].

G) Magnetoelastic biosensors: - defined as amorphous ferromagnetic ribbons whose principle of operation is to measure the change in the magnetic field with time as a result of the magnetic material being exposed to an external force as a result of the correlation event. This type depends not on the piezoelectric material but the magnetic elasticity. In this type, electromagnetic waves pass around the deposited material above the electrode. When a process of linking the bio-deposited receptors on the electrode with the analyte or the target material occurs, a change in the resonant frequency of the electromagnetic wave will occur, meaning that it gets distorted and that the intensity of these waves is proportional to the concentrations of the reactant [73, 74]. Table 3 gives the advantage and disadvantages of transducers. Table 4 describe the biosensor types and their applications

Table 3: The advantages and disadvantages of transduces [16, 75-80].

Transducer	Advantage	Disadvantage
Electrochemical	Low cost, label-free, high selectivity and sensitivity, simple operation, low limited detection.	Detecting take more time, low repeatability and stability, low adaptability to complex clinical specimens.
Optical	Low cost, high selectivity, medium sensitivity, specific, sometimes fast response time, good biocompatibility, and no electric interference.	Interference light incident, narrow range of concentration, need for high energy sources, complex processing steps, and advanced tools.
Electronic (FET)	Low cost, label-free, mass production, fast response time, stable output, require a small number of analytes, simple fabrication, long-term stability, and monitoring.	The complex manufacturing process makes it difficult to replicate and manufacture to integrate these devices into larger sensors, sensitive to temperature, the fabrication of several different layers on the gate is not perfect.
Mass-based	Medium cost, label-free, high specificity and sensitivity, fast response time, sample operation, economy.	Take more time to change, has a long time for incubating, requires several steps for immobilization, causes problems in the regeneration of surface crystal, requires several steps for drying and washing, and has low sensitivity in liquid.
Thermal	Fast response, low cost, high sensitivity, high specificity to analyte, simple fabrication, and control.	Performance Influenced by pH, samples require preparation, poor reproducibility, and did not show sensitivity toward optical and electrochemical analytes.
Magnetoelastic	Low cost, label-free, highly sensitive and specific, rapid, simple fabrication and configuration, wireless.	Pick-up coil, its applications are limited at high frequencies due to eddy current.

Table 4: Biosensor types and their applications [21, 81-94].

Biosensor	Application
Conductometric	Calibration analysis, detection of heavy metals, protein markers, and chemicals.
Potentiometric	Ion-Selective Electrode (i.e. pH meter). Determination of CO_2, sugars, pesticides, urea, neurotransmitters, etc.
Amperometric	Bio/chemical-sensing, deposition, detection of urea, alcohol, glucose, cholesterol, and amino acids.
Voltammetric	Electrode kinetics, analyte redox peak, reversibility.
Impedance	Kinetics of electrodes, corrosion, biosensing, electro-deposition.
Optical	DNA, immunosensors, localized SPR, metallic nanoparticles, receptor, SPR imaging, and liposome.
Fluorimetric	Availability of iron or water in cell populations or plants, water in the microbial environment, and measurement of biochemical oxygen demand.
Chemiluminescence	Detection and quantification of heavy metal, environmental, and food quality monitoring.
Colorimetric	Water- and foodborne pathogens.
Electronic (FET)	The clinical investigation, food analysis, biological research, and environmental.
Piezoelectric	Protein, DNA, cholera toxin, food pathogens detection.
Acoustic	Bio/chemical-sensing, Medical.
Thermal	Bio/chemical-sensing, deposition, food industry, enzyme thermistor.
Magnetoelastic	Food safety, and bio-security, determine blood coagulation time.

6. Method immobilized bioreceptors on the transducer surface.

The functionality of biological sensors depends particularly on the correct binding between the bioreceptors and the transducer surface. Bioreceptors are attached to the electrode surface by a process called immobilization. Therefore, the correct immobilization method must be chosen in order to design a biological sensor with good properties such as sensitivity, selectivity, and minimum detection limits. Because choosing the wrong installation method can affect the work of biological materials. The immobilization technology depends on several factors, for example, the nature of the biological elements, the type of electrode used, and the physical and chemical properties of the target substance (the analyte). The immobilization process can be defined as immobilizing vital receptors such as enzymes, peptides, and others on the surface of the transducer or the support. One of the benefits of the stabilization process is the possibility of using the stabilized biomolecules for as long as possible while maintaining their effectiveness when used repeatedly, thus reducing the costs of producing the sensors. It also maintains its sensitivity to the effects of changing ionic forces and pH. In general, there are two methods of immobilizing enzymes: physical and chemical immobilizing [95-97]. Figure7 shows methods of immobilized bioreceptors.

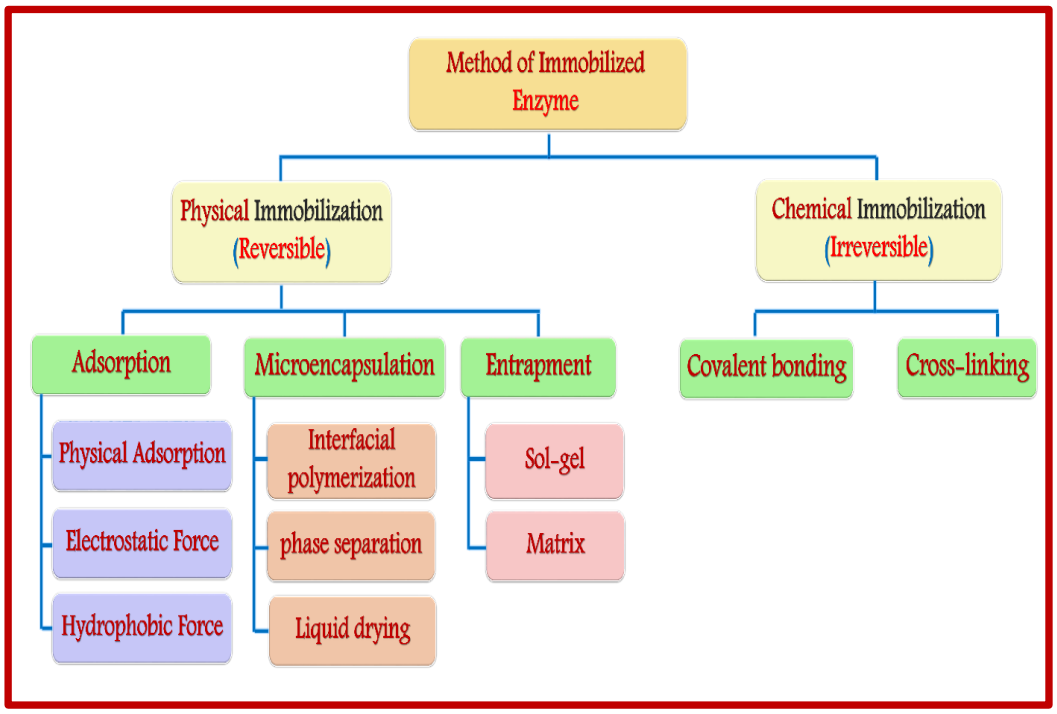

Figure 7: Flowchart of methods of immobilized bioreceptors.

First) Physical Immobilization: - is a stabilization technique that does not include forming chemical bonds between the electrode surface and the biological recognition element. It includes several methods: physical adsorption, encapsulation, microcapsule, and liquid gel.

I) Adsorption: - It is the process of adhesion of molecules or ions to the surface of the adsorbent. This method includes several types, including physical adsorption, adsorption by electrostatic forces, and water-repellent adsorption.

Physical Adsorption: - It is considered one of the oldest and simplest methods used in installation operations that do not require any chemical reactions. This technique involves the binding of bioreceptors to the electrode surface through Van der Waals bonds, hydrogen bonds, or hydrophobic interactions [98].

Electrostatic Force: - is a physical immobilization process in which electrostatic forces immobilize the bioreceptors to the electrode surface. This depends on the charge difference between the transducer surface and the biomolecules. Some conditions must be considered when using the fixation process: the enzyme's acid-base (isoelectric points) and the reactant medium or solution [99].

Water-repellent: - is a physical stabilization process that includes hydrophobic reactions due to the interaction between enzymes and the support surface. This method does not involve chemical reactions but rather changes in entropy. When the adsorption process occurs on the surface of the electrode, the bonds formed will work to separate the water molecules, so the randomness decreases, i.e., an increase in entropy [100].

II) Entrapment: It is a cheap and simple physical stabilization process by which the bioreceptors are confined within a matrix (a network of pores by a polymer membrane) without any direct attachment to the electrode surface. The polymeric membrane only allows molecules of small molecular weight to diffuse into the matrix and prevents their exit. The

reservation process is done through two mechanisms: reservation by liquid gel and reservation by capsule [101].

Sol-gel Entrapment: - The most common stabilization method. It is used to confine the enzyme within a polymeric membrane matrix consisting of several pores. These pores are prepared by condensation, hydrolysis of metal oxides, and hydrolysis of metal oxide. This method is distinguished from other fixation methods by the ease of controlling the size and shape of the membrane pores during its preparation. Furthermore, it does not require any modifications in the covalent bonds, nor is it thermally and chemically stable. It can define as polymerizing the solution due to the decomposition and condensation of the material's water at low temperatures, resulting in optically transparent glass. Since the chemical bond works to inactivate the trapped molecule, the biological molecule is confined within a matrix covalent network [102].

Matrix Entrapment: - It is a restriction method that uses matrices of pores or polymerized gels (e.g., silica gel, starch, pectate) to trap enzymes. One disadvantage of this method is the leakage of material retained through the pores upon use and low reproducibility. That leads to a loss of biosensor activity unless the enzymes are reinforced with polymerized materials [103].

III) Micro-encapsulation: - It is a technique in which the biomolecule is physically and chemically immobilized inside a semi-permeable spherical polymeric membrane with a drop ranging from one to one hundred micrometers. This membrane may be a polymer, and its preparation requires suitable conditions [104]. In general, the membrane can be prepared in three ways:-

Interfacial polymerization: - is a technique in which an aqueous mixture of a hydrophilic monomer and an enzyme are mixed in an organic solvent. This mixture of two phases of liquids is called an emulsion. An emulsion is a mixture of two phases, one continuous and the other dispersed. The scattered phase means the liquid is dispersed in the other phase, which is the continuous phase. The monomer is added to the organic solvent and then stirred well, which leads to the formation of a film of polymeric monomer at the boundary between the two solutions. This membrane surrounds the enzyme so that it works to trap it inside [105].

Coacervation (or phase separation): - It is a technique in which polymers are dissolved in organic solvents and then filtered to remove impurities. After that, the first organic solvent is mixed with a second organic solvent that does not dissolve the polymer [106].

Liquid drying: - This method is used to avoid enzyme damage from monomers. It can be defined as a technique in which the polymer is dissolved in a hydrophobic organic solvent in an aqueous solution of enzymes, forming the first emulsion while the colloidal substances present in the fine droplets of the caustic solution work to form a second emulsion. The organic solvent is then dried in a vacuum oven to form a capsule-shaped micro polymeric membrane surrounding the enzyme [106]. Figure 8 shows this mechanism.

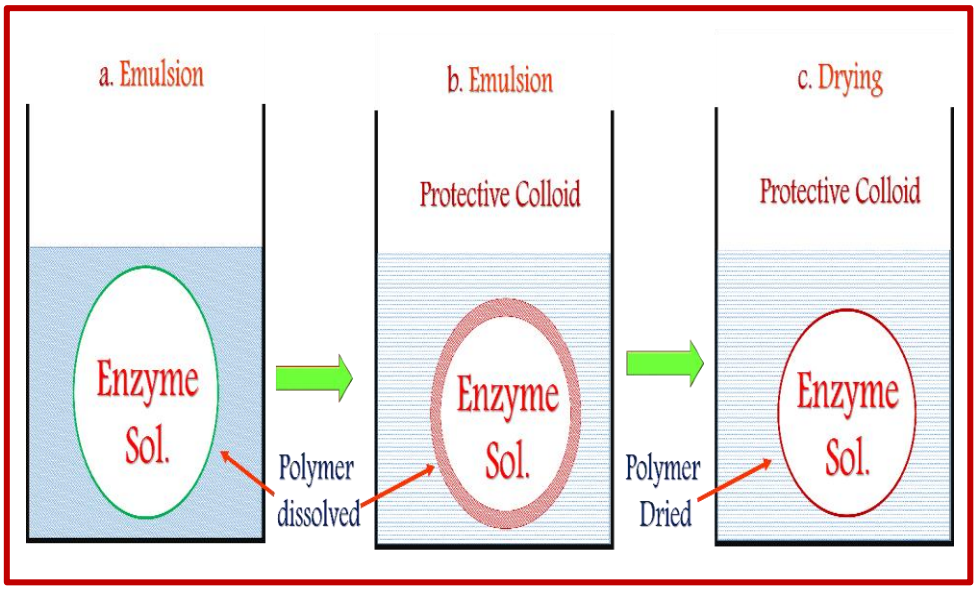

Figure 8 : Micro-encapsulation using the liquid drying method. Reproduced from Hartmeier[106].

Second) Chemical Immobilization: - is the second stabilization technique that includes forming chemical bonds between the electrode surface and the biological recognition element. It includes two methods, namely, covalent bonding and cross-linking.

Covalent Bonding: - is the most commonly used method of immobilizing biological identification elements through covalent bonds either in a layer of a membrane (surface or internal) or directly on the surface of the transducer. The immobilization process involves enzymes in a membrane matrix; two steps prepare covalent bonds and functional polymers. The binding process is based on the interaction between the same functional groups of the enzyme and the electrode surface. This method uses nucleophilic groups for coupling, like CO_2H, SH, NH_2, OH, and imidazole. Also, functional groups use aspects of amino chains in immobilization processes in cases that are not necessary for the enzyme's catalytic activity [96, 107, 108].

Cross-linking: - is the process of forming covalent bonds between the inactive regions of biological detection elements, like proteins and enzymes, by inert multifunctional groups around an inactive region of the support surface material. Glutaraldehyde is the most widely used as a multifunctional agent for the binding process. These functional groups, in turn, form three-dimensional clusters of proteins strongly attached to electrode surfaces with each other as a cross shape. Some important conditions must be observed when preparing these bonds, for example, the ideal temperature, acidity, ionic bonding strength, and incubation period for the chemical reaction and washing process after the preparation for removing unconnected biological material. Table 3 shows the immobilization methods' advantages and limitations [107, 108]. Figure9 shows methods of immobilized bioreceptors.

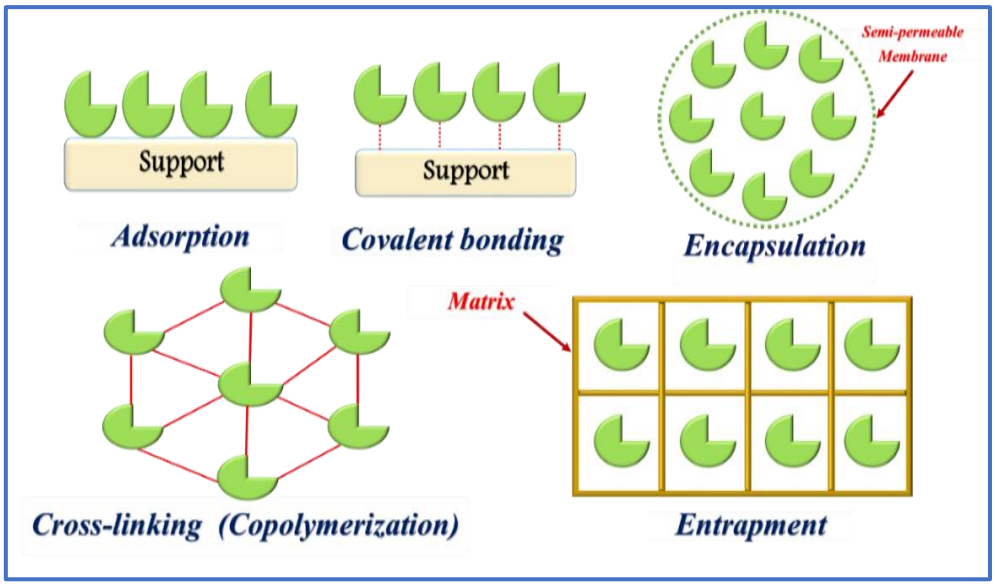

Figure 9 : Methods of immobilized bioreceptors.

Table 5: Advantages and disadvantages of Immobilization methods [109-113].

Technique	Advantages	Disadvantages
Adsorption	Simplest and cheap, it causes less damage to the enzyme attached, no regents needed and is reversible, so it allows for the regeneration of enzymes, simple preparation, and no modification of enzymes.	Less efficiency, very weak bonding, more enzyme leakage, short response time, sensitivity to pH, temperature, and ionic media, desorption of enzymes from a substrate, and blockage of the active site.
Entrapment	A simple and cheap method, suitable for different large bioreceptors, and pore size can be changed, not affecting the enzyme activity, not causing any chemical change in the supporting, immobilization with multiple enzymes together.	Limitation of pore size diffusion, leakage of enzymes, less change of conforming to changes, chance of bacterial contamination, slow response time due to substrate diffusion.
Micro-encapsulation	The cheap method, possible immobilization of large quantities of an enzyme, controls polymer thickness.	Limitation of pore size, only a small substrate can cross from the polymeric membrane.
Covalent Bonding	No leakage of enzymes, short response time, uniformity of distribution of receptors on the electrode surface, and strong coupling with a substrate.	High cost because it requires biomolecules in large quantities, and chemical modification can lead to the loss of a functional group of the enzyme.
Cross-linking	It is cheap, has ease of preparation, chemical strength bonds, has high adsorption, and has no leakage of enzymes.	Difficulty in controlling the reactions and the low occurrence of changes in the active enzyme sites when the binding process occurs

7. Some Applications of Biosensors

Cancer cells: - cancers are cells caused by a genetic deviation that leads to the body's failure to kill old cells and replace them with others. Thus, the increase in old cells leads to forming of an area of dead cells called a cancerous focus, whose size does not exceed a micrometer [114-116]. Sensors are used to measure the percentage of proteins produced by cancer cells. That is done by attaching antibodies to cancer cells (Polyethylene Glycol (PEG) proteins) on

the surface of quantum dots. When the patient is injected with a solution containing these granules, these anti-cancer cell proteins will guide the granules to the area where the cancer cells are located to stick to them only. And when exposed to ultraviolet rays by laser, these rays will irritate the quantum dots, resulting in a glow that clearly and accurately shows the areas of the spread of cancer cells [117, 118].

Glucose: - is a small sugar molecule produced by the photosynthesis process of green plants. Medical sensors are used to monitor blood sugar level by measuring the glucose percentage in diabetic patients. The percentage of glucose is determined using organic sensors made of porous polymers installed on the surface of any body part. When the glucose level is low, these organic sensors send signals to the patient's mobile phone to alert him to take an immediate insulin dose. The three generations of biosensors were used to know the glucose concentration [119, 120].

Cholesterol: - is a fatty layer that increases the percentage of heart disease due to hardening (reduced flexibility) of the arteries and high blood pressure due to lack of oxygen in the blood and thus a defect in the functional performance of vital organs. Its danger increases when those fatty layers are exposed to sudden breakage, causing blood clots and blockage in the blood vessels and arteries. The causes of increased cholesterol on the walls of blood vessels are determined by using quantum dots and nanoparticles of magnetic materials in early detection. Also, using a biological sensor called a molecular beacon [121], a single strand of DNA with fluorophore and quencher at opposite ends [122] with dimensions ranging between 4-5 nm. It is injected into the body (as a nanocapsule) and flows with the blood. It acts as a watchdog to monitor the genes that cause fat deposition. This data is transmitted and recorded as signals in organs outside the body. Optical sensors were used to determine the cholesterol concentration [123-125].

Urea: - is produced mainly from nitrogenous compounds and the metabolic breakdown of proteins in the liver of mammals and some fish. Optical biosensors are used to determine the urea concentration in the human body. Its concentration in a healthy body ranges from 2.5 to 7.5 mmol. In other words, any increase or decrease indicates a defect in liver function. Optical sensitizers consist of enzymes catalyzing a urease reaction and conjugating with acrylate globules. Polymeric hydrogels are used to stabilize urease enzymes to monitor urea concentration. Modified Fluorine-doped Tin Oxide (FTO) glass is used to detect urea in the Field Effect Transistor (FET) biosensor [124, 125].

Safety Food: - Sensors are used to detect the safety of food packaged inside packages. That is done by instilling nanosensors inside food packages to monitor the condition of the food product preserved internally and externally. These nanosensors detect any change resulting from microbial or bacterial activity in the food product. The detection process is inferred through the gradual change of the colors of the nanosensors inside the food package. These sensors are extremely accurate in detecting the lowest concentrations of microbes. Immunosensors have a use for this purpose [126, 127].

Environmental Pollution: - Sensors are also used to know the percentage of environmental pollution that harms human health, for example, knowing the percentage of toxins in sewage water through the oxidation processes of organic pollutants such as organophosphates used as an insecticide, which is being studied to find out its damage to the environment. Aptamers, antibodies, DNA, and enzymes are preferred as bioreceptors for environmental monitoring [128, 129]. Figure10 shows the applications of biosensors.

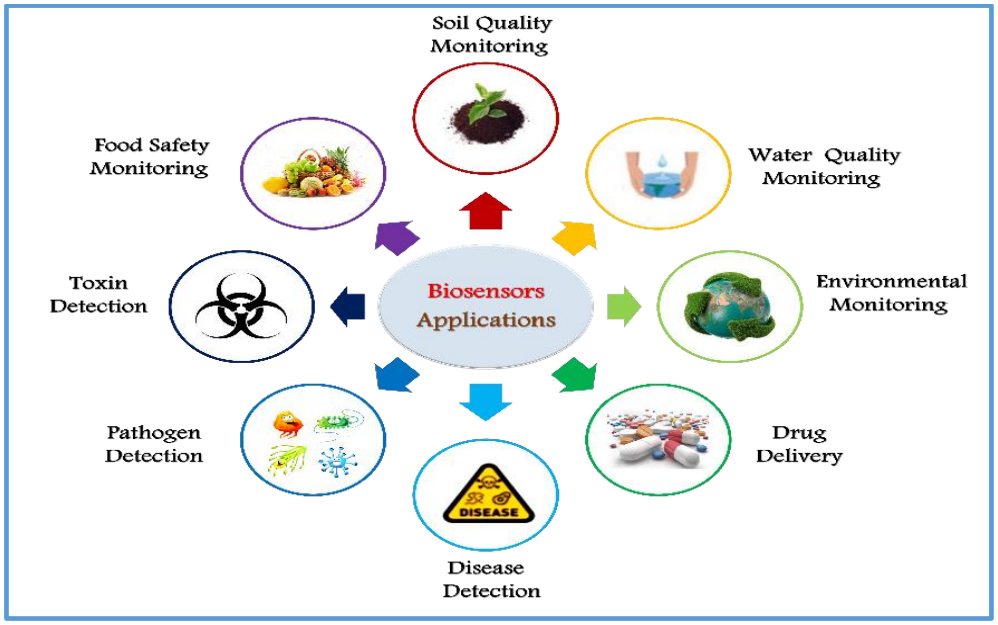

Figure 10: Biosensors applications.

8. Challenges of Biosensors

Despite the development of biosensors and the diversity of their applications in various fields, there is a gap between these developments and the number of commercially available biosensors causing a great challenge. These challenges are represented in the difficulty of obtaining sensors with accuracy, specific sensitivity, and repeatability for each use so that they give reliable results. As for the agricultural fields, the food industry, and the monitoring of chemical pollutants, the challenges of this type are its resistance to water and the open air so that it maintains its efficiency during repetitive work. At present, and with the presence of repeated infections from Coronavirus disease, the polymerase chain reaction (PCR) technique used in diagnosis takes a long time, requires expensive, complex equipment to install, and requires highly experienced personnel. In addition to problems related to low sensitivity that may give false negative or positive results [130-133].

9. Conclusion

Biological sensors are used in laboratories and hospitals for biomedical diagnosis of the patient and follow-up of disease development. In addition, it is used in other areas such as food safety control, drug discovery, and environmental monitoring, such as discovering the proportion of toxins in water due to some pollutants such as factory waste and fertilizers. Biosensors run an extensive study on the biological interactions between biological receptors and analytes, as well as an appropriate choice to immobilize the electrode surface recognition element correctly to ensure the durability of the sensor at each use. In addition, biosensors require chemicals on the sensor surface that are anti-environmental. The rapid diversification in the use of biosensors in various applications over the past decades is mainly due to the accuracy of the materials used (such as nanomaterials) in the manufacture of the biosensor structure, which ensures its high quality in addition to the technology used in manufacturing and the interrelationships in scientific research between various disciplines, for example, between physics and biology, as well as between engineering and biological disciplines.

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