RECENT DEVELOPMENTS IN BIOSENSORS: AN OVERVIEW

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CANDIDATE'S DECLARATION

I, Mansi sharma, 2k21/MSCCHE/30 of M.Sc Chemistry, hereby declare that the project Dissertation titled "Recent developments in biosensors: An overview" which is submitted by me to the Department of Applied Chemistry, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science, Chemistry is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition.

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I hereby certify that the Dissertation titled "Recent developments in biosensors: An overview" which is submitted by Mansi sharma, 2k21/MSCCHE/30 of Department of Applied Chemistry, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the Degree of Master of Science, Chemistry, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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ABSTRACT

According to conventional definitions, a biosensor is a self-contained analytical instrument that combines a biological recognition system with a physiochemical transducer for the detection of target molecules by converting recognition signal into detectable output signal. There are a number of different types of biosensors that have been effectively used in the environment, biomedical, and food industries to find and get rid of some contaminants, whether they are living or not. The most popular sensors used nowadays include enzymatic, optical, surface plasmon resonance, DNA, phage, and bacterial sensors. The need for academics and scientists to have a solid understanding of the various types of biosensors available in these and other sectors is growing. The fundamental characteristics of biosensors, the many biological materials employed, and information on the most significant types of biosensors now used primarily in the food sector, agriculture sector, medical field and industrial sector etc.

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MANSI SHARMA

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CHAPTER-1

Introduction

1.1 General Introduction

The fathers of biosensor are regarded to be Dr Leland and C. Clark. In 1962, they developed the idea of using a biological sensing component to find different analytes. The analytical tool known as a “biosensor” converts a biological response into an electrical signal [1,2]. Together with physicochemical detectors, they serve as analyser for chemical detection. The term “biosensor” was coined by Cammann and its meaning was introduced by IUPAC. Based on their mechanisms, the materials employed in biosensors are divided into three groups: the biocatalytic group, which comprises enzymes; the bio affinity group, which comprises antibodies and nucleic acids; and the microbe-based group, which comprises microbes. It is composed primarily of two components: a bioreceptor or biorecognition element that recognises the target analyte and a transducer that transforms the recognition into an electrical signal [3]. The transduction process can be carried out using optical, electrochemical, thermometric, piezoelectric, magnetic, micromechanical, or a combination of one or more of the aforementioned methods. A bioreceptor could be a tissue, microorganism, organelle, cell, enzyme, antibody, nucleic acid, or a bio-mimic [4]. The target analyte is recognised by the bioreceptor, and the transducer transforms the corresponding biological responses into equivalent electrical signals. The biosensor's amplifier reacts to the transducer's small input signal by producing a large output signal that has all of the essential input signal waveform characteristics. The signal processor then processes the amplified signal so that it can be later stored displayed and analysed [5].

1.2 Characteristics of Biosensor

Selectivity: When choosing a bioreceptor for a biosensor, selectivity is an important quality to take into account. A bioreceptor identifies a specific target analyte molecules in a sample that contains undesired pollutants and admixture compounds.

Sensitivity: The lowest concentration of analyte that may be reliably identified or recognised in the fewest steps at low concentrations (ng/mL or fg/mL) to confirm analyte traces in the sample.

Linearity: The findings of the measurements are more precise when there is linear graph. The substrate concentration can be detected at higher levels when linearity (straight line) is increased.

Response time: 95% of the findings are obtained in the time allotted.

Reproducibility: Precision (similar output when the sample is measured more than once) and accuracy (capacity of a sensor to generate a mean value that is closer to the actual value when the sample is measured each time) are characteristics of reproducibility time. When the same sample is tested more than once, the biosensor needs to be able to generate findings that are exact.

1.3 Structural Design of Biosensor

1.3.1 Architectural design

For the detection and measurement of glucose in any liquid, a potentiometric enzyme-based electrode was created as the first biosensor [6]. However, an examination of current studies shows that a lot of effort has been put into making laboratories smaller and more financially stable in order to build portable, small/nanoscale, and multifunctional biosensors these days [7]. However, the fundamental components of the biosensors - a bioelement and a sensing element-remained the same. A bioelement is any

organic organism that can detect a particular analyte from the medium of interest without reacting to any other potentially curious or interfering species. The biosensor's signal-transducing component: the sensing element- can take the form of any magnetic, optical, electrical, or electrochemical transducing mechanism [8]. The necessary criteria, such as quick response time, dependability, mobility, productivity, and long-lasting stability, have generally remained the same while choosing various substances/factors as the components of biosensors. The following is a summary of the key elements that must be taken into account when designing high performance biosensors: a) immobilization/fabrication of the bio-analyte in its natural configuration, b) high accessibility of the reception sites to the species of interest, and c) effective adsorption of the analyte to the employed support [9-10]. The design of biosensors should actively take into account these requirements.

1.3.2 Coupling of bio-element and senor element

Several phenomena have been presented for the efficient integration of the biological/organic recognition factor into the sensor. Here, only four primary coupling processes that have been frequently used to achieve the desired result have been illuminated: covalent amalgamation, matrix entrapment, membrane immobilisation, and physical adsorption encapsulation. When an organic substance becomes trapped in a certain SPM (semipermeable membrane) that is positioned at the sensor element, membrane entrapment takes place. In this type of analysis, the membrane acts as a separating phase between the organic component and the analyte [11]. Using a coupling technique that relies on physical intermolecular interactions (hydrophilic/hydrophobic forces, van der Waals forces, ionic forces, etc.), a bioelement is joined to a sensor this type of coupling is known as physical adsorption immobilisation [12]. Similar to this, matrix immobilisation is the term used when porous materials, such as sol or gel matrixes,

are used as limiting. The matrix encapsulation serves as a medium for the biological element and directly interacts with the sensing element [13]. Covalent coupling is the term used to describe a sort of interaction when the bioelement is directly linked to the sensor [14].

1.4 Components of Biosensor

1.4.1 Bioreceptors

The efficacy of the biosensor is determined by how specifically bioreceptors interact with the chemical of interest. There are three types of bioreceptors: Since enzyme sensors have a high substrate selectivity, they are widely used. Chemoreceptors, antibodies (immune-bioreceptors), and nucleic acids are examples of bioaffinity receptors that bind to specific ligands to create permanent complexes. The DNA and RNA sequences used by hybrid receptors are complementary to a single sequence found in the target.

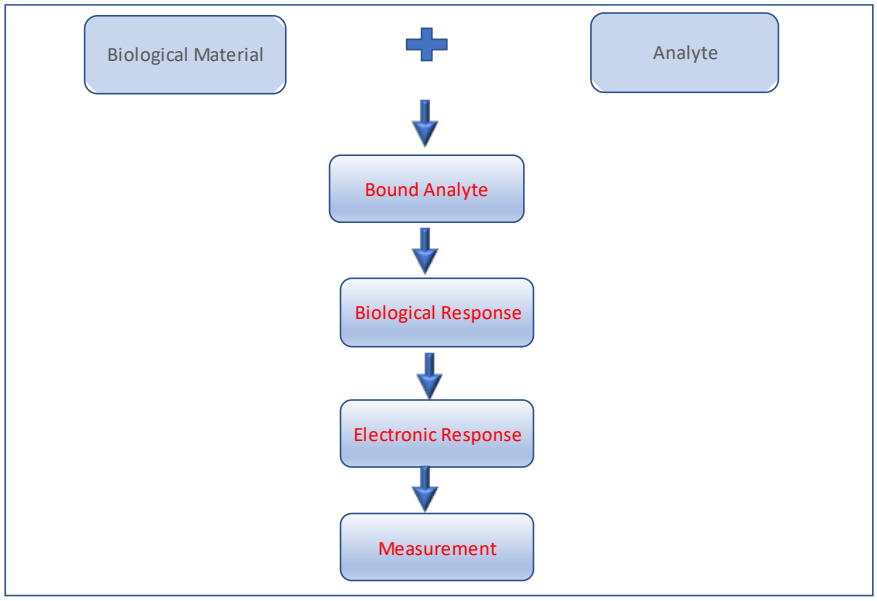
1.4.2 Transducers

Bioreceptor biological recognition is transformed by transducers into a detectable signal that can be measured and is proportionate to the target concentration. The kind of signals the bioreceptor emits will influence the transducer selection. Electrochemical biosensors are based on the monitoring of electroactive species produced or absorbed by the bioreceptor. Depending on the particular molecule, transduction is accomplished using an amperometric, potentiometric, or conductometric approach. The target concentration is directly correlated with the current produced by an electroactive species' chemical reaction to an applied voltage by the amperometric transducer. However, the selectivity of the amperometric devices is governed by the redox potential of the electroactive species present in the sample. This is bad because the signal that was

observed might actually be noise from another chemical species. Potentiometric transducers work by producing a working electrode potential that is proportionate to the active species concentration in relation to a reference electrode. Conductometric biosensors, meanwhile, rely on variations in conductivity brought on by biological processes. Thermal transducers are thought of as a small, temperature-detecting microcalorimeter. Thermal transducers have a wider range of applications because most complete microbial cell- or enzyme-catalyzed reactions result in the generation of heat. An oscillating quartz crystal submerged partially or entirely in a liquid makes up a piezoelectric transducer. Enzymes, antibodies, and antigens are used to measure and connect the variations in quartz crystal vibration frequency to the target analyte based on changes in the sample's physicochemical parameters, such as viscosity, density, and conductivity. Optical transducers use light phenomena including UV-Vis absorption, bio- or chemiluminescence, fluorescence or phosphorescence, reflection or scattering, and the refractive index to identify substances.

1.5 Principle of biosensor

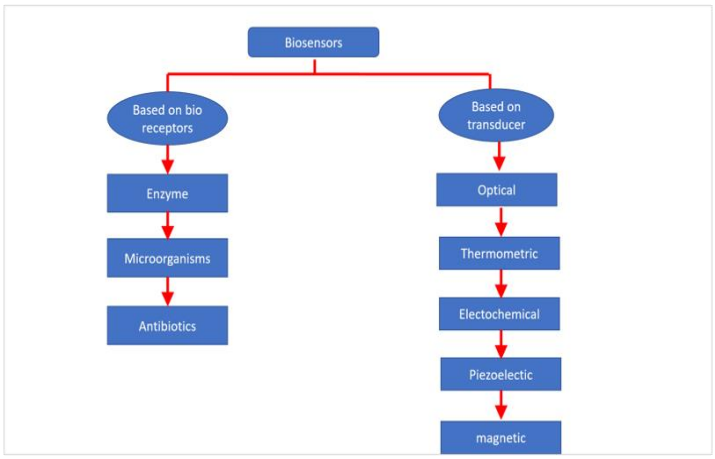
Traditional methods (physical or membrane trapping, non-covalent or covalent binding), immobilise the required biological material, frequently an enzyme. This organic material is immobilised and in close proximity to the transducer. The analyte binds to the biological substance to create a bound analyte, which then causes the measurable electrical reaction. Sometimes the analyte undergoes conversion into a product that may involve the release of heat, oxygen, electrons, or hydrogen ions. Product-linked changes can be converted by the transducer into electrical signals that can be amplified and measured.



Types of biosensor

The following two categories of biosensors are

- based on the physical modifications that transducers will measure
- based on the sensor's biological component



1.6.1 Biosensors can be classified into different groups depending on the method of signal transduction:

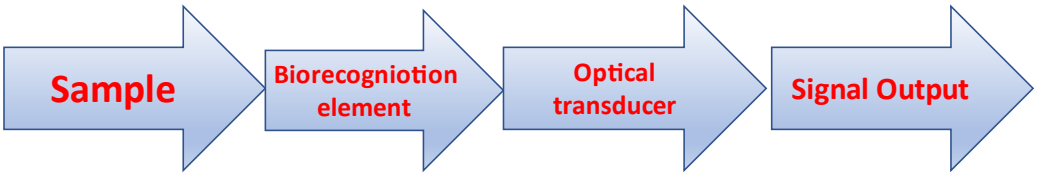
- **Optical**

- **Electrochemical**
- **Thermometric**
- **Piezoelectric**
- **Magnetic**

1.6.1.1 Optical

Optical biosensors have a number of advantages over conventional analytical techniques because they enable the direct, in-situ, and label-free detection of a wide range of biological and chemical substances. Optical detection is accomplished by combining an optical field with a biorecognition component. Optical biosensing with and without labels can be broadly divided into two general modes. In a nutshell, the interaction between the substance being examined and the transducer produces the measured signal in a label-free manner. In contrast, label-based sensing generates the optical signal using a label and a colorimetric, fluorescent, or luminescent approach. The analysis of blood glucose levels is the most commercially successful use of a biosensor, or the portable glucose metre used by diabetics. But in some circumstances, such as when an antibody interacts with an antigen Labelling can change the binding characteristics when a label is conjugated with one of the bioreactants, which introduces systematic inaccuracy into the biosensor analysis. By employing label-assisted sensing in conjunction with enzymatic oxidation, simple molecules like glucose can be found. High specificity, sensitivity, tiny size, and cost-effectiveness are only a few of its benefits. multiple sophisticated idea and extremely interdisciplinary methods are used in the development of new optical biosensors, including microelectronics, microelectromechanical systems (MEMSs), micro/nanotechnologies, molecular biology, biotechnology, and chemistry [15-16]. The development of optical biosensor technology has accelerated dramatically over

the last ten years. The biotechnology, environmental, and healthcare industries have dominated research and development on optical biosensors. In the fields of medicine, the environment, and biotechnology, there are many potential applications for biosensors, and each one has specific requirements for the concentration of the analyte to be measured, the output precision necessary, the sample concentration necessary, the time needed to complete the probe, the time needed to allow the biosensor to be reused, and the system cleaning requirements [17].



1.6.1.2 Electrochemical

The two basic parts of an electrochemical biosensor are a molecular recognition layer and an electrochemical transducer, which converts biological data coming from a binding event into an electrical signal and then displays it on a readout device. In other words, signals produced the electrode surface is converted into a signal for use in quantitative analysis after the active contact between the analyte and bio-recognition element. This sort of biosensor may identify target diseases in air, water, and on seeds in a variety of settings, including greenhouses, fields, and post-harvest storage containers.

Plant antibodies and DNA are more abundant among all the potential biological sensing components connected to a transduce are beneficial and used in point-of-care tests to find plant pathogens. According to Cassedy et al., the high sensitivity and specificity of antibodies are their most desirable qualities. Only the target antigens can be detected by them at extremely low concentrations, and all other antigens receive no signal from them. Also, a biosensor must have the ability to demonstrate high affinity levels and little to no interactions with other reagents throughout tests in order to function properly. Once the biomolecular contact that develops on the surface of the transducer between the analyte and antibody is the essential basis of antibody-based immunosensors [18-21].

1.6.1.3 Thermometric

Thermometric biosensors take advantage of the heat absorption or evolution that is a key characteristic of biological reactions. Here is reflected as a rise in the reaction medium's temperature. Earlier calorimetry research used direct monitoring of the change in heat to determine the degree of reaction (for catalysis) or the structural dynamics of biomolecules in the dissolved state [22-23]. The development of thermometric devices, however, was facilitated by its use in biosensors. They primarily gauge variations in fluid temperature that occur after an appropriate substrate reacts with the mounted enzyme molecules. In its simplest form, thermometry is the measuring of temperature. A thermometer is the most basic type of such a device and is frequently used to measure body or ambient temperature. But regular mercury based thermometers are restricted not just by the toxicity of metallic mercury but also by how sensitive they are to temperature [24]. Simple mercury thermometers are, however, restricted by their temperature sensitivity as well as the toxicity of metallic mercury. The heat is sensed by sensitive thermistors in thermometric devices according to similar principles. Common names for such devices include enzyme thermistors. The cost of operation and the somewhat lengthy

experimental procedures limited the use of calorimetric instruments for everyday use. However, several of these drawbacks were overcome by the development of the enzyme thermistor, which was based on flow injection analysis and included a heat-sensing element with an immobilised biocatalyst. In the last two decades, a number of instruments have been developed that combine the calorimetric, enzyme catalytic, immobilisation on appropriate matrices, and flow injection analytical principles [25-26].

1.6.1.4 Piezoelectric

The standard quartz crystal microbalance, which consists of a thin, circular quartz plate with metallic electrodes placed on the opposing sides, serves as the primary example of piezoelectric transducers in this review [27-28]. The active sensing surface is defined by the overlap of the electrodes. Both bulk acoustic wave devices (BAW) and thickness shear mode (TSM) are used. Electrodes used in biosensing applications are frequently made of gold. The fundamental resonance frequency, which ranges from 5 to 30 MHz, is determined by the thickness of the quartz plate. Many reviews and textbooks have covered the fundamentals of operation modes (active one based on oscillator, passive impedance scanning), drive circuits, and theories describing the observed resonant frequency fluctuations of the piezoelectric sensor [29]. The Sauerbrey equation which describes the directed relationship between mass and frequency shifts in measurements in the presence of liquids, is not always true, and the observed response is frequently significantly higher than theoretically anticipated. From a practical standpoint, piezoelectric biosensors supposedly low sensitivity is actually more than adequate for the required analytical purpose. The last five years' worth of trends in the subject will be summarised in this review; the earlier literature has already undergone a thorough evaluation [30].

1.6.1.5 Magnetic

Magnetic nanoparticles have significant application value in drug analysis and biological detection. Complex activities including sample mixing, separation, and detection can be performed by tagging biomolecules with magnetic materials and utilising molecular recognition technology. To facilitate sample separation and identification under magnetic field gradients, scientists tag molecules with magnetic materials Johnson, etc. a magnetic counter used in magnetic immunoassays to find molecules that have been magnetically tagged. Additionally, once the discriminator is marked with nanomagnetic particles and paired with a target recognition device on the surface of the tumour to find the tumour, the distribution and placement of magnetic particles can be assessed in vitro [31]. Chmela and other researchers have suggested a fresh, quick method for detecting biological material using a microscope. a high-temperature superconducting DC quantum interface device and a paramagnetic nanoparticle-based microscope for biological samples (SQUID). Magnetic nanoparticles are created during a brief magnetic field pulse after the immobilised antibody magnetic particles are first suspended in a solution. Without antibodies, the particles move in a Brownian manner in the absence of a magnetic field, leading to free particle dispersion and the absence of a detection signal. The target substance is analysed using the signal gathered from the squid. Nanoparticles move with the target molecule in the sense of Neal relaxation, resulting in a slowly decaying magnetic signal. Shorter detection times derive from this technology's ability to directly identify tagged molecules without separating nanoparticles that are not linked to the molecule to be detected [32].

1.6.2 Based on the sensor's biological component

1.6.2.1 Enzyme

In essence, a biocatalyst is a protein molecule that, like a key fitting a lock, identifies a certain target chemical. Once attached, it changes the material into a

chemically distinct product. This product frequently consists of something that is simple to detect, like a chemical that produces light. In the presence of oxygen and adenosine triphosphate (ATP), the enzyme like luciferase combines with the substance luciferin to produce oxyluciferin, a chemically distinct molecule that produces light. Many commercially available biosensors exploit this reaction some of which are employed to find bacterial contamination or poisonous soil [33].

1.6.2.2 Microorganisms

Typically, yeast or bacterium cells are the microorganisms employed in biosensors. Typically, one of three potential methods is used by this kind of biosensor. The target analyte serves as the microorganism's food. The microorganism-based biosensors that identify biodegradable organic substances are the most often utilised. The immobilisation of the microbes onto electrochemical transducers enables the measurement of the rate of organic compound metabolism. Microorganisms employed in biosensors can become less active when exposed to a wide variety of harmful substances. Because of this, general toxicity screening is a particularly good application for these biosensors. Optical or electrochemical transducers can be used to detect the bacteria' respiration. Microorganisms that have undergone genetic engineering are able to detect the presence of specific materials [34].

1.6.2.3 Antibiotics

These are proteins that the immune systems of living things produce in response to the presence of “foreign” microorganisms (bacteria and viruses). Antibodies, in contrast to enzymes, recognise and bind to certain molecules instead of catalysing reactions. They may typically be produced for the detection of particular industrial compounds and are more easily customised [35-36].

1.6.2.4 Cell

Cell-based sensors are a type of biosensor that depend on the ability of living cells to recognise internal and external cellular environments conditions, physical characteristics, and produce reaction through the cooperation of jolt and cell as the biospecific detecting component [37]. Microorganisms, such as parasites and microscopic organisms, can be used as biosensors to identify specific atoms or the overall "status" of the surrounding situation [38]. Additionally, proteins found in cells can be utilised as bioreceptors for the recognition of particular analytes. In general, a biosensor based on living cells is exceptional compared to other types of biosensors that contain materials that have been taken from living things. These types of biosensors have both benefits and drawbacks. The typical natural settings under that the cell can endure for an extended period of time where necessitate the regulation of the physical and synthetic parameter of condition are what primarily regulate the recognition of this biosensor's outermost reaches. However, the main limitation with cell-based biosensors is the security of the cell, which depends on a number of factors, including disinfection, longevity, biocompatibility, and so forth. The effectiveness of a cell-based sensor is also dependent on particle selectivity, where a cell-based sensor has low microbiological sensor selectivity because of the multi-receptor conduct of the in place cells [39]. Due to its advantages over a biosensor based on chemicals, scientists continue to favour cell-based sensors despite these complications. Due to its advantages over a biosensor based on chemicals, scientists continue to favour cell-based sensors despite these complications. The cell-based biosensors are relatively less sensitive to interference from solutes and more resilient to unfavourable temperature and pH values than chemical-based biosensors, but they shouldn't be used in the long run if an issue with the cells dying

should arise. As a result of the dynamic nature of the cells, a longer lifespan than with enzymatic sensors can be anticipated.

CHAPTER-2

Applications of Biosensor

There is a growing focus on highly advanced sensors created for use with biological matter monitoring and measuring of the environment, biomedicine, etc. Biosensors are used widely in fields including pathology, environmental monitoring, criminology, screening and monitoring of public and individual health, and the food sector for safety**.** Various applications of biosensor are shown here in pictorial representation.

2.1 INDUSTRIAL

The manufacturing sector is being affected by biosensor technology more and more, and there are tremendous opportunities for its growth. Applications in fields where quick detection, high sensitivity, and specificity are crucial need to continue to be a driving force behind scientific advancement and commercialization [40-41]. The following list of probable industrial uses for biosensor technology is provided: All

manufacturing industries in need of a quick, affordable way to monitor industrial effluent. Chemical, culinary, and pharmaceutical sectors evaluate water quality the quantitative and differential analysis of petrol mixtures from chemical operations and products, as well as analytical quality control and monitoring. petrochemical industry study of volatile organic compound characterization, clean up, and post-closure monitoring of polluted land and hazardous waste sites through in-situ operations as a glucose sensor, lactate sensor, alcohol sensor, biochemical oxygen demand sensor, microbe sensor, *E.coli* biosensors for food, fish, meat, and poultry flesh sensors, and product quality evaluation sensors [42-43]. In this field, biosensors may be used to monitor microbial biomass, product information, and substrate levels, among other things. There are several off-line procedures available right now, but they are inconvenient and time-consuming because samples must be extracted (and frequently diluted) for analysis. However, the requirement for steam sterilisation in many food and pharmaceutical fermentations to avoid microbial contamination hinders the development of biosensors for fermentation. Unless there is a separate sample leak from the main process to a remote testing site, this is obviously not compatible with biosensors.

2.2 Health care

2.2.1 Biosensor in Cancer Research

The type of detection is determined by the biosensor measuring approach either label-free or not. While some methods (such as fluorescent experiments) only allow the analyte molecules that have been labelled to be recognised by the bio recognition element in order to produce an electro active signal, the key of label-free detection is the direct binding of the original, unaltered analyte molecule to the bio reorganisation component (enzymes, fluorescent compounds). Because of their remarkable affinity for cancer cells, metal nanoparticles are frequently used in cancer research [44]. Chemical synthesis and

genetic engineering techniques are frequently used to incorporate certain markers into the tested molecule. Sadly, the label's attachment may dramatically change the evaluated molecule's properties. Markers may also bind to molecules other than the target, and when utilising living cells, they may disrupt metabolism. All of the aforementioned factors make label-free solutions much more popular. Present-day label-free techniques include surface Plasmon resonance and quartz crystal microbalance (QCM) (SPR). These methods enable real-time monitoring and study of the kinetic/thermodynamic interactions between two complementary molecules, where one molecule is immobilised on the surface [45].

2.2.2 Biosensors for cardiovascular diseases diagnostics

One of the leading causes of death is regarded as cardiovascular disease worldwide. For such disorders to be successfully diagnosed, an early and quick diagnosis is necessary. Several biomarkers, including myoglobin, B-type natriuretic peptide (BNP), cardiac troponin I, C-reactive protein (CRP), interleukins, and interferons, are now recognised for use in the medical and nontechnological fields. These cardiac signature biomarkers made use of a variety of biosensor technologies, including magnetic, optical, acoustic, and electrochemical ones. Even while some of these biomarkers have the potential to be important diagnostic tools in the medical field and have predictive value independent of prior conventional risk variables, few of them have achieved this. Using the Troponin biomarker, patients with probable acute coronary syndrome have been identified and risk classified [46-47].

Biosensors for Markers of CVDs

To identify the biomarker for CVDs, biosensors have been created. These biosensors were made using a variety of nanomaterials. Due to their improved performance, nanotubes, nanowires, metal nanoparticles, and polymer-based

modifications are typically favoured in these researches enhancing surface area, sensitivity, and selectivity qualities of analytes [48-51]. Due to CVD events and high mortality rates, the serum's rising levels of cardiac biomarkers are crucial. Therefore, rapid, trustworthy, and accurate detections of these biomarkers are essential. Because CVD biomarkers' substantial concentrations fluctuate between pM and nM, very sensitive detection techniques are also required.

Types of Transducers for Detecting CVD Biomarkers

The substance of the transducers affects how well the electrochemical technique works. In these investigations, the substrate serves as the working electrode. Low noise signals and repeatable results for the analytes should be provided. The choice of electrodes is influenced by a number of variables, including potential range, electrical conductivity, surface reproducibility, mechanical qualities, cost, and hazardous effects. The most popular electrodes are those made of noble metals like platinum, gold, carbon-based electrodes, and mercury. Since mercury electrodes have drawbacks, solid electrodes are especially favoured. Its anodic component has a limited potential range, making it unable to study the oxidation of substances or biological molecules. Substrates include nickel and copper electrodes, platinum, gold, silver, and other noble metals and carbon-based compounds. A large range of potential exists for gold and platinum electrodes, and they also offer a quick electron transfer mechanism.

2.2.3 Biosensor Technologies for Covid-19 Pandemic

The COVID-19 virus in the air can be found and measured with the help of a biosensor. It effectively addresses the difficulties posed by biological constraints and technical constraints. With the majority of its transmission occurring from person to person, this technology helps determine how long a virus can survive in the air. Also, it aids in the diagnosis of illnesses caused by infections. It automatically evaluates

numerous laboratory tests as well as the source of several infectious diseases in the atmosphere. The information gathered by biosensors can be used by healthcare facilities for remote screening of a broad population, including those who are in quarantine, patients in nursing homes, and those who are vulnerable and at high risk while at home. To address the growing difficulties in virus diagnosis, it is advised that the current biosensing technologies need to be continuously improved. The COVID-19 virus moves from person to person throughout the world under the current situation, necessitating an early diagnosis of this virus kind [52].

Biosensors used in covid

Nucleic acid based biosensor, optical biosensors, aptamer-based, antigen-Au/Ag nanoparticles-based electrochemical biosensors, and Surface Plasmon Resonance (SPR) are examples of cutting-edge biosensors used to detect RNA-viruses [53]. Biosensors may be useful biological instruments for quick, precise, portable, and more optimistic diagnosis for the pandemic that is currently affecting the world's economies and people [54-55]. A dual the most significant protein in the SARS-CoV is the nucleocapsid (N) protein, which serves as an analytical marker for extremely sensitive virus identification. As a suitable clinical method, localised surface plasmon coupled fluorescence (LSPCF) fiber-optical biosensing tools were created for the detection of SARS-CoV N nucleocapsid protein in human serum. The developed platform is easy to use and has a linear range and detection limit that are appropriate [56].

For the purpose of detecting the N protein of coronaviruses while experimental research, SELEX, or systematic evolution of ligand by exponential enrichment, was employed. The SARS-CoV N protein was detected using an immunoassay based on an aptamer-antibody hybrid that was quick and accurate [57]. As a potential treatment for the clinical severe acute respiratory syndrome coronavirus 2, a functional plasmonic

biosensor with the plasmonic photothermal (PPT) effect coupled with localised surface plasmon resonance (LSPR) sensing transduction was developed. (SARS-CoV-2) diagnosis in order to develop diagnostic coronavirus biosensors. Through nucleic acid hybridization, the two-dimensional gold nanoislands (AuNIs) functionalized with complementary DNA receptors can perform a sensitive detection of the chosen sequences from COVID-19. The created system has special qualities like high sensitivity and specificity [58].

2.3 Biosensors in plant biology

Plant science has advanced thanks to novel new tools in DNA sequencing and molecular imaging. While enzyme substrates, receptors, and transporters are difficult to measure with the same precision as intracellular localization and ions and metabolite levels using conventional mass spectrometry methods. It lacked crucial details concerning its behaviour and location. Yet, this data may be exploited quickly and effectively with the use of biosensors [59-60]. Develop strategies to visualise the real process, such as changing one metabolite to another or starting a signalling event, in order to measure dynamic processes under physiological settings. By having the sensor respond dynamically, this visualisation is possible [61]. The first protein sensor was created by Roger Tsien's lab to monitor caspase activity and regulate calcium levels in active cells. The FRET between two spectral variants of GFP served as the foundation for these sensors. incorporates Cameleon sensor-based high time resolution imaging of calcium oscillations [62-64]. Biosensors can be used to locate missing elements that are involved in the analyte's metabolism, regulation, or transport. The sucrose FRET sensor, which is in charge of identifying proteins, transports the sucrose effluent from the mesophyll and loads it in the phloem. When glucose is introduced to starved yeast cells, fluorometer-based experiments using a FRET sugar sensor can successfully identify sugar transporters

that can start working right away. Assays using yeast cytoplasm or find the genes that alter vacuolar pH and explain the use of biosensors for gene screening in situations. The biosensor is built on a molecular recognition event that has developed organically, frequently with high selectivity and with an appropriate affinity for working under endogenous substrate concentrations. This is one of the advantages of enzyme-based electrochemical sensors. A study reveals that redox enzymes catabolize a number of plant hormones, which increases the potential for selective, enzyme-based biosensors. when suitable throughput imaging techniques are available [65-66].

2.4 Environmental applications of biosensors

2.4.1 Biosensors for pesticide detection

Pesticides, insecticides, and herbicides with a high toxicity and deadly potential have been used extensively in agriculture for decades. For instance, potato, maize, wheat, and rice crop fields are frequently treated with pesticides. Repeated exposure to some pesticides over time may result in allergies, breathing issues, or even cancer, and their high toxicity may have an impact on the environment. Pesticide sales in 2011 were over $20 billion greater than they were in 2000 [67]. Pesticide analyses are therefore becoming more and more significant. In general, gas chromatography or high-performance liquid chromatography are employed to find pesticides, but these processes take a long time and need a lot of work. For quick and fast pesticide detection, biosensors may be a good alternative method. Despite harming the environment and people's health, organophosphorus is a common pesticide. It is necessary to create techniques for accurately analysing these pesticides. Enzymatic biosensors have been extensively studied for this purpose due to their stability, sensitivity, and accuracy. Based on the inhibition of enzymes, optical, calorimetric, electrochemical, and piezoelectric biosensors

have been created to measure pesticides among the several kinds of enzymes employed [68].

2.4.2 Biological Oxygen Demand

In trash streams and sewers, microorganisms typically break down organic compounds to produce hazardous chemicals. The quantity of atomic oxygen(O_2) needed by microbes to survive in waste water-and primarily during the breakdown of organic compounds-is known as the biochemical oxygen demand (BOD). This causes the environmental pollution of water sources to increase. Nisshin Denki Electric Co. Ltd. created the first commercially produced biosensor for measuring BOD levels in 1983 [68-69].

2.4.3 Polychlorinated biphenyls (PCBs)

While being useful for pest management, polychlorinated biphenyls (PCBs), which are non-biodegradable compounds used in a range of pesticides and herbicides, also produce PCB buildup in the soil. These PCBs enter the human body after being absorbed by crops and result in major health problems, most frequently cancer. The most promising application of biosensors in recent years for the immunological biosensors have provided accurate detection of these organic substances in foods and soils, which monitor the interaction between antigens and antibodies using piezoelectric transducers [68-71].

2.4.4 Heavy metals

Because they cannot be easily biodegraded, heavy metals pose the greatest hazard to human health and their hyper-accumulation results in a variety of unsuitable health problems. Several biosensors have been very effective in identifying and keeping track of the dangerous amounts of heavy metals that could result in adverse health

consequences [72]. The utilisation of genes that are resistant to specific kinds of heavy metals, such as copper, mercury, tin, and cobalt, is necessary for bacteria-based cell biosensors [73]. These sensors' reliance on heavy metals is based on the conjugation of genes that are resistant to the metals with some luminescent proteins, like as luciferin, so that they can respond when the metals come into contact with their cytoplasm. These biosensors work by inhibiting these heavy metals by metal ions on various enzyme types, and then specifically detecting those inhibitions with various types of biosensors. The successful detection of urease enzyme action inhibiting mercury ions (Hg^{+2}) was accomplished using amplimetric biosensors. The same urease enzyme inhibited cobalt, nickel, mercury, gold, and lead, allowing for the monitoring of dangerous levels using fibre optic sensors [74-76].

2.4.5 Nitrogen compounds and microbial detection:

To monitor dioxins, nitrates, E. coli, and chemicals similar to dioxins, commercial biosensors have also been developed and utilised successfully. Airborne pathogens and pollutants can both be monitored using microbe-based biosensors. It is possible to employ phage-sensors to find airborne harmful bacteria [77].

2.5 Biosensors in food quality

In the food business, it is evident that many batch activities are being replaced by processing that is ongoing and highly automated. As a result, there is a growing need for instruments that can automatically control quality throughout the process and at the very end so that the current status of the process can be characterised [78]. Biosensors undoubtedly provide real-time monitoring of a specific analyte for the food business as well as feedback control. Not only will this boost food safety, but it will also result in less effective control, fewer jobs, and time and energy savings control, fewer jobs, saving of time and energy [78]. In various food businesses, biosensors can be employed as

analytical tools, particularly for determining the composition, level of contamination, and on-line control of the fermentation process of raw materials and processed meals. Considering the wide range of research on biosensors for the food sector, their use for any analyte in this field is still limited [79-81].

The Food Matrix's Monitoring of Microorganism Activity

A good microbiological environmental surveillance system can identify issues and promote complete microbiological safety via early warning of potential microbial dangers in food products. As a result, the microbiological aspects of food safety have been thoroughly studied for many years. Maintaining food protection, for instance, has long been a key component of government programmes in several nations. To stop dangerous pollutants from entering the food chain, management measures have been set up [82]. The Centres for Disease Control and Prevention (CDC) contend that significant attention needs to be paid to the impact that microorganisms including bacteria, viruses, and fungi have on human existence . Because the adoption and oversight of microbiological food safety lead to enhanced productivity, higher wages, sustainable development, and better living conditions, it has been urged that politicians implement proper food safety policies to improve global nutrition and food security [83].

Food safety for microorganisms is very different from food safety for chemicals. Microbes can enter the food chain at any moment, despite the fact that chemical pollutants and additives often do so at specified amounts [84]. As a result, on this level, food laws are fairly simple everywhere.

A high level of protection of human life and health should be guaranteed in the pursuit of community goals, according to the EU General Food Law [85], for instance. The sanitary qualities of the manufacturing system are also intimately related to the microbiological safety of consumer items. Implementing suitable sanitary practises is

crucial under these circumstances for the protection of the finished good. For the assurance of these procedures, it is crucial to assess the effectiveness of such approaches [86]. In actuality, these inspection procedures are demanded by all food safety rules. As a result, scientists are working very hard to develop efficient and quick procedures that may fulfil the demands of daily inquiry and monitoring of food production [87]. Monitoring food chain contamination necessitates a variety of analytical techniques as well as the application of sophisticated, automated apparatus that has only recently been created for the purpose of contaminant detection [88].

2.6 Biosensor in Smart Packaging

Throughout the world, there have been several instances of food product contamination in recent years. Although *Escherichia coli*, viruses, listeria, and other pathogens in salmonella, tuna, poultry, dairy products, etc. have not resulted in food-borne illnesses in the United States, there is a rising consumer desire for technology development to ensure the safety of food goods. The environment in which items are packaged and delivered to consumers typically determines the quality of food. It is essential to comprehend the mechanism of meat rotting in order to use indicators or sensors to determine the freshness of meat. Technology for smart food packaging has enhanced the exchange of and monitoring of food quality data by integrating indicators, sensors, and radio frequency identification (RFID) into packaging. With this technology, producers and consumers may now track a product's history through key links in the food supply chain. Several indications and sensors, including freshness sensors and time/temperature indicators, have been created for smart packaging in order to monitor the integrity of food goods. indicators or sensors that employ analytics for quality-indicating characteristics. An electrode's surface should ideally have a biological component immobilised on it so that it can mediate an electrochemical reaction and

provide an electrical signal that is proportional to the concentration of the analytes. An RFID tag or other microelectronic device will be operated by creating electron flow from the signal, which will be amplified. Data gathered from the biosensor may be traced and monitored during the manufacture, distribution, and consumption of fresh items to assure their safety thanks to the convergence of bio sensor and RFID technology [89].

Integrators for time-temperature

The oldest method of food quality control to be established for commercial application was TTI because the majority of fresh items are distributed, handled, and stored in the cold chain. By adopting continuous and irreversible colour movement or development based on mechanical, biological (enzymatic, microscopic), photochemical, diffusion, and solid state polymerization reactions [90]. TTIs can depict a whole or partial history of the temperature to which a product was exposed. These processes are temperature-dependent, and as the temperature rises, the rate of the reactions accelerates. Lipase enzyme was utilised in the first-generation TTIs to reflect pH-dependent colour changes brought on by lipid hydrolysis [91-93]. As freshness indicators of food products, biological reaction-based TTIs based on enzymes and microorganisms have an advantage over other types of TTIs since they can more precisely reflect the actual course of biological meat deterioration processes. Meat deterioration is primarily caused by microbial growth and enzymatic autolysis. The inclusion of TTIs in packaging materials for frozen fish products [94-95], dairy goods [96], fresh and frozen meat products [97-102], frozen fruits and vegetables [98-99], and other items is straightforward.

Metabolites as metrics for evaluating quality

An indicator/sensor can provide direct information [103] as opposed to TTIs, which provide indirect information on the quality and freshness of food based on the temperature to which the product was exposed. Several metabolites, including glucose,

lactic acid, CO_2, O_2, volatile nitrogen compounds, and biogenic amines, are generated in the head space within the sealed environment under normal packing circumstances without the application of special scavenging agents [104]. By adding an indication or sensor that can recognise these analytes into packing materials, it is potentially conceivable to detect spoilage. Therefore, these metabolites can be utilised as quality-indicating parameters.

2.7 Metabolic engineering

The requirement to construct microbial cell factories for the synthesis of chemicals is beginning to be driven by environmental concerns and the unreliability of petroleum-derived goods. Researchers believe that a sustainable bioeconomy needs metabolic engineering as a key technology. Additionally, they anticipate that microorganisms rather than petroleum extraction or refining are used to manufacture a sizable part of fuels, basic chemicals, and medications from renewable sources. Avoid touching the plants. The enormous capacity for variation also necessitates effective screening techniques to choose people who exhibit the desired phenotype [105]. The earlier technique used enzymatic assay analysis related to spectroscopy, however they had a low throughput. There is a chance that Harris Heague Screening, Fluorescence Activated Cell Sorting (FACS), or Cell Survival may migrate to avoid these barrier coded biosensors that permit cell metabolism in vivo monitoring. The FRET sensor had ligand-binding peptides sandwiched in between a pair of donors and acceptor fluorophores. The peptide has subtracted the conformational change if it is bound to the target ligand, which may cause the signal to move without altering the FRET change. Natural sensory proteins called transcription factors are produced in response to environmental changes in order to decrease gene expression for high throughput. They suggest a lack of orthogonality and background noise. Riboswitches are a component of the third class of biosensors. The

regulatory region of mRNA controls the transcription of the protein it encodes by preferentially coupling to the ligand and changing itself. RNA is already transcribed, which makes it reasonably quick and independent of protein-protein or protein-metabolite interactions in contrast to TF-based biosensors. In bacterial systems, ribosomes have undergone substantial manipulation during the past few decades [106].

2.8 Applications in tissue engineering:

The viability of various tissue engineering applications, such as the creation of organ specific on chips and preserving the 3-D integrity and configuration of cell cultures, is greatly impacted by the use of biosensors. Here, the fate of tissues and cells is directly correlated with the presence of small biomolecules (such as adenosine, glucose, hydrogen peroxides, etc.) in the medium. The ability to transform and convey a wide range of signals (physical and chemical) into and out of the medium is a strength of living metabolic cells. These signals could take on any shape, including changes in protein composition, pH, ionic concentration, or oxygen uptake, among others. As a result, tracking these incoming/outgoing analytes could be used to get information about the cell in real time [106].

2.8.1 Nucleic acids, DNA, genes:

There are direct connections between DNA encoding and genetic diagnostics in a number of fundamental research-related domains. Therefore, the use of biosensors in relation to nucleic acids is unquestionably important. A typical DNA-specific sensor entails the following three steps: a) adding probes to the substrate film; b) Through analogue base pairing, making contact with the necessary DNA sequence; and c) reading out the chemical signal produced as a result of base interaction in the form of an analytically useful signal . Quantum dots and the use of nanomaterials are also being overused in this context. Accurate and reliable H_2O_2 content measurements are crucial

for tissue engineering as well as therapeutic applications. Its composition directly reflects the oxidative stress that cells experience or the tissue hypoxia in people. Currently, a number of analytical methods, including titration, electrochemistry, and photocatalysis, can be used to recognise H_2O_2 [107]. High concentrations of this extremely unstable species in any biological system are extremely harmful and must be avoided since they can induce cytotoxicity in people as well as a wide range of plants, animals, and microbes [108].The majority of the methods used for H_2O_2 quantification in the field of tissue engineering are electrochemical in nature, which presents a number of challenges to the user (poor detection, low sensitivity, limited mobility, and application limitations on the organic system) . Due to the production of biosensors with very high stability and accuracy, enzyme-based biosensing has lately established itself in this area as well [109-110]. This type has received a lot of attention lately, which may be explained by the development of stable sensor assemblies that still contain fully functionalized enzyme binding sites after they have been deposited over stiff electrodes or surfaces [111].

2.9 Application of biosensors in agriculture

Due to their high toxicity and significant harm to the environment and public health, pesticide residue analysis is a major concern. Chromatography (GC) or high performance liquid chromatography (HPLC) are typically used for pesticide analysis. These techniques, however, need for time-consuming extraction and clean up procedures that lengthen analytical times and raise the possibility of mistakes. The field of biosensor development is expanding in response to the need for quick, easy, cost-effective, and selective pesticide detection methods. The fundamental idea behind developing biosensors is the relationship between a pesticide's toxicity and drop in the activity of a biomarker, like an enzyme. This undertaking can be measured by using various transducers, to identify various enzymatic reaction substrates or products. Cholinesterases

are specifically inhibited by pesticides with organophosphorus and carbamates. Acetylcholinesterase (AChE) is an enzyme that catalyses the breakdown of acetylcholine into acetic acid and choline, or thermometry for detecting the various enzymatic reaction substrates or products. In the development of AchE-based biosensors, some authors have used a pH-sensitive transducer to measure the pH shift brought on by the release of acetic acid during the enzymatic reaction [112]. An optical fibre biosensor was described for the detection of the pesticides propoxur and carbaryl, which are frequently used insecticides in vegetable crops. A pH indicator (chlorophenol red) that was covalently attached to glass beads with regulated pores served as the optical transducer. The pH-sensitive layer's colour altered according to the carbamate concentration in the sample solution when there was a constant acetylcholine concentration present.

Conclusion

As biosensors contribute to the next wave of medical advancements, industrial advancements, and numerous other sectors, they are quickly becoming the focus of the most intense study. Our existing bio diagnostic capabilities in terms of selectivity, sensitivity, robustness, and cost efficiency will be significantly improved by advances in bio nanotechnology enhanced sensitivity and downsizing methodologies. In future researchers will be able to further change these biosensing components to strengthen them to advancements in the creation of biosensors. This technology's ability to combine highly sensitive electrochemical detection with selective biochemical identification gives it practical utility. Thus, interdisciplinary efforts that transcend traditional fields are necessary for the development of novel biosensors. Biosensor development is accelerated and the field of biomedicine is revolutionised by several interdisciplinary knowledge combinations. Finally, we may infer from the aforementioned facts that biosensors and bioelectronics have been utilised in numerous fields, including healthcare, life science research, the environment, food, and military applications. The study is ongoing to improve the biosensor's sensitivity for successful use.

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