MAHSA International Journal of Health and
Medicine, V4, Issue 1; September, 2024
e-ISSN: 2805-5705

Review Article **Open Access**

Recent Development and Application of Biosensors in Biological Analysis

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Received: 18 September 2024 Accepted: 25 September 2024 Published: 28 September 2024

Abstract

Biosensors have emerged as versatile analytical tools for detecting and quantifying various biological substances, with applications spanning medicine, food safety, and environmental monitoring. This review highlights recent advancements in medical biosensors, including in vitro diagnostic, continuous monitoring, and wearable devices. While significant progress has been made in miniaturization and integration, the clinical application of electrochemical biosensors remains a significant milestone. Challenges in device commercialization, such as enhancing stability, selectivity, and sensitivity, must be addressed. The integration of biosensors with the Internet of Things (IoT) holds promise for improving disease surveillance and management, particularly in the context of COVID-19 diagnostics.

Keywords: Biosensors; Medical Diagnostics; Optical Detection; Electrochemical Sensors, Wearable Technology

Introduction

A biosensor is a device that detects biological substances and converts their concentrations, along with other indicators such as pH, into electrical signals for analysis. It is an analytical tool or system comprised of immobilized bio-sensitive materials, such as enzymes, antibodies, antigens, microorganisms, cells, tissues, nucleic acids, and other bioactive substances, which serve as recognition elements. These elements work in conjunction with appropriate physiochemical transducers, including oxygen electrodes, photosensitive tubes, field effect tubes, and piezoelectric crystals, and signals amplifying devices [1]. A biosensor is composed of a molecular recognition part (sensor) and a conversion part (transducer). The molecular recognition element underpins the selective measurement capability of the biosensor, acting as a physical or chemical transducer that converts signals emitted by bioactive substances into electrical signals. All types of biosensors share a common structure: one or more related bioactive materials (biofilms) and physical or chemical transducers (sensors) that transform signals from bioactive substances into electrical signals. The combination, utilizing modern microelectronics and automatic instrumentation technology to process biological signals, constitutes biosensor analysis devices, instruments, and systems [2]. Currently, biosensors are utilized for the detection of various body fluid samples, including blood, interstitial fluid, saliva, tears, urine, and sweat. Biosensors are advancing towards miniaturization, wearable format, and bedside detection [3]. They find applications in diverse fields such as medicine, food safety, and environmental monitoring. This review emphasizes recent advancements in medical biosensors, covering three distinct types: in vitro diagnostic biosensors for detecting blood, saliva, or urine samples; continuous monitoring biosensors (CMBs); and wearable biosensors. In recent years, significant progress has been made in the development of in vitro diagnostic biosensors, including those based on CRISPR/Cas systems and enhanced integrated biosensing devices such as lateral flow assays (LFA) and microfluidic/ electrochemical paper-based analytical devices (μPAD).

Wearable Biosensors

The widespread adoption of smartphones has led to an increasing demand for biosensing systems that can be integrated with these devices to control wearable biosensors and receive real-time biosensing data [4]. Recent advancements in smartphone technology have enabled the development of smartphone-based biosensor systems, which are now playing a critical role in AI-assisted biosensors for patient data processing, storage, sharing, and user interface management. These systems, in conjunction with cloud biosensors, perform three primary functions: sensing, observation and reaction.

The bioreceptor is the outermost part of the biosensor, directly interfacing with the analyte (target) during operation. Commonly used biological receptors include aptamers, enzymes, whole cells, DNA, and antibodies, and their construction typically involves the immobilization or adsorption of biomolecules onto the biosensor surface. The adhesion technology of biomolecules remains focused on enhancing the selectivity and sensitivity of biosensors [5]. Various types of sensors can be utilized in biosensor manufacturing, depending on the biochemical interactions involved. For instance [6], if a biometric phenomenon outputs data in the form of light, the transducer used would be an optical photodetector capable of converting incident light into measurable electrical data. Consequently, the collected data is digitally processed using signal simulation platforms that employ different notch filters, low-pass, or

high-pass simulations and amplifiers to display the quantized signal in a readable form. Display units in biosensors can vary, including computer-based, liquid crystal display (LCD) [7], or printer-based graphic displays for signal estimation. Furthermore, the display output signal pattern can be adapted to user requirements, allowing the final information to be presented as graphs, tables, images, or digital formats for better interpretation and differentiation.

The integration of computer technology with biosensors is increasingly prominent. Deep learning (DL), a machine learning (ML) technique, is employed to train computers to perform human-like tasks [8]. For complex tasks, DL relies on neural networks (NN), which require substantial processing power. Advances in processing power and data analysis have enabled DL algorithms to observe, learn, and respond to complex situations. Depending on the task, DL algorithms can utilize supervised learning, unsupervised learning, or reinforcement learning. The 2020 deep learning model "AlphaFold" successfully predicted protein structures from amino acid sequences, solving a long-standing scientific challenge [9].

Since S.J. Updick et al. developed the first glucose biosensor in 1967 [10], various methods have been proposed for fixing the sensing film including direct chemical binding, polymer carrier techniques, and polymer membrane binding methods [11]. The advent of microfluidic technology in the 1990s and the integration of biosensors with microfluidic chips have opened new technical prospects for drug screening and gene diagnosis [12]. Given that enzyme membranes, mitochondrial electron transfer system particle membranes, microbial membranes, antigen membranes, and antibody membranes possess selective recognition functions for the molecular structures of biological substances, they act catalytically for specific reactions, endowing biosensors with high selectivity.

However, a notable disadvantage is theinstability of the biologically cured membrane. Biosensors are primarily utilized in clinical diagnostics, monitoring during treatment, the fermentation industry, food safety, environmental monitoring, and robotics [13].

Wearable Biosensors

An optical biosensor is the most common type of biosensor. It mainly includes general optical measuring instruments, laser interference type, grating, encoder, and optical fiber type optical sensors and instruments. It is designed to detect whether the object is present or not, or to conduct motion detection for various industrial, automotive, electronic products, and retail automation [14].

Among all optical biosensors, surface plasmon resonance (SPR) optical biosensor is the most common and widely used one [15]. Several subsequent research efforts have focused on the development of optical biosensors, particularly evanescent waves and surface plasmonic resonance (SPR) since the 1980s. Over the past decade, researchers have focused on the miniaturization, specificity, responsiveness, and cost-effectiveness of optical biological sensors. New advances in optical biosensors are contributing to the fields of biotechnology, environmental research, agriculture, food inspection and safety, disease diagnosis, and medical facilities [16].

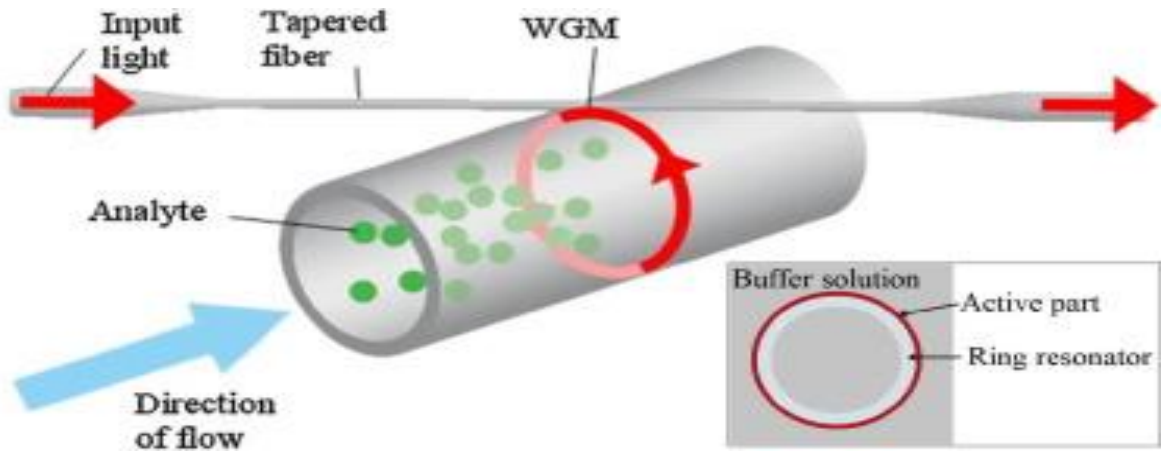

Figure 1. Schematic Illustration of optical waveguide biosensor

Optical ring resonator biosensors change in light behavior due to the interaction of the fading field of the resonant light in the resonator with particles in the environment. Figure 1 shows an opto-fluid ring resonator (OFRR) that achieves excellent marker-free detection of breast cancer using microfluidics and optical ring resonators [17]. Optical ring resonator biosensors have fast response times and are less expensive.

The challenges of implementing optical ring resonator biosensors in various fields such as pharmaceuticals, medicine, and food safety have been discussed, being able to convert specific optical signals into signals for detection [18]. A metamaterial waveguide ring resonator which increases the interaction between the optical field and analyte and a plasma ring resonator which is easy to manufacture and has low loss transmittance are proposed [19]. Optical ring resonators have been integrated with microfluidic environments and have recently been successfully tested.

The optical waveguide biosensor consists of a sensitive layer, a cladding layer, and a waveguide layer placed on the substrate. The optical change near the guide surface caused by wave scattering is used as the detection mechanism in the optical waveguide biosensor. Typical optical waveguide biosensors are characterized by high sensitivity, flexibility, and resolution. Metal-insulator-metal (MIM) waveguides based on Mach-Zender interference and Bragg reflection are designed for sensing and communication applications, and highly sensitive detection of mycotoxins using planar waveguide-based optical biosensors has been reported [20]. In fluorescent luminescence optical biosensors, the use of photodiodes or photomultiplier tubes to detect the light emitted by the fluorescent luminescence process shows the typical structure of fluorescent biosensors, as well as traditional optical biosensors and their relevance to metal-enhanced fluorescence (MEF) platforms [21]. Due to the rapid development of fluorescence and luminescence-based biosensors, many authors have attempted to conduct detailed studies of two-dimensional (2D) materials due to their excellent electrical, optical, mechanical, and other properties, which have also recently attracted the design of fluorescent biosensors. A novel labeling-free, inexpensive, and color-indicating cholesteric liquid crystal has been demonstrated for the detection of biomolecules [22]. Two nanoparticle-based nonlabelled immunosensors with photoluminescence in the strong visible region of titanium dioxide have been used for rapid analysis of salmonella

infection. Carbon-labeled nucleotides and GO have been used to design fluorescent biosensors for mercury detection. Hu et al. designed a fast and sensitive fluorescent biosensor to detect DNA emitted from visible to near-infrared regions [23].

cross-linking. Glucose Oxidase based biosensors are mainly used for glucose sensing. Strabini et al. developed a microneedle-shaped biosensor that monitors blood sugar in intestinal fluid.

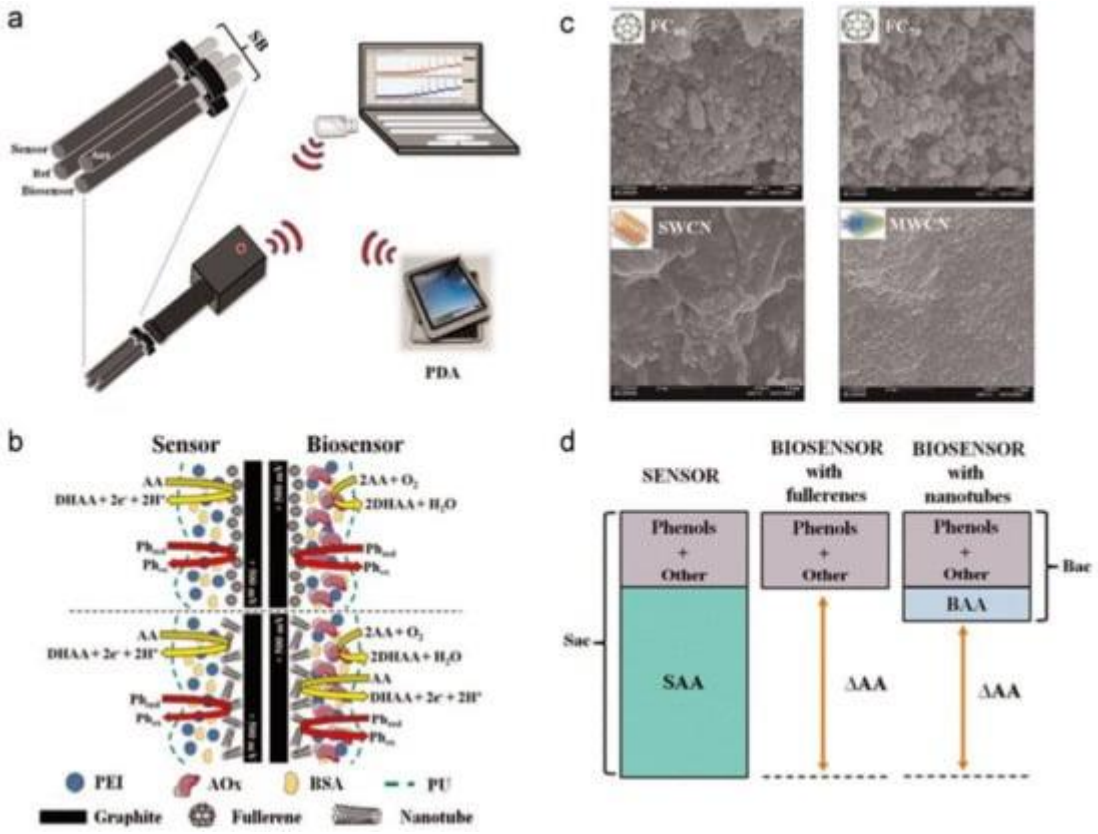

Figure 2. Pseudo-reference electrode, the working electrode, and auxiliary electrode, (b) CSEM image of biosensor surface modified with different materials, (c) schematic diagram of the sensor with the modified surface, and (d) operation of the sensor

Biological Biosensor

To improve efficiency and reduce the cost of enzyme electrodes, different types of electrodes have been specially modified using nanomaterials and sometimes replaced with carbon electrodes. The method uses newly designed oxidase enzymes, spermine, and polyamine, which are captured in a gel of polyvinyl alcohol and reduced on a Prussian blue-modified carbon-based electrode [24]. Another method is to form a barrier on the electrode surface, trapping enzymes on the electrode surface by physical interception or

They fitted a glucose biosensor to the back of the needle that could detect the presence of glucose in the intestinal fluid within 30 seconds with ±20 percent accuracy. The second-generation enzyme electrodes developed by depositing gold on PC membranes have also been used to manufacture electrochemical biosensors. The detection limit (LOD) of glucose was 36 µM through the use of mediator (Ferrocenylmethyl) trimethylammonium. Functional parameters can also be calculated

using enzyme electrodes because the food contains antioxidants (produced by chemicals in the food). These biosensors have been used to monitor antioxidants and ascorbic acid in orange juice, blueberries, and kiwi using modified graphite and fullerenes, as shown in Figure 2a. Figure 2b shows the freeze-scanning electron microscope (CSEM) image of the biosensor, while Figures 2c and 2d show the schematic diagram and working principle of the biosensor respectively. Due to the oxidation of enzymes, the current is reduced, which helps to monitor and measure the presence of ascorbic acid in the sample.

Aptamers can also be used to detect antibodies. Aptamers are highly selective ribonucleic acid (RNA) and single-stranded deoxyribonucleic acid (DNA) that bind to and detect specific antibodies. Different aptamers have different affinities, and based on these affinities, they can be used to develop low-LOD biosensors. Castillo et al. used dendritic polymer structures to develop voltammetry biosensors for the detection of a mycotoxin called aflatoxin B1 (AFB1) in food. For AFB1 concentrations of 0.1 ~ 10 nM, the biosensor has a LOD of 0.40 nM, and the biosensor has been successfully tested on contaminated peanut extracts and peanut snacks. Scarano et al. built a piezoelectric material-based biosensor to detect this protein in human blood serum. Compagnone et al. developed a biosensor using a gold-modified quartz crystal array. Using PLS-DA analysis, the biosensor was able to detect 95% of odorous chocolate samples. Zuccaro et al. developed a graphene-based biosensor that monitors the behavior of topoisomerase IB, which is present in human DNA. The interaction between enzymes and graphene substrates was analyzed by determining the field-effect properties of the biosensor. The biosensor provides real-time analysis and could be used for drug screening in the future. DNA hybridization is an important feature, and its detection is very helpful in all areas of biology. Biosensors with high selectivity and sensitivity can be used to detect DNA hybridization. Mariani et al. reported a method for detecting genomic human DNA (obtained from lymphocytes) without the use of the polymerase chain reaction (PCR) amplification process. The gold nanostars were arranged into a sandwich model based on the analyte to be detected in the DNA, and the surface plasmonic resonance (SPR) imaging tool was used as the detector. A LOD of 10 pM was obtained using this method. In another published work, Karel Lacina et al. observed a reduction in impedance response due to the binding of positively charged proteins (Figure 3). These hypotheses were confirmed using gel electrophoresis, which seems promising as a simple tool for such applications.

Electrochemical Biosensors

The ampere biosensor is a standalone integrated device that provides accurate quantitative analysis information based on the electrical flow generated by oxidation. Typically, these biosensors have response times, energy ranges, and sensitivity comparable to potential biosensors [25]. In the ampere biosensor, the output current of the sensor is analyzed and used in the sensing process. The sensitivity of the ampere biosensor is determined by comparing the current obtained from different analyte concentrations. The biosensor uses just two electrodes, one to apply a voltage and the other to measure the current flowing through the device. The sensitivity of this glucose sensor is affected by changes in temperature and pH [26]. The sensitivity of the glucose sensor is measured by the change in current per mM concentration in an area of one square centimeter. Impedance and potential biosensors belong to electrochemical biosensors [27].

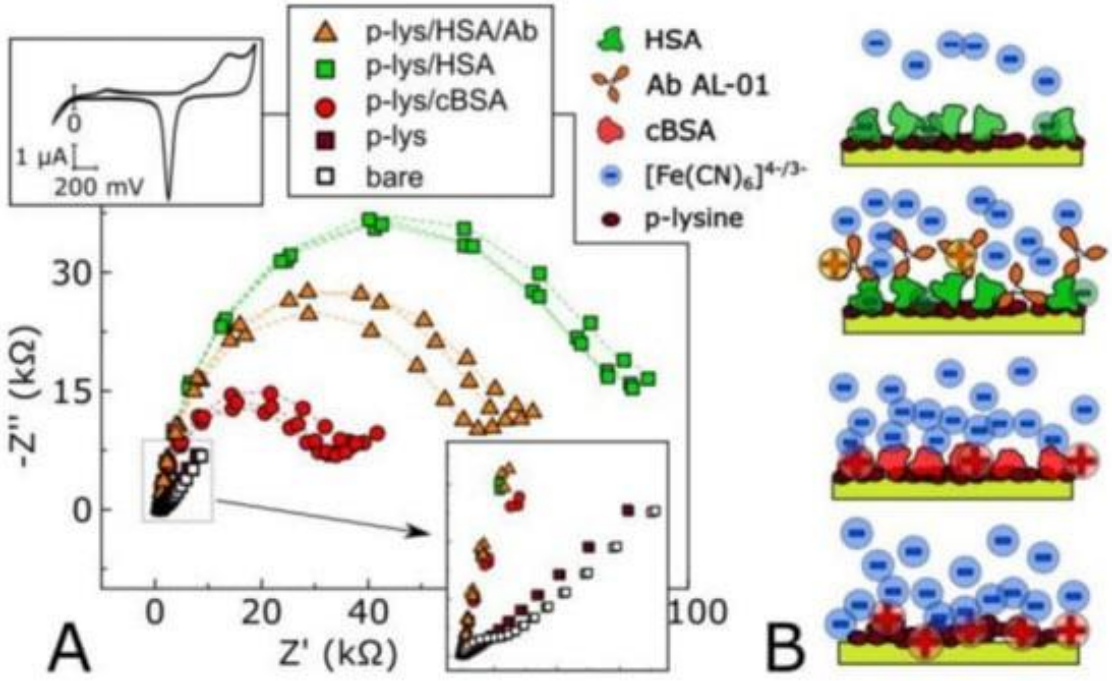

Figure 3. (A) Visual Diagram of the electrode process and (B) corresponding gel electrophoresis proof of the charge of the compound used at experimental pH values.

An impedance biosensor is constructed by fixing the biometric element to the electrode surface. It reports the target analyte by measuring and monitoring the electrical impedance signal that is proportional to the activity of the analyte. Electrochemical biosensors that use the impedance change to detect the analyte or biological entity are called impedance biosensors. The most commonly used technique in this approach is electrochemical impedance spectroscopy (EIS)[28]. Using EIS, the properties of the bulk electrode and the processes occurring at the electrode interface can be easily determined. The EIS spectrum is obtained as either a Bode diagram or a Nyquist diagram, both of which are functions of frequency [29]. The Nyquist diagram consists of semicircular regions on the axis representing the electron transfer process, followed by straight lines depicting the diffusion process. When electron transfer is a fast process, the Nyquist chart shows only a straight line, while slow electron transfer is shown by a large semicircular region. Here, the resistance to electron transfer is equal to the diameter of the semicircle. The Bode graph, on the other hand, is a logarithmic graph in which the logarithms of phase (Φ) and impedance (Z) are plotted with respect to the frequency (logν). In EIS, there is a very small variation in signal amplitude. In addition, impedance measurement does not depend on the presence of REDOX pairs, because biosensors measure biological events using reagents such as antibodies, enzymes, bacteria, viruses, etc. In impedance biosensors, emphasis is placed on generating amino, carboxyl, and similar groups on the electrode surface to capture antibodies, which is the most important part when developing impedance biosensors. Because it ensures the durability and repeatability of the sensor [30].

In addition, nanomaterials are also being used for such purposes. King et al. used EIS to

determine the concentration of bacteria in fermenters used in the laboratory. The biosensor was composed of PDMS polymer, a gold-plated silicon wafer, and a borosilicate glass tube. The biosensor successfully detected the presence of Escherichia coli in the fermenter at a frequency of 0.01 MHz AC for 13 hours. MCF-7 cancer cells were detected using EIS. On the polypyrrole-NHS electrode, anti-C-Cerbb-2 was captured by a covalent link and the sensor successfully detected cancer cells, showing a sensitivity of 100-10,000 cells per ml.

Ankan et al. investigated the induction of Escherichia coli (O157:H7) using an antigen-antibody binding mechanism, where antibodies were covalently attached to the surface of PANI films and conducted EIS studies to investigate the sensitivity and performance of the sensor, measuring and recording changes in impedance as bacterial concentrations were increased [31]. The biosensor is highly sensitive to E. coli and can be used in the laboratory. Rushworth et al. developed a biosensor for detecting Alzheimer's amyloid-beta oligomers. By increasing the current flowing through the biosensor, the bonding of oligomers increases, thereby reducing the impedance of the biosensor (Figure 4) [32].

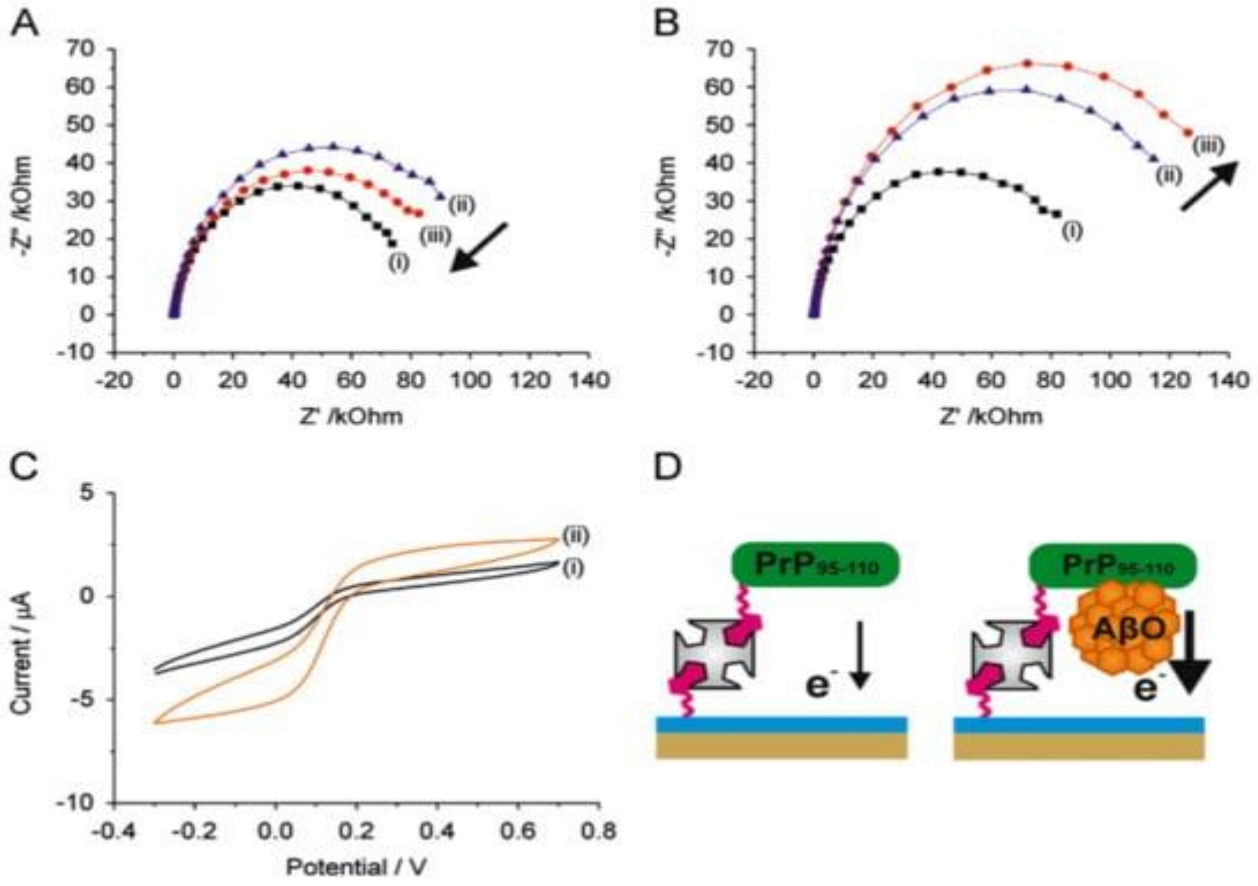

Figure 4. (A, B) EIS Diagram, (C) CV study of AβO by biosensor, and (D) diagram showing an increase in surface conductivity caused by AβO.

In contrast, the working principle of the potential biosensor is that there is a potential difference between the working electrode and the reference electrode, and the species measured is not consumed as in the ampere biosensor. By comparing its activity with the reference electrode's, its response is proportional to the analyte concentration. When the highly stable and accurate reference electrode is used, the greatest advantage of potential biosensors is their sensitivity and selectivity. Potentiometry is the most commonly used electrochemical technique in the field of sensors, is cost-effective, and can be used in a variety of ion concentrations [28]. Most sensors developed using potentiometric methods are available on the market. These sensors can be easily manufactured, and reducing their size does not affect their performance. The use of potential tools in the biosensor field opens many new doors for diagnostics and sensing.

The two main advantages of using potential biosensors are: the generated signal is in the form of potential, the biochemical components used are part of the receptor, and potential biosensors in the form of tattoos have been developed for monitoring human sweat. Potential biosensors prepared by coating a gold electrode with polypyrrole and using horseradish peroxidase as a biochemical agent have been developed to detect tumors, hepatitis B, digoxin, and troponin. Recently, a potential biosensor with a gold electrode and an extended FET transistor was used to detect interleukin in LOD 1 pg mL-1. Acetylcholinesterase is used as an antibody to produce mercaptan adsorbed on the electrode. Mishra built a tattoo-shaped biosensor to detect G-nerve agents using potentiometric methods [33]. In this biosensor, the tattoo sensor is designed in the form of a skull, with one eye as the reference electrode and the other as the working electrode. Figure 5 shows the concept, design, printing, and application on human skin.

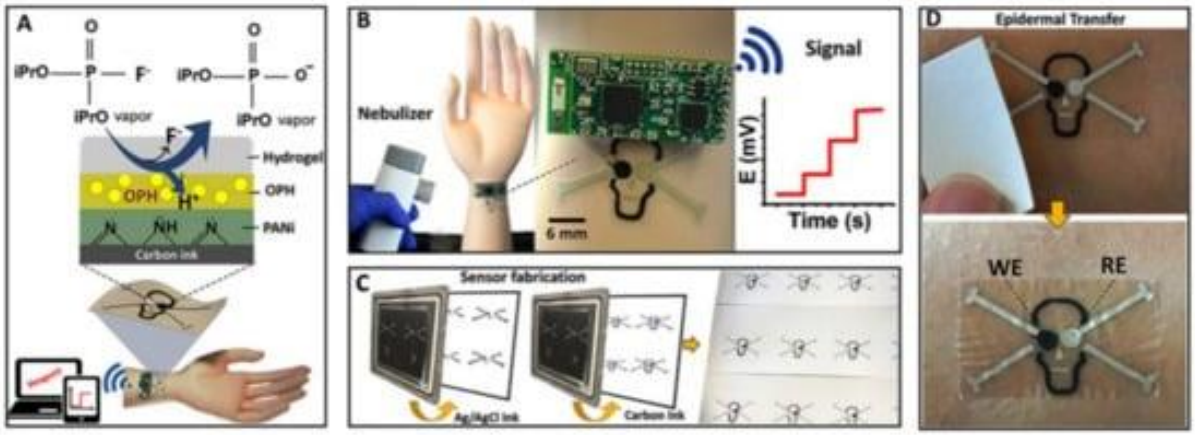

Figure 5. Schematic Diagram of a tattoo-shaped potential biosensor. (A) Concept of the biosensor, (B) the design of the tattoo biosensor, (C) the printing process of the biosensor on paper, and (D) the successful transfer and removal of tattoos from human skin.

Applications of Biosensors

The use of biosensors for the detection of blood glucose levels in diabetic patients has witnessed rapid growth, currently accounting for approximately 80% of household biosensor applications worldwide. Beyond glucose monitoring, electrochemical biosensors have also been employed in the detection of various infectious diseases, such as urinary tract infections, as well as the identification of pathogens and microorganisms in urine samples [34]. Notably, electrochemical biosensors have been integrated into digital watches and wearable bands to enable the effective detection of cardiovascular diseases and heart failure - growing global health concerns responsible for millions of deaths annually. These integrated, cost-effective, and efficient biosensing devices hold promise for saving lives through early disease detection [34].

Fluorescent-based electrochemical biosensors have been utilized to monitor enzyme levels in cancer patients. These biosensors are designed to detect the presence of specific analytes and generate corresponding fluorescent signals, which can be detected and quantified. Such biosensors have demonstrated efficacy in the early detection of a variety of diseases, including inflammation, arthritis, cancer, viral infections, cardiovascular issues, and metastases [35]. Furthermore, electrochemical biosensors have become an integral component of drug discovery programs, enabling the monitoring of drug effects during both pre-clinical and post-clinical evaluations. More recently, these biosensors have been successfully employed to guide surgical procedures through imaging techniques and to monitor the effects of drugs on disease progression [35].

Cancer remains one of the leading causes of death and a significant barrier to global life expectancy improvements. According to GLOBOCAN, 2020 saw 19.3 million new cancer cases and nearly 10 million deaths worldwide. With over 200 variants affecting more than 60 organs, cancer presents a complex challenge [36]. While some tumors may remain dormant indefinitely, metastasis accounts for 90% of cancer-related deaths. Early therapeutic interventions are crucial, as they are most effective when pre-cancerous or pre-metastatic tumors are localized within an organ. Consequently, the early, sensitive, and effective detection of cancer via specific biomarkers is a critical focus in contemporary scientific research [37].

According to the National Cancer Institute (NCI), a biomarker is defined as a biological molecule, such as a protein (secreted proteins or cell surface proteins) or nucleic acid (RNA transcripts or genome sequences associated with malignant cells), that can indicate the presence of cancer within the body. Assessing the levels of specific cancer biomarkers in a patient's blood, urine, stool, or saliva can facilitate early cancer diagnosis, detect tumor recurrence, predict cancer risk, and monitor treatment efficacy. However, significant challenges exist in early-stage cancer biomarker detection, primarily due to their extremely low concentrations in plasma and the variability in normal levels among individuals influenced by diet, lifestyle factors (e.g., smoking), age, comorbidities, and genetics. Moreover, the concentration of a single biomarker is typically insufficient to confirm malignancy, necessitating the simultaneous detection of multiple biomarkers for accurate and early cancer detection [37].

Most alcohol metabolism in the human body is catalyzed by alcohol dehydrogenase, which converts ethanol in the cytoplasm of liver cells to carcinogenic acetaldehyde. This compound is then oxidized to acetic acid in the mitochondria by aldehyde dehydrogenase. Acetate can be excreted into the bloodstream,

further metabolized to produce CO_2, H_2O, or fatty acids, or enter intermediate metabolism as acetyl-CoA. Experimental evidence suggests that alcohol can also be produced from the metabolic pathway of food, precluding its classification as a true cancer biomarker. Aromatic compounds and nitriles, exogenous pollutants, primarily originate from excessive exposure to pollution, radiation, smoking, and alcohol consumption. Despite their exogenous nature, they are relevant to follow-up studies in cancer patients as many are carcinogenic and toxic. These compounds, typically stored in fatty tissue, are released gradually and in substantial amounts through respiration in cancer patients. Peroxidation makes these compounds reactive enough to damage proteins, DNA, and polyunsaturated fatty acids [38], leading to the degradation of the body's natural repair processes and the accumulation of pollutants over time. This process contributes to age-dependent diseases, such as cancer. While breath cancer biomarkers generally lack specificity and may have other bodily sources, they can be effectively combined with other biomarkers for early cancer detection [39].

The human saliva proteome encompasses the comprehensive repertoire of proteins present in the oral cavity. Saliva is known to harbor over 2,000 distinct proteins and peptides that fulfill diverse biological functions within the mouth. Intriguingly, approximately a quarter of the salivary proteome overlaps with the plasma proteome. However, the proteomic analysis of saliva presents distinct advantages over that of blood for the screening of low-abundance proteins and the even distribution of salivary peptides [40]. Mass spectrometry and Raman spectroscopy have emerged as promising techniques for the sensitive monitoring of salivary proteins, enabling the differentiation between healthy and diseased states. Specifically, alterations in the levels of lactate dehydrogenase (LDH) in saliva have been shown to aid in the detection of oral cancer. Salivary LDH levels are significantly elevated in patients with oral cancer and oral submucosal fibrosis compared to healthy individuals, suggesting the potential utility of salivary LDH as a biomarker for the diagnosis of these specific diseases [41].

Sweat is a translucent biological fluid produced by sweat glands under the stimulation of the sympathetic nervous system. This system is located in dermal tissue rich in nerve fibers and capillaries, and is involved in the host defense against infection and body temperature regulation. Sweat is composed of over 99% water, with the remaining fraction comprising trace amounts of nitrogenous compounds (e.g., urea, amino acids), metallic and non-metallic ions (e.g., potassium, sodium, chloride), and metabolites (e.g., pyruvate, lactic acid), rendering it slightly acidic (pH 4.0 - 6.8) [42].

As a sparsely utilized, sterile biological fluid that can be collected non-invasively, sweat has garnered increasing interest for biomarker screening, particularly in the context of proteomics and metabolomics advancements. The most prominent example is the sweat test for the early detection of cystic fibrosis (CF), which utilizes chloride levels as biomarkers. Typically, sweat chloride concentrations above 60 mmol/L indicate positive (classic) CF, while levels between 30 and 60 mmol/L suggest atypical CF. However, sweat gland dysfunction is not unique to CF and has been observed in various other diseases [43]. Recent studies have reported the potential of sweat-based metabolite profiling for the detection of lung cancer, with a specificity and sensitivity of 80% and 79%, respectively, compared to healthy smoker controls [44]. In contrast to imaging and biopsy, sweat-based analysis offers a convenient, minimally invasive, cost-effective, and widely accepted approach for cancer diagnosis by quantifying circulating

tumor cells, proteins, DNA, and miRNAs [45]. Colorimetric, optical, and electrochemical biosensors have emerged as attractive options for rapid, sensitive, and quantitative detection of cancer biomarkers in sweat and other biological fluids. Colorimetric sensors rely on visual color changes corresponding to biomarker concentrations, while optical sensors utilize light-based phenomena, and electrochemical sensors convert biomolecular interactions into quantifiable electrical signals [46, 47]. The development of these biosensing technologies is a crucial step towards enhancing prognostic and treatment options, particularly in the early stages of cancer, by enabling continuous and in vivo monitoring of dynamic cancer-related biomarkers [49].

Future Perspectives

Despite significant advancements in the development of miniaturized, minimally invasive, portable, and wearable biosensors for disease surveillance, the clinical application of electrochemical biosensors remains a significant milestone. The commercialization of biomarker-based biosensors faces major challenges, particularly in device miniaturization and microfluidic integration. Electrochemical biosensors predominantly utilize nanostructured materials and nanocomposites, which are anticipated to be increasingly employed in cancer diagnostics in the future. However, enhancing the stability and repeatability of electrochemical sensor manufacturing is essential, along with significantly improving the selectivity and sensitivity of cancer biomarkers. Moreover, the simultaneous detection of multiple cancer biomarkers using dual sensors may be crucial for reliable cancer detection, especially in the early stages of the disease. Future sensors integrated with the Internet of Things (IoT) will have the capability to receive stimuli and wirelessly transmit signals to loggers and analyzers. For instance, integrating IoT sensors into COVID-19 diagnostic protocols can facilitate the detection of SARS-CoV-2 in remote and inaccessible areas, enabling precise and targeted management of COVID-19 outbreaks. Such IoT-enabled sensors could substantially reduce the time and human resources required by traditional public health management systems, offering a more efficient approach to disease surveillance and control.

Biosensors are catalyzing a paradigm shift in various disciplines, from healthcare and environmental monitoring to food safety and industrial processes. By leveraging their ability to detect and quantify specific analytes with high sensitivity and selectivity, biosensors are emerging as indispensable tools for molecular analysis. As the field continues to evolve, several development trends are influencing the trajectory of biosensor development and application. Firstly, Miniaturization is a dominant force, driven by the demand for continuous, real-time monitoring in diverse settings. Wearable and implantable biosensors, some even capable of being ingested, are poised to revolutionize healthcare by providing non-invasive monitoring of vital physiological parameters. This trend towards portability is further amplified by the rise of point-of-care (POC) diagnostics. Biosensors are enabling rapid, accurate, and cost-effective testing at the patient's bedside, a game-changer for healthcare delivery, especially in resource-limited settings. POC devices are being developed for various applications, including infectious disease diagnosis, glucose monitoring, and pregnancy testing. Secondly, the complexity of biological systems demands simultaneous analysis of multiple analytes. Multiplex biosensors, employing sophisticated techniques like microarrays and electrochemical impedance spectroscopy, are enabling comprehensive profiling of biomarkers, paving the way for personalized medicine and early disease detection. This ability to generate multi-dimensional

analytical data has also fueled the integration of Artificial Intelligence (AI) and Machine Learning (ML) algorithms into biosensor platforms. This synergy allows for real-time data processing, pattern recognition, and predictive modeling, leading to enhanced sensitivity, specificity, and the potential for automated diagnosis and personalized treatment strategies.

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