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Fabrication of composite-based biosensors for rapid disease detection

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A B S T R A C T

Biosensors are a fundamental component of point-of-care diagnostic technologies, which are essential for early detection and real-time health monitoring. They play a vital role in improving healthcare outcomes and making a significant societal impact by facilitating rapid diagnostics and disease management. This review explores the fundamentals of biosensors, including their operational principles, key components, and mechanisms, as well as the use of composite materials and their applications in disease detection. Furthermore, it discusses important performance metrics such as sensitivity, specificity, stability, and reproducibility.

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1. Introduction

Point-of-care (POC) diagnostics enable early detection and real-time health monitoring, crucial for improving treatment outcomes [1-4]. Biosensors significantly contribute to this by supporting rapid, on-site disease detection and monitoring disease progression, ultimately enhancing quality of life [5-8]. The demand for biosensing systems that reliably detect physiological signals and biomarkers, with biocompatible surfaces for safe device–human interaction, drives ongoing innovation in sensing materials, strategies, and device structures [9]. Biosensors are compact devices that allow in situ analysis and POC testing, transforming biological responses into electrical signals [1]. They eliminate the need for traditional laboratory methods, offering benefits such as low cost, speed, and reliability. Advances in nanobiotechnology have enhanced biosensor capabilities, enabling more straightforward alternatives to complex techniques like CT, RT-PCR, ELISA, and lateral flow assays [10, 11]. A biosensor integrates a biological recognition element, such as DNA, enzymes, antibodies, or cells with a transducer that can be

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electrochemical, optical, or mechanical [12]. These sensors are vital for early disease detection, monitoring health signals, and assessing treatment effectiveness [13]. Recent progress has seen significant improvements in transducing materials, device architecture, and miniaturization, though challenges remain, especially for wearable and implantable devices that interface seamlessly with soft tissues [14].

Therefore, effective healthcare increasingly relies on innovative, real-time sensing technologies capable of translating biological and chemical signals into measurable outputs [15, 16]. This review covers the basics of biosensors, working principles, core components, composite materials and their applications in detecting infectious diseases, cancer biomarkers, metabolic and chronic illnesses, along with discussions on performance and ongoing challenges.

2. Fundamentals of biosensors

Biosensors are devices designed to identify specific biological markers, such as proteins, DNA, RNA, or cells, and convert their interactions into measurable electrical signals for digital output [17]. They typically comprise biological components like nucleic acids, enzymes, cell receptors, tissues, proteins, or engineered molecules such as antibodies and aptamers, paired with physical or chemical transducers, including optical, electrical, piezoelectric, or electrochemical elements within a compact system [10, 18].

2.1. Key components

A biosensor integrates analytes, bioreceptors, transducers, and output systems to quantify markers like cancer indicators. These analytical tools process biological samples using specialized detecting molecules in conjunction with electronic sensors and transducers to gather relevant information [17]. Fig. 1. illustrates key elements and selected parts of a typical biosensor.

2.2. Working principles

Development of biosensors depends on the target analytes such as cancer or immune markers, or genetic material found in biological samples [19]. A typical biosensor includes a) bioreceptors that selectively bind the analyte, b) an interface where biological recognition occurs, generating a signal, c) a transducer that converts this signal into an electronic form, which is amplified and processed by circuitry and software, then d) presented via a display or interface for the user [9]. Biosensors can analyze a range of samples, including bodily fluids, food, cell cultures, or environmental samples [17].

2.3. Types of biosensors

Classification varies based on the types of bioreceptors and transducers used, with immobilization strategies for biorecognition components on the transducer surface being essential [5]. Overall, biosensors can be classified into three groups i.e., based on 1) receptor type e.g., biocatalytic (enzymes), immunological (antibodies), or nucleic acid-based (DNA) 2), transduction method e.g., electrochemical, optical, piezoelectric, or thermal and 3) application field e.g., medical, environmental, or wearable devices [10, 18, 20]. Commercial biosensors are also categorized as laboratory-based or portable. All biosensors require a stable interface to ensure reliable and high-performance sensing [20]. Fig. 2 highlights the flow from analyte input to digital output, involving molecules such as proteins, DNA, enzymes, and antibodies, with transducers categorized as optical, electrochemical, piezoelectric, or thermal depending on their detection mechanisms and transducer systems [10, 17, 18].

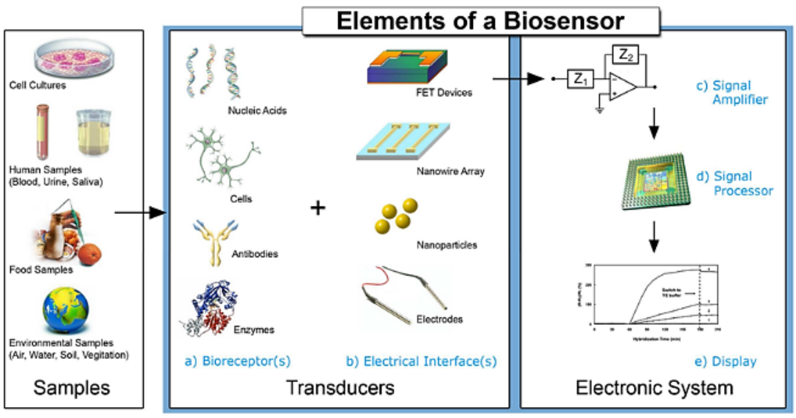

Fig. 1. Key elements and selected parts of a typical biosensor [9].

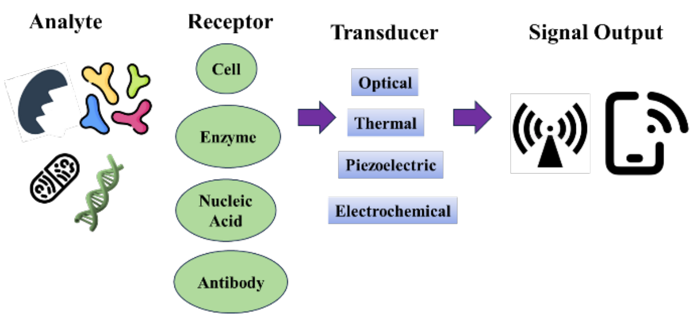

Fig. 2. Overview of the biosensor device workflow.

2.3.1. Types of biosensors based on transduction method

Optical Biosensors detect interactions between microorganisms and target analytes by measuring photons such as luminescence, fluorescence, or color changes, in UV, visible, or near-infrared ranges, rather than electrons [21]. Electrochemical Biosensors rely on redox reactions, measuring changes in current, voltage, or other parameters driven by electron transfer, with electroactive materials playing a key role [13].

Piezoelectric Biosensors measure variations in resonant frequency of piezoelectric crystals caused by mass changes during biochemical interactions, like antibody-antigen binding or DNA hybridization. They include devices like quartz crystal microbalances and surface acoustic wave sensors, which translate mechanical deformations into electrical signals. When external forces, such as blood pressure, deform the crystal, electric dipoles polarize, generating measurable currents proportional to the applied pressure, used in applications like bacterial lysis monitoring [22-25].

Thermal Biosensors detect heat produced or absorbed during biochemical reactions. They use temperature changes, measured by sensitive thermistors or calorimetric devices, to infer reaction dynamics. These sensors often employ flow injection techniques with immobilized enzymes and differential temperature measurement, offering high stability and affordability, though they have historically faced challenges like sensitivity issues [26-29].

Each type provides unique advantages for detecting biological interactions, offering diverse tools for medical diagnostics, environmental monitoring, and microbiology research [20].

3. Composite materials in biosensors

Nanomaterials, polymers (including conducting polymers and biopolymers), and their combinations are commonly used in biosensor interfaces [30]. Advances include monolayer membranes and 3D structures, with growing applications of nanocomposites. Biosensors are versatile tools in fields like food safety, defense, environmental monitoring, and healthcare [20, 31, 32]. Conducting polymers (ICPs) and their composites are particularly valued for their biocompatibility, efficient electron transfer, and ability to immobilize biomolecules such as glucose, DNA, cholesterol, aptamers, and cancer cells [33, 34].

3.1. Types of composites (polymer-, metal-, and carbon-based)

Composites in biosensors can be broadly categorized into several types. Polymer-based composites play a crucial role, with conductive polymers often used to coat electrodes or immobilize receptors [33], while biopolymers such as chitosan, agarose [20, 35], and hydrogels provide biocompatible matrices that facilitate immobilization of biomolecules and enable efficient analyte diffusion. Hydrogels, which are water-rich networks, can be functionalized with nanoparticles or biomolecules to further enhance sensor performance [14]. Inorganic materials like metal oxides, including CuO, NiO, Fe_2O_3, and TiO_2, are valued for their catalytic activity and electrical properties, making them effective electrocatalysts in biosensing applications [12]. Metal-organic frameworks (MOFs), characterized by their crystalline and porous nature, offer high stability, tunability, and functionalization capabilities, making them ideal for the sensitive and selective detection of biomedical analytes through various methods such as electrochemical, fluorescence, or colorimetric assays [36]. Carbon nanomaterials, especially carbon nanotubes (CNTs) and graphene, provide exceptional electrical and mechanical properties; CNTs are often employed in diagnostics and drug delivery, whereas graphene enables highly sensitive detection of volatile organic compounds (VOCs) related to disease diagnosis [12]. The integration of nanomaterials like graphene with polymers or biomolecules has significantly improved biosensors by enhancing their sensitivity, lowering detection limits, and increasing selectivity [1]. For example, in research by Villa et al., a carbon nanotube-based immunosensor was successfully used to detect rheumatoid arthritis antibodies in serum, demonstrating the potential of these composite materials in advanced biosensing technologies [37].

Another study highlighted that incorporating graphene, either alone or in composites, enhances biosensor performance by extending dynamic ranges, lowering detection limits, and improving selectivity and miniaturization [38]. Furthermore, recent research focused on composites of conducting polymers (CPs) and graphene, which combine their exceptional electrical, mechanical, and chemical properties, leading to increased interest and application in advanced sensor design [39]. Fig. 3 demonstrates the diagram of hydrogel-based composites used for health monitoring and disease diagnosis.

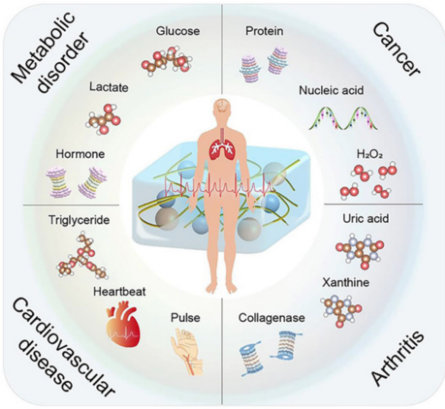

Fig. 3. Diagram of hydrogel-based composites used for health monitoring and disease diagnosis [14].

4. Fabrication techniques

The fabrication of affordable, flexible biosensors using organic electronics and high-throughput printing techniques offers significant advantages for chemical and biological detection. Advances in organic materials and synthesis have improved sensitivity, stability, and specificity, enabling detection of a wide range of analytes [40]. A key step in biosensor development is depositing (nano)materials onto conductive electrodes to enhance performance by increasing surface area, supporting enzyme immobilization, and boosting catalytic and bioaffinity properties [41].

Microfluidic devices benefit from their high surface-to-volume ratio, enabling efficient fluid management, reduced reaction volumes, and precise temperature control, all at low cost [42]. Cutting-edge printing and deposition methods are transforming biosensor manufacturing by increasing throughput, miniaturizing features, and lowering costs. Techniques like inkjet, screen, microcontact, gravure, lithography, plasma modification, and laser printing are emerging as effective tools for patterning biomolecules and materials at micro- and nano-scales, paving the way for scalable, high-performance biodevices [43]. Fig. 4 shows the different fabrication methods employed in creating miniaturized microfluidic biosensors.

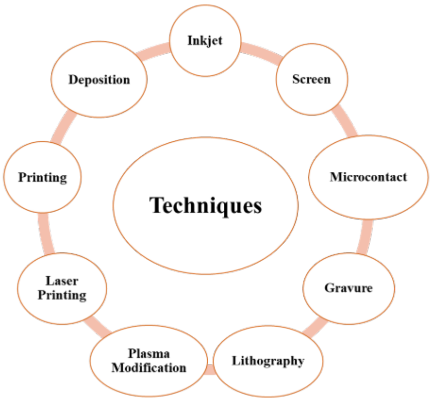

Fig. 4. Different fabrication methods employed in creating biosensors.

5. Applications in disease detection

Biosensors have broad applications in disease detection, exemplified by rapid tests for COVID-19, home pregnancy kits, cancer markers, pathogen identification, and glucose monitoring. They are vital in disease management, food security, and environmental safety due to their high specificity, portability, and low cost [5, 15]. Different applications of biosensors are shown in Fig. 5.

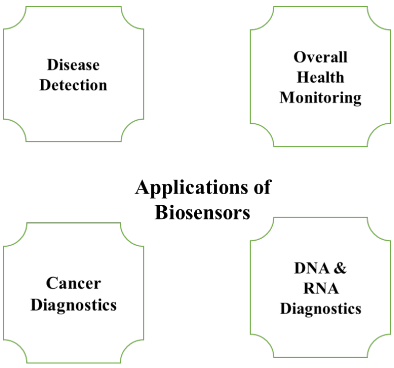

Fig. 5. Different applications of biosensors.

5.1. Detection of infectious and metabolic diseases

In infectious disease detection, especially for COVID-19, biosensors, particularly electrochemical ones based on conducting polymers, offer promising alternatives to traditional methods like PCR and CT scans [44]. These biosensors are advantageous because they are rapid, sensitive, and suitable for point-of-care and home use, although challenges remain regarding their stability and interaction with biomarkers [17]. Studies show they can detect various COVID-19 biomarkers such as viral RNA, proteins, and whole viruses [44].

For metabolic and chronic diseases, breath analysis and VOC detection provide non-invasive diagnostic tools. Recent research employs molecularly imprinted polymers and nanostructured electrodes to detect viral proteins like SARS-CoV-2 with high sensitivity and specificity, facilitating rapid virus identification [1]. Similar approaches are used to monitor immune responses, such as detecting antibodies against COVID-19 [45].

In diabetes management, biosensors measuring biomarkers like glycated albumin complement traditional glucose tests, especially when HbA1c results are unreliable. Bimetallic nanomaterial-based biosensors on microelectrodes enable sensitive, broad-range detection of diabetes biomarkers [46].

Additionally, biosensors are being developed for infectious diseases such as Zika virus, where rapid, low-cost electrical biosensors utilizing aptamers and advanced flow techniques can detect viral proteins within minutes, significantly enhancing diagnostic speed and accuracy [47].

Baradoke et al. developed an electrochemical sensor for SARS-CoV-2 antibodies using gold nanoparticles on screen-printed electrodes with immobilized Spike protein. It offered rapid detection with a limit of 2 ng/mL, providing an effective tool for monitoring immune response to COVID-19 [48].

5.2. Cancer biomarkers

In cancer diagnostics, biosensors enable early detection by identifying biomarkers like microRNA-21, which is overexpressed in many cancers. Innovative paper-based electrochemical biosensors using gold inkjet printing are cost-effective and capable of detecting miR-21 at very low concentrations, making them suitable for resource-limited settings. Biosensors also hold potential in monitoring cancer progression, metastasis, and the effectiveness of treatments, offering quicker diagnostics and real-time disease management [17, 49-52].

6. Performance evaluation and challenges

Biosensors, including piezoelectric and electrochemical types, are highly sensitive and selective devices that utilize materials like piezoelectric crystals and conducting polymers (CPs) [24, 25, 33]. Piezoelectric mechanisms show promise as alternative signal transduction methods if issues like non-specific binding and sensitivity are addressed. Conversely, biorecognition molecules such as antibodies, DNA, or aptamers, often face hurdles related to stability, nonspecific adsorption, and small analyte detection, which limit their widespread commercial use despite extensive research [12]. Moreover, electrochemical biosensors, especially when combined with nanomaterials, offer high sensitivity, simplicity, and low cost. However, challenges such as high detection limits and inconsistent reproducibility remain. Recent advancements include wearable glucose sensors and sweat analysis patches [11]. Recent innovations involve combining CPs with graphene-based materials (CP/GE composites), which enhance flexibility, surface area, stability, and recognition capacity [44]. High-sensitivity DNA biosensors based on graphene field-effect transistors (GFETs) have demonstrated scalability and reproducibility, with potential for rapid, inexpensive DNA hybridization and sequencing, advancing genomics and diagnostic applications [53].

Notably, Ping et al. developed a scalable, highly reproducible (>90%) process for fabricating label-free DNA biosensors using GFETs functionalized with single-stranded DNA. The sensor's Dirac point voltage shifted systematically with target DNA concentration, with a detection limit of 1 fM for 60-base DNA. Tests with mismatched DNA confirmed that mismatch position affects hybridization strength, highlighting the potential for fast, cost-effective, and precise DNA detection and sequencing [53].

Overall, key challenges involve effectively capturing biorecognition signals and converting them into measurable outputs such as electrical, optical, or acoustic signals. Improving transducer performance by increasing sensitivity, response speed, reproducibility, and detection limits (down to single molecules) is essential. Miniaturization via micro- and nano-fabrication techniques is also crucial, as nanomaterials provide high surface area and conductivity [12, 54].

In the third generation, it was shown that enzymes are integrated directly into the sensing element, enabling electron transfer without mediators, which reduces costs and allows repeated measurements [11]. Next-generation biosensors are crucial for early disease detection and point-of-care diagnostics due to their portability, rapid results, and multiplexing abilities [53].

7. Conclusion

Biosensors are emerging as valuable tools in disease management, particularly offering great promise for cancer detection and monitoring. They can provide rapid, precise measurements of cancer cells and metastasis, evaluate the effectiveness of anticancer treatments, analyze cancer biomarkers, and assess drug performance at specific target sites. Overall, biosensors aim to shorten diagnostic times and track therapeutic outcomes. Developing scalable, highly sensitive, and selective all-electronic biosensors is essential for advancing research and practical applications in disease and pathogen detection.

Author contributions

Mehrasa Nikandish: Conceptualization, Writing—Original Draft Preparation, and Writing—Review and Editing**. Hawraa Alsayegh:** Investigation, Writing—Original Draft Preparation, and Visualization. **Mojtaba Karbalaee:** Writing—Original Draft Preparation and Writing—Review and Editing. **Narjes Sadat Yadollahi Nooshabadi:** Investigation and Writing—Review and Editing**. Mohammad Borhan Abazari:** Writing—Original Draft Preparation and Writing—Review and Editing.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

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