Biosensors in Alzheimer’s Disease: Emerging Tools for Early Diagnosis

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Abstract. Alzheimer’s disease (AD), a prevalent neurodegenerative disorder, has experienced a marked increase in incidence due to global population aging, imposing substantial challenges on healthcare systems. Conventional diagnostic approaches are typically applied only after the onset of overt cognitive impairment. They are often constrained by operational complexity, high cost, and invasiveness, limiting their utility for early detection. In recent years, biosensor technology has emerged as a promising tool for the early, rapid, and non-invasive AD diagnosis due to its high sensitivity. This review summarizes the advances and applications of biosensors in AD diagnosis and patient care from 2020 to 2025, with a particular focus on electrochemical and optical biosensors for detecting key AD-related biomarkers, including β-amyloid, Tau, phosphorylated Tau, and exosomal miRNA. Strategies for multiplexed biomarker detection to enhance diagnostic accuracy are also discussed. Moreover, the review highlights the use of biosensors in daily patient management, encompassing real-time health monitoring, optimization of pharmacotherapy, and behavioral interventions. Despite existing sensitivity, specificity, standardization, and clinical translation challenges, biosensor technologies are progressively moving toward multi-modal sensing, integration with artificial intelligence, and combination with microfluidic platforms. This review aims to provide insights into the early diagnosis and personalized management of AD and to outline prospective directions for future research in this field.

Keywords: Alzheimer’s Disease; Electrochemical Biosensor; Nanomaterials.

1. Introduction

Alzheimer’s disease (AD) is one of the most common human neurodegenerative disorders, clinically characterized by a progressive decline in multiple cognitive domains, including memory, learning ability, language, and executive function, ultimately leading to global dementia [1]. With the intensifying global population aging, the incidence and burden of AD are increasing significantly. Epidemiological statistics indicate that approximately 50 million people worldwide are affected by dementia, of which more than 60–70% of cases are attributed to AD, and the number of patients is projected to double or even triple by 2050, posing a substantial challenge to healthcare systems and public health resources [2].

Pathologically, AD is primarily characterized by the deposition of β-amyloid (Aβ) plaques, neurofibrillary tangles caused by tau hyperphosphorylation, synaptic structural and functional impairments, and persistent neuroinflammation in the central nervous system [3]. Current studies suggest that the onset and progression of AD represent a complex, multi-factorial, and multi-stage pathological process, influenced not only by genetic susceptibility but also by environmental factors and lifestyle [4].

Early diagnosis of AD is crucial for delaying disease progression and optimizing intervention strategies. Unfortunately, conventional clinical diagnostic methods are typically applied only after the patient exhibits noticeable cognitive deficits or functional impairments, making it challenging to capture the latent or early stages of the disease [5]. Moreover, these methods often rely on neuroimaging, cerebrospinal fluid (CSF) analysis, and neuropsychological assessments. These are complex, costly, and time-consuming and involve invasive procedures (e.g., lumbar puncture) that may affect patient compliance. These limitations significantly constrain the application of traditional methods in large-scale population screening and early clinical diagnosis.

In contrast, the rapidly developing field of biosensor technology has shown great potential for early, rapid, and non-invasive or minimally invasive diagnosis through highly sensitive detection of AD-related specific biomarkers, such as Aβ, tau, and phosphorylated tau. Beyond early diagnosis, biosensors also hold promise in the daily management of AD patients, including real-time health monitoring, optimization of pharmacotherapy, and behavioral interventions.

This review focuses on the applications and innovations of biosensors in the early diagnosis and daily care of AD over the past five years (2020–2025). The relevant scientific literature published between 2020 and 2025 was retrieved from the ScienceDirect, PubMed, and Google Scholar databases using the following keywords: biosensor, electrochemical immunosensor, optical biosensor, Alzheimer's disease, amyloid beta, tau protein, apolipoprotein E, and behavior detection.

2. Biosensors for Alzheimer's Disease Diagnosis

Biosensors, which are composed of bioreceptors, transducers, technologies, and detection systems, can be classified into various types [6]. This review primarily focuses on electrochemical biosensors, optical biosensors, and nanomaterial-enhanced sensors to recognize biomarkers and their diagnostic performance. Common biomarkers to diagnose Alzheimer's disease include β-amyloid (Aβ), tau protein, phosphorylated tau protein (P-tau), and exosomal miRNAs.

2.1 Biomarker Recognition by Biosensors

Electrochemical biosensors convert biomolecular recognition events into measurable electrical signals (current, voltage, or impedance changes) by integrating biorecognition elements such as antibodies, aptamers, enzymes, or single-stranded DNA with electrochemical transducers [7, 8].

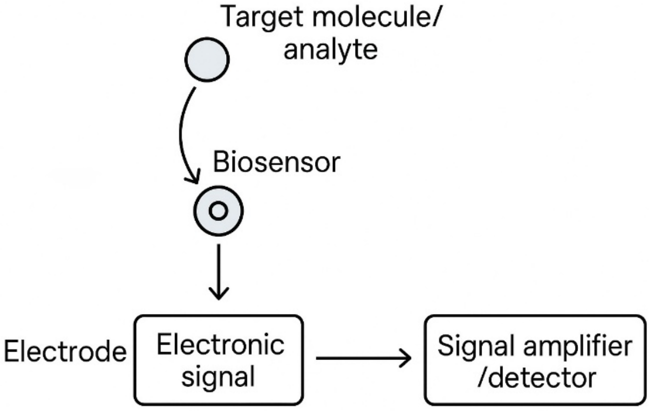

Figure 1. Mechanism of Electrochemical Biosensor

The schematic above illustrates the basic working principle of electrochemical biosensors: target analytes are specifically recognized and bound by receptors, generating signals that can be processed and quantified.

In the early diagnosis of Alzheimer's disease (AD), electrochemical biosensors have been extensively studied for their capacity to detect disease-related biomarkers. Among these, β-amyloid (Aβ), particularly Aβ42, is considered a critical biomarker, and numerous studies have focused on developing electrochemical biosensors specifically targeting this peptide [9–11]. For example, a CNT–metal–porous graphene hybrid (CNT-MGH) nanofork array (n-IDA) biosensor has been designed for the detection of Aβ42 in blood samples, thereby enabling early AD diagnosis [12]. Similarly, a polyadenine-assisted signal displacement aptamer biosensor has been employed to detect Aβ biomarkers precisely [11]. Beyond electrochemical techniques, optical biosensors have also been developed, such as an impedance immunosensor based on indium tin oxide–polyethylene terephthalate (ITO-PET) electrodes modified with 3-glycidyloxypropyltrimethoxysilane (GPDMMS) and specific anti-Aβ42 antibodies, which enabled rapid, selective, and highly sensitive quantification of Aβ42 [9]. In addition, molecularly imprinted polypyrrole-based biosensors have utilized artificial receptors to achieve specific recognition of Aβ [13].

Tau proteins, especially their phosphorylated forms (P-tau181 and P-tau231), also serve as essential biomarkers for AD [14,15]. To facilitate their detection, nucleic acid aptamer-based electrochemical sensors have been developed for identifying serum P-tau231, offering promise for rapid AD screening [16]. Furthermore, electrochemical biosensors integrating bifunctional nanozyme-based signal amplifiers have been reported, significantly enhancing the sensitivity of tau protein detection [17].

Exosomal miRNAs represent another promising class of biomarkers, with electrochemical biosensors demonstrating the capability to detect miRNA-34a cost-effectively and non-invasively [18]. Moreover, programmable plasmonic nanostructure biosensors have enabled the precise quantification of circulating exosomal miRNAs [19]. Although most of these systems are based on electrochemical principles, their success in biomarker detection provides a solid foundation for expanding into optical biosensor approaches.

Given single plasma biomarkers' relatively low diagnostic accuracy, multiplexed detection strategies have attracted considerable attention for improving AD diagnosis [20]. Recent studies have reported electrochemical biosensors capable of simultaneously detecting multiple AD biomarkers. For instance, a printed electrochemical biosensor based on vertical graphene (VG) modified with gold nanoparticles (VG@nanoAu) enabled the concurrent detection of four plasma biomarkers—Aβ40, Aβ42, T-tau, and P-tau181—thus facilitating multidimensional biomarker analysis [20]. Similarly, an electrochemical immunosensor utilizing a superhydrophilic droplet array could detect the same panel of biomarkers, further supporting the potential of multiplexed approaches in enhancing diagnostic performance [14].

Electrochemical biosensors for AD biomarker detection commonly employ techniques such as electrochemical impedance spectroscopy (EIS), cyclic voltammetry (CV), and differential pulse voltammetry (DPV) [21]. For instance, an impedance-based biosensor enabled label-free quantification of plasma P-tau181, distinguishing individuals with mild cognitive impairment, AD patients, and healthy participants [15].

The advancement of biosensors in early AD diagnosis has greatly facilitated early intervention and management. These devices offer non-invasive, low-cost, and rapid diagnostic tools suitable for large-scale screening and point-of-care testing (POCT) [22]. By detecting AD biomarkers in blood, they provide the potential to diagnose the disease before clinical symptoms emerge, even during asymptomatic stages, thereby affording valuable treatment time and mitigating AD's social and economic burden.

Future research on electrochemical biosensors for the early diagnosis of Alzheimer’s disease (AD) is expected to advance along several promising directions. One important avenue is the development of multimodal sensing platforms that integrate electrochemical methods with other detection modalities, such as optical and acoustic techniques. This combination allows for cross-validation of signals and amplification of responses, thereby further enhancing sensitivity and diagnostic accuracy. Terahertz metamaterial sensors, in particular, have shown considerable potential in biosensing applications and may be coupled with electrochemical strategies to achieve high-sensitivity detection of biomolecules, microorganisms, and cells [23].

Another direction involves expanding the scope of so-called “liquid biopsy” applications. While blood remains the most commonly studied sample, other bodily fluids such as saliva, urine, and tears represent valuable alternatives for AD biomarker detection. Exploring these less invasive samples could significantly reduce patient discomfort and improve compliance while also broadening the accessibility of diagnostic testing.

In addition, integrating electrochemical biosensors with artificial intelligence (AI) and big data analytics offers substantial opportunities for refining diagnostic models. The vast datasets generated by biosensor measurements can be coupled with AI and machine learning algorithms to extract complex patterns that may be imperceptible through traditional analysis. AI has already demonstrated distinct advantages in processing large-scale and heterogeneous biomedical data, and its application to early AD detection is exemplified by the use of deep learning for the interpretation of MRI images. Combining such approaches with biosensor-derived data could create more robust, accurate, and clinically applicable diagnostic systems [24].

2.2 Emerging Optical Biosensing Platforms and Technologies

2.2.1 Nanomaterial-Enhanced Optical Sensing

Owing to their unique physicochemical properties, nanomaterials have been widely employed in constructing optical biosensors to enhance sensitivity and selectivity [25]. Nanoparticles, nanowires, and quantum dots have demonstrated outstanding potential for detecting AD-specific biomarkers. For example, MXene ($Ti_3C_2T_x$) materials, with their large surface area, biocompatibility, excellent conductivity, and good aqueous dispersibility, have been applied in the development of cholesterol-detecting biosensors; similar materials are expected to be applicable for AD biomarker detection [26].

2.2.2 Surface Plasmon Resonance (SPR) Biosensors

Surface plasmon resonance (SPR) biosensors are highly sensitive optical analytical tools based on the principle of SPR, which arises from the resonant oscillation of free electrons on a metal film under specific incident light conditions. When light impinges on the metal–dielectric interface at a particular angle, surface plasmons couple with the electromagnetic waves of the incident light, leading to a significant change in the reflected light intensity. This change is susceptible to refractive index variations caused by molecular binding or dissociation at the interface. By monitoring variations in the angle or intensity of the reflected light, SPR biosensors enable real-time, label-free detection of molecular interactions, such as antigen–antibody binding, nucleic acid hybridization, or protein recognition, thereby allowing both qualitative and quantitative analysis of target biomolecules.

A schematic of the SPR principle is shown below.

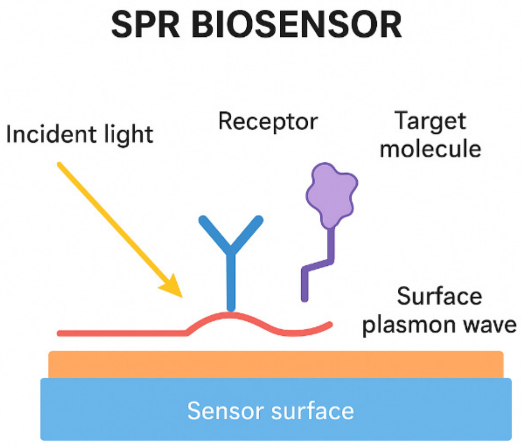

Figure 2. Molecular mechanism of SPR sensor

SPR technology has attracted considerable attention in biosensing due to its label-free, real-time, and highly sensitive characteristics [27]. Although relatively few reports directly describe SPR-based optical sensors for AD, the technique has demonstrated significant potential in cancer cell detection. For instance, cancer cells can be identified by monitoring shifts in the resonance wavelength [28]. This principle applies equally to the binding interactions between AD biomarkers and their corresponding receptors.

2.2.3 Optical Coherence Tomography (OCT) and OCT Angiography (OCTA)

Optical coherence tomography (OCT) is an imaging technique based on the principle of low-coherence interferometry. By measuring the time delay and intensity variations of reflected or scattered light at different depths within a sample, OCT reconstructs high-resolution cross-sectional images of tissues, enabling non-invasive visualization of microscopic biological structures. The underlying principle is illustrated in the schematic below.

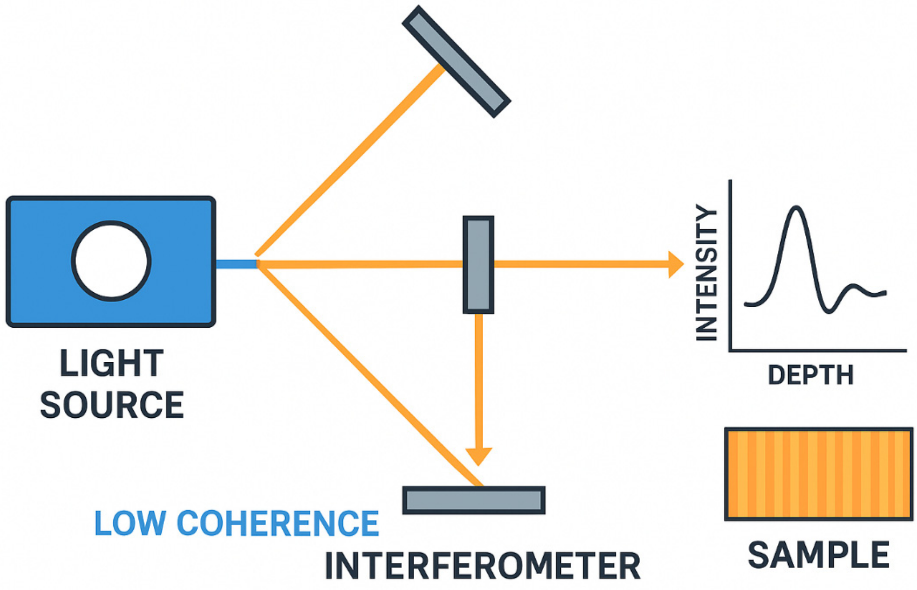

Figure 3. How OCT Biosensor Works

These two non-invasive imaging techniques are potential tools for early AD diagnosis [29, 30]. Changes in retinal vascular density and the foveal avascular zone (FAZ) may serve as potential ocular biomarkers for AD [29]. Although these techniques are imaging-based rather than conventional biosensors, they exploit optical principles to capture microscopic alterations within biological tissues, providing valuable insights for early optical diagnosis of AD.

Despite the considerable promise of optical biosensors for the early detection of Alzheimer's disease (AD), several significant challenges remain to be addressed. One of the most pressing issues is sensitivity and specificity. In complex biological samples such as blood, biomarker concentrations are generally very low and accompanied by numerous interfering substances, necessitating extremely high analytical precision levels [31]. To overcome this barrier, future research should prioritize the development of novel nanomaterials and innovative sensing mechanisms that can enhance detection performance and reliability.

Another major limitation is the lack of standardization and clinical translation. Most optical biosensors remain at the laboratory-based research stage, with few undergoing rigorous large-scale clinical validation. Transitioning these technologies from bench to bedside requires addressing regulatory hurdles, production costs, and usability challenges, which are critical for achieving widespread clinical adoption.

In addition, given AD's multifactorial nature, it is essential to pursue multiparametric integration in optical biosensor design. AD involves complex interactions among genetic, environmental, and lifestyle factors. Therefore, future biosensors should be capable of simultaneously detecting multiple biomarkers while incorporating broader datasets to establish more comprehensive diagnostic models.

Finally, integrating optical biosensors with microfluidic technology offers another promising direction. By combining sample processing, biochemical reactions, and detection within a single miniaturized platform, microfluidic-assisted optical biosensors could facilitate point-of-care testing (POCT), making early AD diagnostics more accessible, rapid, and user-friendly [32].

Addressing these challenges will be essential for advancing optical biosensors from experimental prototypes to practical and clinically relevant diagnostic tools, ultimately contributing to more accurate and accessible early AD detection.

3. Conclusion

This review comprehensively summarizes the latest advances in biosensor applications for Alzheimer’s disease (AD) diagnosis and daily care over the past five years (2020–2025). Studies indicate that biosensor technologies, particularly electrochemical and optical biosensors, offer great potential for early, rapid, non-invasive or minimally invasive AD diagnosis by enabling highly sensitive detection of specific biomarkers such as β-amyloid (Aβ), Tau protein, and exosomal miRNAs. Combined detection strategies targeting multiple biomarkers—for instance, electrochemical biosensors based on vertical graphene simultaneously detecting four plasma AD biomarkers—significantly enhance diagnostic accuracy.

Despite remaining challenges—such as further enhancing sensor sensitivity and specificity in complex biological samples and effectively translating laboratory findings into clinical practice—the field's future direction is clear. Multimodal sensing platforms, in-depth liquid biopsy applications, and integration with artificial intelligence and big data are expected to advance biosensor technologies. By providing more accurate, convenient, and cost-effective detection methods, biosensors have the potential to fundamentally transform early diagnosis and management of AD, thereby alleviating the societal and healthcare burdens associated with global aging.

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