

Alzheimer's Disease Diagnosis in the Preclinical Stage: Normal Aging or Dementia

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Abstract—Alzheimer's disease (AD) progressively impairs the memory and thinking skills of patients, resulting in a significant global economic and social burden each year. However, diagnosis of this neurodegenerative disorder can be challenging, particularly in the early stages of developing cognitive decline. Current clinical techniques are expensive, laborious, and invasive, which hinders comprehensive studies on Alzheimer's biomarkers and the development of efficient devices for Point-of-Care testing (POCT) applications. To address these limitations, researchers have been investigating various biosensing techniques. Unfortunately, these methods have not been commercialized due to several drawbacks, such as low efficiency, reproducibility, and the lack of accurate identification of AD markers. In this review, we present diverse promising hallmarks of Alzheimer's disease identified in various biofluids and body behaviors. Additionally, we thoroughly discuss different biosensing mechanisms and the associated challenges in disease diagnosis. In each context, we highlight the potential of realizing new biosensors to study various features of the disease, facilitating its early diagnosis in POCT. This comprehensive study, focusing on recent efforts for different aspects of the disease and representing promising opportunities, aims to conduct the future trend toward developing a new generation of compact multipurpose devices that can address the challenges in the early detection of AD.

Index Terms—Biosensors, wearable technology, Alzheimer's disorder, disease hallmarks.

I. INTRODUCTION

EARLY diagnosis of chronic diseases is a crucial aspect of health promotion as it enables timely intervention and helps alleviate their significant societal and economic burden. Alzheimer's disease (AD) is widely recognized as a progressive chronic disease that primarily affects individuals aged 65 and above on a global scale [1]. By 2020, there were already

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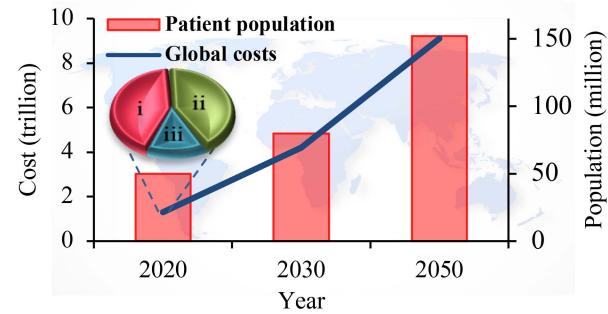


Fig. 1. Projected growth rate of AD patients and their global costs, estimated rise in involved cases and the societal burden from 2020 to 2050. The details of disease's global cost, including (i) the social costs of 42.3%, (ii) the indirect costs of 41.7 %, and (iii) the medical costs of 16%.

50 million individuals affected by AD. This irreversible neurodegenerative disorder is rapidly increasing due to the aging population, with a projected growth rate of 60% from 2020 to 2030, and 204% by 2050 [2]. Consequently, the estimated worldwide societal cost of Alzheimer's disease is anticipated to reach a staggering \$9.1 trillion by 2050 [3], as illustrated in Fig. 1(a). While, as evident, the indirect and social costs of this disease are attributed to a significant portion of the total expenses (Fig. 1(b)) [4].

Currently, the AD continuum encompasses distinct phases: preclinical, mild, moderate, and severe stages. Clinically, AD dementia onset involves gradual symptoms like memory loss and behavioral changes, ultimately impacting the patient's daily life and necessitating long-term care [5]. However, over a silent phase lasting years, early signs correlate with molecular and structural changes in the brain, detectable through altered AD biomarkers. Despite extensive research endeavors, the pathogenesis of Alzheimer's disease remains unclear. Notably, the major hypotheses regarding this neurological disorder indicate that the preclinical stage of AD commences with abnormal alterations in amyloid beta (A β) and tau proteins, leading to the accumulation of plaques and tangles in the neocortex and entorhinal cortex. These neurological developments bear similarities to age-related changes seen in normal aging. Over time, individuals at risk of AD may transition to a stage known as mild cognitive impairment (MCI), bridging the gap between normal aging and AD. Thus, the ability to diagnose this disorder during its preclinical stage can exert a profound influence on disease management,

allowing for distinguishing between individuals experiencing normal aging and those afflicted by Alzheimer's dementia to postpone the symptoms and control its progression [6].

At present, Alzheimer's diagnosis can be realized using diverse clinical practices and measurements, including cognitive tests, physical exams, CSF or blood analysis, and neuroimaging techniques considering the disease complexity and its similarities with different subtypes of dementia. In fact, these unique abilities can reveal abnormalities in the structure and function of the brain manifested as alterations in the cognitive, physical, and molecular systems of an involved person [7]. Brain imaging techniques are a crucial part of AD diagnosis, which can directly evaluate the structural, functional, and molecular changes of the patient's brain. Currently, structural and functional MRI, as noninvasive approaches, pose significant effects in assessing AD patients by examining the anatomy changes and determining the brain activity or its network connectivity [8], [9]. EEG/MEG can also manifest the functional changes (neuronal activity) of the brain regions involved in AD neurodegeneration. This can be carried out under the condition of applying cognitive activities or even in the resting-state EEG/MEG, which is more comfortable to perform with AD patients and eliminates the difficulties of completing the required tasks. While, the challenge remains to conduct clinical tests for elderly population at regular intervals, particularly in AD mass screening. In line with recent evidence, abnormalities in EEG/MEG characteristics may be associated with cognitive impairments over different stages of the AD continuum [10], [11]. Thus, EEG can be remarkable in the future trend of AD diagnosis, considering its potential in brain imaging, noninvasive nature, and cost-effectiveness [12], in particular by gaining a lot of attention in developing as reliable, user-friendly wearable devices [13]. Nevertheless, EEG as cost-effective and noninvasive imaging technique with high temporal resolution compared to MRI methods, suffers from low spatial resolution due to the distance between the source signal and the measurement electrodes. Additionally, its sensitivity to artifacts and external factors leads to a relatively low reliability or even low accuracy, resulting in challenges for the early detection of AD and discrimination from other neurological disorders [7], [14]. Furthermore, the lack of monitoring molecular changes in the AD continuum in these different noninvasive imaging methods makes them insufficient to directly diagnose and determine the type of disease.

Therefore, molecular PET imaging, though invasive, can be highly promising for the early detection of AD dementia by targeting the changes of specific and non-specific AD biomarkers in the brain, particularly when combined with the MRI test. Despite the high reliability of this technique in AD detection, its utility can be limited owing to the low availability, high cost, and invasiveness [7], [8]. Additionally, for this in-vivo molecular assessment of AD biomarkers, the approved radiotracers for clinical evaluation of AD are limited (particularly for novel high-potential biomarkers). Given these limitations, cognitive tests, physical exams, and CSF or blood analysis are usually conducted on a patient with suspected symptoms before undergoing brain imaging. In fact, these tests, which can evaluate the cognitive behavior and physical and molecular abnormalities of

a person involved in memory impairments, can play a critical role in diagnosing the disease or even eliminate unnecessary expensive tests. However, CSF analysis is an invasive and expensive method to manifest molecular changes of individuals with cognitive declines. In addition, the present tools for investigating physical behavior are bulky, textile-based devices, which are not useful for long-term monitoring [15], [16]. Table I summarizes the advantages and limitations of present clinical methods for diagnosis of the AD continuum. Accordingly, these available techniques cannot be appropriate choices for detecting Alzheimer's disorder in its preclinical stage.

These highlight an urgent need to provide different mechanisms to reliably monitor the physical and molecular abnormalities of an older adult in daily life toward the early detection of AD. Consequently, biosensors can be viable alternatives to these methods by enhancing their performance for repeatable, reliable, and accurate identifications while prediction algorithms (machine learning) can aid in precisely analyzing the data to detect the disease in its preclinical stage. Considering the impact that Alzheimer's disease can have on an individual's biological, physical, and physiological functions, biosensors can be designed to detect biological quantities [15] and assess body behavior characteristics [17]. In the first classification for detecting biological markers, changes in AD biomarkers of various body fluids can be converted into measurable signals through sensitive transduction mechanisms. Such biosensors show promise in the early detection of Alzheimer's disease [15]. For the second category, recent contributions have reported advances in harnessing various indicators, such as abnormal changes in physical, physiological, and ocular behaviors of Alzheimer's patients, to aid its early-stage detection [18], [19]. Nonetheless, these non-invasive biosensors in addressing Alzheimer's detection often exhibit bulkiness while require to be worn for a long time [20].

Here, we aim to provide a detailed overview of AD-related markers and biosensing techniques to summarize the latest advances in the early detection of Alzheimer's disorder and represent different opportunities. First, recent developments to identify various high-potential biomarkers and behavioral hallmarks for early diagnosis of this dementia are studied. Cutting-edge biosensing structures, tailored to address various biological and behavioral issues, are subsequently reviewed and compared. Within this section, the advantages and current limitations of each mechanism are examined to show the high potential of different methods in this context. Thus, according to current challenges and critical demands, several concepts of developing new biosystems through merging different technologies are discussed to make a new insight into the future of identifying early-stage Alzheimer's disorder.

II. BIOMARKERS AND PROMISING HALLMARKS FOR DIAGNOSING ALZHEIMER'S DISORDER

Elderly adults living with Alzheimer's disease suffer from various irreversible cognitive and physical difficulties. Alzheimer's dementia may be inherited (by hereditary genes) or occur sporadically due to unknown causes (lifestyle, tumors, a stroke, or even viruses and toxins). While the primary causes of this

TABLE I
ROLE OF CLINICAL PRACTICES CONSIDERING THEIR SUPERIORITIES AND LIMITATIONS IN AD DIAGNOSIS AND ITS EARLY DETECTION

Clinical practice		Advantages	Challenges in AD detection	Limitations in early diagnosis and mass screening
Neuroimaging	MRI	- Non-ionizing radiation, high resolution, high sensitivity, preferred for frequent imaging, direct monitoring of the brain's structural and functional changes	- Loud noise, high cost, longer time to take the image, the lack of molecular imaging, sensitivity of fMRI to artifacts	- Relatively low availability, high cost, difficulties to perform for long-term monitoring, labor-intensive, the lack of molecular tracking
	PET	- Molecular imaging of the brain, high reliability and specificity, the potential of utilizing in early AD detection	- Low-access, highly expensive, invasive or minimally invasive, limitations on in-vivo approved biomarkers	- Invasive, low availability, highly expensive, the lack of approved substances for in vivo molecular tests (novel promising biomarkers), inappropriate for long-term monitoring
	EEG	- Assessing brain functions by tracking neuronal activity, high temporal resolution, cost-effective, noninvasive, easy to use compared to other imaging, high-access, the potential to be an automated and user-friendly wearable device	- Low spatial resolution, relatively low reliable, the lack of molecular imaging, sensitivity to environmental noises and artifacts	- The lack of molecular tracking, relatively low reliability, sensitivity to environmental noises and artifacts
Cognitive and physical tests		- Noninvasive, relatively convenient to perform, providing indirect data on functional and structural changes of AD patients	- Low accuracy with sensitivity to several interferences, bulky textile-based devices, the lack of data on molecular changes	- Low accuracy, sensitivity to interferences, bulky textile-based devices, the lack of molecular monitoring, clinical tests
CSF or blood analysis		- High sensitivity, monitoring the molecular changes of AD patients, high accuracy, availability	- Invasive or minimally invasive, expensive, labor-intensive, the lack of monitoring the brain	- Invasive or minimally invasive, high cost, labor-intensive

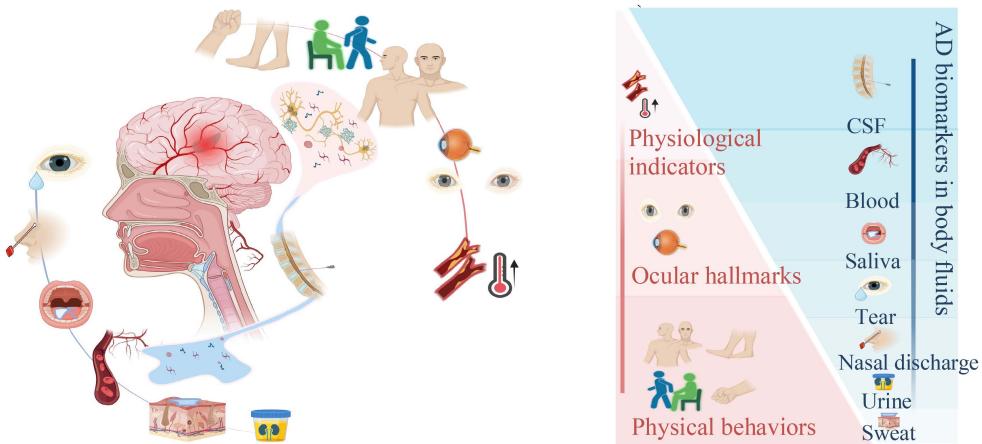


Fig. 2. Effect of Alzheimer's neurodegenerative disorder on various body fluids and organs recognized as biological markers and body behavior hallmarks with emphasizing the extent of studying in each category based on conducted research. Created with BioRender.com.

neurodegenerative disorder are still not completely understood, multiple theories explain the AD continuum by focusing on the abnormal changes in its pathogenic proteins, namely amyloid beta and tau, occurring in different regions of the brain. According to the neuropathological cascade, the disorder initiates with the accumulation of extracellular A β , leading to the formation of senile plaques in the entorhinal cortex and hippocampus. The process gradually expands and is accompanied by the development of neurofibrillary tangles, which result from the phosphorylation of tau inside neurons, triggered by A β . These structural alterations ultimately cause neurodegeneration, which leads to brain atrophy [21].

In line with the progression of neuronal cell damage, given the brain's central role in regulating bodily functions, behavioral activities can also be influenced in individuals afflicted with

Alzheimer's. As a consequence, various physical or behavioral symptoms, such as gait variabilities or balance difficulties, can manifest across different stages of the disorder [22]. Therefore, apart from cognitive behaviors, Alzheimer's characteristics can be classified as biological markers and body behavior indicators, as depicted in Fig. 2.

A. Biological Markers (Biomarkers)

Pathological features of Alzheimer's disease mostly overlap with different kinds of dementia and other neurodegenerative disorders. Accordingly, biomarkers can play critical roles in the diagnosis of this neurological disorder and tracking its progression using imaging techniques and body fluid analysis. Additionally, their impact on examining how therapies

TABLE II
ADVANCES IN IDENTIFIED AD BIOMARKERS, CONSIDERING HIGH-POTENTIAL ONES IN EARLY DIAGNOSIS OF ALZHEIMER'S DISORDER

Biosamples	Identified AD biomarkers based on AT(N) classification	Promising biomarkers in early detection
CSF	A β pathway: A β_{42} , A $\beta_{42}/A\beta_{40}$, A $\beta_{42}/A\beta_{38}$ [5] Tau pathology: t-tau [24], p-tau181, p-tau231, p-tau235, p-tau217 [25], phosphorylation occupancies at T217 and T205 [26], MTBR-tau243 (particularly in combination with pT205/T205) [27], the tau ratios, including p-tau/A β_{42} , t-tau/A β_{42} , and (p-tau or t-tau)/endogenous peptides [28] Neurodegeneration: - neuronal injury biomarkers; neurogranin [29], NfL, VILIP-1 [5, 30] - neuroinflammation biomarkers related to microglia activation and reactive astrocytes; programulin, CX3CL1 in CX3CL1/CX3CR1 signaling, sTREM2 [31], YKL-40, GFAP [5], IP-10 [32]	A $\beta_{42/40}$ [21], A β oligomers [33], BACE-1 protein [34], neurogranin, YKL-40, GFAP [5], programulin, CSF miRNAs [35]
Blood	A β pathway: A $\beta_{42/40}$, APP $_{669-711}/A\beta_{1-42}$, and A $\beta_{1-40}/A\beta_{1-42}$ ratios [36] Tau pathology: p-tau181, p-tau217, p-tau231, and their combinations [5, 37] Neurodegeneration: NfL, YKL-40, GFAP [16, 38]	p-tau217, p-tau231 [39], NfL, GFAP [40]
Saliva	A β pathway: increased level of A β_{42} (a negative correlation with CSF) [41] Tau pathology: p-tau [41] Neurodegeneration: lactoferrin, AchE, GFPA [41, 42]	A β_{42} , lactoferrin [42]
Tear	A β pathway: A β_{42} (limited data) [43, 44] Tau pathology: t-tau [43]	A β_{42} [44] and miRNAs [45], perspectives: A $\beta_{42}/A\beta_{40}$ and lactoferrin (no data) miRNAs [48]
Nasal secretion	A β pathway: soluble amyloid beta oligomers [46] Tau pathology: t-tau, p-tau, and p-tau/t-tau ratio [47]	
Urine	A β pathway: amyloid beta protein (controversial) [49] Tau pathology: P-S396-Tau [50]	AD7c-NTP [51], formaldehyde metabolism, formic acid [49, 52]
Sweat	Dopamine (a different non-specific biomarker) [15]	-

may affect dementia development is significant. A β abnormalities, tau aggregations, and neurodegeneration (represented in Table II) are the biomarker signatures of Alzheimer's disease classified by the AT(N) system [1]. Among these categories, beta-amyloid and tau proteins have been marked as specific or core biomarkers of AD, while neurodegeneration is the later consequences of abnormal changes in A β and tau isoforms. Beta-amyloid is a product of Amyloid Precursor Protein (APP) cleaved by β -secretase (BACE-1) and γ -secretase. According to the amyloid hypothesis, the increased level of sticky A β protein in the brain serves as the primary trigger for the onset of Alzheimer's disorder. The accumulation of this protein can cause the formation of extracellular plaques, primarily composed of the A β_{42} peptide, with the presence of A β_{40} . As a consequence, this process results in a reduction of the soluble form of the A β_{42} in the extracellular fluid, leading to lower concentrations in CSF [5], [6]. However, β -amyloid reduction can also be observed in bacterial meningitis, normal aging, some other neurodegenerative diseases, or dementia [5].

The tau pathway is another specific aspect of the AD continuum, which is hypothetically accelerated by the deposition of A β [23]. The role of tau is crucial in the pathology of Alzheimer's disease due to its synergistic effect with amyloid beta biomarkers, offering enhanced specificity in diagnosing the disease, particularly during the preclinical stage and its progression. Tau protein is the intracellular component of neurons, regulating the cytoskeletal dynamics of neural cells. The imbalance of hyperphosphorylated tau and its aggregation lead to the formation of neurofibrillary tangles, ultimately resulting in neuron dysfunction and subsequent cell death. Thus, the concentrations of total tau (t-tau) and phosphorylated tau (p-tau) show higher levels in CSF samples obtained from AD at-risk patients compared to those without the condition [5].

Over time, the A β pathway and tau pathology cause neuronal injury, neuroinflammation, and neurodegeneration in AD patients. Such processes are identified by changes in various non-specific markers expressed in most neurological disorders. Neuronal injury is related to the damage of individual neurons, characterized by releasing intracellular proteins from the dead neurons into the extracellular space (brain fluids) [29], [30].

Beyond neurons, AD progressively affects the functionality of glial cells, specifically astrocytes and microglia, both of which play vital roles in supporting and enveloping neuronal cells. These non-neuronal cells are involved in the inflammatory response of the nervous system, known as neuroinflammation. In the AD pathway, neuroinflammation has a critical role in the gradual decline of neurons and the impairment of their function during neurodegeneration [32].

Recently, several biological markers and their ratios have been identified in various body fluids. The recent advances in these biomarkers, considering their potential in early AD detection, are summarized in Table II. In light of the significance of molecular monitoring in AD diagnosis, targeting high-potential biosamples for the detection of disease biomarkers while weighing their advantages and limitations can significantly contribute to early AD diagnosis and its prediction. The CSF analysis, though invasive, is currently a clinical method to aid specialists in detecting Alzheimer's disorder, particularly in assessing abnormal symptoms. Furthermore, based on rapid advances in developing and validating blood-based biomarkers, a precise test for evaluating these biomarkers may be often efficient to study the presence of AD pathology in several patients with typical symptoms, without necessitating a comprehensive CSF analysis. It is valuable because of the convenience and minimally invasive nature of collecting this biosample from individuals when compared to CSF [37], [53].

TABLE III
PROSPECTIVE OCULAR HALLMARKS AND BODY BEHAVIORAL INDICATORS IN ALZHEIMER'S DETECTION

Markers	Invasive or minimally-invasive markers	Noninvasive potential indicators in early diagnosis
Ocular hallmarks	AD proteins in the eyes: - A β ₄₂ and A β ₄₀ peptides in vitreous humor, aqueous humor, and lens [54, 55] - t-tau and NFL changes in vitreous humor [54]	Changes in eye tissue characteristics (particularly in the retina and cornea): thinner nerve fiber layer, abnormalities in retinal capillary levels, vasculature changes, reduced metabolic activity [18]
Physical behaviors		Motor dysfunction symptoms: 1- Changes in body movement symptoms: - impaired gait quantified by various parameters, such as stride length, step rate, velocity, and cadence, particularly stride-to-stride feature [56] and toe off - slow walking, poor balance, disability of fine motor skills [57] - declines in finger and hand skills, Low handgrip strength [58] 2- Changes in physical activities like increased duration of sedentary activity [59] 3- Head turning sign (HTS) [60]
Physiological indicators	Increment in core body temperature [61]	- Body temperature fluctuations [61] - Elevated blood pressure variability (BPV) [62]

Nonetheless, research on noninvasive body fluids with a close relationship to the brain system remains limited. Saliva can be a valuable biofluid for the detection of neurodegenerative disorders due to the direct relation of the salivary gland with the brain and noninvasiveness. Tears, easily accessible, and intriguing biofluids, have the potential to reflect the neurodegenerative processes associated with various disorders due to their connection to the central nervous system. In addition, most CSF proteins can be detected in tear samples, suggesting tears as a suitable source for investigating AD pathology. Nasal discharge also holds the potential to be an appropriate noninvasive fluid for reflecting the development of neurological disorders. It can be bold by considering the direct effect of brain changes on the olfactory system during the AD continuum manifested as the biological signatures of AD within various regions of the olfactory system and olfactory decline in the early stages [35], [42], [44], [47]. However, due to the lack of sufficient data, there remains a deficiency in the standardization of unified protocols for analyzing AD biomarkers in these valuable biofluids, and it is imperative to devote more attention to such samples in the future research trends of AD pathology.

On the other hand, despite the importance of sweat or urine in wearable technology, the detection of small quantities of proteins in such diluted samples poses several challenges using present sensing techniques. Thus, research on identifying biomarkers in these high-potential biosamples has been limited in the context of AD diagnosis, emphasizing the need for innovative biosensing methods for further studies on these samples. It is also worth noting that despite recent findings in AD fluid biomarkers, the cross-talk of A β -tau proteins and mechanisms underlying neuronal injury and inflammation in cognitive decline are not fully understood. Because of that, there is a lot of attention to analyzing the trajectory of gene expression and regulation of transcription factors during the disease process [63]. Such research may provide valuable insights into a better understanding of the disease process, its

progression, and the variabilities observed in reported data for biomarkers during the disease development. Additionally, these efforts can lead to the discovery of new specific hallmarks for early diagnosis of AD and its treatment.

B. Body Behavior Indicators

The second category of AD characteristics is related to abnormal changes in ocular features, physiological, and physical behaviors of the body. Impairments in daily activities and eye movements are some examples of this group, as classified in Table III. Recently, these hallmarks are gaining more attention to consider in the early detection of Alzheimer's dementia thanks to their noninvasiveness and accessibility. However, the portion of studies in this group is less compared to the emphasis on biomarkers depicted in Fig. 2.

1) Ocular Hallmarks of AD: Eyes can provide new insight into the study of neurodegenerative diseases. Alzheimer's dementia is one of the neurological disorders that results in a range of effects on eye function and its parameters. These changes represent promising biomarkers for diagnosing AD in the preclinical stage, which can be categorized as invasive and noninvasive markers.

Invasive ocular biomarkers refer to AD pathogenic proteins found in the inner layers and fluids of the eyes. While various changes in eye tissue characteristics can be considered as noninvasive ocular hallmarks of AD. Multiple retinal changes (structural and microvascular) have emerged as biomarkers linked to AD pathology, including a thinner retinal nerve fiber layer, degeneration of ganglion cells-inner plexiform, abnormalities in retinal capillary levels, retinal vasculature changes, and reduced metabolic activity [64]. These characteristics are typically examined through non-invasive imaging techniques, such as optical coherence tomography (OCT) and optical coherence tomography with angiography (OCTA) [18], [65]. Furthermore, a progressive decline in corneal nerve fiber density, shorter fiber length, and diminished branch density in the cornea may be

strongly associated with cognitive decline and AD dementia, which have been observed by corneal confocal microscopy (CCM) [18], [54].

As a dynamic intraocular behavior, abnormalities in pupillary dilation of AD patients during cognitive tests may be a high-potential biomarker for early AD [66]. Moreover, eye blink rate (BR) can be an extraocular noninvasive candidate to reveal mild cognitive impairment. Elevated blink rate may potentially serve as an early symptom preceding the progression of Alzheimer's disease [55], [67].

Also, because of high similarities in neural and vascular structures of the eyes with the brain, AD can affect oculomotor behavior, leading to regulation changes in eye movements. Several parameters, such as changes in saccadic movements, smooth pursuit, and reduction in eye movement velocity, have been reported as early hallmarks of Alzheimer's disorder [68]. These errors or latency in eye movements are the impact of injury or neuronal damage in the cortex, which may become evident many years before the appearance of clinical symptoms [17], [55]. Taken together, due to the lack of correlation in the results of independent studies, comprehensive research is still necessary to confirm the ability of employing such interesting biomarkers in reliable diagnosis of AD. Therefore, several ocular signs have been recently reported as early AD hallmarks, which are summarized in Table III.

2) Physiological Markers: Body physiological systems are appropriately tuned to produce adequate blood flow for the brain operation. As a result, there is a deep connection between brain function and blood pressure [69]. Moreover, based on preliminary findings, the core body temperature of AD patients is above normal levels in healthy controls, which might be the effect of local neuroinflammation in the brain, exacerbating AD progression [61]. While such markers need more research to precisely validate their role in AD pathology, measuring them as early markers of cognitive impairment may be impressive in a multi-parameter system to continuously monitor the status of older adults, in particular those at high risk of this dementia.

3) Activity Indicators and Movement Behaviors: Various regions of the brain are gradually affected during Alzheimer's continuum, resulting in cognitive and motor dysfunctions over time. Although the underlying mechanism of neural network changes in such deficits has not been significantly studied during the disease progression [22], [70], various physical symptoms related to motor problems have been associated with developing AD. They include changes in daily activities, head and body movement behaviors. Recent advances in recognizing these indicators are classified in Table III. There is some evidence suggesting that these non-cognitive behavioral changes may serve as valuable phenotypic hallmarks during the preclinical stage, facilitating the prediction of Alzheimer's disorder progression [19]. Taken together, due to the lack of correlation in the results of independent studies, comprehensive research is still necessary to confirm the validity of such interesting biomarkers in reliable diagnoses.

Finally, to provide an overview and as a comparative study, the AD biological markers, ocular and behavioral hallmarks

with their advantages and challenges for AD diagnosis are summarized in Table IV. According to this table, one can conclude that there is a variety of high-potential markers, weighing their advantages and limitations, which can be simultaneously measured in a sensing platform for studying the disease and monitoring patients with or at risk for AD dementia.

III. STATE-OF-THE-ART BIOSENSING MECHANISMS AND DEVELOPMENTS IN AD DIAGNOSIS

Since the markers can signify the underlying biological, physiological, and physical processes in diseases, there are different types of biosensors.

Biological sensing platforms are utilized to identify biomarker concentrations in various biofluid samples. In such structures, label-based detection mechanisms need preparation steps for labeling secondary antibodies to detect biological targets using specific properties of labels. Label-free biosensors, on the other hand, utilize specific transduction mechanisms to quantitatively translate biological interactions into various signals [71]. Therefore, the functional characteristics of these biological systems significantly rely on the use of suitable biorecognition elements and high-throughput bio-transducers. Bioreceptors act as interface elements that facilitate the conversion of biological reactions into transducer signals. By choosing appropriate bioreceptors, a transducer should be properly designed to convert induced biological characteristics to a measurable signal. This part plays a critical role in the sensitivity of biological sensors and their limit of detection (LOD), which can be relied on electrochemical, optical, and microelectromechanical (MEMS) techniques [72].

On the other hand, biosensors can be applied for the detection of behavioral changes associated with different diseases. These structures can be wearable or non-wearable, in which the selection of the sensing mechanism is dependent on the specific indicators involved. These biosensors can be more popular than present methods for AD diagnosis. However, available wearable biosensors in this context are often bulky, posing challenges for extended daily use over a long period [20], [73].

A. Electrochemical Biosensors

Label-free electrochemical (EC) transducers are classified as electrodes, field effect transistors, and photoelectrochemical structures, as depicted in Fig. 3. In electrodes based on two or three fingers (Fig. 3(a)), potentiometric biosensors typically rely on two ion-selective electrodes to measure changes in voltage caused by variations in target entities. The role of these biosensors is significant in measuring key electrolytes because of their acceptable performance, affordability, and ease of use in wearables [74]. Meanwhile, potentiometric methods require higher selectivity, sensitivity, stability, and flexibility. Surface modification of electrodes by various nanomaterials or nanostructures, such as Au nanostructures and reduced graphene oxide (rGO), can increase the stability of these biosensors. Gold nanoparticles as tagged probes can also enable multiplex detection of ions and improve sensor sensitivity [75]. However,

TABLE IV
VARIOUS KINDS OF HALLMARKS EVALUATED IN AD DEMENTIA REGARDING THEIR POTENTIAL TO MERGE IN A SENSING PLATFORM TOWARD AD DIAGNOSIS

Indicators	Body targets	Superiorities	Current limitations	The potential of merging in a platform
Biomarkers	CSF	- Direct connection with the brain, reliability, clinical validity, standardized methodology	- Invasive and laborious sampling techniques, high cost	
	Blood	- Accessibility, minimally invasive sampling, cost-effectiveness	- Inconsistent changes in core biomarkers, lack of standardization, low concentrations of biomarkers	
	Saliva	- Direct relation of salivary glands to the brain, equivalency to serum, noninvasive sampling, easily accessible	- Lack of sufficient data in assessing AD biomarkers, non-specific methodology, very low concentrations of AD biomarkers	
	Tear	- Simple and noninvasive sampling, a close relation of eyes with the brain, being intermediate between CSF and serum	- Few studies on AD biomarkers, limitations in sample volume and reproducibility, non-specific methodology	
	Nasal discharge	- Direct association between the olfactory system and the brain, noninvasive sampling	- Limited research in AD detection, lack of providing a correlation with CSF biomarkers, inconsistent data due to different sampling techniques from different regions	
	Urine	- Noninvasiveness, easy to collect, no limitation in sample volume or repeatability	- A handful of research on specific biomarkers, inconsistency, very low concentrations of AD biomarkers	
	Sweat	- High accessibility, the potential for continuous monitoring, noninvasiveness, attractive in wearables	- Lack of data on specific and non-specific AD biomarkers, very low concentrations of biomarkers	
	Ocular markers	Eye movements Pupil dilation Blink rate	Noninvasiveness, high accessibility as daily activities and physical features, the ability of real-time, continuous, and long-term monitoring	
Physical or behavioral hallmarks	Physiological indicators	Blood pressure Body temperature	Overlapping with other diseases, lack of sufficient research to differentiate these markers in AD dementia, affecting by various interfering factors, the need for continuous monitoring	
	Body behaviors	Movements Sedentary behavior Fine motor skills Head turning sign		
				▪ Tear AD biomarkers, pupil dilation, and eye movements ▪ Tear AD biomarkers, pupil dilation, and core body temperature ▪ Tear AD biomarkers, blink rate, head turning ▪ AD biomarkers in nasal discharge, head turning, head acceleration, body temperature ▪ Urinary biomarkers, core body temperature, body acceleration (for body movement), and sedentary behavior ▪ Sweat-based AD biomarkers, arm or wrist movements in fine motor skill, blood pressure, and body temperature

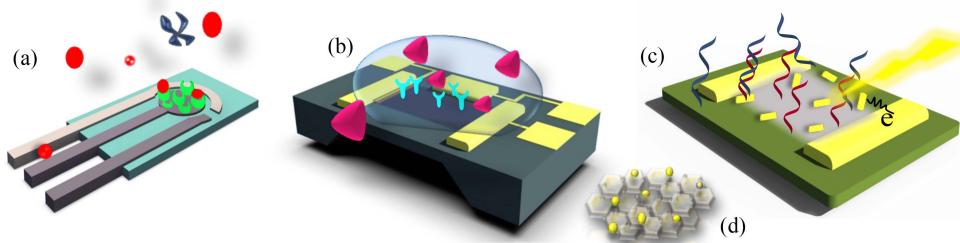


Fig. 3. Schematic description of electrochemical biosensing mechanisms to depict their basic principles for the detection of biological species: (a) an electrode-based biosensing device functionalized by bioreceptors on the working electrode, (b) transistor-based structures, modifying the gate electrode or channel by biorecognition elements for biosensing, (c) photoelectrochemical biosensing method based on converting photon energy into electrical current by photoactive materials for sensitive detection of biomarkers, (d) taking advantages of nanomaterials and nanostructures for surface modification of electrochemical biosensors.

employing nanostructures can pose a challenge to the repeatability and reproducibility of biosensors.

Amperometry is a popular biosensing technique to study metabolic processes by enzymatic recognitions. In amperometric structures, the working electrode is functionalized by enzymes to measure the redox reaction of analytes, monitoring current changes between electrodes under a constant voltage

[76]. These biosensors can be efficient for wearable devices due to their appropriate sensitivity and selectivity, as well as easy fabrication [74], [77]. However, to identify biospecies in various biosamples, higher sensitivity, and lower detection limit are required owing to low concentrations of metabolites found in different body fluids. Consequently, 2D nanostructures and nanomaterials [77] have been motivated to modify the sensing

surface of electrodes and enhance their sensitivity. Moreover, organic chemical transistors can be suitable alternatives for electrode ones [75].

On the other hand, in most cases, voltammetric biosensing is applied for the quantification of bio-affinity interactions between biomarkers and bioreceptors, employing electroactive labels for signal amplification. The supply voltage applied on the working electrodes of these sensors can be adjusted in different forms, which is important to precisely analyze biosensing mechanisms and improve biosensor sensitivity [76]. Cyclic voltammetry is a popular technique based on measuring the current response of biochemical reactions over scanning the triangular cyclic voltage. In the differential pulse voltammetric (DPV) method, a fixed-amplitude pulse is applied on a step potential as electrode voltage, whereas square wave voltammetry (SWV) is based on the superimposition of a staircase ramp and a symmetrical square wave. As a result, current changes are indicative of biological interactions on working electrodes, resulting from direct redox processes or labeling techniques. DPV and SWV show higher sensitivity and lower detection limit compared to CV. However, among these analytical techniques, square wave voltammetry is preferred because of combining the advantages of cyclic and pulsed approaches [76], [78]. Overall, there is a need for improved sensitivity and detection limit in voltammetry methods using bare electrodes for various applications. Therefore, modified layers, including nanomaterials or nanostructures, specific polymer films, and 2D metallic composites, have been widely reported to be employed on electrode surfaces, resulting in improved sensitivity and precision of biosensors [78]. However, the low selectivity of voltammetry biosensors in complex media (i.e., blood serum) poses a significant challenge. This is particularly relevant due to the presence of multiple redox-active species and the sensing mechanism employed by these biosensor structures [79]. Besides, the size and amount of nanostructures have significant effects on the sensitivity of biosensors, which can affect the sensor simplicity and reproducibility. Recently, a study has shown that using edge-plane pyrolytic graphite electrodes relying on an advanced SWV method can address some issues for electrochemically characterizing human serum without pre-treatment of the samples or surface modification [79]. In this spectroscopy-like method, the role of choosing electrodes and parameter changes in SW pulses has been studied under different serum samples.

Organic transistor biosensors have the potential to simultaneously convert biological interactions and amplify electrical signals. This determines their advantages over simple electrochemical transducers (electrode-based) [82]. As can be seen in Fig. 3(b), these devices are implemented to quantify target biomolecules interacted by immobilized biorecognition elements on the gate or channel of transistor structures. These biological interactions can change the sensing interface properties (i.e., capacitance or conductance) of the p-type or n-type transistor. Consequently, in organic transistor biosensors, taking advantage of nanostructures, such as ZnO, MoS₂ nanopores, carbon nanotubes, nanowires, copolymers, and graphene sheets (or nanoribbons) on the gate or channel makes them highly sensitive devices for biosensing [83], [84]. In addition to enhancing

the sensing surface by nanomaterials, a concave surface like crumpled graphene showed higher sensitivity than a flat one [84]. However, providing this specific pattern of graphite sheets leads to complexity in the sensor implementation. In another manner, applying square-wave voltage (AC voltage) on the gate electrode instead of DC voltage can significantly enhance the signal responses generated by organic transistors [85]. While transistor-based biosensors commonly offer low power consumption, appropriate sensitivity, and flexibility, the fabrication and biofunctionalization of electrochemical transistors tend to be more complicated than electrode ones. This complexity can also include the necessity for high-precision readout circuits to achieve a high signal-to-noise ratio [83].

In a different mechanism, merging the electro-optical properties of photoactive nanomaterials with electrochemical sensing methods results in photoelectrochemical (PEC) biosensors (Fig. 3(c)). Electrochemical electrodes or organic transistors are frequently modified with photoactive materials to serve as PEC biosensors. In these structures, the illumination of a light source in the ultraviolet or visible optical spectrum can excite photoactive semiconductor nanomaterials, leading to a photocurrent response in biosensors. Because of the impact of UV light on the performance of biomolecules, visible light is the preferred choice for exciting desired photoactive nanomaterials in this kind of biosensor. Binding the target molecules to specific bioreceptors can subsequently change the photoelectrical signal produced by physical or chemical reactions under light illumination [82]. Due to the importance of photoactive nanomaterials in converting light energy to photoelectrical signals and their role in analytical performance, various kinds of active transducers have been introduced. These materials can be categorized as semiconductors (i.e., ITO, TiO₂, quantum dots) and the combination of semiconductors with other semiconducting structures or carbon-based nanomaterials [82], [83]. PEC biosensors are intriguing because of their advantages, such as fast response, cost-effectiveness, and proper selectivity. Additionally, these structures represent low background signals with appropriate sensitivity due to separating their input source (light) and output signal (current) and merging optical and electrochemical transducing mechanisms. Nevertheless, their complexity and additional light stimuli to excite active materials should be taken into account. Ensuring high stability, addressing the pretreatment requirements of real samples, and achieving signal amplification in sensitive applications are also significant challenges for PEC biosensors. Furthermore, the use of nanoparticles or nanowires to facilitate biomolecule identification in such biosensors can affect their repeatability and reproducibility. In conclusion, given the compromise between the performance of electrochemical biosensors and their complexity and repeatability, there is still a significant gap in developing high-performance EC biosensors for reliable recognition of biomolecules in real samples, particularly in the context of affinity-based biosensing and multiplex detections. Considering the accessibility of screen-printed electrodes, a wide range of electrochemical sensors has been employed to investigate Alzheimer's biomarkers based on various surface modification techniques [82]. Accordingly, the best results in the electrochemical biosensing trend for detecting

TABLE V
DEVELOPMENT OF LABEL-FREE BIOSENSING MECHANISMS IN DETECTING DIFFERENT ASPECTS OF ALZHEIMER'S DEMENTIA

Mechanism	Method	AD marker	Characteristic	Sample	Detection technique
Electrochemical	Glassy carbon electrode (SnO ₂ nanofiber modification) [71]	A _β ₄₂	LOD: 0.638 fg/mL	Plasma	Impedance spectroscopy
	ITO electrode (β -CD/rGO modification) [80]	A _β ₄₀	LOD: 0.69 fg/mL	Serum	Capacitive
	Au electrode (3D polymer modification)[81]	A _β oligomers	LOD: 10 ⁻³ fM	Animal brain	CV and EIS
	Glassy carbon electrode modified by graphene and mesoporous silica [82]	ApoE4	LOD: 10 fM	Plasma	DPV
	Electrodes modified by rGO [83]	BACE1	LOD: 1 fM	Spiked serum	CV and DPV
	Photoelectrochemical electrode modified by Au nanoparticles and MoSe ₂ nanosheets [84]	Tau-381	LOD: 0.3 fM	Serum	Photocurrent measurement
	Diode [85]	TNF- α	LOD: 10 fM	Human serum	I-V response
	Carbon electrode modified by gold nanowires and rGO [82]	miRNA-137	LOD: 1.7 fM	Human serum	DPV
	Array of transistors based on densely carbon nanotube sheets [86]	A _β ₄₂ , A _β ₄₀ , t-tau, and p-tau181	LOD: 2.13 fM, 2.20 fM, 2.45 fM, and 2.72 fM	Plasma	Resistance measurement
	Shape-code LSPR [87]	A _β ₄₀ , A _β ₄₂ , and tau proteins	LOD: 34.9 fM, 26 fM, and 23.6 fM	Mimicked blood	Dark-field microscopy
Optical	Dual-channel SPR [88]	ApoE ϵ ₄	LOD: 10 fM	Serum	Prism-based
	Gold nano-urchins LSPR [89]	A _β ₄₂ fibrillation	Tracking structural changes over the fibrillation (in nM)	Buffer	Intensity modulation of LSPR
	Nanoplasmonic metasurface [90]	Tau and α Syn	Extracting fingerprints	CSF	ImmunoSEIRA
BioMEMS	Optical fiber [91]	Tau-441	LOD: 1 pM	CSF	Lossy-mode resonances
	Electrically tunable grating plasmonic [92]	-	Evaluation of neuron cell activity in AD	Human nucleus pulposus cells	Intensity modulation of SPR
	Atomic force microscopy (AFM) [93]	Fibrils and tangles	Morphology of AD pathogenic proteins	PBS buffer and red blood cells	AFM Imaging

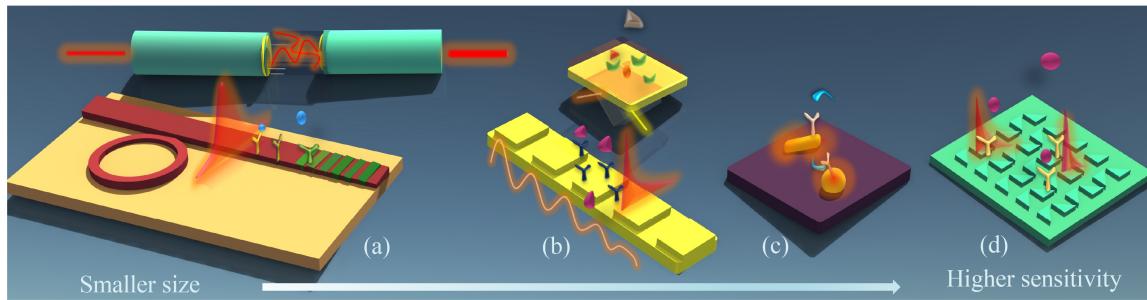


Fig. 4. Description of various optical platforms and their potential to confine electromagnetic waves for detection of biological interactions: (a) photonic biosensing using cavities and resonators in waveguides or fibers, (b) SPR biosensors relying on prism-based detection methods or grating patterns, (c) LSPR biosensing by nanoparticles, and (d) metasurfaces as nanophotonic bio-systems.

various biomarkers of Alzheimer's dementia are addressed in Table V.

B. Optical Biosensors

Optical biosensing has been gaining widespread attention due to the ability of remote sensing, miniaturization (in nanoscale), wide dynamic range, and high precision [94]. Label-free optical biosensors can be divided into affinity-based photonic and plasmonic structures. Waveguides and microfibers are fundamental photonic structures that realize optical transmission through total internal reflection. This mechanism traps light within the core

thanks to differences in the refractive indices of the core/cladding interface [95]. However, a part of the electromagnetic fields, as evanescent waves, propagates in their cladding layer with a lower index. These evanescent waves decay exponentially in the vicinity of optical interfaces with a decay length of about a few hundred nanometers. Such confinements can enhance the light-matter interactions, yielding a refractive index (RI) sensing surface to evaluate affinity-based biological processes [95]. As a result, these main optical elements can serve as the foundation for various interferometers and cavities to provide evanescent field-based structures for refractometric biosensing, as depicted in Fig. 4(a).

In Mach-Zehnder interferometer biosensors, the sensitivity is tuned by the structure and length of the sensing arm. Thus, taking advantage of long arms in various shapes, ring resonators [96], guided-mode resonances [97], and tapered microfibers [98] in the sensing layer can improve the biosensor sensitivity.

Whispering gallery mode resonators are other well-known photonic structures relying on evanescent-field biosensing. Trapping light in a circular dielectric, such as micro rings, microspheres, microdisks, and toroidal shapes, induces the oscillation of electromagnetic waves at specific wavelengths within the resonators, generating evanescent waves on their surfaces [94]. Consequently, their resonant wavelength is dependent on the resonator geometry (size and shape). Due to the nature of such resonators, light is strongly confined into the structure, resulting in an ultra-narrow spectral linewidth and high quality factor. Therefore, these kinds of biosensors can be remarkable choices for high-precision biosensing, such as label-free sensing of single biospecies [99] and investigation of kinetics and dynamics of molecular interactions [100].

Fabry-Perot interferometers [101], [102] and photonic crystal (PC) cavities [103] have been also used as photonic biosensors. Fabry-Perot cavities operate based on multi-beam interferences of electromagnetic waves passed through two highly reflective spaced surfaces. Therefore, the changes in both the distance between reflective surfaces and the refractive index of the gap can be utilized to tune a Fabry-Perot resonator as an affinity-based biosensor. Accordingly, Fabry-Perot optical fibers can be appropriate choices for biosensing purposes in which applying the Vernier effect [101] or 2D materials (rGO nanosheets) to enhance energy transfer [102] can significantly improve the biosensor sensitivity. Additionally, photonic crystals are multi-dimensional dielectric cavities that can detect a variety of biological elements for disease diagnosis. Periodic patterns of these structures in one, two, or three directions affect wave propagation by forming photonic bandgaps [103]. Meanwhile, a local defect in their periodic structure results in occurring a sharp resonance peak within the bandgap spectrum, which can offer a highly precise detection mechanism for monitoring biomarkers through strongly confined resonances.

Photonic biosensors based on dielectric materials show low losses and high quality factors, particularly in the case of optical resonators and cavities. These characteristics are crucial for achieving precise biosensing. Furthermore, the incorporation of on-chip optical sources and photodetectors, considering the compatibility of silicon photonics with CMOS fabrication, presents an appealing prospect for the production of portable devices for lab-on-chip applications. However, it is important to note that they often exhibit a low sensitivity, which is due to a small overlap between their confined electromagnetic fields and tiny biomolecules compared to nanoplasmonics.

Beyond the diffraction limit, the coupling of phonons and free electrons of metal/insulator interfaces excites plasmon polaritons [104]. These plasmons can be propagated or localized with a decay length in the plasmonic surface. Surface plasmon resonance (SPR) is a well-known method in biosensing, taking

advantage of plasmon polariton propagation in a flat or corrugated metal-dielectric surface to improve sensor sensitivity, as modeled in Fig. 4(b). In these structures, evanescent-field SPR biosensors are mounted on a prism, fiber, or waveguide in order to satisfy matching conditions in exciting plasmon polaritons. Consequently, plasmonic sensors show high sensitivity to refractive index changes near the metal-dielectric interface, triggered by alterations in analytes. While these structures have the ability to control electromagnetic fields at the nanoscale, the decay length of evanescent waves remains comparatively significant, considering the typical size of biological species. This can affect the biosensor sensitivity due to limited interactions of plasmonic fields with target biomolecules. Furthermore, because of the optical losses of metallic parts, plasmonic biosensors intrinsically represent broad resonance bands, resulting in a low quality factor in the biosensing performance. On the other hand, localized surface plasmons (LSPs) are collective oscillations of electrons in metallic nanostructures exposed to incident light (Fig. 4(c)). Due to the high surface-to-volume ratio of metal nanoparticles, LSP resonances (LSPR) show strong light confinement and high dependency on the nanoparticle size or shape and refractive index of the surrounding medium, yielding in a high sensitivity to biomolecular interactions [105]. Thus, LSPR biosensors represent high surface sensitivity, while they are less sensitive to RI changes in the bulk of a medium compared to SPR. LSPR-based biosensors can be simple spherical nanoparticles or designed in various shapes to increase biosensor sensitivity, such as nanodisks, nanocubes, nanorods, and nanostars [95]. These structures suffer from a low figure of merit and Q-factor owing to high losses, which can be enhanced by Fano resonances [106], hybrid structures using van der Waals materials [104], and by engineering chiral nanoparticle features [105].

Moreover, the widespread utilization of nanoplasmonic biosensors for biomolecular interaction analysis is hindered by several limitations, such as the complexity and high resolution of detection systems and the high sensitivity to fabrication tolerances (leading to difficulties in manufacturing). Plasmonic metamaterials are other nanostructured arrays based on periodic patterns of various metallic shapes, such as rods, holes, or split-ring resonators. These topologies have emerged to improve biosensing performance by the enhancement of field localization and control of plasmons. In such devices, the ability to converge plasmon polaritons and localized modes in an array can be remarkable for strong interactions in biosensing [107].

Nonetheless, due to the low figure of merit of plasmonic structures, including SPR, LSPR, and metamaterials, using advanced optical materials as alternatives in nanophotonics is of great interest. For instance, the resonance of dielectric meta-atoms in subwavelength resonators is interesting in biosensing applications. High-index dielectric materials in optical metasurfaces can enhance light confinement near the sensor surface and provide high-quality hotspot regions with strongly localized fields, illustrated in Fig. 4(d). In addition, dielectric metasurfaces can be manipulated to show very high quality factors relying on quasi-Bound State In the Continuum (BIC) resonances caused by breaking the symmetry of meta-atoms. Recently, 1D and 2D van der Waals (vdW) materials, including carbon nanotubes

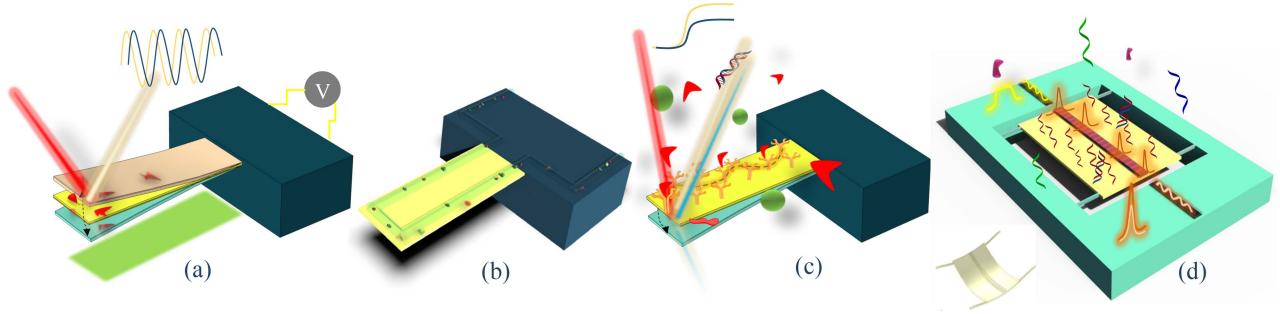


Fig. 5. BioMEMS sensors for quantification of biospecies and biological interactions: (a) mass-based biosensors formed by a conventional cantilever resonator, (b) a modified cantilever with an embedded microfluidic channel to improve the quality factor of the sensing mechanism, (c) surface stress-based biosensing mechanism relying on free-space optical detection systems, and (d) an architecture for surface stress biosensing using on-chip measurement methods.

and graphene sheets with their chemical derivatives, have represented new insights into optical sensing. This is bold, especially in surface-enhanced spectroscopies, thanks to the unique optical and electrical properties of these materials that give rise to tightly confined electromagnetic fields [108]. It is worth mentioning that while several efforts have been conducted to simultaneously enhance the key characteristics of optical biosensors, there is an inevitable trade-off between these parameters, which should be carefully assessed to meet diverse demands.

Apart from the use of optical spectroscopies, fluorescent probes, and colorimetric methods to study Alzheimer's disorder, optical biosensors have been relatively interested in the detection of AD biomarkers [87], [88], [89], [90]. In Table V, advances in photonic and plasmonic biosensors for investigating various aspects of Alzheimer's are represented.

C. BioMEMS Sensors

In light of the capability of MEMS technology to produce highly sensitive, miniaturized structures for a wide range of applications, BioMEMS has emerged to improve the performance of biomedical systems [72], [109]. In affinity-based BioMEMS sensors indicated in Fig. 5, transducers have been utilized for measuring very low concentrations of biomolecules relying on two different mechanisms. Indeed, these transducers can identify biomolecular interactions through mass-bound changes or surface stress phenomenon. Mass-based transducers convert any mass changes bounded to the MEMS surface to optical or electrical signals in a dynamic manner. For this purpose, a suspended substrate, such as a cantilever or membrane, can be driven by an external force to oscillate in its resonant frequency. This resonance frequency is very sensitive to mass changes occurred on both sides of the MEMS structure. As can be shown in Fig. 5(a), the frequency shift can then be monitored by an optical (laser beam deflection) or electrical detection (piezoelectric) system. Mass-based biosensors are predominantly favored for gas sensing applications, as the operation of MEMS resonators in fluids has been constrained by the significant impact of damping factors on their quality factor [72]. However, by a sensitive optical approach, the nanomechanical fluctuations generated from coated bacteria on an atomic force microscopic cantilever

have been precisely studied to analyze the bacteria activity [110]. On the other hand, the use of an embedded microchannel on the transducer surface can guarantee a high-performance mass-based biosensor for sensitive detection of analytes depicted in Fig. 5(b). Accordingly, cell growth rate has been appropriately investigated using an array of mass-based cantilever biosensors, which provide adequate delay for passing single cells through an embedded microchannel [111].

In a different scenario, the static behavior of a BioMEMS transducer is targeted to sense biological elements using surface stress-based biosensors (Fig. 5(c)). Based on the operating principle of these biosensors, one side of a movable structure should be functionalized by biorecognition elements, whereas the other side is passivated. The binding of biomarkers with specific receptors in active sites releases surface stress, leading to changes in the energy balance of the MEMS surfaces. This differential stress then triggers a static deflection in the BioMEMS transducer, depending on the binding events. The movements can be eventually measured by capacitive, piezoresistive, and optical techniques [72], [112]. Compared to capacitive and piezoresistive approaches, sensitive detection of biomolecules in low concentrations or even for single cells [113] can be appropriately realized by optical setups.

Following the principles of surface stress-based biosensors, surface stress generation is completely proportional to the characteristics of biological processes, such as the amount and type of binding events occurred on the surface. Thus, one can conclude that the bio-functionalization step plays an important role in the mechanical operation of these biosensors and significantly influences the sensor sensitivity. In other words, optimal connectivity of biological interactions on active sites of the surface can satisfy large forces to produce appropriate reactions. These imply that designing highly sensitive bio-transducers and employing a high packing density of bioreceptors immobilized on the surface through simple methods (i.e., self-assembly monolayer) can result in a very low limit of detection for measuring proteins, down to sub-femtogram levels. Interestingly, such results can be realized by microstructures without the necessity for utilizing any labels or nanoparticles [114], [115]. Furthermore, the capability of using an array of microcantilevers in a platform offers the use of reference cantilevers to eliminate interference

factors by differential signals. Moreover, the BioMEMS arrays can facilitate multiplex detection of biomarkers. All these potentials highlight the significance of employing BioMEMS sensors for monitoring very low concentrations of biomarkers in Alzheimer's disease. To attain this goal, there is a growing demand to advance the detection mechanism of BioMEMS sensors for integration onto a chip, depicted in Fig. 5(d). Monitoring the current changes of FET transistors implemented on cantilever surfaces or using a tunable surface stress-based membrane in a Fabry-Perot resonator have been proposed as alternatives to the conventional free-space laser method [116], [117]. Moreover, novel designs of BioMEMS sensors can be promising choices in obtaining high-performance devices to facilitate the detection of very small changes in biological interactions without comprising specific features of a high-resolution cavity [118].

Despite the high potential of BioMEMS sensors and probes to study diverse indicators of diseases, BioMEMS methods have rarely been applied to study Alzheimer's disorder, which is specified in Table V. However, based on the biomechanical basis of AD neuropathological alterations and the ability of AFM to examine the morphology of AD pathogenic proteins [93], it is worth noting that BioMEMS sensors can be high-throughput and cost-effective devices in the future trend of AD.

D. Biosensors for Detection of Various Indicators in Health Monitoring

Chronic diseases crucially need cost-effective continuous monitoring for health assessment and managing the disease risk. Besides biomarker detection, biosensors can also be ideal tools for sensing physical behaviors or physiological markers, including eye movements, heartbeat, body motions, body temperature, and blood pressure. As a result, there is a wide range of sensing platforms to detect these indicators classified as wearable or non-wearable devices. In the past few years, advances in biocompatible materials and the ability to realize various key features in wearable technology have led to developing a vast variety of wearable systems [73], [120], [121]. Biocompatible and flexible materials, such as Parylene, poly-dimethylsiloxane (PDMS), and silicon-based materials, are one of the main components of a wearable structure, in particular skin-based biosensors. Furthermore, 2D nanomaterials, such as graphene, MXenes, and MoS₂, can be employed to enhance the performance of biosensing in health wearable biosensors because of appropriate optical, electrical, or physicochemical properties [122]. However, developing new materials that can be recyclable, breathable, or even more stretchable to adapt to electronic skins is still a major concern in this context [120]. Power sources, sensors, communication circuits, or even microfluidic channels are other units of wearable biosensors that contribute to data capturing and processing. Power sources are critical parts of wearable structures as they provide regular power to integrated sensors, especially for long-time monitoring. Consequently, there is an urgent need for self-powered biosensing using energy harvesters. To address this challenge, different innovative possibilities, including physical activity of the body, body temperature, biofuel cells, and leveraging solar energy,

have been emerging to produce energy-efficient equipment [123]. In another case, the transduction mechanism of sensors in wearable structures is determined by the specific requirements of the health monitoring device. Potentiometric and amperometric electrochemical methods offer intriguing sensing capabilities for wearable applications, enabling the measurement of redox changes in target analytes present in sweat, tears, or saliva. While the role of MEMS methods, including piezoelectric, piezoresistive, or capacitive transducers, is to monitor abnormal changes in various organs (eye, hand, or leg movements) or physiological characteristics (temperature, heart rate, and pressure). On the other hand, optical sensors on a flexible substrate can serve as colorimetric, fluorescence, plasmon resonance, or whispering gallery mode sensing approaches to detect target hallmarks [123], [124]. As a result, taking advantage of optical and MEMS technologies in an engineered structure can develop flexible photonic chips for artificial smart skin to detect human motions [124].

Obtained signals from sensors should be appropriately transmitted to a smart device for processing data by various algorithms. It can be carried out by wireless communications or by recording visual data. Wireless techniques require custom circuitry, amplifiers, and radio frequency (RF) antenna, while visual recording is free from any on-chip electronic circuits or related power sources [125]. Transferred data can then be analyzed by artificial intelligence and machine learning methods to provide an autonomous wearable device.

In the process of developing wearables, several important factors come into play, including more miniaturization, high sensitivity, and high precision while achieving reliability. In addition, the ability to sense multiple healthcare indicators in a single unit is the evolution of multi-modal wearables. Regeneration of affinity-based biosensors embedded in a wearable system is also important for the reusability of the device, especially in long-term monitoring. Finally, energy harvesting can be merged with sensing mechanisms in a specific design to enhance such biosystems.

Non-wearable biosensors show the opportunity to continuously record patients' activities without the need for wearing or charging them, thus minimizing disruption to daily routines. For instance, eye trackers, motion sensors, door contact sensors, temperature sensors, and bed mat sensors can be used in naturalistic environments to collect data from individuals. These biosensors hold significant value for home-based monitoring of neurodegenerative disorders due to their ability to track the progressive nature of impairments [17], [119]. However, it is important to note that the use of these sensors is limited to study a few indicators in the healthcare context. Moreover, they do not match the capabilities of wearable ones when it comes to precision or resolution. Indeed, non-wearable sensors typically assess general behavior and cannot provide detailed information about physical activity, especially in monitoring the motion of various body organs.

As Alzheimer's disorder affects the physical and physiological characteristics of individuals over time, wearables can play vital roles in AD diagnosis or its prediction. However, most

TABLE VI
DEVELOPMENT OF WEARABLE AND NON-WEARABLE SYSTEMS IN
DETECTING PHYSICAL AND OCULAR INDICATORS
OF ALZHEIMER'S DEMENTIA

Mechanism	Device or Sensor	Physical indicator
Wearable	Infrared and proximity sensors mounted on the head (glasses or virtual reality eye trackers [17])	Eye movements, including eye blink rate, pupil diameter, saccade, and gaze
	Inertial sensors: 3-axis accelerometers and gyroscopes mounted on waist, feet, ankles, or legs [17, 119]	Gait behavior and balance
	Wrist-worn inertial sensor [17]	Sedentary behavior
Non-wearable	Force sensor mounted on legs [17]	Walking speed and gait analysis
	Wireless system containing various sensors [17, 20]	Daily activity by monitoring movement and acceleration values
	Depth sensors [17]	Body movement
	Eye trackers on a desk, infrared cameras, and handheld pupillometers [17, 119]	Eye-related hallmarks

wearable sensors employed for the diagnosis of AD patients are bulky and textile-based devices, which are summarized in Table VI. Finally, Table VII is represented to provide a summary of biosensors and offer a comparative study of different biosensing mechanisms, taking into account the advantages and challenges in their applications. Consequently, this table introduces the prospects of using various biosensing platforms for the study and detection of AD.

IV. DISCUSSION AND OUTLOOKS

Early AD detection or its screening in the elderly population is an urgent not only in diagnostic domains but also for developing therapeutic strategies. At present, despite a wide range of studies on discovering a complete cure, pharmacological treatments for Alzheimer's are based on lightening the symptoms (symptomatic-based) to only postpone the progression of the disease. Based on the ATN classification framework and diverse biomarkers, there are a lot of valuable endeavors to find new medicines for removing dysfunction of various beta-amyloid, tau, and neuroinflammation targets over the AD continuum or disease prevention (disease-modifying based) [126]. Among these, anti-amyloid therapy has gained more attention (advances), considering the significance of beta-amyloids as the central event of AD pathology in the amyloid cascade hypothesis. Various types of anti-A β monoclonal antibodies have been investigated to target soluble and insoluble A β species. The majority of them have not satisfied the requirements, representing small clinical impacts and safety concerns. These suggest further understanding of the causes of neurodegeneration to improve results in individuals with symptomatic AD [24].

Tau is another core biomarker of AD targeted for AD therapeutic goals. While multiple symptomatic and disease-modifying based strategies have been applied to this target, there is no clear evidence of appropriate clinical efficiency of tau-targeting therapies in the early stages of Alzheimer's to date [127].

Besides A β and tau therapeutic candidates, several targets related to neuroinflammatory pathways of the AD continuum are under assessment stages for the disease-modifying treatment. Targeting various factors of the peripheral immune system or activating microglial cells as immune responses to A β pathology by motivating its different regulating components are emerging mechanisms in AD therapy. However, the molecular targeting of immune cells can present difficulties owing to the dynamic behavior of immune responses and the complex communication that takes place among various cell types [128].

In sum, the available pharmacological treatments can only be beneficial for AD patients to temporarily keep their independence and enhance the quality of their life. Nevertheless, AD treatments pose several challenges and limitations, which affect their efficacy in clinical trials. Such therapies are mostly not disease-modifying based strategies, and AD progression can make the drug useless or less effective in managing the disease. As a result, they may be more effective in asymptomatic early phases of AD when neurodegeneration is not accelerated by the core AD characteristics. Moreover, drug delivery to the central nervous system can be significantly restricted by the blood-brain barrier membrane, leading to inefficient outcomes for truly assessing the drug impact. Side effects of each treatment on individuals can also be serious and cause a limited population to study the drug impact. All these highlight the importance of timely interventions by targeting effective early biomarkers, which need accurate detection of the disease in the early or preclinical stages [128], [129].

In line with focusing on the development of these treatments, evidence shows that prevention strategies and non-pharmacological therapies, such as enhancing cognitive abilities, more physical activities, and dietary changes, may aid in reducing impairments during the AD continuum. Accordingly, the ability of AD screening may revolutionize the future of harnessing this chronic disease in terms of prevention, timely interventions, or appropriate treatments [129]. Concerning the importance of Alzheimer's early detection, numerous research studies have been carried out to identify various specific and non-specific hallmarks of this dementia. Moreover, several biosensing techniques have been introduced to enhance the study of diverse markers in biosamples, physiological functions, or physical behaviors. Nevertheless, many factors should be taken into account in identifying biomarkers and developing biosensors for precise and early diagnosis of AD during its preliminary stages.

A. Biological Perspectives

From a biological viewpoint, some aspects merit consideration.

- First, it is essential to achieve alternative noninvasive samples to CSF for assessing AD biomarkers based on the

TABLE VII

COMPARISON OF DIFFERENT KINDS OF BIOSENSORS, CONSIDERING THEIR POTENTIAL TO USE IN THE DIAGNOSIS OF ALZHEIMER'S DISORDER

Targets	Biomarkers			Physical and behavioral hallmarks	
Biosensing mechanisms	Electrochemical	Optical	MEMS	Wearable	Non-wearable
	- Electrode-based	- Photonic	- Mass-based	- Electrical	- Electrical
	- Transistor-based	- Plasmonic	- Surface stress-based	- Optical	- Optical
Methods	- Photoelectrochemical	- Nanophotonic		- MEMS	- Electromechanical
					- Imaging techniques
Advantages					
	Simplicity to be integrated, low detection limit, rapid detection, high sensitivity using nanostructures	High sensitivity in nanoscale, high precision, high quality factor (cavities and resonators), real-time response, miniaturization, tunability for biosensing	High sensitivity, high precision using optical detection, rapid response, miniaturization, reliability (precise results using differential signals), cost efficiency by mass production in microscale	Continuous monitoring, the ability to detect and analyze various physical and physiological characteristics in a platform, miniaturization, high precision	Portability, contactless sensing, long-term monitoring
Challenges	Low repeatability and reproducibility (using nanostructures), complicated high-resolution readout circuits with high signal-to-noise ratio, signal amplification by electroactive substances in affinity-based biosensors, high sensitivity to pH changes of medium nanostructures	High-resolution free-space optical setup, precise alignment, high sensitivity to size and shape of nanoparticles, optimized for a specific range of RI, relatively complex and expensive fabrication	Free space optical setup, external actuators for dynamic mode biosensing, low quality factor of dynamic mode sensing in liquids, relatively low sensitivity, data transferring	Bulky to use (in some cases), technical difficulties, regeneration and reusability, relatively low sensitivity, data transferring	Low sensitivity or precision, high cost, the need for collecting data in clinics (in some cases) or a specific location in patients' houses
Potentials in AD detection	<ul style="list-style-type: none"> ▪ Nanophotonic biosensors for highly precise detection of AD core biomarkers ▪ Surface stress-based BioMEMS sensors for highly sensitive detection of AD biomarkers ▪ Mass-based BioMEMS sensors (combining by optical methods) to precisely study changes in fibrils and tangles during the AD continuum ▪ Wearable biosensing of various biological, physiological, and behavioral markers in a small compact device by different sensors, including electrochemical, optical, and BioMEMS inertial and pressure sensors 				

NIA-AA or ATX(N) classification system. While blood-based biomarkers have drawn growing interest as a potential biofluid in AD diagnosis, the utility of blood or plasma samples in clinical trials is constrained owing to the inconsistent data (in particular, A β core biomarkers) and a lack of standardized methodology. This inconsistency may be the result of several factors, such as the expression of A β by cells, masking of these peptides by plasma proteins, and its very low concentrations in the plasma compared to CSF. In addition to blood-based biomarkers, other body fluids such as saliva, urine, nasal secretion, and tears have been recently aimed to identify AD biological signatures. However, the current state of sparse research conducted on these biosamples reveals the lack of sufficient data for characterizing Alzheimer's biomarkers in these noninvasive fluids. This may be affected by two significant limitations: the lack of reliable and cost-effective devices to precisely measure very low concentration changes in such biofluids and the difficulty of collecting a broad range of real samples from elderly people to do the test in a laboratory. Therefore, further unified research is crucial to appropriately determine the AD-specific and promising biomarkers in these biosamples of at-risk patients using highly sensitive platforms and validate them by association

with CSF or PET biomarkers during the AD continuum. Moreover, extensive focus on tear, saliva, and nasal secretion samples as high-potential noninvasive fluids may open new perspectives in the future of screening Alzheimer's dementia for POCT applications thanks to their close relationship with the brain and simple sampling, as summarized in Table IV. Enhancing the ability for multiplex detection of various AD biomarkers (both specific and promising non-specific biomarkers) can also provide a more comprehensive understanding of conflict data and facilitate the discrimination of this dementia from other neurodegenerative disorders, in particular in its early diagnosis.

- Beyond developing biological markers, the identification of physiological and behavioral hallmarks of this neurological disorder can play important roles in the disease diagnosis. While these indicators hold promise for early-stage AD diagnosis because of their noninvasive and readily accessible nature, their development requires careful consideration of several factors. The abnormal physical behaviors or physiological functions attributed to this dementia may not be specific regarding the similarities between Alzheimer's disease and other types of dementia (or even other neurological disorders). In addition, various interfering parameters can affect these characteristics.

As a result, finding the correlation of such hallmarks with CSF and PET biomarkers of Alzheimer's disease over its progression is crucial for their validation, achieving specificity in early-stage diagnosis, and predicting AD development. For this purpose, the occurrence of each promising marker should be properly modeled in this neurodegenerative disease associated with changes in AD core biomarkers. Furthermore, multimodal experiments need to be performed on a large statistical population and repeated at frequent intervals to provide a specified framework for AD trajectory.

As the outcome, providing a strong association between these two different aspects of AD dementia is necessary, which can be impressive in the early diagnosis of this neurodegenerative disorder or predicting the disease progression for POCT applications using simultaneous detection of both biological and physical (or physiological) hallmarks.

B. Perspectives in Biosensing

According to the current limitations in diagnostic tools and the demands for measuring very low concentrations of AD biomolecules in various biofluids, especially in early diagnosis, emerging high-performance biosensing platforms can bridge the gaps in diverse studies for the early detection of AD. Therefore, several points and opportunities should be taken into account in affinity-based biosensors.

- Regarding recent advances in electrochemical biosensors, appropriate sensitivity and low detection limit (femtomolar level or lower) are usually achieved by using luminescence tags, quantum dots (QD), or Au nanoparticles. Luminescent labels and QDs make the biosensor a labeling-based method, which needs laboratory preparation steps. For Au nanoparticles, the size, shape, and amount of nanocomponents influence the sensor characteristics, leading to low reliability, low repeatability, and low reproducibility. Additionally, these structures necessitate highly precise readout circuits, which result in bulky and expensive detection systems. Therefore, given the significant role of electrochemical techniques in wearable biosensors, focusing on structural and functional changes of the sensor architecture can enhance their performance and may revolutionize their utilization in various applications, in particular for AD diagnosis. In fact, the changes can be tailored in innovative patterns under different control methods to enable multiplex sensitive detection of biomarkers.

- For optical biosensors employed in AD detection, functional characteristics are completely dependent on the nanoscale size of sensors. LSPRs or nanostructures (based on nanoparticles) offer higher sensitivity compared to SPR ones thanks to their few nanometer size. However, this advantage comes at the cost of increased dependency on fabrication tolerances, leading to reduced repeatability and reproducibility of biosensors. Besides, plasmonic structures suffer from the need for precise alignment in nanoscale and high-resolution, complicated detection systems, which have currently limited their utility in the early detection of Alzheimer's biomarkers. Thus, modern optical technologies such as engineered metamaterials and

metasurfaces can be more reliable while keeping high sensitivity in detecting low biomarker concentrations, signifying their high potential in AD diagnosis. It can be bold by taking advantage of the optoelectrical properties of various emerging materials (as structural materials) to improve their characteristics and provide a tunable array for the detection of multiple biomarkers in Alzheimer's dementia.

- BioMEMS sensors can be promising platforms in the future research of this neurological disease, relying on their advantage and the biomechanical basis of AD neuropathological alterations (Table VII). Surface stress-based biosensors can be appropriately designed and implemented in microscales (as an array) to be highly sensitive structures in detecting multiple biomarkers for a vast dynamic range. In addition, these biosensors can be more stable in background noises compared to electrochemical or optical ones. Consequently, these reliable structures can be implemented to efficiently detect various biomarkers, maintaining their repeatability and reproducibility. This can be addressed by novel designs of BioMEMS platforms relying on tunable optical methods to provide ultra-high sensitivity for studying very low concentrations of biomarkers in the Alzheimer's screening for POCT applications. Furthermore, mass-based biosensors (with a single-cell resolution) can be cost-effective and appropriate alternatives to study some aspects of the disease, such as the structural changes of aggregated proteins during the AD continuum. Hence, BioMEMS has a high potential for precisely sensing AD biomarkers and may contribute to its pathological studies.

Furthermore, with a deep look at the physical and physiological changes of patients, behavioral symptoms of the disorder can be observed in the body.

- Eye trackers, cameras, inertial, temperature, and acoustic sensors constitute the main parts of wearable and non-wearable sensing platforms, which should be enhanced to reliably and conveniently detect the physical symptoms of Alzheimer's disorder. From the perspective of AD diagnosis, wearable biosensors are expected to undergo miniaturization and become more compact. Accordingly, MEMS technology has the potential to significantly impact the development of such biosensors thanks to its capability to provide highly sensitive miniaturized devices in micro/nanoscales. For instance, sensitive BioMEMS accelerometers, pressure, and acoustic sensors, as well as optical MEMS structures, can be very interesting in detecting early indicators. It can be remarkable when these various sensors, with their circuits, can be fabricated on a small device for multimodal detection of AD symptoms (using the compatibility of MEMS and CMOS technology).

Finally, the potential of merging various biomarkers and behavioral hallmarks for the preclinical diagnosis of AD highlights the importance of multipurpose small platforms for detecting various biological and behavioral indicators of the disease at the same time. Regarding the fast development of wearable biosensors and taking advantage of regeneration techniques, tiny wearable devices can be realized for daily usage of elderly adults in POCT applications to monitor the important changes in at-risk individuals, as depicted in Fig. 6.

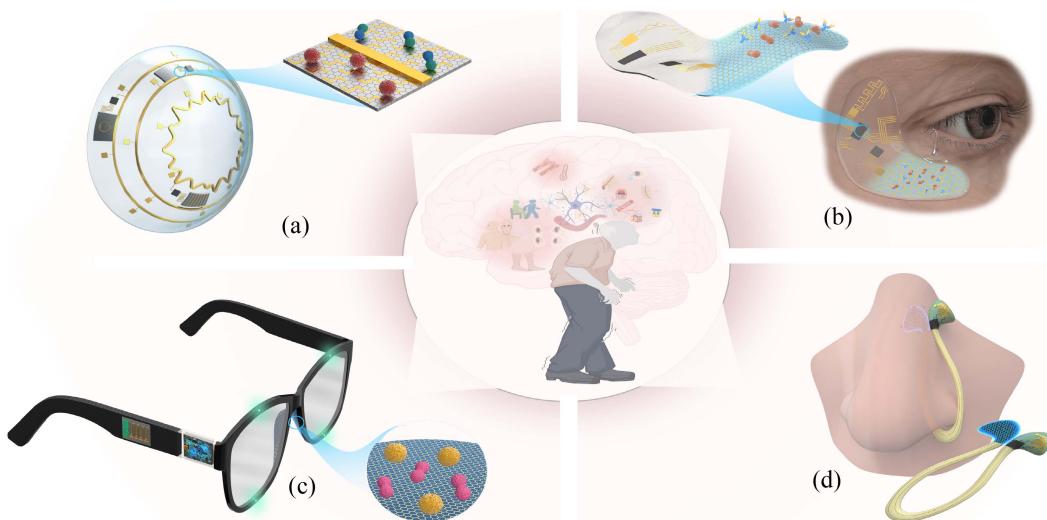


Fig. 6. Schematic description of high-potential wearables for the early detection of Alzheimer's dementia by assessing various AD hallmarks: (a) a contact lens for monitoring tear-based biomarkers and various ocular hallmarks, (b) an eye flexible pad to study AD tear biomarkers, physiological parameters and ocular characteristics, (c) a smart glasses including various sensors to evaluate multiple biomarkers and physical indicators, and (d) a nose-mounted device for identification of nasal discharge biomarkers, body temperature and head turning sign.

- 1) From a perspective, smart lenses have the potential to be intriguing for ongoing research of AD in POCT applications by simultaneous monitoring of diverse AD hallmarks. Notably, pupil dilation, as one of the intraocular hallmarks of AD, which is usually quantified by pupilometers, has a significant effect on the intraocular pressure of the eyes. As a result, increased pupil dilation in older populations can be detected by eye pressure sensors (under a different pattern of eye pressure changes compared to glaucoma). Considering eye blink rate changes and eye movement indicators in Alzheimer's continuum, an advanced lens can be realized not only to assess tear-based biomarkers (i.e., core biomarkers of AD) by highly sensitive optical or electrochemical microsystems but also to measure BR, eye movements, and the intraocular pressure by optical, MEMS inertial and pressure sensors on a platform (Fig. 6(a)).
- 2) Also, merging different biosensors in wearable structures as a flexible pad on the face skin can lead to the continuous quantification of AD-related characteristics, including tear-based biomarkers, head turning or tremor, body temperature, and eye blink rate. A schematic description of this smart pad mounted on the face skin is depicted in Fig. 6(b).
- 3) Smart glasses can be promising devices for simultaneous measuring of several behavioral and biological markers, such as blink rate, eye movements, or gaze by optical sensors, tear-based biomarkers by a sensitive biosensor mounted on the nose pads, and head turning or tremor using MEMS sensors (Fig. 6(c)).
- 4) A specific pattern of nose-mounted structures can also be designed for detecting nasal secretion biomarkers, core body temperature, and the head turning sign (or tremor), illustrated in Fig. 6(d). Such a device can include affinity-based and temperature sensors on its internal part,

making contact with nasal secretion (nasal discharge), and sensitive MEMS inertial sensors in the external pad on the skin.

- 5) Besides, identifying AD biomarkers in sweat can accelerate the implementation of several wearable biosensors, such as smartwatches, rings, and shoes, to detect the combination of sweat-based biomarkers, blood pressure, body temperature, and body movements in AD diagnosis.

To conclude, these projected biosensors can be invaluable for two key reasons: first, to gain a better understanding of the interplay between the biochemical and biomechanical behavior of Alzheimer's disease on the body, and second, to facilitate the development of cost-effective, efficient biosensors in POCT for early screening of AD patients in the preclinical stage.

V. CONCLUDING REMARKS

Given the increased cases of Alzheimer's disease as a global health issue and its societal burden, there is an urgent need for its early detection. Biosensors and the disease hallmarks can play important roles in the future of diagnosing AD continuum.

Nowadays, CSF analysis is a clinical technique to identify AD biomarkers in patients. However, CSF sampling is invasive and laborious, making it inappropriate for most adults for mass screening of early-stage dementia. Therefore, noninvasive biofluids can be alternatives to study core and promising biomarkers of Alzheimer's disorder for diagnostic and research objectives. In addition to biochemical effects, abnormal physical and physiological behaviors may reveal the disease's status in AD pathology. Nonetheless, there are still several challenges to detecting the disease by these markers and their clinical utility, including the lack of standardization, specification, conflicting results in different experiments, and processing protocols. Furthermore, the fact that physical or behavioral activities have various unknown interfering factors in daily life emphasizes the

essential of comprehensive research on these parameters to be specified in the preclinical detection.

All these requirements highlight the importance of developing high-performance, reliable, and cost-effective platforms, not only for diagnostic tests but also for advancing research objectives (i.e., disease diagnosis and drug delivery tests for treatment). For this purpose, the utilization of advanced technologies such as MEMS and emerging optical systems can enable miniaturization and precision, leading to a new generation of bio-devices that can detect AD biomarkers at an early stage. Additionally, the integration of wearable systems with diverse micro/nanoscale sensors (for simultaneous quantification of biological and physical changes) can enable continuous detection of different types of Alzheimer's hallmarks. In the initial concept, this has the potential to uncover links between biological and physical characteristics of AD, alongside their association with the disease progression. This can be highly valuable for screening and early diagnosis of this neurological condition in POCT. The consideration is particularly significant regarding the challenges faced by the elderly population in undergoing multiple tests and the similarity of initial symptoms to the effects of normal aging.

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