

Review

Enhancing Biological Field Effect Transistors (Bio-FETs) Performance for Alzheimer's Disease Diagnostics: Microfluidics and Artificial Intelligence Integration

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Abstract: Alzheimer's disease (AD) diagnostic workflows are undergoing a paradigm shift from symptom-centric cognitive assessment to biomarker-guided pathological stratification, fuelling an urgent need for minimally invasive analytical tools to quantify ultralow-concentration pathological markers within peripheral biofluids. Biological field-effect transistors (Bio-FETs) stand out as competitive label-free transducers for ultrasensitive biomolecular detection; nevertheless, persistent drawbacks including unstable solid-liquid interfaces, severe signal drift, and limited multiplexing capacity impede their real-world clinical deployment. This review first outlines high-specificity circulating AD biomarkers and elaborates the fundamental transduction principles of Bio-FET sensors, before systematically dissecting two complementary hardware–software strategies to mitigate intrinsic device defects: microfluidic chip integration and artificial intelligence (AI)-assisted data processing. Microfluidic engineering standardizes pre-analytical sample manipulation, precisely regulates on-chip biochemical reactions, and facilitates monolithic sensor integration, whereas AI algorithms streamline microchannel layout optimization, refine biomolecular signal deconvolution, suppress electronic noise, and unify device quality management. Jointly, the combinatorial microfluidic-AI framework creates a clinically feasible route for decentralized, multiplexed, high-fidelity liquid biopsy screening of early Alzheimer's disease.

Keywords: Alzheimer's disease; biomarkers; Bio-FET biosensor; microfluidics; artificial intelligence

1. Introduction

The clinical diagnosis and management of Alzheimer's disease (AD) are undergoing a landmark paradigm transition from symptom-dependent cognitive evaluation to biomarker-guided pathological stratification, as formalized by the classic Amyloid/Tau/Neurodegeneration (ATN) research framework proposed by the NIA-AA workgroup [1–4]. Per the unified NIA-AA diagnostic consensus, the identification of prodromal AD hinges on accurate quantification of core pathological markers, including cerebrocortical amyloidosis reflected by the plasma $A\beta_{42}/A\beta_{40}$ ratio and tau phosphorylation represented by p -tau₁₈₁ and p -tau₂₁₇, alongside markers indicative of progressive neuronal loss [1,5]. To fully delineate the heterogeneous multi-pathological cascades underlying AD onset and progression, contemporary diagnostic pipelines have integrated emerging peripheral biomarkers, such as neurofilament light chain (NfL) for axonal injury, glial fibrillary acidic protein (GFAP) for astrocytic reactivity,



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soluble TREM2 (sTREM2) for neuroinflammation, and tissue-specific microRNAs that reflect epigenetic remodeling [6–8]. Detecting these molecular fingerprints in accessible peripheral biofluids enables a minimally invasive, low-cost diagnostic modality, circumventing the drawbacks of invasive cerebrospinal fluid (CSF) lumbar puncture and expensive positron emission tomography (PET) neuroimaging [5]. However, the clinical deployment of peripheral liquid biopsy strategies faces substantial translational barriers originating from the intricate composition of biofluid matrices. These AD-specific biomarkers exist at ultralow concentrations ranging from attomolar (aM) to femtogram-per-milliliter (fg/mL), while their signals are masked by a massive excess of high-abundance endogenous proteins with concentrations over nine orders of magnitude higher, imposing formidable analytical limitations on conventional detection technologies [9].

To tackle the aforementioned analytical bottlenecks in AD liquid biopsy, biological field-effect transistors (Bio-FETs) have evolved as ultra-sensitive bioelectronic transducers for capturing trace pathological biomarkers at early disease stages [10–12]. Structurally, Bio-FETs represent three-terminal solid-state sensors constructed by coupling semiconductor channels with high-specificity biorecognition elements, including antibodies, oligonucleotide aptamers, and biocatalytic enzymes [13,14]. The signal conversion relies on the solid-liquid interfacial region, where specific biomolecular binding rearranges local surface charge and modulates the electrostatic potential of the underlying semiconductor layer; such interfacial electrostatic perturbation is directly converted into real-time electrical readouts. Distinct from conventional optical detection, this label-free transduction scheme eliminates cumbersome multi-step fluorescent labeling and amplification workflows, enabling rapid, ultrasensitive quantification of target biomolecules [11]. Benefiting from the above merits, Bio-FET-based sensing technologies have driven remarkable progress spanning clinical pathology testing, personalized disease surveillance, and environmental biomonitoring.

Low-dimensional nanomaterials, including one-dimensional silicon nanowires (SiNWs) and carbon nanotubes (CNTs) as well as two-dimensional atomic-layer materials (graphene and transition metal dichalcogenides, TMDs), endow Bio-FETs with outstanding electrostatic properties to support direct label-free potentiometric transduction and superior transconductance [11,13,15]. Such remarkable electrostatic responsiveness renders Bio-FETs uniquely suited for quantifying AD-associated biomarkers (p -tau₂₁₇, $A\beta_{42}$, neurogranin) that exist at attomolar concentrations, close to the detection threshold in peripheral biofluids [3,16]. Benefiting from their ultrahigh surface-to-volume ratio, nanostructured semiconductor channels can generate robust electrostatic gating effects over the whole conductive path upon binding with trace charged target proteins [17]. This core physical mechanism converts subtle biomolecular recognition events into distinguishable macroscopic electrical signals without pre-amplification of analytes. Compared with mainstream centralized laboratory techniques such as enzyme-linked immunosorbent assay (ELISA) and single-molecule array (Simoa), the inherent electronic amplification of Bio-FETs eliminates bulky optical components, intricate enzymatic reaction sequences, and multi-stage fluorescent labeling workflows [18,19]. In addition, mature complementary metal-oxide-semiconductor (CMOS) manufacturing technologies allow the fabrication of high-density Bio-FET sensor arrays on monolithic silicon substrates [14]. Such compatibility with industrial semiconductor processes enables scalable, low-cost production of compact, all-in-one diagnostic chips tailored to decentralized point-of-care (POC) AD screening [20].

Although Bio-FETs exhibit remarkable capacity for AD biomarker detection, their practical clinical deployment is fundamentally hampered by interconnected biophysical, chemical, and electrochemical constraints originating from the transducer–electrolyte interface [21–23]. To rationally contextualize these challenges, the clinical biomarker profiles and baseline transduction physics discussed in this review are systematically structured to highlight how integrated microfluidic hardware and artificial intelligence (AI) software specifically resolve these intrinsic bottlenecks. Specifically, conventional Bio-FET transducers deployed in crude physiological biofluids suffer from four pervasive operational limitations: (1) Severe Debye electrostatic screening, where high-salinity matrices ($I > 150$ mM) construct an electrical double layer (EDL) that shrinks the effective sensing Debye length (λ_D) to less than 1 nm and masks biomarker charges [21,24,25]; (2) Mass-transport constraints in laminar flow regimes, which severely delay analyte diffusion and binding kinetics at femtomolar-to-attomolar concentrations; (3) Non-stationary baseline drift and low-frequency $1/f$ flicker noise, which obscure subtle potentiometric binding signals over continuous operation; and (4) Device-to-device fabrication heterogeneity inherent to low-dimensional nanostructured channels (e.g., graphene or carbon nanotubes). To mitigate these interfacial physical and operational limitations, contemporary Bio-FET development has centered on intelligent sensing frameworks that fuse microfluidic hardware with machine learning (ML) computational tools [26,27]. In this review, we systematically examine these two mutually reinforcing technical pathways. On the hardware frontend, microfluidic lab-on-a-chip systems enable automated on-chip desalting, dynamic boundary-layer mixing, biomolecular enrichment, and standardized parallel sample delivery. On the software backend, AI and ML pipelines drive microchannel hydrodynamic optimization, suppress electronic flicker noise, compensate for

continuous baseline drift, correct for structural chip-to-chip variances, and deconvolve complex multi-biomarker profiles. Furthermore, we outline critical translational hurdles—including the batch-to-batch reproducibility of nanostructured channel materials and the necessity for large-scale multi-cohort clinical validation—and propose future engineering pathways toward compact, fully integrated Bio-FET platforms for decentralized early-stage Alzheimer’s disease liquid biopsy screening.

To ensure a comprehensive and objective overview, a systematic literature search was conducted across PubMed, Web of Science, and IEEE Xplore databases for articles published between January 2015 and February 2026. The search strategy utilized combinations of primary keywords including: (“field-effect transistor” OR “Bio-FET” OR “graphene transistor”) AND (“Alzheimer’s disease” OR “*p*-tau217” OR “ $A\beta_{42}/A\beta_{40}$ ” OR “GFAP” OR “NfL”) AND (“microfluidics” OR “lab-on-a-chip”) AND (“machine learning” OR “artificial intelligence” OR “baseline drift compensation”). Only peer-reviewed journal articles written in English were included.

2. The New Landscape of Alzheimer’s Disease Biomarkers: High-Specificity Targets

The clinical practicability of advanced Bio-FET sensing systems relies on multiplexed biomarker panels capable of distinguishing AD neuropathology from other neurodegenerative disorders via minimally acquired blood specimens. Such panels must deliver superior diagnostic specificity to discriminate Alzheimer’s disease from clinically similar pathologies, including frontotemporal dementia, Parkinson’s disease, and vascular cognitive impairment. To accommodate the dynamic, complex pathology of Alzheimer’s disease (AD), the original 2018 National Institute on Aging–Alzheimer’s Association (NIA-AA) ATN framework—encompassing Amyloid- β (A), Tau (T), and Neurodegeneration(N)—was expanded in the 2023 revised diagnostic criteria into the ATNISV framework. This updated system incorporates three additional physiological domains: Inflammatory/immune(I) response, Structural/vascular(S) injury, and Synaptic/neuronal dysfunction(V). By categorizing fluid and imaging biomarkers across these six distinct partitions, the ATNISV matrix provides a standardized biological classification system that enables precise staging across the complete AD continuum, from preclinical asymptomatic phases to overt clinical dementia (Figure 1). Current biosensing development has gradually moved beyond non-specific pan-neuronal injury markers toward molecular analytes closely linked to the canonical amyloid and tau pathological cascades. Hyperphosphorylated tau isoforms, especially *p*-tau₁₈₁ and *p*-tau₂₁₇, stand out as ultrasensitive circulating readouts that mirror early cortical amyloid- β ($A\beta$) aggregation and neurofibrillary tangle formation [28,29]. The plasma $A\beta_{42}/A\beta_{40}$ ratio serves as another core metric for quantifying cerebral amyloid plaque burden at preclinical disease stages. In addition, glial fibrillary acidic protein (GFAP), a marker of reactive astrogliosis and neuroinflammation, exhibits strong predictive performance when combined with amyloid and tau biomarkers in multiplexed detection panels [3,29,30]. Quantification of these low-concentration, disease-specific analytes in heterogeneous peripheral biofluids imposes stringent requirements on Bio-FET platforms, which must simultaneously attain ultralow limits of detection and reliable differentiation of multiple target biomolecules.

This review strategically focuses on high-specificity, ultra-low-abundance biomarkers in peripheral blood, a scope that uniquely leverages the femtomolar sensitivity and label-free capabilities of Bio-FETs. To ensure rigor, these targets are categorized into validated (e.g., plasma $A\beta$, *p*-tau_{181/217}, NfL with established Bio-FET detection), emerging (e.g., plasma GFAP, *p*-tau₂₃₁ with preliminary validation), and potential tiers. Notably, plasma *p*-tau₂₀₅ is explicitly classified as a potential target; while it exhibits exceptional clinical specificity for tauopathy, its direct detection via Bio-FETs remains a prospective frontier awaiting empirical validation rather than an established capability. This restructuring clarifies that current Bio-FET success is limited to specific validated markers, while others like *p*-tau₂₀₅ represent critical future opportunities.

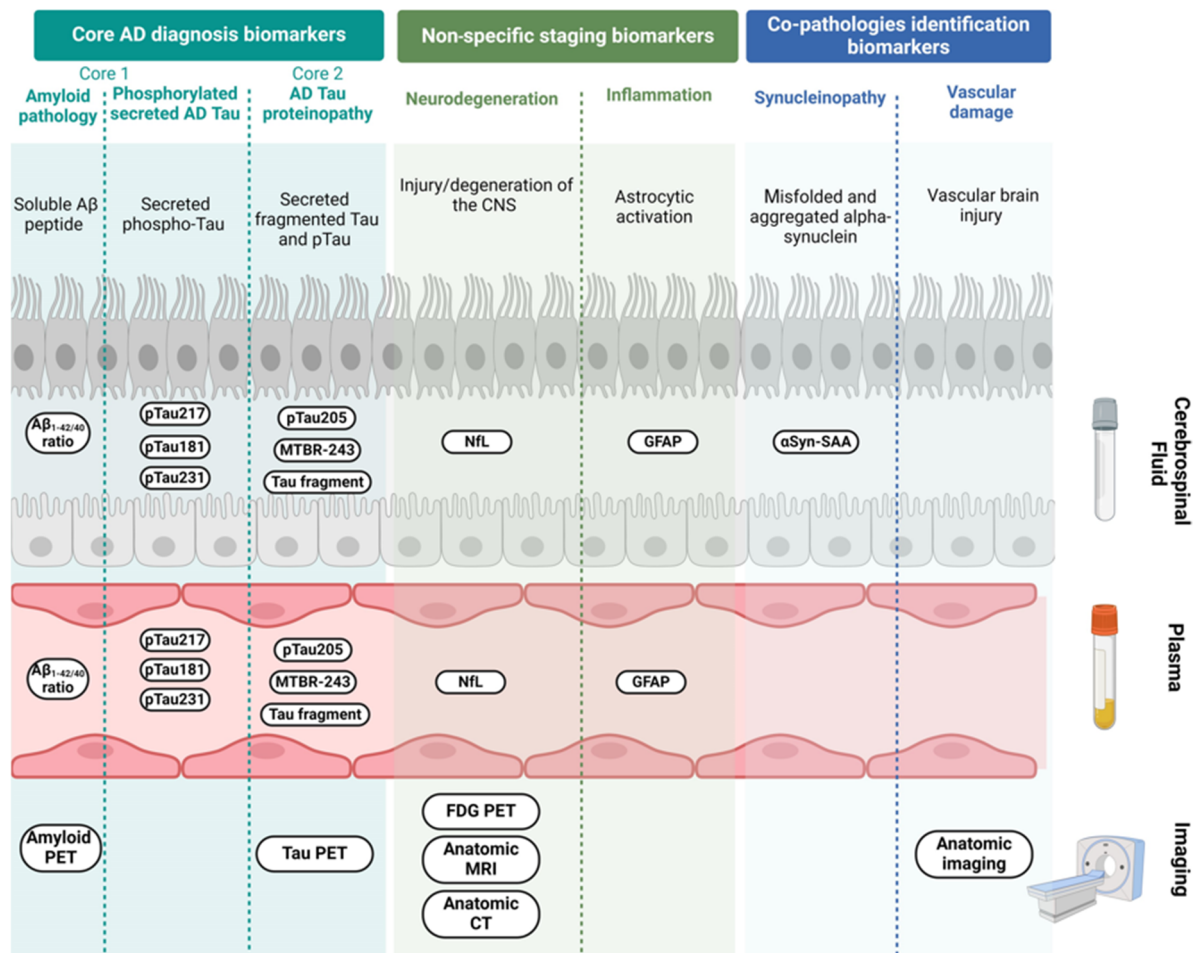


Figure 1. ATNISV pathological classification and mainstream diagnostic modalities for Alzheimer's disease (AD). The 2023 revised ATNISV framework—encompassing Amyloid- β (A), Tau(T), Neurodegeneration(N), Inflammatory/immune(I), Structural/vascular(S), and Synaptic/neuronal dysfunction(V)—expands upon the initial NIA-AA ATN criteria with four categorical partitions, allowing improved delineation of the complete AD pathological spectrum and standardized integration of fluid and imaging biomarkers. Reprinted from [31], under the terms of the Creative Commons Attribution License.

2.1. Phosphorylated Tau-217(*p-tau*₂₁₇)

As one of the most promising liquid biopsy analytes, phosphorylated tau 217 (*p-tau*₂₁₇) is acknowledged as the most pathologically specific circulating biomarker for Alzheimer's disease [3,29]. From a pathophysiological perspective, *p-tau*₂₁₇ acts as a key molecular mediator linking cerebral amyloid- β (*Aβ*) deposition to subsequent tau-driven neuronal degeneration. Notably, plasma *p-tau*₂₁₇ concentrations increase at an extraordinarily preclinical stage of AD, with elevations detectable up to two decades prior to the emergence of clinical cognitive deficits and far earlier than observable neocortical neurofibrillary tangle formation [32,33]. Such early elevation strongly correlates with the spatiotemporal progression of brain *Aβ* plaques validated via amyloid positron emission tomography (PET), providing a valuable molecular readout to track the incipient pathogenic cascade of AD [34]. In clinical practice, plasma *p-tau*₂₁₇ exhibits superior diagnostic performance relative to other tau isoforms including *p-tau*₁₈₁ and *p-tau*₂₃₁. It delivers over 95% diagnostic accuracy for discriminating AD from non-AD tauopathies and vascular cognitive disorders, effectively reducing misdiagnosis rates across demographically diverse patient cohorts [35,36].

Despite the prominent diagnostic value of plasma *p-tau*₂₁₇, its routine clinical quantification is hindered by its ultralow physiological concentration, which generally falls within the sub-picogram to low-picogram per milliliter range in peripheral blood [37,38]. Capturing such sub-femtomolar biomolecular interactions without pre-amplification of target analytes poses substantial engineering obstacles to Bio-FETs development. Reliably transducing these weak localized biorecognition signals mandates Bio-FET architectures with maximized channel transconductance (gm) and finely tuned solid-liquid interfacial chemistry. Additionally, sophisticated signal conditioning modules for noise attenuation and baseline stabilization are indispensable to shield faint biomarker readouts from thermal drift and low-frequency 1/*f* flicker noise interference [39,40].

2.2. Amyloid-Beta 42/40 Ratio ($A\beta_{42}/A\beta_{40}$ Ratio)

The plasma $A\beta_{42}/A\beta_{40}$ ratio constitutes a core metric for blood-sourced Alzheimer's disease diagnosis, serving as a robust non-invasive surrogate for cerebral amyloid deposition. Early mass spectrometric analyses have validated tight quantitative correlations between peripheral $A\beta_{42}/A\beta_{40}$ values and the gold-standard amyloid PET as well as cerebrospinal fluid (CSF) $A\beta_{42}/A\beta_{40}$ readouts [41,42]. Owing to the strong hydrophobicity of $A\beta_{42}$, this peptide readily undergoes self-aggregation and accumulates as insoluble amyloid plaques inside brain tissue, leading to a selective reduction of circulating $A\beta_{42}$ relative to the more stable, abundant $A\beta_{40}$ isoform. Tracking this relative concentration shift, instead of quantifying individual $A\beta$ species alone, delivers a resilient biomarker signature for the detection of preclinical amyloid pathology [43]. Such ratiometric quantification intrinsically offsets interindividual discrepancies in baseline peptide levels and systemic metabolic clearance, eliminating analytical bias commonly observed with single-marker detection and yielding liquid biopsy outcomes highly consistent with amyloid PET findings [44].

A core technical bottleneck restricting Bio-FET-based quantification of the $A\beta_{42}/A\beta_{40}$ ratio originates from the high sequence homology between $A\beta_{42}$ and $A\beta_{40}$; the two peptides differ merely at two hydrophobic C-terminal residues (isoleucine and alanine). Distinguishing such subtle structural disparities through potentiometric readouts imposes stringent requirements on the molecular specificity of the sensor solid-liquid interface. To mitigate interfering cross-reactive signals, Bio-FET surfaces are typically modified with high-selectivity biorecognition elements, including conformation-specific antibodies and custom-designed DNA aptamers that selectively bind the distinct steric conformations of each peptide's C-terminal domain [10,45,46]. Additionally, active microfluidic splitting modules can be monolithically integrated with sensor arrays to mitigate run-to-run deviations and chronic baseline drift. Such architectures allow a single blood specimen to be evenly partitioned into multiple parallel independent transistor channels [47]. Synchronized real-time quantification of $A\beta_{42}$ and $A\beta_{40}$ on a unified chip consequently generates a standardized, self-referenced $A\beta_{42}/A\beta_{40}$ readout, which is well-suited for point-of-care AD screening applications.

2.3. Phosphorylated Tau-205 ($p\text{-tau}_{205}$)

Phosphorylated tau 205 ($p\text{-tau}_{205}$), recognized as a representative tauopathy biomarker within the updated 2023 ATNISV framework, has emerged as a promising circulating indicator for staging AD pathology. Mechanistically, $p\text{-tau}_{205}$ is closely associated with the formation and propagation of cortical neurofibrillary tangles (NFTs) and thus reflects more advanced tau aggregation following the initial phases of amyloid- β deposition and early tau phosphorylation [48,49]. In contrast to $p\text{-tau}_{217}$, which becomes elevated during the preclinical phase of AD, plasma $p\text{-tau}_{205}$ appears to increase predominantly during the middle-to-late prodromal stages, in parallel with the extension of tau pathology into neocortical regions and progression to higher Braak stages [50,51]. Moreover, peripheral $p\text{-tau}_{205}$ levels show a strong correspondence with the cerebral burden and topographical distribution of NFTs as assessed by tau positron emission tomography (PET), supporting its utility for tracking the progression of established tau pathology [48]. A recent meta-analysis shows plasma $p\text{-tau}_{205}$ still possesses moderate diagnostic accuracy for AD, with a pooled sensitivity of 76.6% and specificity of 86.0% [52]. Although its sensitivity for detecting preclinical AD is lower than that of $p\text{-tau}_{217}$, $p\text{-tau}_{205}$ provides complementary value when combined with earlier amyloid- and tau-related biomarkers, thereby enabling more refined pathological stratification across the AD continuum.

Although $p\text{-tau}_{205}$ is a vital tauopathy biomarker for multi-parametric AD liquid biopsy, dedicated Bio-FET platforms for circulating $p\text{-tau}_{205}$ quantification remain underexplored. Featuring label-free electrostatic transduction, ultrahigh sensitivity and microfluidic multiplexing capacity, Bio-FETs support synchronous measurement of $p\text{-tau}_{205}$ alongside canonical AD biomarkers to achieve comprehensive pathological assessment across the AD continuum, ranging from early $A\beta$ deposition to mature neurofibrillary tangle progression [53]. However, multiple technical obstacles restrict reliable clinical detection of $p\text{-tau}_{205}$ using Bio-FETs. Its ultralow plasma concentration demands high-performance sensors to resolve faint binding signals in high-ionic, protein-rich plasma. Parallel quantification of homologous tau isoforms ($p\text{-tau}_{181}$, $p\text{-tau}_{217}$, $p\text{-tau}_{205}$) also raises risks of antibody cross-reactivity stemming from neighboring phosphorylation epitopes, impairing multiplexed detection specificity [54]. Furthermore, sensor signals are susceptible to non-specific adsorption, thermal drift and low-frequency flicker noise [55]. Rational surface biofunctionalization for epitope-specific recognition combined with AI-driven signal deconvolution and noise suppression can mitigate these challenges. Integrating $p\text{-tau}_{205}$ into multiplexed Bio-FET panels enables refined AD pathological stratification, promising precise diagnosis and longitudinal monitoring of disease progression.

2.4. Glial Fibrillary Acidic Protein (GFAP)

Phosphorylated tau (*p*-tau) and amyloid- β (*A β*) constitute the cornerstone circulating biomarkers for evaluating canonical Alzheimer's disease (AD) pathological lesions. Nevertheless, accumulating clinical cohort evidence has identified glial fibrillary acidic protein (GFAP)—an intermediate filament protein exclusive to astrocytes—as a sensitive and robust indicator reflecting early pathological transformation during AD progression. Amid the evolving framework of AD liquid biopsy, GFAP acts as a pivotal reactive biomarker that links cerebral neuroinflammatory cascades to upstream amyloid- β plaque deposition. Distinct from non-specific markers of axonal degeneration, peripheral GFAP concentrations correlate dynamically with early reactive astrogliosis and deliver over 90% accuracy for AD diagnosis and differential discrimination [56]. GFAP exhibits unique responsiveness to astrocytic overactivation, a pathological event directly initiated by nascent cerebral *A β* plaque accumulation, which sets it apart from pan-axonal injury biomarkers [57,58]. Such superior sensing capacity renders plasma GFAP a powerful peripheral predictor of total brain amyloid load, facilitating reliable risk stratification for patients prone to subsequent clinical dementia long before cognitive impairment manifests. From a translational perspective, integrating GFAP into multi-biomarker detection panels substantially improves overall diagnostic performance and provides non-invasive access to track neuroinflammatory signaling pathways that govern the early progression of AD [59].

Although plasma GFAP concentrations in AD patients exceed 54.1 pg/mL—several orders of magnitude higher than circulating *p*-tau₂₁₇ levels—GFAP imposes unique analytical obstacles when measured via Bio-FET sensors due to its intrinsic interfacial binding characteristics [60]. GFAP monomers intrinsically tend to self-polymerize into intricate intermediate filament networks. Upon immobilization at the solid–liquid interface, such polymeric assemblies generate uneven surface charge distribution and random molecular alignment relative to the semiconductor channel [61]. Such heterogeneous molecular configurations severely compromise the repeatability of potentiometric electrical responses. To address this analytical limitation and achieve stable signal transduction, Bio-FET sensing surfaces require precisely engineered surface modification schemes, among which nanostructured self-assembled monolayers (SAMs) represent a viable solution [62–64]. By finely regulating surface ligand coverage and the spatial orientation of recognition receptors, rationally designed SAM interfaces suppress localized GFAP aggregation, alleviate non-specific macromolecular biofouling, and homogenize heterogeneous polymer binding behaviors to yield consistent, quantifiable electrical outputs.

2.5. Neurofilament Light Chain (NfL)

Phosphorylated tau (*p*-tau) and amyloid- β (*A β*) are etiopathologically specific signature biomarkers for Alzheimer's disease (AD). By contrast, neurofilament light chain (NfL)—a fundamental structural protein constituting the axonal cytoskeleton—acts as a highly sensitive pan-biomarker for generalized neuroaxonal damage across neurological disorders [65,66]. During AD progression, peripheral NfL concentrations increase progressively alongside continuous axonal breakdown and white matter tract destruction. Distinct from *p*-tau₂₁₇ and GFAP that closely mirror AD-specific pathological cascades, NfL exhibits limited disease selectivity; its plasma elevation is observed in a broad spectrum of neurological injuries, such as traumatic brain injury, multiple sclerosis, and frontotemporal dementia [67,68]. Despite insufficient diagnostic specificity for AD alone, NfL possesses unmatched sensitivity for long-term prognostic monitoring. Circulating NfL concentrations exhibit robust correlations with the progression of whole-brain atrophy, ventricular enlargement, and longitudinal cognitive deterioration. From the perspective of biosensing translation, integrating NfL into multiplexed Bio-FET detection panels delivers a quantitative readout for tracking neurodegeneration progression and therapeutic efficacy over time, which complements the pathological stratification capacity of amyloid and tau biomarkers [69,70].

From a biophysical perspective, NfL is an elongated, highly anisotropic fibrous protein with a central α -helical coiled-coil rod domain, capped by a negatively charged C-terminal tail enriched with glutamic acid residues [71]. Owing to its large aspect ratio and asymmetric architecture, randomly immobilized NfL molecules adopt disordered orientations at the solid–liquid interface. This irregular molecular arrangement situates the protein's dominant charge-bearing regions at uneven distances away from the semiconductor channel. A considerable fraction of bound NfL molecules therefore protrudes beyond the confined Debye screening length (λ_D), which severely weakens potentiometric gating efficiency and introduces severe signal fluctuations [72]. To mitigate this spatial sensing limitation, Bio-FET surfaces require rationally designed, site-specific surface modification schemes. The combination of well-ordered, low-density self-assembled monolayers (SAMs) and domain-targeted affinity ligands (e.g., nanobodies that selectively bind the charged C-terminal segments) confines captured NfL molecules in a well-aligned conformation proximal to the transistor channel. Such precise spatial arrangement strengthens electrostatic coupling within the Debye screening region, alleviates steric hindrance effects, and

transforms heterogeneous axonal injury molecular signatures into stable, quantifiable electrical outputs with excellent repeatability.

It is important to note that the quantitative metrics cited throughout this review—including diagnostic accuracy (AUC), sensitivity/specificity percentages, and detection limits (fM/aM)—are derived from representative studies and current state-of-the-art reports in the field. While these values demonstrate the high potential of Bio-FET technology, the underlying evidence for many of these specific claims primarily stems from small-scale, single-center, or proof-of-concept cohorts. Consequently, while the reported figures reflect the current technical capabilities, they should be interpreted as preliminary benchmarks rather than definitive clinical standards. We explicitly acknowledge that large-scale, multi-center longitudinal studies are required to validate these metrics across diverse populations and to confirm their robustness in real-world clinical settings. Future research must prioritize these rigorous validation steps to transition from promising experimental data to clinically approved diagnostic criteria.

3. Overview of FET-Based Biosensors

3.1. Device Architecture: Constituent Materials and Structural Modules

From the perspective of biomedical microelectronics, biological field-effect transistors (Bio-FETs) are three-terminal microelectronic devices composed of source, drain, and gate electrodes, wherein nanostructured semiconductor channels function as core signal transducers [11]. The working mechanism is governed by tunable charge transport: externally applied gate bias generates an electric field to modulate the concentration of charge carriers inside the channel, thus adjusting the steady-state drain-source current [73]. When biased within the sensitive linear operating region, the conductive channel exhibits extreme susceptibility to subtle external electrostatic disturbances. Such structural design enables Bio-FETs to serve as high-performance solid-state transducers, converting dynamic biochemical interactions at the solid-liquid interface into readable analog electrical outputs without optical labeling or secondary signal amplification [74].

To tailor transducers for clinical liquid biopsy scenarios, semiconductor channels are fabricated from low-dimensional nanomaterials to fully expose active sensing surfaces to analyte-containing media. One-dimensional (1D) nanomaterials including silicon nanowires and carbon nanotubes deliver ultrahigh surface-to-volume ratios; electrostatic signals generated by captured biomolecules can permeate and modulate the entire conductive pathway of the channel [75,76]. In comparison, two-dimensional (2D) nanomaterials feature atomically thin planar geometries that strengthen capacitive coupling with liquid matrices [77] (Figure 2). Graphene exhibits outstanding carrier mobility and fast signal response, yet the absence of an intrinsic bandgap introduces prominent leakage current and background noise. By contrast, transition metal dichalcogenides (e.g., molybdenum disulfide) possess inherent bandgap structures capable of restraining baseline noise and boosting transconductance, rendering them promising candidates for low-power, high-sensitivity point-of-care diagnostic chips [15].

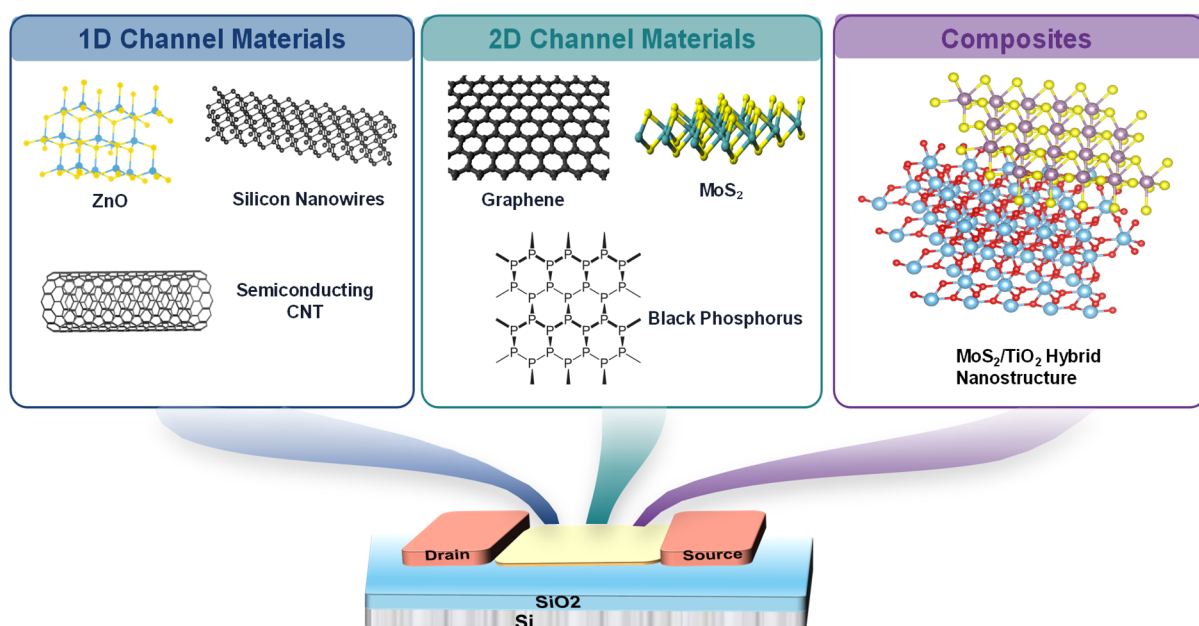


Figure 2. Overview of representative one-dimensional (1D) and two-dimensional (2D) nanomaterials for FET biosensor channel construction.

Surface biofunctionalization of the semiconductor-electrolyte interface with target-specific biorecognition elements endows Bio-FETs with clinical detection capacity. Specific binding between biomarkers and immobilized receptors triggers local charge rearrangement and reorientation of molecular dipoles at the sensing surface. Such biomolecular recognition modulates interfacial potential, imposes capacitive gating on the underlying semiconductor channel, and shifts the transistor threshold voltage accordingly [72,78]. Nevertheless, measurement in high-ionic-strength clinical biofluids (whole blood, cerebrospinal fluid, etc.) leads to the accumulation of mobile counterions at the interface to form an electrical double layer (EDL). The EDL imposes electrostatic shielding that isolates the intrinsic charge of bound biomarkers from the semiconductor channel. The critical spatial range of this shielding effect is defined as the Debye length, which confines the effective sensing region to an ultrathin nanoscale layer [79]. For reliable clinical detection, rational structural design is required to anchor target-receptor complexes within this nanometer-scale active zone, thereby avoiding signal attenuation caused by electrostatic shielding that would otherwise disable biosensor responsiveness to disease biomarkers.

3.2. Transduction Mechanism: Interfacial Electrostatics and Physical Behaviors

Bio-FET sensing originates from field-effect electrostatic modulation occurring at the solid–liquid interface. Charged biomolecules captured via specific biorecognition act as localized chemical gates to tune semiconductor band bending and the density of charge carriers within the channel [22]. For p-type semiconducting channels, the adsorption of negatively charged biomolecules triggers upward band bending, enriches majority hole carriers, elevates channel conductance, and shifts the threshold voltage toward positive values. Conversely, negatively charged analytes deplete free electrons in n-type channels through downward band bending, leading to reduced electrical conductivity (Figure 3). The magnitude of threshold voltage shift exhibits a quantitative correlation with surface biomolecular charge density and interfacial capacitance, laying the theoretical foundation for label-free signal transduction in Bio-FET devices [76,80,81].

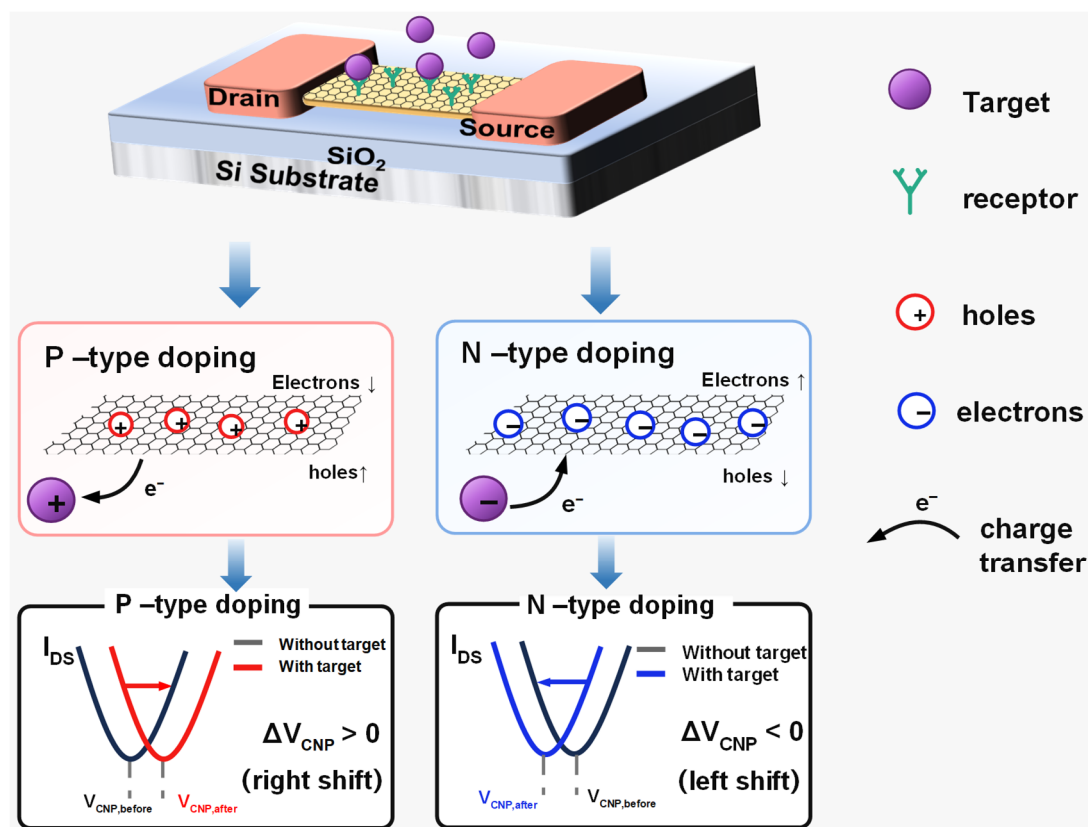


Figure 3. Working principle of graphene-based Bio-FETs relying on interfacial charge transfer. The specific binding of charged target molecules triggers charge exchange at the graphene surface, altering carrier concentrations in p-type and n-type graphene channels. This effect drives characteristic shifts of the charge neutral point (V_{CNP}), enabling label-free quantification of biomolecular targets.

Unfortunately, Debye electrostatic screening originating from electrolyte media drastically impairs the analytical performance of conventional Bio-FETs when deployed in clinical biofluids. Dissolved ions self-

organize into interfacial Stern and diffuse layers that insulate the intrinsic charge of captured biomolecules. The effective screening distance, defined as the Debye length, follows an inverse correlation with the ionic strength of aqueous solutions [82]. Clinical matrices with high ionic content, including plasma and cerebrospinal fluid (CSF), compress the Debye length to less than 1 nm. Such severe electrostatic shielding masks most target biomolecular charges, triggering pronounced signal attenuation or false-negative detection outcomes and forming a critical physical barrier hindering clinical translation [82,83]. To mitigate this constraint and reverse sub-Nernstian signal decay in complex biological matrices, asymmetric dual-gate Bio-FET configurations have been proposed as an effective engineering solution [84]. These devices integrate a high-capacitance liquid top-gate and a low-capacitance solid back-gate, allowing stable operation within the subthreshold region, where channel current varies exponentially against minor perturbations of interfacial potential. The inherent capacitive mismatch between the two gate electrodes delivers on-chip electrostatic signal amplification, achieving super-Nernstian sensitivity that surpasses the classic thermodynamic limit of 59.2 mV/dec. This design therefore facilitates ultrasensitive quantification of trace disease biomarkers in crude, unprocessed clinical biofluids [85].

3.3. Application to Alzheimer's Disease: Clinical Translation of Bio-FET Sensors

Bio-FET technologies tackle a critical unmet demand in Alzheimer's disease (AD) clinical management: the development of ultrasensitive, minimally invasive, low-cost diagnostic instruments (Table 1). The ongoing shift toward blood-derived AD biomarkers hinges on quantifying pathogenic proteins including amyloid- β_{42} ($A\beta_{42}$) and phosphorylated tau 217 (p -tau₂₁₇). These species traverse the blood–brain barrier and enter peripheral circulation at ultralow concentrations, generally at the femtogram-per-milliliter scale [86]. Conventional reference immunoassays such as ELISA and single-molecule array (Simoa) suffer from cumbersome multi-step labeling workflows, excessive reagent waste, and reliance on costly centralized laboratory equipment [87]. In contrast, Bio-FETs deliver direct label-free potentiometric signal conversion to overcome the above drawbacks. When engineered with high-transconductance nanomaterial channels (e.g., molybdenum disulfide and graphene) and miniaturized biorecognition probes, Bio-FET devices can capture subtle surface charge shifts triggered by trace target biomolecules. Such combinatorial design achieves ultralow limits of detection reaching femtomolar to attomolar magnitudes directly within complex biological matrices, facilitating the identification of preclinical AD pathology years prior to the emergence of cognitive manifestations [12,88].

Table 1. Representative Bio-FET biosensors for the detection of Alzheimer's disease biomarkers.

Platform	Target	Main Results	Clinical Matrix/Scale
Graphene SGFET	p -tau ₂₁₇	Linear response from 10 fg/mL to 100 pg/mL; 18.6 mV/decade in PBS	Maintained ~90% sensitivity in human serum albumin [88]
CNT FET	$A\beta_{42}/A\beta_{40}$	Reproducible sub-femtomolar detection with dynamic range $> 10^4$	Full human serum; mass-produced semiconducting CNT films [10]
Graphene FET panel	$A\beta_{40}/A\beta_{42}/p$ -tau ₁₈₁ / p -tau ₂₁₇ /NfL	Femtomolar plasma detection plus ML-based AD staging	Multicenter human plasma cohorts; AUC > 0.94 for composite panel [12]
CNT-FET	p -tau ₂₁₇	3 fM–30 pM linear range; 1.66 fM LOD	Mechanism consistent with electrostatic gating; clinical validation still pending [37]

LOD: Limit of Detection; CNT: Carbon Nanotube.

AD exhibits pronounced pathological and clinical heterogeneity, such that single-biomarker measurement fails to deliver robust, precise diagnostic outcomes. Bio-FET arrays are uniquely suited for on-chip multiplexed biomolecular profiling, supporting simultaneous quantification of core biomarkers consistent with the canonical Amyloid-Tau-Neurodegeneration (ATN) diagnostic framework [1,4,89]. High-density transistor arrays can be manufactured on monolithic silicon or graphene substrates via microfabrication patterning and orthogonal surface biofunctionalization. Each independent sensing channel is modified with target-specific biorecognition elements to capture characteristic AD pathological signatures in real time: the plasma $A\beta_{42}/A\beta_{40}$ ratio for evaluating early amyloid peptide aggregation, p -tau₁₈₁ and p -tau₂₁₇ for tracking neurofibrillary tangle propagation, and glial fibrillary acidic protein (GFAP) alongside neurofilament light chain (NfL) for evaluating neuroinflammation and axonal degeneration [89]. This multiplexed sensing paradigm acquires holistic molecular fingerprints from microliter-

scale patient specimens. It reduces false-positive risks inherent to single-analyte detection, enables accurate pathological staging of AD, and offers a practical platform for longitudinal monitoring of therapeutic efficacy.

For point-of-care (POC) deployment, Bio-FET-based systems constitute a revolutionary substitute for invasive cerebrospinal fluid lumbar puncture and expensive amyloid positron emission tomography (amyloid-PET) neuroimaging. Monolithic integration of Bio-FET arrays and microfluidic delivery modules yield robust lab-on-a-chip systems capable of generating rapid digital readouts from a single droplet of lightly processed serum, plasma or whole blood [90–92]. The fully electrical transduction mechanism obviates bulky optical excitation hardware, alignment-dependent photodetectors and labor-intensive pre-analytical sample pretreatment. Further integration with portable smartphone-compatible readout devices and on-chip filtration membranes (for separating target proteins from cellular debris) enables fully decentralized AD testing [91]. Such translational advances narrow the gap between high-end central laboratory testing and routine neurodegenerative disease screening, broadening diagnostic accessibility to primary care facilities, remote rural regions and resource-limited medical infrastructures. Realizing these attractive POC diagnostic capabilities heavily relies on seamless integration of Bio-FET transducers with sophisticated microfluidic lab-on-a-chip architectures.

While this review has emphasized ultra-low limits of detection (LOD) as a primary benchmark for the analytical capability of Bio-FETs, it is critical to acknowledge that high analytical sensitivity does not automatically equate to clinical diagnostic superiority. Real-world clinical utility requires a holistic evaluation that extends beyond LOD to include specificity in complex biological matrices, long-term reproducibility, inter-batch variability, and the rigorous validation of diagnostic cutoffs against established gold standards.

We explicitly recognize that many current Bio-FET prototypes excel in controlled laboratory settings but face significant hurdles in achieving the robustness and reliability required for routine clinical adoption. Future research must therefore shift focus from solely optimizing LOD to systematically addressing these clinical performance dimensions, including external validation in multi-center cohorts. Only through such comprehensive validation can Bio-FET platforms realistically complement or replace existing clinical assays.

4. Microfluidic-Integrated Bio-FET Biosensors

Microfluidic lab-on-chip systems have transformed conventional bioanalytical workflows via miniaturization and automation of laboratory operations within microchannel networks (Table 2). Microfluidic biosensing devices monolithically embed diverse transducers alongside fluid delivery, signal acquisition, transduction and readout modules on compact microfluidic substrates [93]. These platforms precisely manipulate fluid volumes ranging from nanoliters to microliters, enabling rapid high-throughput biomolecular quantification with drastically cut sample and reagent usage. Compared with conventional benchtop analytical assays, microfluidic systems deliver improved detection sensitivity, shorter testing durations and lower operational costs [94,95]. The synergistic fusion of microfluidic circuits and sensing elements further elevates overall analytical performance, supporting robust chemical and biomolecular measurement across a broad spectrum of biomedical applications. Consequently, microfluidic-sensor hybrid architectures have evolved into versatile tools applicable to point-of-care diagnostics, clinical biomarker screening, pharmaceutical development and delivery, as well as basic biological investigation [96–100].

Table 2. Comparative performance metrics between conventional clinical analytical workflows and microfluidic chip platforms.

Feature Category	Conventional Laboratory Assays	Microfluidic Integrated Chip Systems
Reagent consumption & cost	Substantial reagent waste, high operational expenditure	Minimal reagent loading, drastically reduced running costs
Sample input volume	Milliliter-scale specimen demand	Nanoliter–microliter ultra-low sample consumption
Total assay turnaround	Hours up to several days	Completes detection within minutes to several hours
Hardware & manpower requirement	Bulky bench-top instruments; mandatory professional laboratory operators	Miniaturized portable hardware, simplified operation with low training threshold
Deployment scenario	Restricted to centralized core laboratories	Decentralized on-site testing, compatible with point-of-care testing (POCT)

Leveraging the above advantages, microfluidic engineering delivers customized strategies to resolve inherent technical limitations of Bio-FET sensors, boosting their analytical performance and clinical translatability. Microfluidic chips enable precise fluid handling for standardized sample loading, online dilution and regulated biochemical reactions, which construct a stable, reproducible liquid microenvironment for Bio-FET measurement [101]. Such hardware integration supports real-time biomolecular tracking and multiplexed target profiling; automated on-chip processing simultaneously minimizes human-induced operational deviations and enhances assay accuracy and repeatability [102]. As a representative example, microfluidic-graphene FET (GFET) hybrid systems leverage low fabrication costs and high throughput to substantially expand the practical deployment of graphene-based biosensors [39,103]. However, existing prototypes suffer from incomplete system-level integration, where pre-analytical sample purification and separation still rely on external off-chip equipment. Fully integrated microfluidic chips that incorporate on-chip separation, purification and sensing modules are therefore critical to unlock the full translational potential of Bio-FET devices.

Driven by the prominent strengths of microfluidic-sensor co-integrated platforms, extensive research has explored combinatorial designs pairing microfluidic circuits with various biosensing modalities to elucidate underlying biochemical interaction mechanisms [102,104,105] (Figure 4). Screening compatible transducers for lab-on-chip assembly is critical to preserve undistorted target signals, which lays a solid foundation for machine learning algorithms to maximize analytical capacity in subsequent signal decoding. Microfluidic biosensing systems inherently generate high-dimensional, noise-contaminated raw readouts stemming from non-specific adsorption, ionic interference, and device-to-device fabrication variation; artificial intelligence and machine learning provide powerful data-driven strategies to tackle these pervasive analytical bottlenecks via intelligent denoising, automatic feature extraction, cross-reactivity correction, and quantitative signal deconvolution. Moving forward, research on microfluidic biosensors will center on boosting detection throughput, reducing manufacturing expenses, developing novel biorecognition probes and transduction schemes, embedding artificial intelligence pipelines for real-time signal processing and on-chip intelligent decision-making, and expanding application boundaries to home-based health monitoring, drug screening, and food safety surveillance [94].

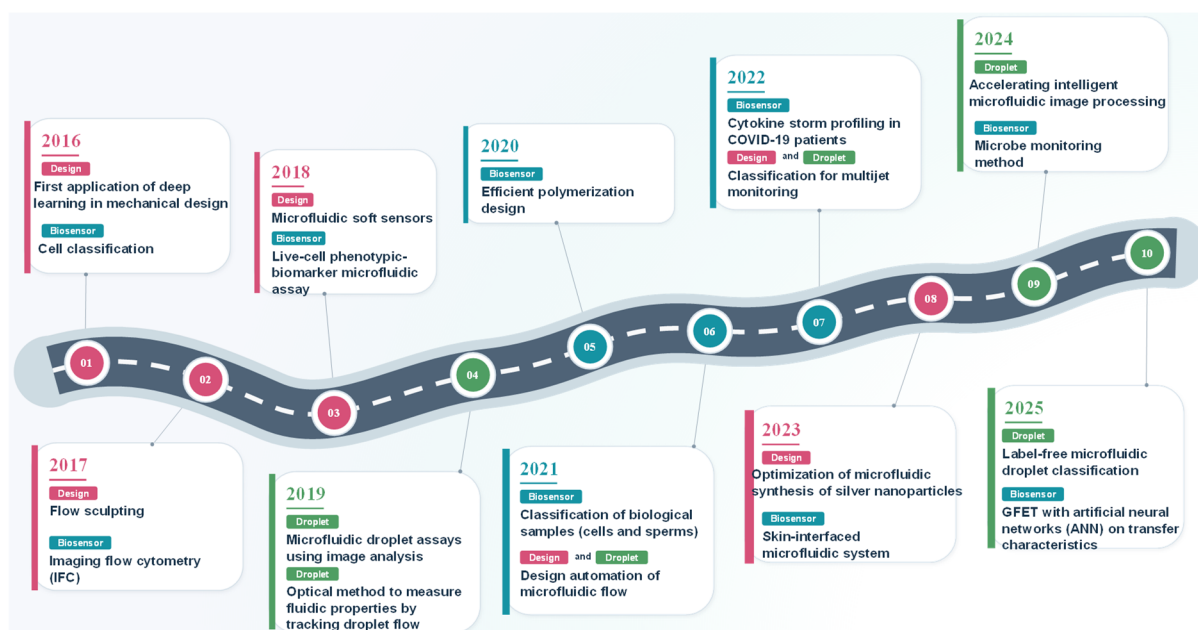


Figure 4. Timeline illustrating key breakthroughs and representative applications of microfluidic biosensing. Adapted from [106], under the terms of the Creative Commons Attribution License.

5. Artificial Intelligence (AI)- and Machine Learning (ML)-Enhanced Bio-FETs

Artificial intelligence (AI) and machine learning (ML) have evolved into core analytical engines that transform low-dimensional Bio-FET transducers into intelligent, self-calibrating platforms by transitioning from single-parameter threshold tracking to multi-dimensional feature extraction [107,108] (Figure 5). In liquid biopsy frameworks for AD, AI/ML integration directly targets three persistent bottlenecks: mass-transport limitations, intrinsic nanoelectronic noise and baseline drift, and signal cross-reactivity [107,109,110]. Crucially, a rigorous distinction must be drawn between experimentally validated AD applications and prospective strategies extrapolated from broader biosensing domains. While multi-marker clinical staging, drift compensation, and

transfer-curve recalibration have been experimentally validated using AD patient plasma, advanced strategies—such as deep-learning-driven microchannel design, wafer-scale defect screening, and generative receptor modeling—remain prospective models derived from related bioelectronic fields that await direct clinical validation in AD biofluids.

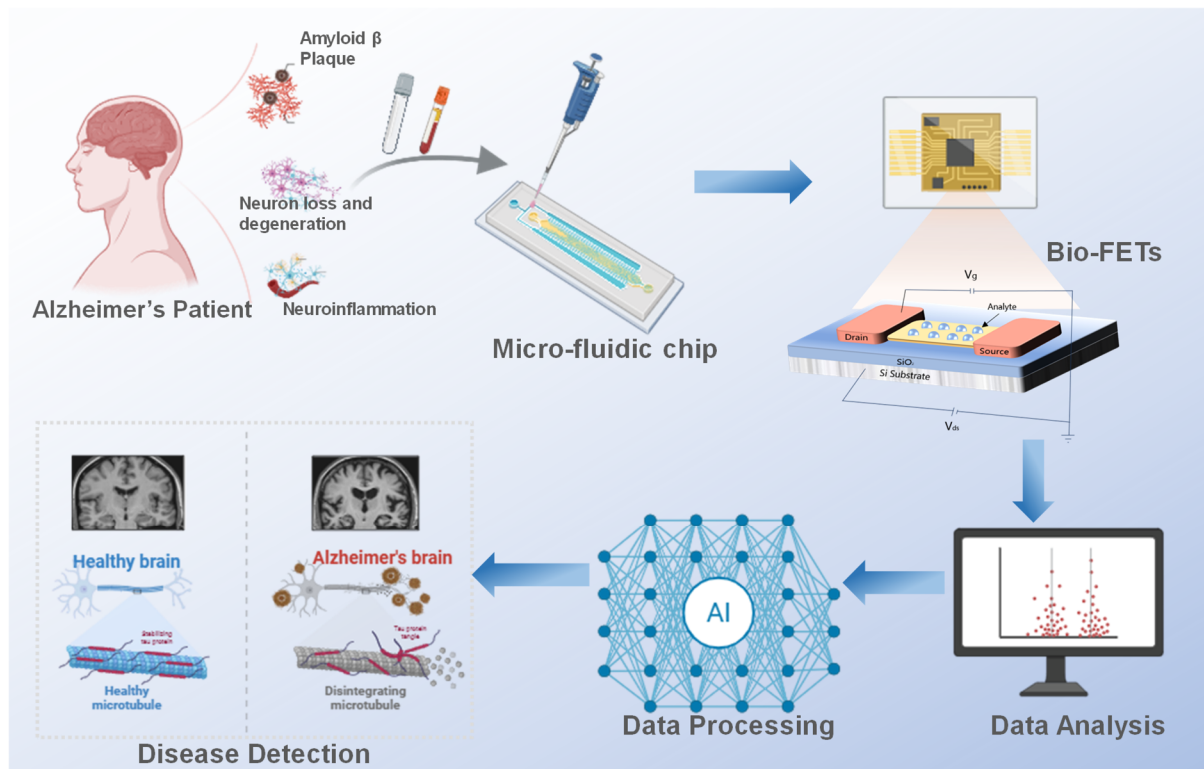


Figure 5. Schematic illustration of the proposed point-of-care testing (POCT) system for Alzheimer's disease enabled by microfluidic Bio-FETs integrated with artificial intelligence (AI).

In microfluidic-integrated Bio-FET platforms, biomolecular capture at the semiconductor interface is often bottlenecked by diffusion-limited mass transport in laminar regimes, where analytes must traverse thick boundary depletion layers before contacting receptor-functionalized channels. Conversely, unoptimized channel geometries generate excessive shear stress that disrupts bound receptor-antigen complexes [106]. To optimize these hydrodynamics, deep learning (DL) architectures—including Convolutional Neural Networks (CNNs, such as U-Net and ResNet topologies) and Gaussian Process Regression (GPR) surrogate models—have served as efficient surrogate models computationally intensive finite-element method (FEM, e.g., COMSOL) simulations [111,112]. Wang et al. recast random microfluidic mixer simulation as an image-recognition problem, using a CNN [113]. Coupled with Bayesian optimization, GPR models iteratively tune obstacle pillar spacing and channel aspect ratios to establish uniform flow velocity profiles [114], accelerate target mass transfer to the Bio-FET surface, and eliminate flow stagnation zones to mitigate non-specific biofouling.

When deployed in raw clinical plasma or cerebrospinal fluid (CSF), Bio-FET transducers suffer from low-frequency $1/f$ flicker noise, thermal baseline drift, hysteresis, and device-to-device structural heterogeneity (e.g., grain boundaries in CVD graphene or chirality variations in carbon nanotubes) that shift the baseline Dirac point (V_{CNP}) or threshold voltage (V_{th}) [115,116]. Rather than relying on single-point electrical shifts, advanced ML algorithms process complete transfer characteristics ($I_{\text{ds}}-V_{\text{gs}}$) or dynamic time-series current ($I-t$) curves [116]. Because individual biomarkers fail to capture the multi-pathological spectrum of AD (combining amyloidosis, tauopathy, neuroinflammation, and neurodegeneration), multi-channel Bio-FET arrays are used to capture composite molecular panels [117]. Supervised ML algorithms act as feature-fusion engines to resolve cross-reactivity among homologous tau isoforms ($p\text{-tau}_{181}$, $p\text{-tau}_{217}$, $p\text{-tau}_{205}$) and non-specific background signals [116] (Table 3).

Table 3. Compiles key performance metrics of state-of-the-art platforms utilizing microfluidic or AI-driven enhancements for Alzheimer's biomarker detection.

Platform/Channel	Target Biomarker(s)	Matrix	Microfluidic/AI Enhancement	Key Translational Contribution	Related Literature
Graphene FET	$A\beta_{42}$, $A\beta_{40}$, p -tau ₂₁₇	Clinical plasma	ANN on full transfer curves	Avoids device-specific recalibration; four-way cognitive-state classification in 72 samples.	[118]
Graphene FET panel	$A\beta_{40}$, $A\beta_{42}$, p -tau ₁₈₁ , p -tau ₂₁₇ , NfL	Plasma	ML biomarker-panel assembly with clinical metadata	Five-marker panel plus age, sex, and education reached AUC > 0.94 for staging	[12]
Microfluidic plasmonic platform	$A\beta_{42}$ monomer, $A\beta_{42}$ oligomer	CSF	Multi-channel microfluidics	Distinguishes $A\beta_{42}$ morphologies using sub- μ L samples and binding kinetics	[27]
Surface-engineered microfluidic platform	$A\beta_{1-42}$, p -tau ₁₈₁	Plasma	Engineered beads, electrostatic bead-microwell pairing, algorithmic calibration	Reduced nonspecific binding and supported longitudinal monitoring in 107 AD and 100 controls	[119]
Smartphone μ PAD	$A\beta_{1-42}$	Artificial plasma	Automated paper microfluidics + YOLOv5	Offline smartphone inference reached 97% accuracy on 1824 images	[120]

ANN: Artificial Neural Network; CSF: Cerebrospinal Fluid.

To overcome the severe batch-to-batch variability caused by structural defects, flake thickness variations, and non-uniform contact resistance in low-dimensional nanomaterial channels, ML pipelines provide automated quality management and interface optimization [121,122]. Computer vision models (e.g., ResNet-18 or VGG-16) trained on spatial optical/AFM images and Raman mapping matrices automatically identify structural defects and monolayer discontinuities across wafer-scale channels [123]. Coupled with automated electrical probing, these classification models automatically flag and exclude out-of-spec transistor channels prior to surface functionalization, dramatically boosting chip yield and array response uniformity [124,125]. Furthermore, ML-guided Molecular Dynamics (MD) surrogate models predict self-assembled monolayer (SAM) packing density and receptor spatial orientation [126,127], helping researchers design surface chemistries that minimize steric hindrance and ensure target biomolecular binding occurs strictly within the Debye screening length.

6. Conclusions and Future Perspectives

Bio-FETs have emerged as a compelling analytical platform for the early screening of Alzheimer's disease (AD), owing to their inherent advantages of label-free transduction, ultrahigh electrostatic sensitivity, and compatibility with high-density multiplexed chip integration. Leveraging these merits, Bio-FETs enable blood-based profiling of multi-dimensional AD biomarker panels covering amyloid deposition, tau pathogenesis, neuroinflammation, and neuroaxonal degeneration, as represented by the $A\beta_{42}/A\beta_{40}$ ratio, phosphorylated tau isoforms, GFAP, and NfL. Unlike single-biomarker detection strategies that fail to accommodate disease heterogeneity, multiplexed Bio-FET systems closely recapitulate the complex pathological spectrum of AD, offering superior capability for accurate disease diagnosis, pathological staging, and longitudinal progression monitoring.

Future research directions should prioritize the development of fully integrated, low-cost, high-throughput lab-on-chip Bio-FET systems that monolithically integrate sample preprocessing, multi-biomarker multiplexed sensing, and intelligent data analytics. The advancement of such compact, intelligent sensing platforms will accelerate the clinical translation of high-performance Bio-FET technology, paving a feasible route toward decentralized point-of-care liquid biopsy for early AD screening and precision neurological healthcare.

Author Contributions

J.W.: conceptualization, writing—original draft preparation; Z.-J.W.: visualization; Z.-A.Z.: investigation; Y.-H.L.: visualization; K.-Y.Y.: validation; J.C.-W.C.: writing—review & editing, supervision. All authors have read and agreed to the published version of the manuscript.

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Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used Gemini to polish language. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the published article.

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