

Recent Advances in Electrochemical Aptamer Sensors: Materials Design, Antifouling Strategies, and Toward Miniaturized and Wearable Applications

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Abstract: Electrochemical aptamer sensors integrate the molecular recognition capability of aptamers with electrochemical or electronic signal readout, offering promising tools for environmental monitoring, clinical diagnostics, point-of-care testing, and continuous molecular monitoring. However, their practical performance is not determined by sensitivity alone. Nonspecific adsorption, interfacial instability, signal drift, impaired electron transfer, and architecture-dependent limitations such as Debye screening remain major barriers to reliable application in complex samples. This review summarizes recent progress in electrochemical aptamer sensors from an architecture- and application-oriented perspective. We first classify major electrochemical aptamer sensor architectures according to their signal-transduction mechanisms, including redox-tagged structure-switching sensors, capture/release or signal-amplified sensors, and field-effect transistor-based aptasensors. We then discuss how electrode fabrication, electrode and interface materials, aptamer immobilization, antifouling strategies, and integrated sensing platforms support or limit these architectures. Rather than evaluating sensors only by detection limit, we highlight the distinct requirements of different analytical scenarios. Endpoint assays may benefit from nanomaterial-enhanced amplification and disposable electrode formats, whereas wearable or implantable monitoring requires reversible recognition, stable baselines, antifouling protection, and calibration-free or calibration-minimized operation. Finally, we discuss remaining challenges and future directions for translating electrochemical aptamer sensors toward robust real-world applications.

Keywords: electrochemical aptamer sensors; electrode fabrication; surface modification; electrochemical signal transduction; miniaturized and wearable applications

1. Introduction

With the rapid advancement of precision medicine, point-of-care testing (POCT) and intelligent wearable health monitoring, there is an increasing demand for analytical devices capable of miniaturized, portable, in situ and continuous measurements [1]. Conventional *ex vivo* techniques, such as high-performance liquid chromatography [2], liquid chromatography mass spectrometry [3], and enzyme-linked immunosorbent assay [4],

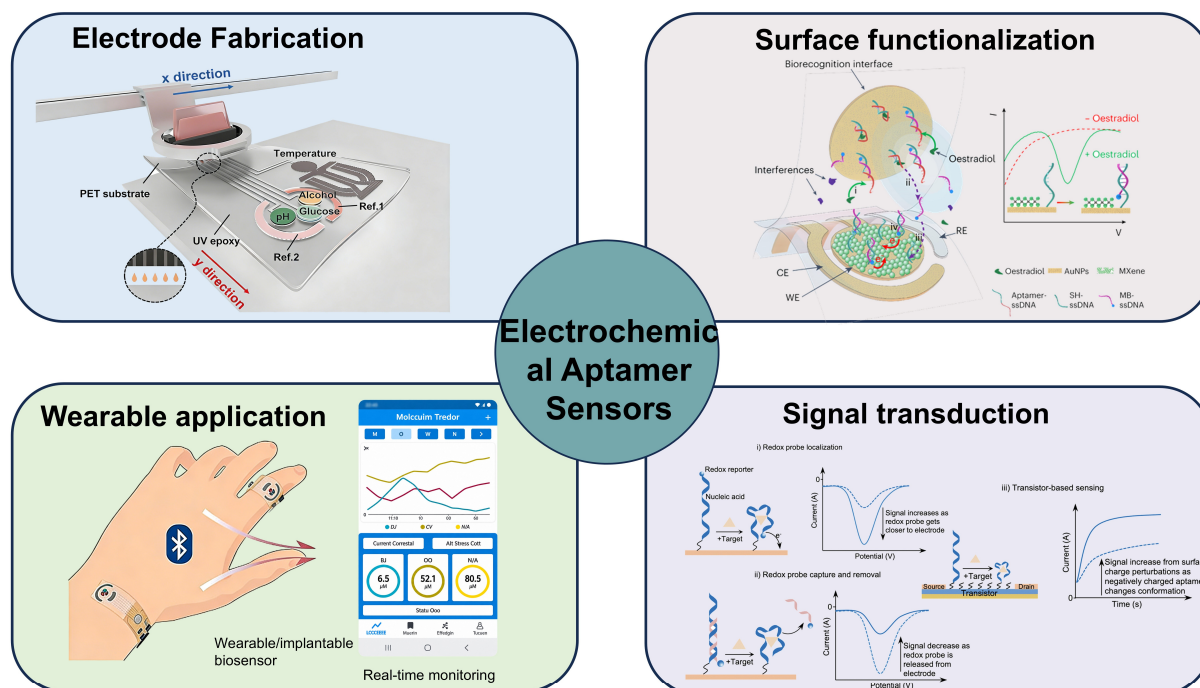


are powerful tools for detecting a broad range of chemical and biological targets, including ions, small molecules, and proteins. However, these methods are typically limited by bulky instrumentation, complex operation, labor-intensive sample preparation, and long assay times, making them unsuitable for rapid on-site or continuous dynamic monitoring [5]. In addition, complex biological matrices introduce further challenges, including nonspecific adsorption, interfacial fouling, and limited sensor stability. These factors can compromise sensing performance in wearable and real-time monitoring scenarios. Therefore, new sensing technologies are needed that combine high sensitivity, rapid response, robust antifouling capability, and facile integration with miniaturized and wearable platforms [6].

Electrochemical analysis represents a well-established and widely applied class of detection techniques, offering high sensitivity, rapid response, and ease of miniaturization and integration [7–9]. These features have enabled its extensive use in clinical diagnostics [10], environmental monitoring [11,12], food safety, and biomedical research [13]. To meet the increasing demand for rapid testing and device miniaturization, electrochemical sensing platforms have attracted considerable attention for point-of-care testing because of their high sensitivity, compact device configuration, low cost, and compatibility with portable signal readout [14,15]. Building on this foundation, electrochemical aptamer sensors integrate highly specific nucleic acid aptamers as molecular recognition elements with electrochemical signal transduction. This design retains the intrinsic advantages of electrochemical detection while improving molecular selectivity and interference resistance through aptamer-mediated recognition. As a result, electrochemical aptamer sensors show great potential for rapid on-site detection, continuous monitoring, and the development of portable and wearable sensing platforms.

Aptamers [6,16–21] are short single-stranded nucleic acid oligonucleotides (DNA or RNA) selected through *in vitro* techniques such as SELEX, and they can recognize a wide range of targets with high specificity due to their well-defined three-dimensional structures. Their small size, structural flexibility, and ease of chemical modification make them particularly suitable for incorporation into electrochemical sensing systems. Compared with traditional antibodies, aptamers provide comparable molecular recognition capability while offering several practical advantages. These include higher physicochemical stability, facile and low-cost synthesis, excellent batch-to-batch reproducibility, convenient chemical modification, low immunogenicity, and extended storage stability [22]. At present, aptamers have attracted significant attention in clinical diagnostics, therapeutics, food safety, environmental monitoring, and biomarker discovery, demonstrating tremendous potential in next-generation biosensing and precision medicine [23–29]. In practical electrochemical aptamer sensors, however, aptamers do not function independently in solution. They must be immobilized onto electrode surfaces, where their orientation, surface density, and conformational freedom are strongly affected by interfacial properties. The electrode therefore serves not only as the signal transduction platform but also as the key regulator of molecular recognition efficiency and signal generation. Factors such as electrode material, surface functionalization, and interface engineering critically determine aptamer immobilization, electron transfer kinetics, and resistance to nonspecific adsorption in complex biological environments. Rational design of electrode structures and bio-interfaces is thus essential for improving the overall performance of electrochemical aptamer sensors.

In this review, we do not aim to provide an exhaustive catalogue of reported electrochemical aptamer sensors. Instead, we seek to establish an architecture- and application-oriented framework for understanding how electrochemical aptamer sensors are designed, optimized, and evaluated. The review first classifies major electrochemical aptamer sensor architectures according to their signal-transduction mechanisms, because these mechanisms define how aptamer–target recognition is converted into an electrical output and therefore determine the intrinsic strengths, limitations, and application suitability of each sensing format. Based on this framework, the subsequent sections discuss electrode fabrication, electrode material selection, aptamer immobilization, antifouling interface engineering, and integrated applications in miniaturized, wearable, and continuous monitoring platforms. As illustrated in Scheme 1, the development of electrochemical aptamer sensors involves the coordinated design of signal-transduction mechanisms, electrode structures, surface chemistry, aptamer presentation, antifouling protection, and device integration. Therefore, electrode materials, catalytic or conductive nanomaterials, immobilization strategies, and antifouling coatings are discussed not as isolated components, but according to how they support or limit specific sensing architectures and application scenarios. For example, reagentless structure-switching E-AB sensors are particularly relevant for reversible and continuous molecular monitoring, whereas capture/release and signal-amplified strategies are more suitable for endpoint assays requiring low detection limits. Field-effect transistor (FET)-based aptasensors provide label-free electronic readout, but their operation in realistic biological media is constrained by Debye screening, nonspecific adsorption, and interfacial instability. By linking signal transduction, sensor architecture, interface design, and application context, this review aims to help readers identify which design features are essential for specific analytical tasks and which reported advantages should be interpreted with caution.



Scheme 1. Overview of aptamer-based wearable electrochemical biosensors: from fabrication to real-time health monitoring applications.

2. Signal-Transduction Mechanisms and Major Electrochemical Aptamer Sensor Architectures

Electrochemical aptamer sensors are first classified here according to their signal-transduction mechanisms, which provide the basis for the subsequent discussion of electrode fabrication, material selection, aptamer immobilization, and antifouling interfaces. The signal-transduction mechanism defines how aptamer-target recognition is converted into a measurable electrical output and thereby determines the response mode, sensitivity, reversibility, operational complexity, and application suitability of each architecture. The major strategies discussed in this review are classified into three categories (Figure 1A): (i) redox-probe localization, (ii) redox-probe capture or release, and (iii) transistor-based electronic readout.

2.1. Redox-Probe Localization

In this strategy, redox-active probes methylene blue (MB) or ferrocene (Fc) are labeled at specific sites of the aptamer. Upon binding with the target molecule, the aptamer undergoes conformational rearrangement, which alters the distance between the probe and the electrode surface [6]. This distance change directly affects the electron transfer rate: when the probe approaches the electrode, electron transfer is accelerated, leading to an enhanced current response; conversely, when the probe moves away, the signal decreases. Therefore, the signal output is governed by distance-dependent electron transfer kinetics, making it a structure-switching-based sensing mechanism.

Structure-switching electrochemical aptamer-based (E-AB) sensors were established well before their recent integration into flexible or paper-based platforms. In an early representative study, Baker et al. [30] introduced an electronic aptamer-based small-molecule sensor in which target-induced folding of a redox-labeled aptamer modulated electron transfer at the electrode surface, enabling rapid electrochemical detection of cocaine. This reagent-free and binding-induced signal-transduction concept was later extended to continuous and real-time monitoring in complex matrices, including the microfluidic E-AB detection of cocaine in undiluted blood serum reported by Swensen et al. [31]. These early studies laid the foundation for subsequent E-AB sensors based on redox-tagged aptamers, reversible target binding, and conformationally regulated electron transfer; this mechanism and its fabrication-dependent signaling behavior have been systematically discussed in previous reviews [32].

Building on this established E-AB mechanism, Yu et al. [33] further integrated redox-labeled aptamers with paper-based electrochemical devices, demonstrating the feasibility of translating E-AB sensing into low-cost and portable formats for on-site small-molecule detection in buffer and bio-samples (Figure 1B). Therefore, this work should be viewed as a platform-level implementation of structure-switching E-AB sensing rather than the origin of this signal-transduction strategy.

However, in this mechanism, the target-induced current change is determined by how strongly aptamer binding alters the electron-transfer rate between the redox reporter and the electrode. Because the signal originates

from conformationally induced changes in reporter–electrode distance rather than changes in the number of surface-bound probes or catalytic amplification, careful structural design of the aptamer and linker is required to obtain a sufficiently large relative current response. Compared with capture/release or signal-amplified aptasensing strategies, the main advantage of structure-switching E-AB sensors lies not in achieving the lowest detection limit, but in their reagent-free, reversible, and continuous readout capability.

2.2. Capture and Release of Redox Probes

Redox-probe capture and release strategies provide a complementary signal-transduction route to structure-switching E-AB sensors. Unlike redox-probe localization mechanisms, capture/release-based systems do not primarily rely on nanoscale motion of a redox tag relative to the electrode. Instead, they regulate the amount or interfacial proximity of signal-generating labels retained at the sensing interface. In a typical design, aptamer-target binding triggers nucleic acid hybridization or strand-displacement reactions, leading to either capture or release of a labeled strand. Probe release decreases the number of signal-generating species retained at the electrode interface, whereas probe capture increases the interfacial signal population.

Because this mechanism changes the population or interfacial accessibility of signal labels rather than only the redox-tag distance, it can provide a larger signal window and, under optimized assay conditions, lower detection limits than simple structure-switching E-AB formats. Xu et al. [34] reported an electrochemiluminescence (ECL)-based aptamer sensor (Figure 1C) using strand displacement reactions for ultrasensitive detection of Cd^{2+} in *Ganoderma lucidum* samples. The sensor employed polymer dots (Pdots) as luminophores and black hole quencher (BHQ) as the energy acceptor to form a signal-off configuration. In the presence of Cd^{2+} , target binding triggered strand displacement, leading to the release of BHQ-labeled DNA strands and restoration of the Pdot luminescence, thereby realizing a signal-off-to-on response. This method achieved a detection limit of 0.006 ppb and was successfully applied to real sample analysis.

Despite their analytical sensitivity, capture/release and strand-displacement-based strategies often require multistep nucleic acid hybridization processes and more sophisticated probe design. These requirements can increase operational complexity and may affect system stability and reproducibility. In addition, the kinetics and thermodynamics of strand displacement reactions are sensitive to ionic strength, temperature, sequence design, and matrix composition, which should be considered when translating these assays from optimized laboratory conditions to real-sample analysis.

2.3. Transistor-Based Signal Transduction

Aptamer-based field-effect transistor (FET) sensors represent a label-free electronic sensing format distinct from redox-tagged electrochemical aptasensors. The concept of aptamer-FET sensing predates its recent implementation in flexible or wearable platforms. For example, early SWNT-FET aptasensors [35] demonstrated that DNA aptamers could be immobilized on transistor channels as molecular recognition elements for real-time protein detection, establishing the feasibility of coupling aptamer–target binding with transistor-based electrical readout. Subsequent studies further extended this concept to graphene, carbon nanotube, nanowire, and metal-oxide transistor platforms for different biomolecular targets.

In FET-based aptasensors, aptamers are typically immobilized on or near the gate/channel surface. Target binding changes the local charge distribution, interfacial potential, or aptamer conformation at the sensing interface, thereby modulating the carrier density in the conductive channel and altering the source-drain current. Because this sensing format does not require redox labels or solution-phase electrochemical reactions, it enables label-free electrical detection and is compatible with miniaturized and integrated electronic devices. However, the practical performance of FET aptasensors is strongly affected by Debye screening in physiological or high-ionic-strength media, nonspecific adsorption, surface functionalization reproducibility, and device-to-device variability. Therefore, the detection of charged, neutral, or zwitterionic targets depends not only on target-binding affinity, but also on aptamer conformational changes, receptor-channel distance, ionic strength, and interface design.

More recently, Wang et al. [36] developed an ultra-flexible and stretchable aptameric graphene field-effect transistor (GFET) nano-sensor for tumor necrosis factor- α (TNF- α) detection (Figure 1D). In this device, an aptamer-functionalized monolayer graphene channel was fabricated on a 2.5 μm -thick Mylar substrate, enabling the sensor to conform to surfaces undergoing large bending, twisting, and stretching deformations. Target binding between TNF- α and the immobilized aptamer altered the carrier concentration of graphene, which was reflected by changes in the transfer characteristics and Dirac point shift of the GFET. The device maintained stable electrical properties and TNF- α sensing responses under repeated mechanical deformation, illustrating the potential of aptamer-FET architectures for flexible and mechanically robust biomarker sensing platforms.

Despite these advantages, the practical application of FET-based aptasensors remains challenging in complex samples. Their responses are highly sensitive to environmental factors, including temperature, ionic strength, pH, and nonspecific adsorption at the sensing interface, which can lead to baseline drift and reduced operational stability. In physiological media, electrostatic signal transduction may be weakened when aptamer-target recognition occurs beyond the effective Debye length. In addition, reproducible large-scale fabrication, stable surface functionalization, antifouling interface design, and reliable signal correction in real-world samples remain important requirements for translating FET-based aptasensors from proof-of-concept devices into robust platforms for point-of-care testing and bioanalysis.

Taken together, these signal-transduction mechanisms impose different requirements on electrode materials and interface design. For redox-probe localization in structure-switching E-AB sensors, the electrode interface must preserve aptamer conformational freedom while allowing efficient distance-dependent electron transfer between the redox reporter and the electrode. Gold electrodes and well-controlled self-assembled monolayers (SAMs) are therefore particularly useful for this mechanism, although additional antifouling modification is often required for operation in complex biological samples. For capture/release or strand-displacement-based sensors, material platforms with high electroactive surface area and good compatibility with nucleic acid hybridization can improve signal output, but excessive surface roughness or dense probe loading may hinder strand exchange and increase background signal. For FET-based aptasensors, graphene, carbon nanotubes, and other transistor-compatible materials enable label-free electronic readout, but their performance depends strongly on Debye screening, receptor-channel distance, surface fouling, and device reproducibility. Thus, electrode materials and interface designs should be evaluated according to the specific signal-transduction mechanism and intended application, rather than by a single metric such as conductivity, surface area, or detection limit.

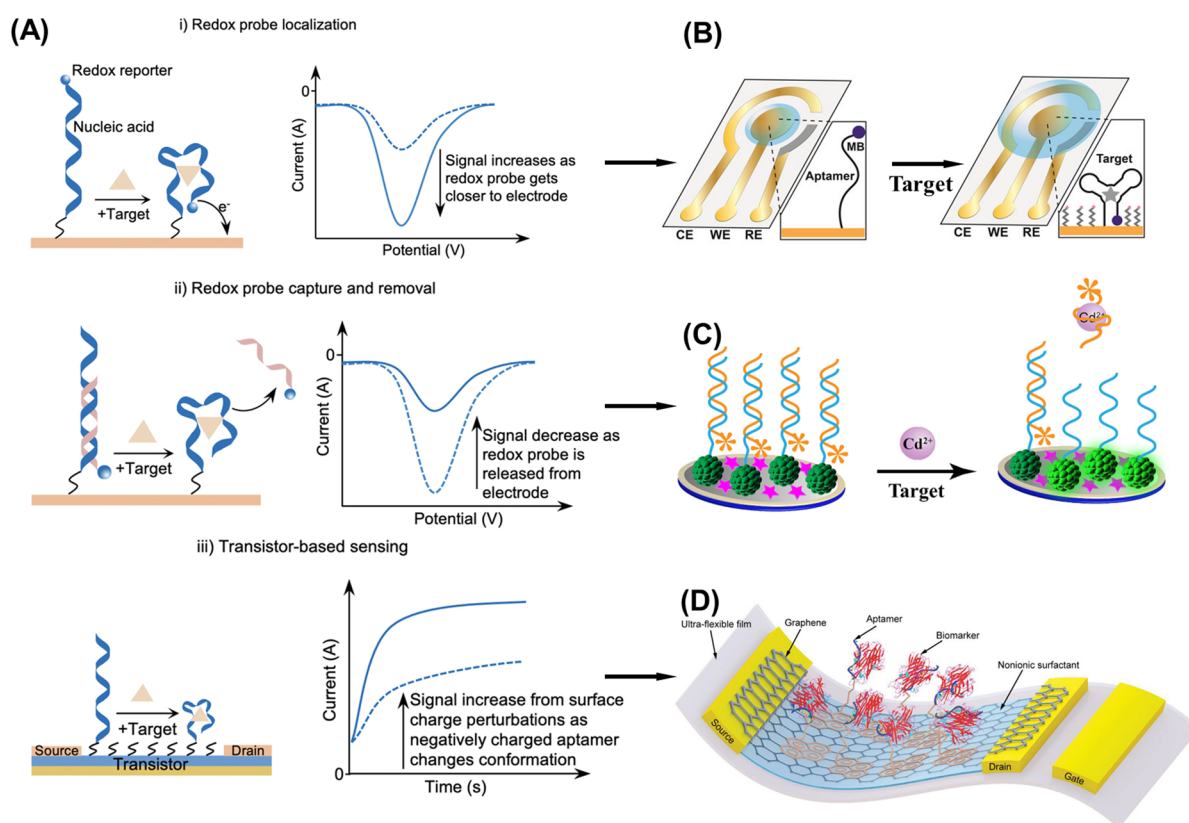


Figure 1. (A) Signal transduction strategies, including redox probe localization, redox probe capture and removal, and transistor-based sensing [6]. Copyright 2024 The Royal Society of Chemistry. (B) Aptamer-modified PEDs for small-molecule sensing [33]. Copyright 2021 Wiley-VCH. (C) Detection of *Ganoderma lucidum* via redox-probe capture/release strategy [34]. Copyright 2025 Elsevier. (D) Schematic design of the ultra-flexible aptameric GFET nano-sensor for TNF- α detection on a thin Mylar substrate [36]. Copyright 2019 Wiley-VCH.

3. Electrode Fabrication and Material Selection

After defining the major signal-transduction architectures of electrochemical aptamer sensors, this section discusses how electrode fabrication strategies and electrode materials should be selected in relation to these

architectures. Electrode design is not a universally beneficial engineering step; its value depends on whether the resulting interface supports the electron-transfer, probe-exchange, or field-effect readout process required by a given sensor type. For structure-switching E-AB sensors, electrode surfaces must preserve aptamer conformational freedom and enable efficient redox reporter–electrode communication. For capture/release or signal-amplified sensors, electrode architectures often need to support high surface loading, probe accessibility, and amplified electrochemical response. For transistor-based aptasensors, the electrode or channel material must maintain stable interfacial charge modulation while minimizing Debye screening, fouling, and device variability. Therefore, the following discussion evaluates electrode fabrication and material selection according to their compatibility with different sensing architectures and application scenarios.

3.1. Electrode Fabrication

The electrode constitutes the central functional platform of electrochemical aptamer sensors, serving not only as a conductive substrate but also as a critical determinant of charge transfer efficiency, the orientation and surface density of immobilized aptamers, and the accessibility of target analytes, all of which collectively govern sensing sensitivity and dynamic response. However, the performance of electrochemical aptamer sensors is frequently constrained by interfacial limitations, including sluggish electron transfer kinetics, insufficient electroactive surface area, and nonuniform aptamer distribution. Accordingly, electrode fabrication has evolved beyond a simple processing step into a key strategy for tailoring interfacial structure and functionality. By regulating parameters such as surface roughness, porosity, conductivity, and chemical functionality, fabrication approaches enable precise modulation of the structure-property relationships at the sensing interface. To address the growing demand for miniaturized, wearable, and point-of-care sensing platforms, diverse advanced manufacturing strategies have been developed to construct electrodes with tunable architectures and reproducible electrochemical performance. Among these, inkjet printing [37], laser-induced graphene (LIG) [38,39], and screen printing [40,41] have emerged as three representative and widely adopted fabrication techniques. These methods differ substantially in resolution, conductivity, scalability, and compatibility with functional materials, thereby offering distinct advantages and limitations for the design of electrochemical aptamer sensors. The following sections provide a comparative discussion of these fabrication strategies, with particular emphasis on their roles in interface engineering and their suitability for sensing applications. Importantly, these fabrication strategies are not interchangeable for all aptasensor architectures. Their suitability depends on whether the target device requires a well-controlled monolayer interface for E-AB sensing, a high-area nanostructured surface for endpoint signal amplification, or a patterned electronic platform for transistor-based readout and system integration.

3.1.1. Inkjet Printing

Inkjet printing [37] is a representative on-demand, mask-free patterning technique that enables high-resolution fabrication of electrode structures with precise spatial control. By digitally designing electrode patterns and directly depositing functional inks onto a variety of substrates, including flexible and paper-based materials, this method provides excellent versatility for device integration and rapid prototyping. From an interfacial engineering perspective, inkjet printing allows programmable control over material distribution, layer thickness, and multi-material integration. This capability is particularly important for constructing hierarchical electrode structures with enhanced electroactive surface area and optimized electron transfer pathways [42]. In parallel, controlled deposition of nanomaterial inks enables the formation of tailored microenvironments for aptamer immobilization, improving both recognition efficiency and signal stability [43].

Inkjet printing offers low-cost, high-throughput, and scalable manufacturing [44], making it particularly attractive for flexible electronics and electrochemical sensor production [45]. For example, Hu et al. [46] employed inkjet printing to deposit gold nanoparticle inks onto cellulose membranes, followed by autocatalytic growth to form highly conductive nanoporous gold electrode arrays, enabling a paper-based three-electrode O₂ sensing system in a single step (Figure 2A). Similarly, Ma et al. [47] developed a fully inkjet-printed strategy by sequentially printing 11 different nanomaterial inks to fabricate a highly integrated, multiparameter sweat sensor patch. By forming interpenetrating interfaces with controlled material loading, the design not only enhanced glucose detection sensitivity but also maintained stable performance after 500 bending cycles, exhibiting minimal signal drift during long-term monitoring. These studies illustrate the unique advantages of inkjet printing for interface engineering, multi-material integration, and scalable fabrication of high-performance wearable sensor arrays.

Despite these advantages, inkjet printing is constrained by factors such as ink formulation requirements, nozzle clogging, and relatively lower conductivity compared to bulk metallic electrodes. Nevertheless, its unique capability for precise patterning and multi-material integration makes it particularly suitable for multiplexed

capture/release assays, flexible E-AB sensor arrays, and integrated wearable platforms where spatially resolved electrode modification and scalable device fabrication are required.

3.1.2. LIG

LIG is a direct-write fabrication technique that converts insulating substrates such as polyimide, paper or textiles [38,39] (Figure 2B) into conductive graphene-like structures via localized laser irradiation. This single-step, mask-free, and reagent-free process enables rapid and scalable electrode fabrication.

A defining feature of LIG is its three-dimensional porous architecture, which provides a large specific surface area [48] and abundant active sites for electrochemical reactions. The interconnected conductive network facilitates efficient electron transport, while tunable micro/nanostructures [49,50] allow modulation of interfacial properties such as roughness, wettability, and functional group distribution. These characteristics are particularly beneficial for enhancing aptamer loading density and improving electron transfer kinetics. For instance, Wang et al. [51] employed LIG arrays on polyimide to construct LIG-Yb-Bi₂S₃/POM heterostructures, which, when coupled with NPY aptamers, enabled ultralow detection of neuropeptide Y in sweat (0.39 fM) under real-time wireless monitoring. Lu et al. [52] further demonstrated a low temperature transfer strategy to deposit LIG onto a 1.5 µm-thick self-adhesive PPH hydrogel, forming ultrathin, soft, and biocompatible conductive films for multifunctional skin sensors and cardiac patches. These examples highlight LIG's versatility in flexible integration, interface modulation, and aptamer-based sensing, offering a low-cost and scalable approach for smart wearable sensors.

Nevertheless, LIG also presents notable limitations. It exhibits restricted substrate compatibility, as the laser-induced graphitization only proceeds efficiently on specific polymer or carbon-rich materials. Moreover, its pattern uniformity and resolution are relatively low and highly sensitive to laser parameters, hindering the fabrication of highly precise microelectrodes. From an architecture perspective, LIG is particularly attractive for wearable or disposable electrochemical aptasensors that require large electroactive surface area and mechanical flexibility, including signal-amplified endpoint assays and flexible E-AB platforms. However, its relatively rough and heterogeneous surface may require additional interface control when precise probe spacing or highly reproducible redox-tag/electrode distances are required.

3.1.3. Screen Printing

Screen printing [40,41] is a widely used technique that transfers conductive inks, such as carbon, graphite, gold, silver, or oxide composites, onto substrates through patterned templates to form electrodes. The method is simple, low-cost, and highly compatible with batch production, making it particularly suitable for disposable and portable electrochemical sensors [53]. Typical screen-printed electrodes (SPEs) [54] integrate working, reference, and counter electrodes on a single planar substrate, achieving miniaturization and portability. By adjusting ink composition and printing parameters, electrode conductivity, surface roughness, and chemical stability can be finely tuned, providing controllable interfaces for aptamer immobilization. Screen-printed graphite carbon electrodes have been widely applied in aptamer-based electrochemical sensors due to their high conductivity and large surface area. Liu et al. [55] reported a multichannel SPDE-based aptamer sensor for heavy metal detection, in which nanomaterial-modified working electrodes enabled selective recognition of Pb²⁺, Hg²⁺, and other ions, with low detection limits, wide linear ranges, and excellent anti-interference performance in complex samples including tap water and environmental matrices (Figure 2C). This work demonstrates the versatility of screen printing for constructing scalable, high-performance electrochemical sensor platforms.

However, SPEs are still associated with several intrinsic limitations. Their fabrication relies on predesigned templates or masks, resulting in limited patterning flexibility and time-consuming customization. In addition, their relatively low resolution restricts the construction of high-precision microelectrode architectures. Precise control over film thickness and uniformity also remains challenging, which may lead to batch-to-batch variation in electrode performance and limit their use in high-resolution nanoscale sensing interfaces. Therefore, screen printing is especially suitable for disposable endpoint assays and point-of-care testing, where low cost, batch production, and integrated three-electrode formats are prioritized. In contrast, for long-term E-AB monitoring or transistor-based electronic readout, additional control over surface uniformity, probe immobilization, and interfacial stability is required.

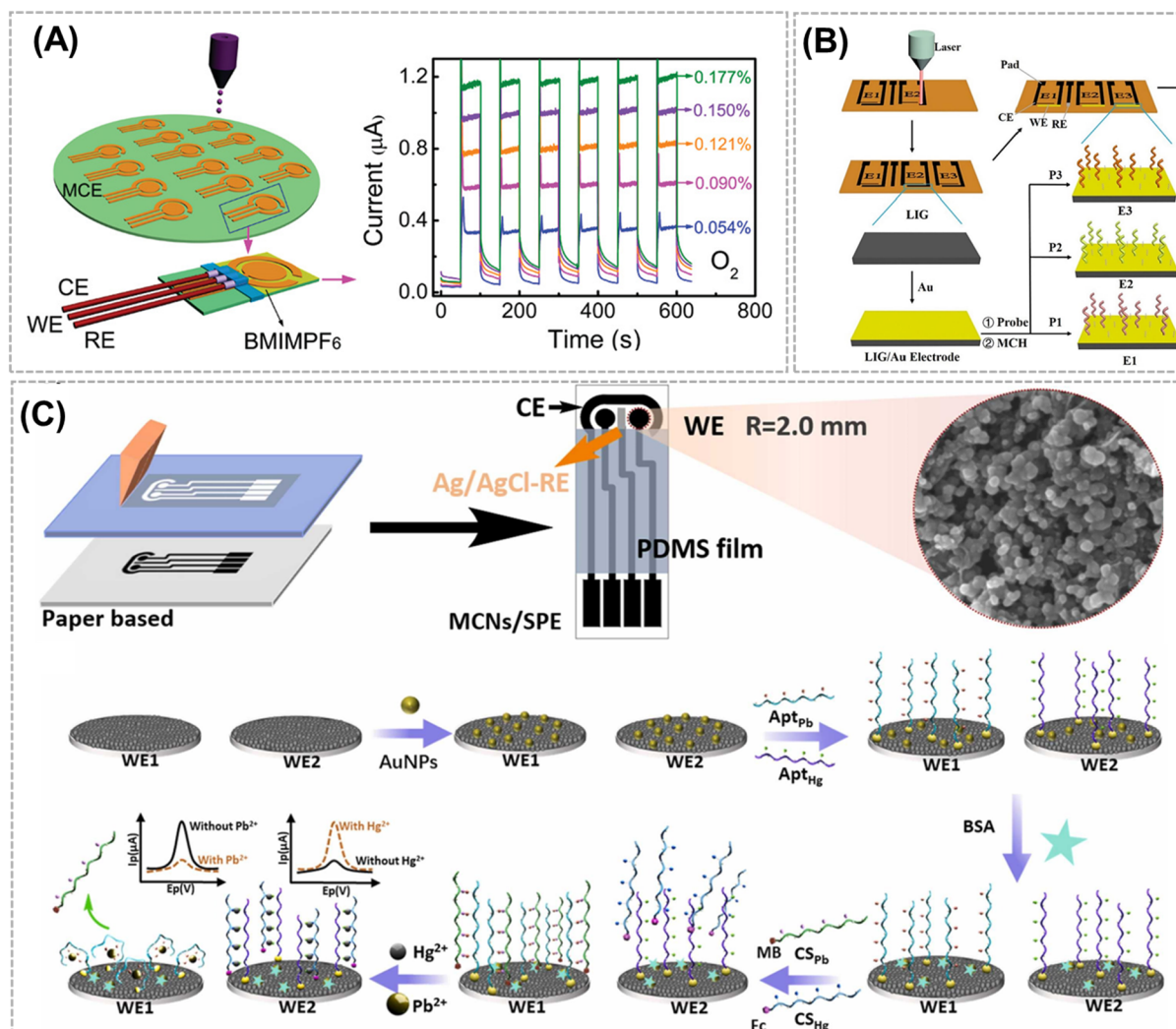


Figure 2. (A) The fabrication process of the oxygen sensor based on inkjet-printed gold electrode arrays [46]. Copyright 2012 American Chemical Society. (B) Fabrication of Au-modified electrodes on PI film via laser-induced graphene (LIG) technology [56]. Copyright 2024 Elsevier. (C) MCNs/SPDE aptasensor: electrode fabrication and dual detection of $\text{Pb}^{2+}/\text{Hg}^{2+}$ [55]. Copyright 2025 Elsevier.

3.1.4. Comparative Analysis of Electrode Fabrication Strategies

To provide rational design guidelines for electrode engineering in electrochemical aptamer sensors, it is necessary to systematically compare representative fabrication strategies based on practical performance requirements. Although inkjet printing, laser-induced graphene, and screen printing are all capable of producing functional electrodes, they exhibit significant differences in structural architecture, electrochemical properties, and interfacial engineering capability, which ultimately determine their suitability for different sensing scenarios. As summarized in Table 1, the key fabrication parameters, including advantages, major limitations, conductivity, surface roughness, scalability, material compatibility, and applications, are systematically evaluated to highlight the trade-offs among different electrode fabrication strategies.

3.2. Selection of Electrode Materials

Because the signal-transduction architectures defined in Section 2 impose different interfacial requirements, electrode materials should be selected according to the sensing mechanism they support rather than treated as universally beneficial substrates. Electrode materials are one of the key determinants governing the performance of electrochemical aptamer sensors. Their electrical conductivity, chemical stability, and interfacial compatibility with biological recognition elements directly influence the sensor's sensitivity, selectivity, and stability. More importantly, electrode materials regulate aptamer immobilization behavior, interfacial electron-transfer kinetics, and resistance to nonspecific adsorption, thereby collectively determining overall sensing performance.

Commonly employed electrode materials can be broadly categorized into three types: metallic and metal oxide electrodes, carbon-based electrodes, and conductive polymer materials. Notably, each material class exhibits distinct advantages and inherent limitations in terms of interface controllability, signal transduction efficiency, and practical applicability, making rational material selection essential for different sensing scenarios.

Table 1. Comparative analysis of representative electrode fabrication strategies for electrochemical aptamer sensors.

	Inkjet Printing	LIG	Screen Printing
Conductivity	Moderate to High (depends on ink formulation and post-treatment)	High (3D porous conductive network with efficient charge transport pathways)	Moderate to High (depends on ink composition and curing conditions)
Surface Roughness	Moderate; tunable via ink formulation	Very High	Moderate
Material Compatibility	Excellent (paper, flexible polymers, textiles, cellulose substrates)	Moderate (mainly polyimide)	High (wide substrate compatibility, including ceramics, plastics, paper)
Scalability	High	Moderate	Very High
Advantages	Mask-free patterning; high design flexibility; precise material placement; compatible with multi-material printing	One-step fabrication; highly porous 3D conductive network	Low cost; mature technology; highly scalable; disposable electrode production
Major Limitations	Requires strict ink rheology; nozzle clogging; limited ink viscosity range	Limited substrates, low uniformity, laser-sensitive	Low resolution, needs mask/template, poor microstructure control
Applications	Flexible/wearable sensor arrays; multiplexed biosensors	Flexible epidermal sensors; sweat monitoring	Mass producing disposable POCT sensors; commercial SPE platforms

3.2.1. Metallic and Metal Oxide Electrodes

Noble metal electrodes (such as Au [57,58] and Pt [59]) are widely utilized in aptasensor fabrication owing to their excellent electrical conductivity, chemical inertness, and controllable surface chemistry. In particular, gold electrodes enable the formation of SAMs [60,61] through Au-S bonding, which allows ordered aptamer immobilization, effective exposure of recognition sites, and enhanced signal stability. These features make gold electrodes particularly suitable for redox-tagged structure-switching E-AB sensors, where controlled probe spacing, monolayer quality, and reproducible reporter-electrode electron transfer are essential for signal generation. Zhang et al. [61] introduced hydrophobic moieties into mixed-thiol SAMs to overcome the fouling limitations encountered in complex biological matrices. By integrating alkyl-terminated thiols into the monolayer, the authors created a partially dehydrated interfacial environment that effectively suppressed protein adsorption without compromising aptamer mobility or electron-transfer efficiency. The resulting hydrophobic SAM-modified gold electrodes exhibited markedly reduced background currents and enhanced signal-to-noise ratios, enabling reliable aptamer-based detection directly in serum and other high-fouling samples. In addition to planar gold electrodes, electrodeposited AuNPs on GCEs have also been used as effective nanostructured interfaces for covalent aptamer attachment [62]. For example, Roushani and Shahdost-fard constructed an ibuprofen nanoaptasensor by immobilizing aptamers on electrodeposited AuNPs/GCE, where the AuNP layer increased the effective surface area and provided a favorable interface for biomolecule conjugation.

Additionally, indium tin oxide (ITO) [63,64], a representative metal oxide material with high transparency and electrical conductivity, has attracted increasing attention for the development of integrated and visualized electrochemical sensing platforms. Compared with noble metals, metal oxides provide additional functionalities such as optical transparency and compatibility with photoelectrochemical systems [65,66], enabling multimodal sensing strategies. For example, Liu et al. [63] developed a near-infrared light-responsive on-off-on photoelectrochemical aptasensor by assembling SnS₂, ZnIn₂S₄, and upconversion nanoparticles onto an ITO substrate, followed by AuNP deposition to facilitate aptamer immobilization. The multilayer heterostructure significantly enhanced charge separation efficiency and light-harvesting capability, enabling ultrasensitive detection of carcinoembryonic antigen with a detection limit of 0.3 pg mL⁻¹.

Despite these advantages, metallic electrodes suffer from relatively high cost and are prone to surface fouling in complex biological environments without additional modification. Meanwhile, metal oxide electrodes often require hybridization with conductive or catalytic nanomaterials to achieve optimal electrochemical performance.

3.2.2. Carbon-Based Electrodes

Carbon materials represent another vital class of substrates for constructing high-performance aptamer sensors. Conventional electrodes such as glassy carbon electrodes (GCEs) [67,68], carbon paste electrodes (CPEs) [69,70], and SPCEs [71,72] are widely used in both laboratory research and portable devices due to their ease of fabrication and excellent chemical stability. In parallel, these materials offer a wide potential window and relatively low background current, which are advantageous for electrochemical detection.

Emerging carbon nanomaterials, including graphene, carbon nanotubes (CNTs), and carbon quantum dots (CQDs), exhibit large specific surface areas, excellent charge-transfer properties, and facile surface functionalization capabilities [73]. These features significantly enhance the effective electroactive area and electron transfer efficiency of electrodes, thereby improving sensing sensitivity [74]. To further exploit these advantages, Su et al. [71] constructed a carbon-based DNA framework nano-bio interface that provided a highly ordered 3D scaffold for anchoring aptamers with controlled orientation and density. This design significantly enhanced electron-transfer efficiency and minimized interfacial noise by reducing steric hindrance and improving recognition-site accessibility. As a result, the carbon-DNA hybrid interface achieved remarkably high sensitivity and an improved signal-to-noise ratio compared with conventional carbon electrodes, demonstrating the advantages of rationally engineered carbon nanostructures for high-performance aptamer biosensing. From an architecture-dependent perspective, high-area carbon interfaces are particularly useful for capture/release and signal-amplified aptasensors, where increased probe loading and enhanced electrochemical response are often beneficial. For structure-switching E-AB sensors, carbon materials can also improve charge transfer, but rough or chemically heterogeneous surfaces may complicate control over probe spacing, aptamer orientation, and redox reporter-electrode distance. Therefore, additional interface engineering is often required to obtain reproducible structure-switching responses. For transistor-based aptasensors, graphene and CNTs can serve directly as conductive channel materials. In this case, their performance depends not only on conductivity, but also on the reproducibility of surface functionalization, receptor-channel distance, Debye screening, fouling resistance, and stability in physiological or high-ionic-strength media.

However, carbon-based electrodes generally lack intrinsic and well-defined surface-active sites for highly specific and controlled biorecognition interface construction. In addition, variations in surface structure and functional groups can lead to reproducibility issues, especially in large-scale fabrication. Therefore, additional surface modification or interface engineering is often required to achieve optimal performance.

3.2.3. Conductive Polymer Materials

Conductive polymers such as polyaniline (PANI) [75], polypyrrole (PPy) [76], and poly(3,4-ethylenedioxythiophene) (PEDOT) [77] possess excellent conductivity, environmental stability, and the ability to form flexible, biocompatible functional layers on electrode surfaces. Compared with rigid inorganic materials, conductive polymers provide mechanically compliant and hydrated interfaces that are more compatible with biological systems, which is particularly advantageous for wearable and bio-integrated sensors. These polymers not only serve as effective immobilization matrices for aptamers but also allow the tuning of their electrical properties through ion doping or copolymerization, enabling signal regulation and amplification. These properties make conductive polymers useful not only as immobilization or amplification matrices in conventional electrochemical aptasensors, but also as active channel materials in transistor-based or OECT-type sensing platforms where mixed ionic/electronic transport contributes to signal transduction.

Furthermore, composite electrodes that integrate conductive polymers with carbon-based or metallic nanomaterials achieve superior electrochemical performance through synergistic effects, offering high sensitivity, stability, and reproducibility [78]. For instance, Li et al. [79] fabricated a coral-like PANI/AuNPs composite electrode via electrodeposition for the detection of prostate-specific antigen (PSA), achieving a detection limit of 0.085 pg mL^{-1} , a wide linear range from 0.1 pg mL^{-1} to 100 ng mL^{-1} .

Overall, electrode materials should not be evaluated only by conductivity, electroactive surface area, or fabrication convenience. Their suitability also depends on how well they support the specific recognition and transduction requirements of each sensor architecture. Metallic electrodes, especially gold-based interfaces, provide well-defined surface chemistry for controlled aptamer attachment and are particularly useful for redox-tagged E-AB sensors. Carbon-based and screen-printed electrodes are attractive for low-cost, disposable, and point-of-care assays,

especially endpoint or capture/release-based formats. Nanostructured metals, carbon nanomaterials, and conductive polymer composites can improve charge transfer and signal amplification, but their rough or chemically heterogeneous interfaces may also increase nonspecific adsorption, background current, and signal drift. Graphene, carbon nanotubes, and conducting polymer channels are relevant to transistor-based readout, but their performance depends strongly on surface functionalization, ionic-strength tolerance, and device reproducibility. Therefore, electrode materials should be selected according to the sample matrix, measurement duration, device format, and signal-transduction requirements defined in Section 2, rather than treated as universally beneficial components.

4. Immobilization of Aptamers on Electrode Surface

Surface modification of the electrode is a crucial step for achieving high specificity and signal responsiveness in electrochemical aptamer sensors. More fundamentally, aptamer immobilization determines the interfacial architecture, including the spatial orientation of aptamers, surface coverage density, and molecular conformational freedom, all of which collectively govern recognition efficiency and signal transduction behavior. Surface modification with aptamers, functional nanomaterials, or interfacial molecular layers can improve sensor performance by regulating both electron-transfer pathways and aptamer presentation at the sensing interface [80,81]. Conductive nanomaterials can increase the electroactive surface area and reduce interfacial charge-transfer resistance, thereby improving electrochemical signal transduction. In contrast, molecular spacers and blocking layers mainly regulate aptamer density, orientation, and spacing, which helps preserve aptamer folding, target accessibility, and reversible target binding. However, the immobilization interface must be carefully optimized. Excessively high probe density may restrict aptamer folding or reduce target accessibility, whereas insufficient surface passivation may increase nonspecific adsorption and background signal. Previous studies on DNA-modified gold electrodes and E-AB sensors have shown that probe surface density and self-assembled monolayer chemistry strongly influence hybridization efficiency [82]. In E-AB sensors, probe packing density and self-assembled monolayer chemistry have also been shown to regulate aptamer-target recognition and electrochemical signal gain [83]. These findings highlight the importance of rationally controlling aptamer density, spacing, and passivation during electrode modification [84].

4.1. Physical Adsorption

Physical adsorption is the simplest immobilization approach (Figure 3A), where aptamers or other functional molecules are adsorbed onto the electrode surface through non-covalent interactions such as electrostatic attraction, van der Waals forces, hydrogen bonding, or hydrophobic interactions [85,86]. The main advantages of this method are operational simplicity and the absence of complex chemical reactions or reagents, making it suitable for short-term detection or rapid screening experiments. In addition, since the physical adsorption process does not involve chemical modification, it preserves the native structure of the aptamer, which is beneficial for preliminary studies. However, due to the weak binding forces, the stability of the adsorbed layer is relatively poor and can be affected by variations in solution composition, ionic strength, or temperature, leading to aptamer desorption or disordered orientation. These factors reduce detection reproducibility and long-term stability [87]. Moreover, physical adsorption does not allow precise control over the spatial density or orientation of aptamers, which limits its application in systems requiring accurate signal regulation.

Therefore, the physisorption strategy is generally not suitable for complex biological samples or long-term monitoring applications, as these scenarios require high interfacial stability.

4.2. Self-Assembled Monolayers

SAMs are formed through spontaneous molecular organization on the electrode surface (Figure 3B), widely used for gold and other SAM-forming materials. By selecting suitable terminal groups (e.g., thiol, carboxyl, or amine), the molecules can assemble into a densely packed and ordered structure that allows fine control of aptamer spatial orientation and density [61,88]. It should be noted that SAMs are typically not used as a standalone immobilization method, but rather as an interfacial engineering strategy in combination with covalent attachment, such as Au-S bonding, thereby enabling precise regulation of the bio-interface. This strategy not only optimizes electron-transfer pathways but also reduces nonspecific adsorption, thus enhancing detection sensitivity and signal fidelity.

However, SAM-based interfaces are still limited by relatively weak stability under harsh electrochemical or biological conditions, potential structural defects such as incomplete packing or domain disorder, and gradual desorption over time, which may compromise long-term performance. In addition, the formation of highly ordered and defect-free monolayers often requires strict control over assembly conditions, making large-scale and highly reproducible fabrication challenging.

4.3. Covalent Chemical Immobilization

Covalent immobilization stabilizes aptamer attachment by forming robust chemical bonds between the aptamer and the electrode surface, significantly enhancing film stability and reproducibility [89]. Common approaches include Au-S bonding [89,90] (Figure 3C) and EDC/NHS esterification crosslinking [91] (Figure 3D). For example, thiolated aptamers can form strong Au-S bonds with gold nanoparticles on Au electrodes, achieving high-density and ordered immobilization. On carbon-based electrodes, EDC/NHS coupling can covalently link carboxyl- or amine-modified aptamers to the electrode surface.

Compared with physical adsorption, covalent strategies provide excellent structural robustness and are suitable for complex sample detection and long-term use. However, they require controlled reaction conditions to avoid damaging the aptamer structure or reducing its binding activity. From an architecture-dependent perspective, aptamer immobilization should be optimized according to the signal-transduction mechanism. For structure-switching E-AB sensors, immobilization chemistry must provide stable attachment while preserving aptamer conformational freedom, controlled probe spacing, and efficient redox reporter–electrode electron transfer. Thiol–gold chemistry combined with well-controlled SAMs is therefore particularly important for this architecture. For capture/release or strand-displacement-based sensors, immobilization should maintain the accessibility of hybridization domains and avoid excessive probe crowding, because steric hindrance can slow strand exchange and reduce signal reproducibility. For transistor-based aptasensors, aptamers must be positioned close to the conductive channel to enable effective interfacial charge modulation, while the immobilization layer must remain thin, stable, and resistant to nonspecific adsorption. Therefore, immobilization strategies should be evaluated not only by attachment stability, but also by their compatibility with conformational switching, probe exchange, or field-effect signal transduction.

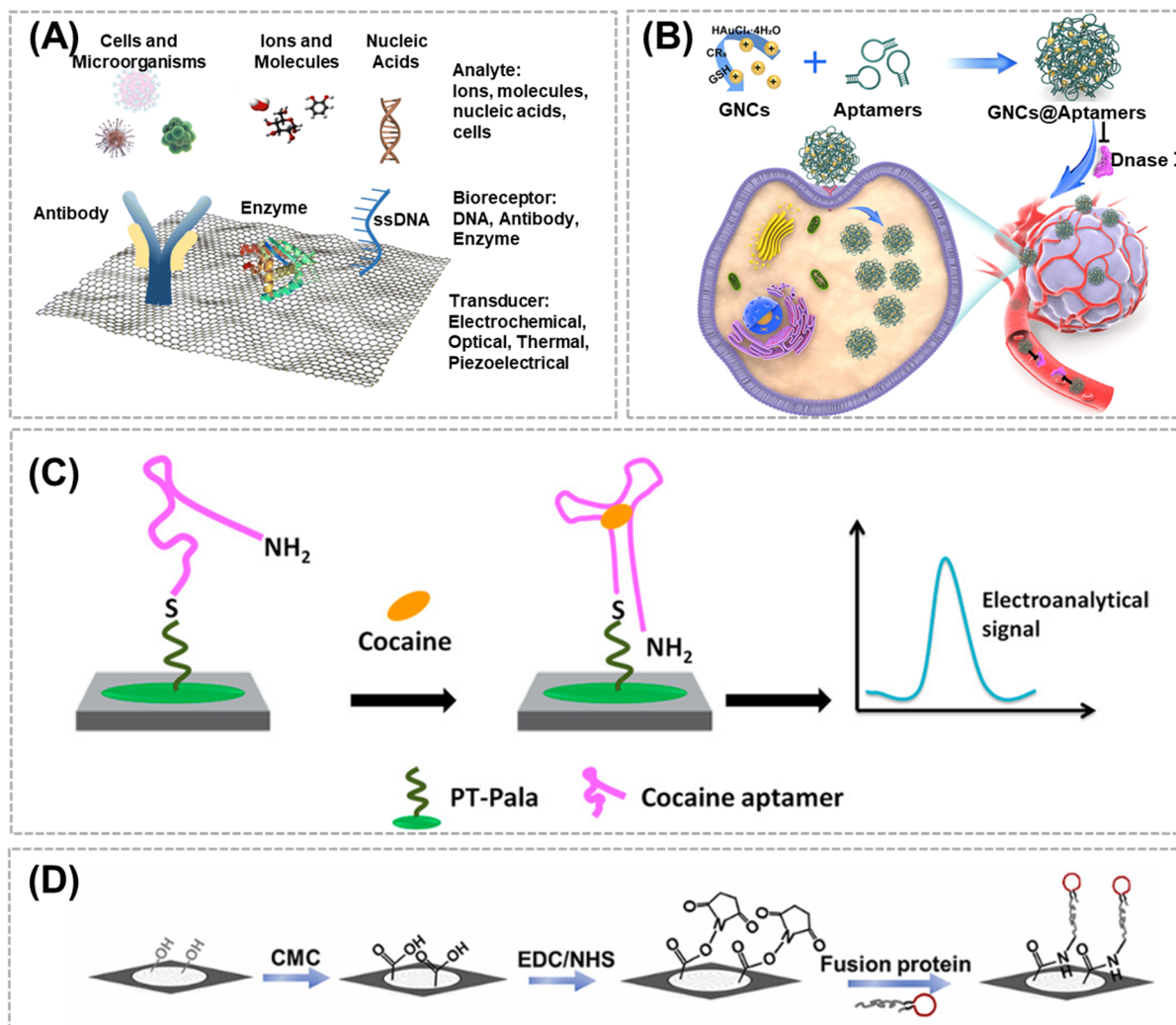


Figure 3. (A) Immobilization of aptamers on graphene via physical adsorption [87]. Copyright 2018 BioMed Central. (B) Aptamer-Functionalized Self-Assembled Monolayers (SAMs) [88]. Copyright 2022 American Chemical Society. (C) Aptamer immobilization onto the sensor surface via covalent coupling [89]. Copyright 2016 American Chemical Society. (D) EDC/NHS aptamer cross-linking on sensor surface [91]. Copyright 2023 Elsevier.

5. Antifouling and Anti-Nonspecific Adsorption

In practical detection environments, electrochemical aptamer sensors are often affected by nonspecific adsorption and matrix interference from serum, whole blood, saliva, sweat, urine, or food extracts. Abundant proteins, peptides, cells, lipids, and other macromolecules may adsorb onto the electrode surface, block aptamer accessibility, alter local mass transport, or disturb interfacial electron transfer. These effects can induce background current changes, signal drift, attenuated sensitivity, and apparent false responses. Therefore, constructing interfaces that suppress nonspecific adsorption while preserving aptamer recognition and efficient electron transfer is essential for reliable electrochemical aptamer sensing in real samples [92]. The development of antifouling strategies can be broadly viewed as a transition from simple blocking layers toward multifunctional interfacial architectures. Early approaches mainly used small-molecule diluents or hydrophilic blocking layers to passivate nonspecific adsorption sites on electrode surfaces. As electrochemical aptamer sensors have been extended from buffer-based assays to serum, whole blood, interstitial fluid, sweat, and other complex matrices, antifouling design has increasingly focused on maintaining molecular recognition, mass transport, and electron transfer during operation in complex samples [93].

Common chemical antifouling strategies include small-molecule diluents such as MCH [94], polyethylene glycol (PEG) and its derivatives [95], zwitterionic polymers [96,97], and short peptide modifications [98]. These materials reduce proteins adsorption by forming hydrophilic or ionically hydrated interfacial layers. However, conventional single-layer coatings still face important limitations, including limited long-term stability caused by desorption or structural rearrangement, and increased interfacial impedance when the antifouling layer is electrically insulating or too dense.

To address these limitations, recent studies have increasingly explored multilayer or composite interface engineering to balance antifouling performance with signal transduction efficiency. For example, copolymerized zwitterionic layers such as SBMA@PDA (Figure 4A) can form highly hydrated surfaces while maintaining favorable interfacial conductivity, enabling low-drift electrochemical aptamer sensing in complex media such as milk and blood [99]. Organic-inorganic hybrid coatings provide another route to combine antifouling protection with efficient electron transfer. For instance, a crosslinked BSA/AuNW/GA coating was designed by integrating gold nanowires with a protein-rich hydrated layer (Figure 4B) [100]. In this configuration, the conductive nanowire network facilitates electron transport, whereas the hydrated protein matrix helps reduce nonspecific adsorption through size exclusion and interfacial hydration. This example demonstrates that hybrid interfaces can help alleviate the trade-off between antifouling protection and electrochemical signal transduction.

Dynamic polymer networks have also been introduced to improve antifouling performance. Appel and co-workers developed polyacrylamide copolymer hydrogel interfaces and used machine-learning-assisted screening to identify compositions with improved resistance to serum fouling (Figure 4C) [101]. These results highlight that hydration, steric exclusion, and polymer network dynamics can jointly contribute to maintaining stable sensing interfaces.

In addition to chemical surface modification, physical diffusion-control layers have been used to block fouling species before they reach the recognition interface. In one membrane-protected E-AB configuration, a porous polysulfone membrane was used as an outer diffusion-control layer to restrict the transport of blood cells and large serum proteins while allowing smaller target molecules to access the aptamer-modified sensing layer (Figure 4D) [102]. This example illustrates how physical size-exclusion barriers can reduce fouling at blood-contacting sensing interfaces. Similarly, hydrogel-based protective coatings, such as agarose layers (Figure 4E), provide hydrated and porous barriers that reduce nonspecific adsorption from complex biological fluids [103]. Hierarchical interfacial architectures, such as nanoscale affinity double layers (NADLs) (Figure 4F), further integrate sample enrichment, matrix separation, and electrochemical sensing, thereby improving analytical performance in complex samples [104].

Importantly, antifouling interfaces should be designed according to the signal-transduction mechanism of the sensor. For redox-tagged E-AB sensors, antifouling layers must suppress nonspecific adsorption while preserving efficient electron transfer between the redox reporter and the electrode. Thick or electrically insulating coatings may reduce protein adsorption but can also attenuate the target-induced current response or slow the apparent response kinetics. For capture/release or strand-displacement-based sensors, antifouling protection should maintain the accessibility of hybridization domains and allow efficient probe exchange at the interface. Excessively dense polymer layers or sterically crowded surfaces may hinder strand displacement and reduce assay reproducibility. For FET-based aptasensors, antifouling layers must be thin, stable, and compatible with interfacial charge modulation, because excessive separation between the recognition event and the conductive channel can further weaken signals already affected by Debye screening. Thus, the suitability of an antifouling coating should be judged not only by its ability to reduce nonspecific adsorption, but also by its compatibility with the required electron-transfer, hybridization, or field-effect transduction process under the intended measurement conditions.

Overall, antifouling interface design has evolved from passive surface blocking toward cooperative regulation of hydration, steric exclusion, mass transport, and electron transfer. Multilayer, hydrogel-based, zwitterionic, and hybrid conductive interfaces do not merely prevent fouling; they aim to preserve aptamer accessibility and signal transduction under realistic operating conditions. Future antifouling strategies should therefore be evaluated not only by reduced protein adsorption, but also by long-term signal stability, response time, reversibility, and compatibility with continuous or wearable electrochemical aptamer sensing [105].

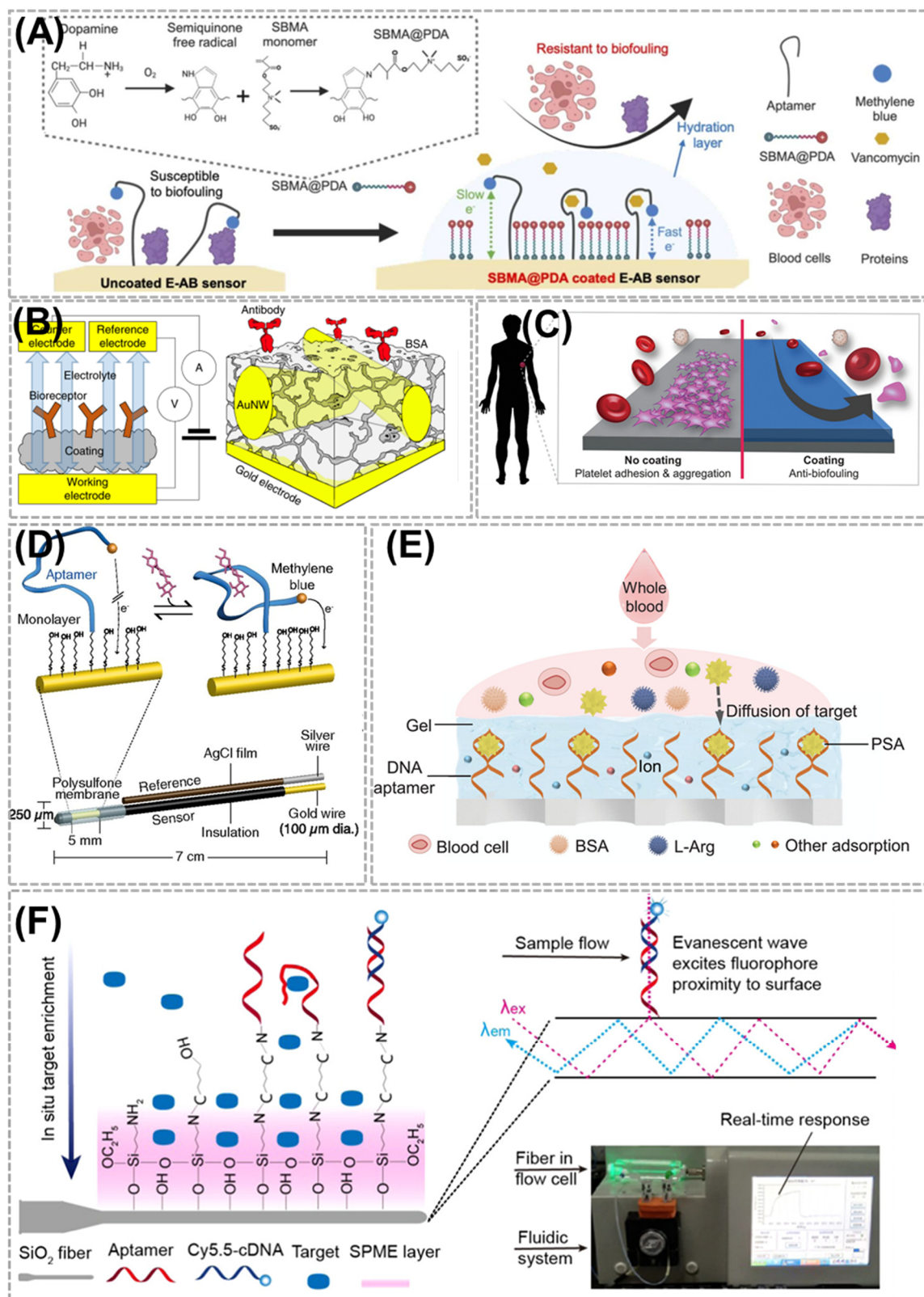


Figure 4. (A) SBMA@PDA zwitterionic coating for antifouling in electrochemical aptamer sensors [99].

Copyright 2026 Elsevier. (B) BSA/AuNW/GA coating for antifouling [100]. Copyright 2019 Springer Nature. (C)

Coating substrates with anti-biofouling hydrogels can mitigate platelet adhesion and aggregation [101]. Copyright 2022 Wiley-VCH. (D) Microporous polysulfone membrane shields the E-AB sensor from blood-cell interference [102]. Copyright 2017 National Academy of Sciences. (E) Antifouling properties of the agarose gel [103]. Copyright 2025 Wiley-VCH. (F) Nanoscale affinity double layer coated on the surface for antifouling [104]. Copyright 2021 American Chemical Society.

6. Applications of Aptamer-Based Electrochemical Sensors in Continuous Monitoring and Wearable Devices

With the rapid development of flexible electronics, microfabrication, and wireless communication technologies, electrochemical aptamer sensors are being extended from laboratory-based analytical platforms toward portable, wearable, and point-of-care applications. Many early electrochemical aptamer sensing systems relied on stationary measurement setups and external electrochemical workstations. Although these systems provided important proof-of-concept demonstrations with high analytical sensitivity and target selectivity, their direct use in on-site diagnostics, personalized health monitoring, and continuous molecular analysis remains limited by device portability, sampling format, operational stability, and system-level integration

The development of wearable and continuous electrochemical aptamer sensors builds on earlier demonstrations of real-time aptamer-based sensing in complex matrices. Before the emergence of fully wearable devices, microfluidic E-AB sensors had already enabled continuous molecular monitoring in undiluted blood serum, and subsequent miniaturized E-AB systems further extended this concept toward real-time in vivo molecular or drug measurements. In this context, microneedle, flexible, and wireless platforms can be regarded as efforts to translate established real-time aptamer sensing principles into more practical sensing formats. Depending on the device design, these systems may address different translational requirements, including minimally invasive sampling, mechanical compliance, portable signal acquisition, wireless communication, and improved operational stability.

6.1. Wearable and Flexible Detection Platforms

Wearable electrochemical sensors represent a vital technological pathway for continuous personal health monitoring. These devices are evolving from external biofluid analysis (sweat, tears) toward continuous in vivo monitoring. Within such systems, aptamers serve as highly selective recognition elements characterized by reversible conformational responsiveness and excellent chemical stability. Their intrinsic flexibility enables reliable recognition even under mechanical deformation and complex physiological conditions, granting unique advantages for non-invasive and minimally invasive detection.

Bakhshandeh et al. [106] reported the Wearable Aptalyzer system, a representative example of aptamer-based wearable sensing (Figure 5A). This device integrates a microneedle array (MNA) with an electrochemical detection module to construct a multichannel sensing platform featuring both mechanical compliance and biocompatibility on a flexible substrate. A thiolated aptamer recognition layer provides highly specific binding toward targets such as glucose, lactate and cortisol, while the electrochemical transduction module enables in situ detection of analytes in interstitial fluid. Structurally, the microneedles slightly penetrate the stratum corneum without stimulating nerve endings, achieving painless, continuous sampling and real-time signal acquisition. The use of highly conductive carbon composites and multilayer encapsulation interfaces significantly enhances signal stability and anti-interference capability, effectively suppressing protein adsorption, ionic fluctuations, and motion-induced noise. This study demonstrates both the structural programmability and interface engineering potential of aptamers within flexible systems, while establishing a wearable sensing paradigm that maintains high sensitivity and reproducibility in dynamic environments. The platform thus lays a foundation for future intelligent POCT systems capable of smart feedback and multi-parameter health management. Gao et al. [107] further developed a flexible multichannel electrochemical aptamer sensing platform for in situ and continuous monitoring of multiple biomarkers within wound microenvironments. A multi-electrode array was fabricated on a bendable substrate, where thiolated or functionally modified aptamers were site-specifically immobilized on each channel to enable parallel detection of parameters such as pH, uric acid, and inflammation-related molecules. To ensure long-term responsiveness in protein-rich and humid environments, the researchers implemented a series of antifouling and encapsulation strategies, including restrictive layers and hydrophilic/hydrophobic composite coatings. Moreover, integration with a signal processing and wireless transmission unit enabled on-skin signal acquisition and remote data communication, representing a major step toward real-time, personalized wound monitoring and wearable biochemical sensing.

6.2. Miniaturization and System Integration

To achieve portable detection and multiparametric simultaneous analysis, miniaturization and system integration have become crucial development trends in electrochemical aptamer sensors. The integration of microfluidics, electrode miniaturization, and 3D printing technologies enables electrochemical aptamer sensors to accomplish sample manipulation, target recognition, signal amplification, and transduction within millimeter- or even micrometer-scale devices. However, the inherent signal attenuation associated with miniaturization has driven the advancement of novel signal amplification mechanisms and transistor-level integrated architectures.

Yu et al. [33] designed a paper-based electrochemical aptamer sensor that exemplifies the synergy between low-cost fabrication and integrated functionality. The study employed wax-printed microfluidic patterns to define liquid flow paths and used electrochemical deposition to form gold electrodes, onto which thiolated aptamers were immobilized to construct the recognition interface. The porous paper substrate facilitated both solution diffusion and electron transfer, while capillary action enabled self-driven sample transport. This system demonstrated nanomolar-level sensitivity in the detection of small-molecule biomarkers, highlighting the potential of paper-based platforms for on-site rapid analysis and resource-limited diagnostics.

In pursuit of high-performance integration, Ji et al. [108] developed an organic electrochemical transistor (OECT)-based electrochemical aptamer sensor (Figure 5B) that seamlessly integrates the molecular recognition layer with the electronic amplification unit, achieving co-localized recognition and signal amplification. Upon aptamer binding to transforming growth factor beta 1, the induced conformational and electrostatic variations modulate the carrier density in the OECT channel, producing in situ signal amplification by 10^3 – 10^4 fold. This strategy significantly enhances the signal response and signal-to-noise ratio (SNR) in microelectrode systems, effectively overcoming the limitations of conventional electrochemical aptamer sensors that rely on external amplification circuits.

Gao et al. [109] reported the PillTrek capsule-based electrochemical platform is a miniaturized system with a total volume below 1 cm³ that integrates a power management module, a wireless communication unit, and multiple sensing elements including aptamer, potentiometric and enzyme modules for multichannel continuous monitoring of various biomolecules in the gastrointestinal tract. (Figure 5C). Within this system, the aptamer recognition module maintains structural stability and reversible binding behavior under high ionic strength and multicomponent biofluid conditions, ensuring both high selectivity and reproducible signal output. This study not only validated the structural robustness and antifouling capability of aptamers in complex physiological environments but also demonstrated their compatibility and scalability in highly integrated systems. By achieving the organic integration of molecular recognition, signal transduction, and wireless communication within a compact capsule, PillTrek establishes a design paradigm for the miniaturization, system-level encapsulation, and continuous in vivo monitoring of electrochemical aptamer sensors.

6.3. Real-Time Monitoring and Wireless Communication

Real-time continuous monitoring represents a critical step toward the clinical translation of electrochemical aptamer sensors. Reagent-free E-AB systems based on reversible conformational switching can generate repeated signal responses during target binding and dissociation, enabling continuous measurements without regeneration or washing steps. This property provides an important basis for molecular monitoring in complex biological environments. With advances in miniaturized electronics, wireless communication, and energy management technologies, electrochemical aptamer sensors are increasingly being integrated with signal processing and data transmission modules, supporting real-time molecular readout and remote monitoring applications [105]. Recent wearable E-AB systems have further advanced from preclinical prototypes toward human studies. For example, Booth et al. reported a pilot phase clinical trial of a wearable electrochemical aptamer-based patch for continuous drug concentration measurement. This study demonstrated the potential of E-AB sensing for minimally invasive therapeutic drug monitoring in humans and represents an important step from laboratory and animal-model demonstrations toward clinical translation [110]. Importantly, drift correction in structure-switching E-AB sensors is not merely a future requirement but has already been experimentally demonstrated in continuous-monitoring settings. Early dual-reporter E-AB designs used a second redox reporter as an internal reference to correct baseline drift in whole blood, thereby improving the reliability of long-duration measurements [111]. Kinetic differential measurement (KDM) provides another important strategy for drift correction in E-AB sensors. In this approach, responses are collected at selected square-wave frequencies that drift in concert but respond differently to target binding. This differential readout suppresses common-mode drift and supports calibration-free or calibration-minimized in vivo molecular measurements [112]. More recent studies using chemically stabilized aptamers, including xenonucleic-acid-employing E-AB sensors [29], have shown that improving probe stability can

substantially reduce in vivo drift and extend continuous monitoring duration [113]. These advances indicate that drift correction is already an integral part of advanced E-AB sensing systems, rather than only a future direction for signal processing.

For example, Tong et al. developed a carbon nanotube field-effect transistor (CNT-FET) aptamer array as an example of spatially patterned multi-aptamer sensing on a single chip (Figure 5D) [114]. In this study, a mixed MESNA/MCH self-assembled monolayer was used to regulate interfacial chemistry, and multiple antibiotic-specific aptamers were inkjet-printed onto the device for the detection of kanamycin, oxytetracycline, and sulfaquinolaxaline. This work demonstrates the feasibility of patterning different aptamer-functionalized transistor channels for parallel electrical readout under the reported assay conditions. However, the reported multiplexed format should not be interpreted as a unique advantage of FET architectures, nor should the reported rapid and ultralow-concentration responses be generalized without considering mass transport, binding kinetics, interfacial confinement, assay geometry, and signal-processing procedures. Therefore, this example is discussed here as a representative FET-based readout design, rather than as definitive evidence that FET aptasensors can universally achieve seconds-scale femtomolar detection or robust operation in realistic biological media.

A critical limitation of FET-based biosensors is that their signal relies on electrostatic modulation at the semiconductor/electrolyte interface. In physiological media, the Debye length is typically less than 1 nm, meaning that charges generated by biomolecular recognition events can be strongly screened before they influence channel conductance. Protein adsorption, nonspecific binding, and interfacial fouling can further alter surface potential, block receptor accessibility, and generate baseline drift. These effects are especially problematic for direct operation in serum, plasma, whole blood, or other protein-rich samples. Some aptamer-FET studies have attempted to address Debye screening by using small-molecule targets and conformationally adaptive aptamers that reposition charged nucleic acid backbones close to the transistor surface. Nevertheless, broader translation of FET-based aptasensors still requires rigorous validation of antifouling chemistry, long-term interfacial stability, device-to-device reproducibility, and performance in minimally processed real samples.

Wireless power transfer and data communication provide another important route toward integrated aptamer sensing systems. Gao et al. integrated wireless communication and energy-coupling modules into an electrochemical detection platform, enabling non-contact signal transmission and remote readout [109]. The system used radio-frequency (RF) energy for wireless power delivery and data transfer, thereby linking molecular recognition, electrochemical signal transduction, and electronic readout in an integrated architecture. Similarly, Gao et al. reported a wireless nanobioelectronic aptamer sensor in which aptamer recognition, electrochemical amplification, and wireless communication modules were integrated within a millimeter-scale device (Figure 5E) [115]. This design enabled real-time in vivo drug monitoring through RF-powered operation and wireless data transmission, highlighting the potential of aptamer-based sensing architectures for implantable or remotely operated bioelectronic systems.

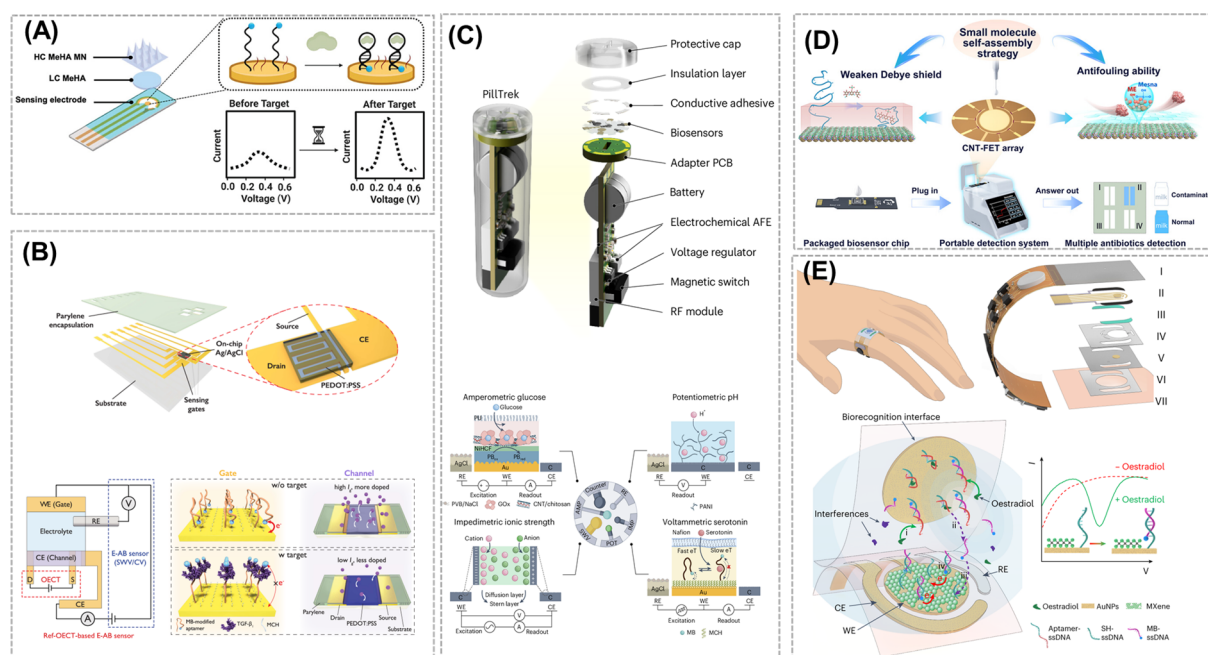


Figure 5. (A) A magnified view of the components of the Wearable Aptalyzer, with a schematic showing the mechanism of signal transduction before and after target capture [106]. Copyright 2024 Wiley-VCH. (B) Schematic

illustration and sensing mechanism of the ref-OECT-based electrochemical aptamer-based sensor for TGF- β 1 detection [108]. Copyright 2023 Springer Nature. (C) Schematic illustration of the inkjet-printed electrochemical sensor array and the fully assembled and exploded views of the PillTrek device [109]. Copyright 2025 Springer Nature. (D) Schematic representation of the CNT-FET aptamer array for multiplexed antibiotic detection [114]. Copyright 2025 American Chemical Society. (E) Schematic illustration of the AuNPs-MXene-based aptamer sensor for reagent-free in situ oestradiol detection and the layered design of the flexible wireless microfluidic wearable patch [115]. Sections I to VII represent plastic substrate interfacing with the FPCB (I), inkjet-printed sensor array (II), carbachol-loaded hydrogels (carbagels) (III), microfluidic channels (IV), biorecognition interface (V), sweat accumulation layer (VI) and the skin (VII). Copyright 2024 Springer Nature.

6.4. Comparative Analytical Performance of Representative Electrochemical Aptamer Sensors

To provide a clearer overview of the analytical performance of representative electrochemical aptamer sensors discussed in this review, typical examples are summarized in Table 2. The comparison focuses on relatively standardized and cross-comparable parameters, including target analyte, electrode material design, detection mode, limit of detection (LOD), linear range, and application scenario. Selectivity and stability are also critical performance indicators; however, they are reported under highly different conditions across studies, including different interfering species, sample matrices, storage periods, mechanical deformation protocols, and continuous-operation times. Therefore, rather than forcing these parameters into a single numerical comparison, we discuss them in the corresponding sections according to the specific sensing architecture and application context.

As shown in Table 2, the reported electrochemical aptamer sensors differ substantially in target type, electrode/material design, signal mode, LOD, working range, and application scenario. These differences indicate that sensor performance cannot be assessed solely by the lowest reported LOD. Instead, analytical parameters should be interpreted in the context of the intended application, such as food-safety analysis, clinical diagnostics, on-site detection, drug monitoring, or wearable bioanalysis.

From an application-oriented perspective, different electrochemical aptamer sensor architectures should not be evaluated by the same performance criteria. Endpoint assays for food safety, environmental monitoring, or laboratory diagnostics often prioritize low LODs, wide linear ranges, matrix tolerance, and compatibility with disposable or low-cost electrodes. In these cases, nanomaterial-enhanced, capture/release-based, or signal-amplified aptasensors can be advantageous. In contrast, wearable, implantable, or continuous monitoring systems require reversible recognition, stable baseline, antifouling protection, rapid signal recovery, and calibration-free or calibration-minimized operation over extended periods. These requirements make reagent-free structure-switching E-AB sensors particularly relevant for continuous molecular monitoring. FET-based aptasensors may be useful for label-free and miniaturized electronic readout, but their practical value should be evaluated together with ionic-strength tolerance, antifouling stability, device reproducibility, and performance in realistic biological samples. Therefore, Table 2 should be interpreted as a representative comparison of application-dependent trade-offs rather than a ranking based only on sensitivity.

Table 2. Analytical performance and application scenarios of representative electrochemical aptamer sensors discussed in this review.

Target	Electrode Material	Detection Mode	LOD	Linear Range	Application	Ref.
Pb ²⁺ /Hg ²⁺	AuNPs@MCNs/SPD Es	DPV	Pb ²⁺ : 8.8 pg mL ⁻¹ ; Hg ²⁺ : 0.7 pg mL ⁻¹	Pb ²⁺ : 0.1–1000.0 ng mL ⁻¹ ; Hg ²⁺ : 0.001–100.0 ng mL ⁻¹	Food or environment	[55]
Thrombin	PtNPs/CNCs	DPV	10 fM	0.05 pM–20 nM	Biomarker	[58]
Streptomycin	MMCM/MGCE	DPV	0.015 nM	0.172–17.2 × 10 ³ nM	Antibiotic residue	[68]
Prostate-specific antigen	PANI/AuNPs/peptide/GCE	DPV	0.085 pg mL ⁻¹	0.1 pg mL ⁻¹ –100 ng mL ⁻¹	Clinical diagnostics	[79]
Cocaine/MDPV	AuNP/SWCNT PEDs	ACV	Cocaine: 1 μ M; MDPV: 0.1 μ M	Cocaine: 0–600 μ M; MDPV: 0–100 μ M	On-site detection	[33]
Vancomycin	SBMA@PDA/AuNPs-MXene	SWV	NR	1.7–106 μ M	Therapeutic drug monitoring	[99]
Glucose/lactate	Hydrogel microneedles/Au	SWV	Glucose: 2.4 mM; lactate: 1.04 mM	Glucose: 0–50 mM; lactate: 0–20 mM	Wearable in vivo	[106]
Oestradiol	AuNPs-MXene	SWV	0.14 pM	0.1–100 pM	Hormone monitoring	[115]

7. Outlook

Electrochemical aptamer sensors have shown considerable promise for portable, wearable, and real-time molecular monitoring. However, their practical translation is still limited by several field-specific challenges that

cannot be solved by sensitivity improvement alone. It is also important to distinguish the application maturity of different aptamer sensor architectures. Nanomaterial-enhanced or sandwich-type electrochemical aptasensors can provide excellent analytical sensitivity in endpoint assays, but many of these systems remain primarily validated in *ex vivo* or short-term detection formats. FET-based aptasensors offer label-free electronic readout, but their operation in physiological media is strongly influenced by Debye screening, nonspecific adsorption, device-to-device variability, and interfacial stability. In contrast, reagent-free structure-switching E-AB sensors have provided some of the most direct demonstrations of continuous molecular monitoring in complex biological environments [102,105]. Accordingly, future development should be guided by application-specific design criteria rather than by a single performance metric. For endpoint or disposable assays, improving sensitivity, simplifying operation, and reducing fabrication cost may remain the primary priorities. For wearable or implantable monitoring, however, the central requirements shift toward reversible signal generation, long-term interfacial stability, antifouling protection, minimized drift, and reliable calibration-free or calibration-minimized readout. Materials and interfaces that improve LOD in short-term assays may not necessarily be suitable for continuous sensing if they introduce irreversible adsorption, unstable baselines, or slow signal recovery.

For applications in complex biological fluids or in *vivo* environments, long-term operational stability remains one of the most critical issues. Continuous exposure to proteins, cells, salts, metabolites, enzymes, and mechanical perturbations can lead to biofouling, aptamer degradation, interfacial passivation, and signal drift. These effects may gradually weaken electron transfer, alter aptamer conformation, or reduce target accessibility, thereby compromising the accuracy of continuous measurements. Recent progress in long-duration E-AB sensing further shows that stable *in vivo* operation requires coordinated optimization of aptamer chemical stability, monolayer integrity, electrode interface, electrochemical interrogation, and device configuration. For example, xenonucleic-acid-employing E-AB sensors have recently enabled continuous, week-long, seconds-resolved *in vivo* drug measurements, highlighting chemically stabilized aptamers as an important strategy for extending operational lifetime and suppressing long-term drift [113].

Another major challenge is the development of calibration-free or calibration-minimized sensing strategies. Many electrochemical aptamer sensors still rely on external calibration curves established under controlled buffer conditions, whereas real samples introduce variations in temperature, pH, ionic strength, nonspecific adsorption, baseline drift, and individual sample composition. Importantly, in structure-switching E-AB sensors, drift correction and calibration minimization are not merely future possibilities but have already been experimentally demonstrated. Dual-reporter E-AB sensors use an additional redox reporter as an internal reference to correct baseline drift in whole blood [111]. KDM further exploits the frequency-dependent signaling behavior of E-AB sensors by comparing responses at selected square-wave frequencies that drift in concert but respond differently to target binding, thereby suppressing common-mode drift during continuous measurements [112]. Dual-frequency and ratiometric interrogation strategies have also supported calibration-free or calibration-minimized *in vivo* molecular measurements [116]. Together with chemically stabilized aptamer interfaces [29,113], these self-referenced electrochemical interrogation strategies provide an important foundation for reliable wearable and implantable E-AB sensing systems, where frequent recalibration is impractical.

Building on these established electrochemical correction strategies, artificial intelligence and machine-learning algorithms may further improve the practical utility of electrochemical aptamer sensors, but they should be regarded as complementary tools rather than standalone solutions [117]. For example, recent electrochemical sensing work has shown that regression-based machine-learning models can assist drift-corrected quantification when combined with dual-channel or dual-pulse interrogation strategies. In future E-AB systems, AI-assisted models may integrate multi-frequency voltammetric responses, dual-reporter or ratiometric signals, electrode impedance, temperature, motion, and historical baseline trends to distinguish true target-induced responses from biofouling, aptamer degradation, mechanical perturbation, and inter-device variability. These approaches should be combined with physically interpretable sensing mechanisms and validated under realistic conditions, including complex biological matrices, long-term operation, mechanical deformation, independent sensor batches, and prospective time-course measurements. In this sense, AI is most likely to support adaptive signal processing based on established E-AB drift-correction methods such as KDM, internal referencing, ratiometric readout, and chemically stabilized aptamer interfaces.

Overall, the next stage of electrochemical aptamer sensor development should shift from simply pursuing lower detection limits toward achieving robust, reversible, and reliable signal output in real-world environments. Key priorities include long-term *in vivo* stability, calibration-free or self-referenced operation, reproducible large-scale fabrication, antifouling interfaces compatible with rapid electron transfer, and integrated systems validated in clinically or environmentally relevant samples. Addressing these challenges will be essential for transforming

electrochemical aptamer sensors from promising laboratory prototypes into reliable tools for point-of-care testing, wearable health monitoring, therapeutic drug monitoring, and continuous molecular diagnostics.

8. Conclusions

Electrochemical aptamer sensors have developed into versatile platforms for molecular recognition and signal transduction, with important progress in electrode materials, aptamer immobilization, nanostructured interfaces, antifouling strategies, and miniaturized device integration. These advances have improved sensitivity, selectivity, and compatibility with complex samples, while different sensing architectures provide complementary strengths. Reagent-free structure-switching E-AB sensors are particularly suitable for reversible and continuous molecular readout, whereas FET-based and nanomaterial-enhanced aptasensors offer useful routes for label-free electrical detection, signal amplification, and device integration. Looking forward, the field should move beyond the isolated pursuit of lower detection limits toward robust and reliable sensing under realistic operating conditions. Long-term molecular monitoring requires not only sensitive electrode interfaces, but also stable aptamer recognition, reproducible surface chemistry, effective antifouling protection, minimized signal drift, and calibration-free or calibration-minimized operation. For structure-switching E-AB sensors, established strategies such as kinetic differential measurement, ratiometric readout, internal referencing, and chemically stabilized aptamer interfaces provide important foundations for continuous monitoring in complex biological environments. Future artificial intelligence or machine-learning tools may further assist adaptive signal processing, but they should be integrated with these physically grounded electrochemical correction strategies rather than treated as standalone solutions. Therefore, future electrode materials, interface designs, and wearable or implantable systems should be evaluated by their ability to sustain accurate, reversible, and stable signal output in real biological or environmental samples. Such system-level development will be essential for translating electrochemical aptamer sensors into reliable tools for point-of-care testing, therapeutic drug monitoring, wearable health monitoring, and continuous molecular diagnostics.

Author Contributions

P.M.: literature investigation, data curation, visualization, writing—original draft preparation; Y.Z.: supervision, writing—review and editing; G.A.W.: conceptualization, funding acquisition, reviewing and editing; Wenqian Feng: conceptualization, supervision, funding acquisition, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used OpenAI's ChatGPT to check grammar and improve the clarity of the original manuscript text written by the authors. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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