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Advances in aptamer-based electrochemical biosensors for disease diagnosis: integration of DNA and nanomaterials

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Aptamer-based electrochemical biosensors (AEBs) have emerged as a highly promising platform for disease diagnostics, offering high specificity, sensitivity, and real-time detection capabilities. These biosensors leverage the unique molecular recognition properties of aptamers and the efficient electrochemical transduction mechanisms to detect various disease biomarkers, including those associated with cancer, cardiovascular diseases, and infectious diseases. A key advancement in this field is the integration of DNA aptamers with functional nanomaterials such as gold nanoparticles (AuNPs), graphene oxide (GO), carbon nanotubes (CNTs), and metal–organic frameworks (MOFs), which significantly enhance sensor performance by improving electron transfer, signal amplification, and biocompatibility. This review comprehensively discusses the fundamental principles of electrochemical biosensors, recent advances in aptamer-based biosensing, and strategies for enhancing sensitivity and stability, particularly through signal amplification techniques and nanomaterial engineering. Furthermore, the challenges related to real-world applicability, including sample matrix effects, sensor miniaturization, and clinical validation, are critically examined. Finally, future perspectives on the development of portable, multiplexed, and point-of-care (POC) biosensors are provided, emphasizing their potential to bridge the gap between laboratory research and clinical diagnostics. The continuous evolution of AEBs, driven by innovations in nanotechnology and bioengineering, is expected to revolutionize disease diagnostics, facilitating early detection and personalized medicine.

1. Introduction

The main Aptamer-based electrochemical biosensors (AEBs) have emerged as a promising tool for disease diagnosis, offering high specificity, sensitivity, and rapid detection capabilities. Conventional diagnostic methods, such as enzyme-linked immunosorbent assays (ELISA) and polymerase chain reaction (PCR), while highly accurate, often require specialized laboratory equipment, lengthy processing times, and skilled personnel.[1] In contrast, electrochemical biosensors, which transduce biochemical interactions into measurable electrical signals, provide a highly efficient alternative for detecting disease biomarkers at ultralow concentrations.[2] Particularly, the incorporation of aptamers—single-stranded DNA or RNA oligonucleotides that selectively bind to specific targets—has further enhanced the analytical performance of electrochemical biosensors. Aptamers exhibit advantages over traditional antibodies, such as greater stability, ease of synthesis, and lower batch-to-batch variability, making them highly suitable for real-time and point-of-care (POC) diagnostics.[3]

Recent advancements in materials science have further expanded the capabilities of AEBs by integrating functional nanomaterials to enhance signal transduction, stability, and biocompatibility. Gold nanoparticles (AuNPs), carbon-based nanostructures such as graphene and carbon nanotubes (CNTs), and metal–organic frameworks (MOFs) have been extensively employed to facilitate electron transfer, amplify electrochemical signals, and provide robust scaffolds for aptamer immobilization.[4] These nanoengineered biosensors demonstrate remarkable improvements in sensitivity, often reaching detection limits in the femtomolar (fM) to attomolar (aM) range, which is critical for the early detection of diseases such as cancer, cardiovascular disorders, and infectious diseases.[5] Moreover, the development of hybrid nanocomposites combining multiple nanomaterials has enabled further enhancements in sensor performance, enabling the detection of multiple biomarkers in a single assay.[6]

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Cancer biomarker detection has been one of the primary focuses of AEB development, with aptamer-functionalized electrochemical sensors demonstrating significant potential for the detection of prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP).[7] Similarly, cardiovascular diseases, which remain the leading cause of mortality worldwide, have been targeted using AEBs capable of detecting cardiac troponin I, myoglobin, and N-terminal pro b-type natriuretic peptide (NT-proBNP).[8] Infectious disease diagnosis has also seen substantial advancements, particularly during the COVID-19 pandemic, where electrochemical aptasensors were employed for the rapid detection of SARS-CoV-2 RNA and spike proteins, highlighting the feasibility of POC diagnostics for real-time pathogen detection.[9]

Despite these advances, several challenges hinder the widespread clinical adoption of AEBs. One major issue is the presence of interfering substances in complex biological matrices, such as serum, whole blood, or saliva, which can affect sensor performance and lead to false-positive or false-negative results.[10] Additionally, the stability of aptamers in physiological conditions, particularly their susceptibility to nuclease degradation, poses a limitation for *in vivo* applications. To address these issues, researchers have explored various stabilization strategies, including chemical modifications such as locked nucleic acids (LNAs) and polyethylene glycol (PEG) conjugation to enhance aptamer robustness.[11] Furthermore, efforts to integrate microfluidic platforms with AEBs have facilitated automation and miniaturization, paving the way for the development of wearable and implantable biosensing devices.[12]

As shown in Fig. 1, this review provides a comprehensive analysis of the latest advancements in aptamer-based electrochemical biosensors for disease diagnosis, with a particular emphasis on the integration of DNA aptamers and functional nanomaterials. The key design principles and mechanisms of electrochemical aptasensors are discussed, followed by an in-depth examination of recent breakthroughs in cancer, cardiovascular, and infectious disease biomarker detection. Furthermore, the review highlights the challenges associated with real-world applications and explores emerging strategies for overcoming these limitations. Finally, future perspectives on miniaturization, portability, and real-time sensing platforms are presented, bridging the gap between laboratory research and clinical applications. Early seminal work by Song *et al.* (2008) and Willner *et al.* (2010) laid the foundation for aptamer-target specificity and electrochemical coupling strategies.

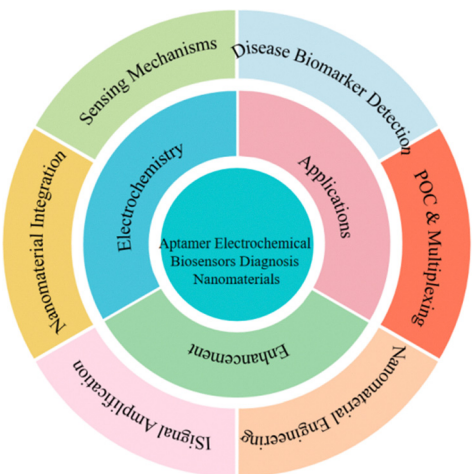

Fig. 1 Summary of this review.

2. Principles of aptamer-based electrochemical biosensing

2.1 Sensing mechanisms: amperometric, voltammetric, EIS, PEC, ISFET

2.1.1 Amperometric, voltammetric, and impedimetric detection. Electrochemical biosensors rely on the direct conversion of biochemical interactions into electrical signals, facilitating the rapid and highly sensitive detection of disease biomarkers. Among the various electrochemical sensing mechanisms, amperometry, voltammetry, and electrochemical impedance spectroscopy (EIS) are the most widely employed due to their ability to quantify analytes with high precision and selectivity.[13] These techniques exploit different electrochemical principles, with amperometric detection measuring current changes associated with redox reactions, voltammetric methods providing information on electroactive species through applied potential sweeps, and impedimetric sensing evaluating interfacial charge transfer resistance. The integration of aptamer-functionalized electrodes in these detection modes has further enhanced biosensor performance, offering significant improvements in sensitivity, detection limits, and real-time analytical capabilities.[14]

Amperometric biosensors measure the current generated by an electrochemical reaction at a fixed potential, making them highly suitable for detecting enzymatic activity or redox-active biomolecules.[15] The principle relies on faradaic electrochemical reactions, where the oxidation or reduction of an analyte at the electrode surface produces a measurable current proportional to its concentration. In aptamer-based electrochemical biosensors (AEBs), amperometric detection is often enhanced by nanomaterial modifications, such as gold nanoparticles (AuNPs) and graphene oxide (GO), which facilitate electron transfer and amplify the electrochemical response.[16] For instance, a recent study demonstrated that an AuNP-modified screen-printed electrode coupled with an aptamer-based sensing platform enabled the ultra-sensitive detection of prostate-specific antigen (PSA) at femtomolar (fM) concentrations, showcasing the potential of amperometric aptasensors for cancer diagnostics.[17] Additionally, enzymatic signal amplification, where horseradish peroxidase (HRP) or glucose oxidase (GO_x) catalyzes redox reactions, has further enhanced amperometric biosensor sensitivity by generating electron donors that participate in electrochemical cycling.[18]

Voltammetry encompasses a range of electrochemical techniques, including cyclic voltammetry (CV), differential pulse voltammetry (DPV), and square wave voltammetry (SWV), each

offering unique advantages for aptamer-based biosensing.[19] CV is widely used to evaluate the redox properties of aptamer-modified electrodes, providing insights into binding interactions and sensor stability.[20] However, DPV and SWV have gained prominence in biosensing applications due to their superior signal-to-noise ratio (SNR) and lower detection limits. These techniques involve applying a series of potential pulses, allowing the selective quantification of target molecules in complex biological samples. In a recent study, a graphene oxide-functionalized aptamer sensor employing SWV achieved picomolar (pM) detection of thrombin, highlighting its potential for cardiovascular disease biomarker analysis.[21] Moreover, the incorporation of redox-active nanomaterials, such as ferrocene and Prussian blue derivatives, has further enhanced the sensitivity and specificity of voltammetric biosensors, enabling real-time, label-free detection of infectious disease markers, including SARS-CoV-2 proteins and viral RNA.[22]

Electrochemical impedance spectroscopy (EIS) is a powerful label-free detection technique that measures changes in the electrical impedance of an electrode–electrolyte interface upon target binding.[23] Unlike amperometric and voltammetric methods, which rely on direct electron transfer processes, EIS detects variations in charge transfer resistance (R_{ct}) and capacitance (C_{dl}), providing valuable insights into molecular interactions at the sensor surface.[24] Aptamer-based impedimetric sensors leverage nanostructured electrode modifications, such as self-assembled monolayers (SAMs) and carbon-based nanomaterials, to enhance binding affinity and minimize non-specific adsorption.[25] A recent study utilizing a graphene-modified impedimetric aptasensor successfully detected amyloid-beta peptides, a key biomarker for Alzheimer's disease, with high selectivity in cerebrospinal fluid samples, demonstrating the clinical relevance of EIS-based aptasensors.[26] Additionally, the integration of machine learning algorithms with EIS data processing has enabled real-time signal interpretation, significantly improving biosensor reliability and diagnostic accuracy.[27]

Overall, amperometric, voltammetric, and impedimetric detection techniques have revolutionized aptamer-based electrochemical biosensing, each offering distinct advantages tailored to specific diagnostic applications. While amperometry provides high sensitivity and straightforward signal quantification, voltammetry enables detailed electrochemical profiling, and EIS offers label-free, non-invasive detection with minimal [sample preparation requirements], as outlined in Table 1. Future advancements in sensor miniaturization, artificial intelligence-driven data analysis, and hybrid electrochemical platforms are expected to further enhance the clinical applicability of these biosensing technologies, bridging the gap between laboratory research and real-world diagnostics. As established in the foundational study by Willner's group, the electron tunneling effects between aptamer conformations and modified electrodes offer mechanistic insights into signal propagation (Willner *et al.*, 2010).

While amperometric detection offers simplicity and high current response, it is often limited by redox reagent dependency. In contrast, EIS provides label-free detection but suffers from sensitivity drawbacks. Therefore, optimal sensing modality selection must consider target analyte properties and matrix complexity.

2.1.2 Signal amplification techniques for ultrasensitive detection. Achieving ultrasensitive detection in electrochemical biosensors requires efficient signal amplification strategies that enhance the transduction of biomolecular interactions into measurable electrical signals. In aptamer-based electrochemical biosensors (AEBs), the binding of a target molecule induces minute electrochemical changes, necessitating amplification methods to improve detection limits, sensitivity, and dynamic range.[28] Signal amplification techniques can be broadly categorized into enzymatic amplification, nanomaterial-based signal enhancement, and electrochemical cycling strategies, each contributing to the improvement of sensor performance for disease biomarker detection. Recent advancements in these methodologies have enabled the detection of biomolecules at femtomolar (fM) and even attomolar (aM) levels, making them highly suitable for early-stage disease diagnostics and point-of-care (POC) applications.[29]

Enzymatic signal amplification relies on the catalytic activity of enzymes to generate electrochemically active species, thereby amplifying the detection signal in proportion to the target molecule concentration. Horseradish peroxidase (HRP), glucose oxidase (GO_x), and alkaline phosphatase (ALP) are among the most widely used enzymes in electrochemical aptasensors.[30] These enzymes catalyze redox reactions that produce electroactive intermediates, enhancing electron transfer at the electrode surface. For instance, an HRP-functionalized aptamer biosensor for cardiac troponin I (cTnI) detection achieved a 10-fold increase in sensitivity by utilizing hydroquinone-mediated redox cycling, enabling detection limits as low as 0.5 fM.[31] Additionally, enzyme cascades, where multiple enzymatic reactions are coupled, have been developed to further boost electrochemical signals. A recent study demonstrated that integrating GO_x and HRP in a dual-enzyme system led to a synergistic amplification effect, significantly enhancing the detection of prostate-specific antigen (PSA) in serum samples.[32]

The incorporation of functional nanomaterials in electrochemical biosensors has revolutionized signal amplification by providing high surface area, excellent conductivity, and catalytic properties. Gold nanoparticles (AuNPs), carbon nanotubes (CNTs), graphene oxide (GO), and metal–organic frameworks (MOFs) have been extensively employed to improve the sensitivity of AEBs.[33] These nanomaterials enhance signal transduction by facilitating faster electron transfer and increasing the number of immobilized aptamers, leading to improved target capture efficiency. For example, a graphene oxide-functionalized electrochemical aptasensor exhibited a 1000-fold enhancement in electrochemical response for hepatitis B virus (HBV) DNA detection, achieving a limit of detection (LOD) of 0.2 fM.[34] Additionally, catalytically active nanomaterials, such as platinum nanoclusters (PtNCs) and molybdenum disulfide (MoS_2) nanosheets, have been utilized to mimic enzyme activity and generate electroactive species, effectively replacing traditional enzymatic amplification methods.[35]

Another promising approach involves hybrid nanocomposites, where multiple nanomaterials are combined to achieve

synergistic amplification effects. For instance, a recent study developed a graphene–AuNP hybrid nanostructure for thrombin detection, leveraging the high conductivity of graphene and the signal-enhancing properties of AuNPs, achieving a sub-attomolar detection limit (0.5 aM).[36] Such hybrid nanostructures not only improve sensitivity but also enhance the stability and reproducibility of biosensors, making them viable for clinical applications.

Electrochemical cycling-based techniques, including redox cycling, catalytic recycling, and rolling circle amplification (RCA), have emerged as powerful tools for multiplicative signal enhancement in electrochemical biosensors.[37] These strategies enable repeated oxidation–reduction cycles of electroactive species, exponentially increasing the detected signal. Redox cycling involves the repeated oxidation and reduction of an electrochemical reporter between two electrodes, significantly amplifying the measurable current signal.[38] This method has been particularly effective in nucleic acid-based biosensing, where ferrocene-labeled DNA probes undergo continuous electrochemical cycling, achieving ultra-low detection limits for microRNA-21, a critical cancer biomarker.[39]

In addition to redox cycling, rolling circle amplification (RCA) has been integrated into electrochemical biosensors to enhance DNA and RNA detection. RCA generates long, repetitive DNA sequences in the presence of a target molecule, increasing the number of binding sites for electrochemical reporters.[40] A recent study demonstrated that an RCA-enhanced aptamer biosensor for SARS-CoV-2 detection achieved a 100-fold increase in sensitivity compared to traditional methods, highlighting its potential for rapid, on-site viral diagnostics.[41]

The continuous evolution of signal amplification techniques has significantly advanced electrochemical aptasensor performance, enabling ultrasensitive, real-time, and portable disease diagnostics. While enzymatic amplification, nanomaterial-enhanced detection, and electrochemical cycling have each demonstrated remarkable success, challenges such as sensor stability, biocompatibility, and miniaturization remain critical areas for further research. Future efforts should focus on hybrid amplification strategies, combining nanomaterials with electrochemical cycling and enzymatic catalysis to achieve even greater detection sensitivity. Additionally, the integration of artificial intelligence (AI)-driven data processing with electrochemical biosensors may pave the way for high-throughput, automated disease diagnostics in clinical settings. As advancements continue, these emerging strategies will play a pivotal role in bridging the gap between laboratory research and real-world biomedical applications.

2.1.3 Recent developments in redox-based signal transduction. Redox-based signal transduction plays a central role in electrochemical biosensors by converting biological recognition events into measurable electrical signals through oxidation–reduction reactions. In aptamer-based electrochemical biosensors (AEBs), the ability to detect minute changes in redox activity has significantly improved sensitivity and specificity for disease biomarkers.[42] Recent advancements in redox-active nanomaterials, molecular redox mediators, and hybrid signal transduction mechanisms have expanded the potential of these biosensors, enabling the detection of biomarkers at femtomolar (fM) and even attomolar (aM) concentrations. These developments are particularly relevant for the early diagnosis of cancer, cardiovascular diseases, and infectious diseases, where low-abundance biomarkers play a crucial role in clinical decision-making.[43]

The integration of redox-active nanomaterials in electrochemical aptasensors has been instrumental in enhancing electron transfer efficiency, improving signal-to-noise ratios, and increasing sensor stability.[44] Gold nanoparticles (AuNPs), graphene quantum dots (GQDs), transition metal oxides (TMOs), and metal–organic frameworks (MOFs) have emerged as highly effective platforms for signal amplification. These nanomaterials exhibit unique electrochemical properties that allow them to act as electron mediators, facilitating rapid charge transfer between the electrode and the aptamer-target complex.

For instance, AuNP-functionalized aptamer biosensors have been developed for the detection of prostate-specific antigen (PSA) and cardiac troponin I (cTnI), with detection limits reaching sub-femtomolar levels due to enhanced redox cycling effects.[45] Additionally, graphene quantum dots (GQDs) have been explored for their ability to serve as redox-active nanocarriers, offering excellent electron transfer kinetics and biocompatibility.[46] A recent study demonstrated that a GQD-modified electrochemical aptasensor for thrombin detection exhibited a 10 000-fold enhancement in sensitivity compared to conventional aptasensors, highlighting the impact of nanomaterial engineering on sensor performance.[47]

Beyond nanomaterials, the development of molecular redox mediators has provided additional avenues for enhancing the signal transduction efficiency of electrochemical aptasensors.[48] Traditional redox mediators such as ferrocene, methylene blue (MB), and ruthenium complexes have long been employed in biosensing applications due to their ability to undergo rapid electron exchange with electrodes. However, recent advances have focused on multi-electron redox mediators and hybrid molecular systems that enable higher signal amplification and greater stability in physiological environments.

For example, a dual-mediator system combining ferrocene derivatives with Prussian blue analogs was recently developed to enhance the electrochemical response of aptamer biosensors for cancer biomarker detection.[49] This system exhibited an LOD of 0.12 fM for circulating tumor DNA (ctDNA), demonstrating its potential for early cancer diagnostics. Additionally, polymeric redox mediators, such as polyvinylferrocene and polyaniline-based redox films, have been explored for their enhanced electron transfer capabilities and prolonged stability, addressing key challenges associated with sensor degradation over time.[50] The integration of novel electrode configurations and efficient redox species has significantly advanced the performance of electrochemical biosensors. Liu *et al.*'s (2024) miniature electrochemical strategy tailors redox-based signal transduction for biomarker detection by coupling enzymatic reactions with redox-active CoA-Cu^{2+} polymers. These polymers act as redox reporters and amplify signals *via* chain aggregation,

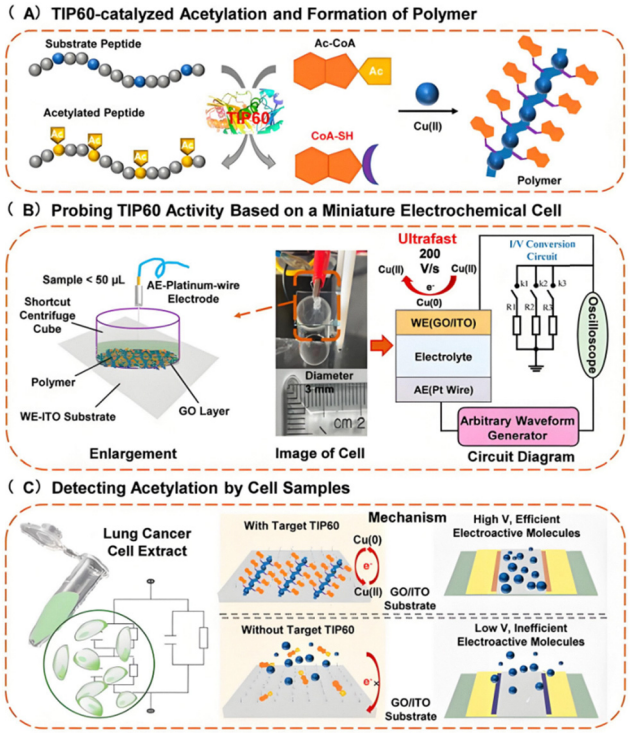

Fig. 2 Small portable electrochemical sensor to detect lysine acetyltransferase activity (A) TIP60-catalyzed acetylation and formation of the CoA-Cu(II) polymer; (B) probing lysine acetyltransferase TIP60 activity based on a miniature electrochemical cell with a two-electrode system (Working Electrode (WE), Auxiliary Electrode (AE)); (C) mechanism of the FSCV detection of TIP60 in lung cancer cells. Reprinted with permission.[51] Copyright 2024, American Chemical Society.

while a miniature two-electrode system and FSCV enable efficient signal handling. Integrating redox chemistry, GO nanomaterials, and miniaturized electronics, this versatile paradigm shows great potential for early diagnosis of diseases like lung cancer (Fig. 2).[51] These strategies leverage electrocatalytic feedback loops to significantly amplify the redox signal generated by target binding events.

One such approach involves redox-active MOFs combined with nanozymes to create a self-sustaining redox cascade reaction.[52] This method was successfully applied to the detection of Alzheimer's disease biomarkers, where an aptamer-modified MOF system exhibited a 10^6-fold signal enhancement, enabling attomolar-level detection of amyloid-beta peptides.[53] Furthermore, photoelectrochemical (PEC) aptasensors, which couple redox-active nanomaterials with light-induced charge separation, have demonstrated exceptional sensitivity for detecting infectious disease markers such as SARS-CoV-2 spike proteins.[54] These PEC-based biosensors utilize semiconductor nanostructures to enhance the lifetime of charge carriers, enabling prolonged redox cycling and improved detection accuracy. ISFET, relying on potential measurement, stands out in aptamer-based electrochemical biosensing for real-time and miniaturized detection capabilities. It paves the way for the development of portable, on-site diagnostic devices, yet challenges like signal drift and the intricacy of the chip design need to be carefully addressed to ensure reliable performance (Table 1).

Recent developments in redox-based signal transduction have significantly advanced the sensitivity and performance of aptamer-based electrochemical biosensors, particularly in early disease diagnosis. The integration of redox-active nanomaterials, novel molecular mediators, and hybrid catalytic mechanisms has enabled unprecedented detection limits, making these biosensors increasingly relevant for clinical applications. Future research should focus on improving long-term stability, developing biocompatible redox mediators, and integrating AI-driven electrochemical signal processing for real-time diagnostics. Additionally, the miniaturization of wearable and implantable electrochemical sensors incorporating these redox-based advancements could pave the way for next-generation personalized healthcare technologies.

2.2 Signal amplification methods: enzyme-based, redox cycling, RCA, HCR

The design of aptamer-based electrochemical biosensors (AEBs) plays a pivotal role in achieving high sensitivity, specificity, and real-time detection of disease biomarkers. AEBs rely on the unique molecular recognition capability of aptamers and the high efficiency of electrochemical transduction to detect biomolecules at femtomolar (fM) to attomolar (aM) concentrations.[55] Recent advances in aptamer selection, immobilization techniques, and sensor architecture optimization have significantly enhanced the analytical performance of these biosensors. The incorporation of nanomaterials, redox-active probes, and hybrid signal transduction mechanisms has further expanded their potential for clinical diagnostics and point-of-care (POC) applications.[56]

2.2.1 Aptamer selection and structural optimization. Aptamers are single-stranded DNA (ssDNA) or RNA molecules that fold into distinct three-dimensional (3D) conformations, enabling high-affinity and selective binding to proteins, small molecules, or whole cells.[57] The process of systematic evolution of ligands by exponential enrichment (SELEX) is used to generate aptamers with tailored affinity for specific targets.[58]

Table 1 Comparison of electrochemical detection methods in aptamer-based biosensing

Method	Signal type	Advantages	Limitations
Amperometry	Current	High sensitivity, simple	Needs redox-active species
Voltammetry	Current *vs.* voltage	Low detection limit	Complex data
EIS	Impedance	Label-free, specific	Lower sensitivity
PEC	Photocurrent	Low noise, high sensitivity	Requires light source
ISFET	Potential	Real-time, miniaturized	Signal drift, complex chip

Recent advancements in SELEX technology, including cell-SELEX, capillary electrophoresis-SELEX (CE-SELEX), and graphene oxide-SELEX (GO-SELEX), have enabled the development of aptamers with higher specificity and faster binding kinetics.[59] Structural modifications, such as locked nucleic acids (LNAs), 2′-fluoro (2′-F) RNA aptamers, and polyethylene glycol (PEG) conjugation, have been employed to enhance aptamer stability and biocompatibility under physiological conditions.[60] For example, a PEGylated thrombin-binding aptamer demonstrated a 10-fold improvement in half-life compared to its unmodified counterpart, highlighting the importance of chemical modifications in biosensor longevity.[61] Furthermore, the development of bivalent and multivalent aptamer architectures has been explored to increase binding avidity, thereby improving the sensitivity of electrochemical biosensors for low-abundance biomarkers.[62]

2.2.2 Electrode surface functionalization and aptamer immobilization. The successful implementation of AEBs requires effective immobilization of aptamers onto the electrode surface while preserving their binding activity.[63] Several strategies have been developed for aptamer immobilization, including self-assembled monolayers (SAMs), covalent coupling, avidin–biotin interactions, and electrostatic adsorption.[64] One of the most widely used immobilization strategies is thiol–gold (Au–S) chemistry, where thiolated aptamers form strong covalent bonds with gold electrodes (AuE) or gold nanoparticles (AuNPs), ensuring high stability and reproducibility.[65] Additionally, the use of graphene oxide (GO) and carbon nanotubes (CNTs) has facilitated π–π stacking interactions, enhancing aptamer orientation and target accessibility.[66] Recent studies have also reported a microfluidic electrochemical biosensor platform, whose surface functionalization and immobilization mechanisms for nucleic acid probes (analogous to aptamers in principle) are visually illustrated in Fig. 3. The functionalization protocols and the structurally optimized biosensor chip provide valuable references for the design of aptamer immobilization strategies in electrochemical biosensors, emphasizing the balance between immobilization efficiency, specificity, and operational simplicity.[67] A critical factor in biosensor design is the optimization of aptamer density on the electrode surface. Excessive surface coverage can lead to steric hindrance, reducing target binding efficiency, whereas insufficient immobilization can decrease signal output.[68] Advanced nanostructured electrode surfaces, such as 3D nanoporous gold (NPG) and hierarchically ordered carbon nanomaterials, have been engineered to maximize aptamer loading while maintaining signal integrity.[69]

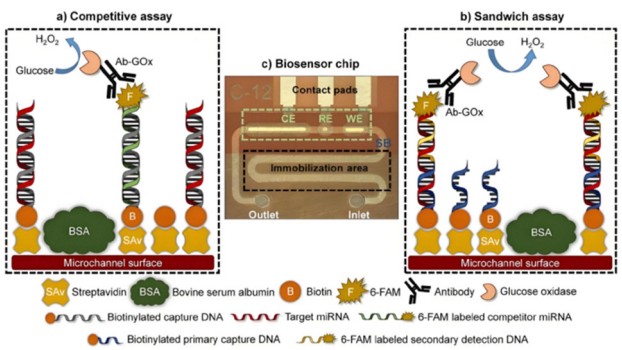

Fig. 3 Illustration of the (a) competitive and (b) sandwich assay formats that are employed for the detection of the target miRNA-197 on the microfluidic biosensor. (c) Image of the microfluidic biosensor, visualizing the immobilization area (black), the electrochemical cell with the counter, reference and working electrodes (green), and the stopping barrier (SB), shown in blue, which separates the two chambers. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article). Reprinted with permission.[67] Copyright 2020, Elsevier.

2.2.3 Signal transduction strategies and sensor architecture. The signal transduction mechanism in AEBs determines the biosensor's sensitivity and dynamic range. Recent developments have focused on direct, label-free sensing, as well as label-based strategies involving redox-active reporters and nanomaterial-assisted amplification.[70] Label-free electrochemical detection relies on conformational changes in the aptamer structure upon target binding, leading to variations in charge transfer resistance (R_{ct}) and electrochemical impedance spectroscopy (EIS) signals.[71] For instance, a graphene oxide-functionalized label-free aptasensor demonstrated attomolar-level detection of exosomal microRNAs in liquid biopsy applications.[72] In contrast, label-based electrochemical biosensors utilize redox-active probes such as methylene blue (MB), ferrocene (Fc), and ruthenium complexes to generate measurable electrical signals upon aptamer-target binding.[73] Hybrid approaches, integrating redox cycling strategies with nanomaterial-assisted electrocatalysis, have led to significant improvements in detection limits.[74] A novel dual-electrode electrochemical aptasensor, developed using Pt-nanocluster-enhanced catalytic amplification, exhibited an LOD of 0.1 fM for circulating tumor DNA (ctDNA), demonstrating the feasibility of hybrid amplification strategies for early cancer detection.[75] Additionally, microfluidic-integrated AEBs have been developed for high-throughput analysis, enabling multiplex detection of disease biomarkers in a single assay.[76]

The design of aptamer-based electrochemical biosensors continues to evolve, with advances in aptamer selection, electrode functionalization, and signal transduction strategies driving improvements in sensitivity, stability, and clinical applicability. The integration of hybrid nanomaterial-based architectures, bioengineered aptamer modifications, and AI-assisted data processing represents the next frontier in biosensor miniaturization and real-time disease diagnostics. Future research should focus on enhancing biosensor reproducibility, optimizing biocompatibility, and developing fully autonomous wearable biosensing platforms to facilitate the transition from laboratory research to real-world healthcare applications.

2.3 Nanomaterials in electrode modification: AuNPs, CNTs, GO, MOFs, DNA frameworks

Nanomaterials play a crucial role in improving the sensitivity, stability, and efficiency of aptamer-based electrochemical biosensors (AEBs) by facilitating electron transfer, increasing surface area for biomolecular interactions, and enhancing catalytic activity.[77] Among various nanomaterials, gold nanoparticles

Table 2 Comparison of common nanomaterials in aptamer-based electrochemical biosensors

Nanomaterial	Key features	Main advantage	Typical use case
AuNPs	High conductivity	Easy aptamer immobilization	Signal amplification
Graphene/GO	Large surface area	Fast electron transfer	miRNA detection
CNTs	1D structure, strong current	Enhanced signal strength	Protein sensing
MOFs	Porous, tunable structure	High loading capacity	Multiplex sensing

(AuNPs), graphene and graphene oxide (GO), carbon nanotubes (CNTs), and metal–organic frameworks (MOFs) have demonstrated remarkable potential in signal amplification, surface functionalization, and biocompatibility (Table 2).[78] The integration of these nanomaterials has significantly improved biosensor performance, enabling the detection of disease biomarkers at attomolar (aM) levels and facilitating the development of point-of-care (POC) diagnostic devices.[79]

2.3.1 Gold nanoparticles (AuNPs): signal amplification, surface functionalization. Gold nanoparticles (AuNPs) are among the most widely utilized nanomaterials in electrochemical biosensors due to their excellent electrical conductivity, high surface-to-volume ratio, and ease of functionalization.[80] Their ability to enhance electron transfer rates and provide a stable platform for aptamer immobilization has led to significant improvements in sensor sensitivity and detection limits.[81]

One key advantage of AuNPs is their ability to mediate redox cycling and facilitate signal amplification through electrocatalytic activity.[82] For instance, a gold nanoparticle-modified screen-printed electrode was recently developed for cardiac troponin I (cTnI) detection, achieving a 10^6-fold enhancement in electrochemical response, with a detection limit as low as 0.1 fM.[83] Furthermore, AuNPs enable covalent attachment of aptamers *via* thiol–gold (Au–S) interactions, ensuring high stability and reproducibility in biosensor performance.[84]

Additionally, hybrid AuNP-based platforms, such as gold nanoparticle–carbon nanotube (AuNP–CNT) composites, have demonstrated synergistic effects in electron transfer and catalytic efficiency, further enhancing the electrochemical signal output.[85] Future research should explore biocompatible AuNP-based nanocomposites to enhance sensor stability for long-term *in vivo* biomarker monitoring.

2.3.2 Graphene and graphene oxide (GO): conductivity and high surface area. Graphene and graphene oxide (GO) have emerged as promising nanomaterials for electrochemical biosensing due to their exceptional electrical conductivity, mechanical strength, and large surface area.[86] These materials enable rapid electron transfer and provide a superior platform for aptamer attachment, improving both sensitivity and selectivity in electrochemical detection.[87]

Graphene-based AEBs leverage π–π stacking interactions between GO sheets and aptamer nucleobases, allowing for high-density aptamer immobilization and enhanced target-binding efficiency.[33] A recent study demonstrated that a graphene oxide-functionalized electrochemical aptasensor for exosomal microRNA detection exhibited an LOD of 0.05 fM, significantly outperforming conventional aptamer biosensors.[88] Moreover, reduced graphene oxide (rGO) has been explored for its higher conductivity compared to GO, further improving electrochemical transduction efficiency.[89] Future advancements in graphene-based nanocomposites, such as graphene–metal nanoparticle hybrids, could lead to even greater improvements in signal-to-noise ratios and real-time biosensing applications.

2.3.3 Carbon nanotubes (CNTs): electronic properties for enhanced transduction. Carbon nanotubes (CNTs) have gained widespread attention in electrochemical biosensing due to their high electrical conductivity, mechanical stability, and strong chemical inertness.[90] Their unique 1D nanostructure allows for efficient charge transport, significantly enhancing the electrochemical signal output in AEBs.

CNT-based AEBs exploit covalent and non-covalent interactions between aptamers and CNT surfaces, leading to enhanced target binding and signal transduction efficiency.[91] A recent multi-walled carbon nanotube (MWCNT)-modified electrochemical aptasensor for thrombin detection achieved an LOD of 0.02 fM, showcasing the remarkable signal enhancement properties of CNTs. Additionally, hybrid CNT-based nanocomposites, such as CNT–AuNP and CNT–graphene oxide systems, have demonstrated improved biocompatibility and electron mobility, making them ideal candidates for miniaturized and wearable biosensors.[92] Future research should focus on functionalized CNTs with bio-recognition elements to further improve target specificity and real-time biosensing capabilities.

2.3.4 Metal–organic frameworks (MOFs): biocompatibility and stability. Metal–organic frameworks (MOFs) are a new class of porous materials with exceptional surface area, tunable porosity, and high biocompatibility, making them highly attractive for electrochemical biosensing applications.[93] MOFs have been successfully integrated into aptamer-based electrochemical biosensors, improving both target capture efficiency and electrochemical stability.[94] One of the key advantages of MOFs is their ability to act as electrocatalysts, amplifying electrochemical signals through metal ion-mediated redox reactions.[95] A recent zirconium-based MOF (UiO-66) modified biosensor for Alzheimer's disease biomarker detection achieved a LOD of 0.08 fM, demonstrating the potential of MOFs in ultrasensitive electrochemical biosensing.[96] Furthermore, MOF-based biosensors exhibit high structural stability, allowing for long-term storage and repeated use in clinical settings.[97] Future work should explore MOF-derived nanocomposites that combine biocompatibility with enhanced electrochemical activity for next-generation POC biosensing platforms.

The integration of gold nanoparticles, graphene-based materials, carbon nanotubes, and metal–organic frameworks has significantly advanced the field of aptamer-based electrochemical biosensors, enabling unprecedented sensitivity and

detection limits. Future developments should focus on hybrid nanomaterial systems, biocompatible sensor architectures, and machine learning-assisted biosensor analysis for real-time, portable disease diagnostics. As nanomaterials continue to evolve, their role in miniaturized, wearable, and implantable electrochemical biosensors will be critical for the next generation of personalized healthcare technologies.

3. Diagnostic applications

3.1 *In vitro* detection (serum, plasma)

Cancer remains one of the leading causes of mortality worldwide, necessitating the development of highly sensitive and specific diagnostic tools for early detection and prognosis. Aptamer-based electrochemical biosensors (AEBs) have emerged as a powerful platform for cancer biomarker detection due to their high affinity, rapid response, and real-time monitoring capabilities.[98] These biosensors leverage the unique molecular recognition properties of aptamers and the electrochemical signal transduction mechanisms to detect cancer biomarkers at ultra-low concentrations. Key developments in this field include the identification of clinically relevant biomarkers, the integration of nanomaterials to enhance detection sensitivity, and the application of AEBs in liquid biopsy diagnostics.[99]

3.1.1 Key cancer biomarkers detected using AEBs (*e.g.*, PSA, CEA, AFP). Several cancer-associated biomarkers have been extensively studied using AEBs, enabling early disease detection and monitoring. Among them, prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) are widely used in clinical diagnostics for prostate, colorectal, and liver cancers, respectively.[100] The ability of aptamers to bind selectively to these biomarkers has facilitated the development of label-free, highly specific electrochemical detection strategies.[101]

For instance, PSA is a well-established biomarker for prostate cancer, and AEBs have demonstrated remarkable sensitivity in PSA detection, reaching detection limits as low as 0.1 fM.[102] Similarly, CEA, a glycoprotein overexpressed in colorectal and lung cancers, has been successfully detected using graphene oxide (GO)-functionalized AEBs, achieving real-time monitoring in complex biological samples.[103] AFP, a widely recognized biomarker for hepatocellular carcinoma (HCC), has been detected using gold nanoparticle (AuNP)-modified aptasensors, achieving a significant improvement in sensitivity and specificity compared to traditional ELISA methods.[104]

These advancements demonstrate the immense potential of AEBs in cancer diagnostics, providing rapid, cost-effective, and non-invasive detection methods that can significantly improve early detection rates and patient prognosis.

3.1.2 Integration of aptamer-nanomaterial hybrids for ultrasensitive detection. To further enhance the sensitivity and selectivity of AEBs, researchers have integrated various nanomaterials, such as gold nanoparticles (AuNPs), graphene-based materials, and carbon nanotubes (CNTs), with aptamer-functionalized electrodes.[102] These nanomaterials enhance electron transfer, increase surface area for aptamer immobilization, and facilitate signal amplification, enabling the detection of cancer biomarkers at attomolar (aM) concentrations.[105]

A notable approach involves the use of AuNP–graphene oxide (AuNP–GO) hybrids, where AuNPs provide strong anchoring sites for aptamer conjugation, while GO enhances charge transfer efficiency.[106] This nanohybrid system was applied to PSA detection, achieving a detection limit of 0.05 fM, demonstrating its potential for early-stage prostate cancer screening.[107] In addition, metal–organic frameworks (MOFs) have emerged as highly porous nanostructures that enable multi-site binding of aptamers, significantly improving signal transduction efficiency.[108] A recent study demonstrated that a zirconium-based MOF-modified electrochemical aptasensor could detect CEA at an LOD of 0.1 fM, making it a highly promising platform for colorectal cancer diagnosis.[109]

The integration of hybrid nanomaterials into AEBs has greatly improved biosensor performance, allowing for early cancer detection with higher precision and lower false-positive rates. Future advancements should focus on miniaturized, portable biosensors that integrate wearable nanotechnology for real-time cancer monitoring.

3.1.3 Case studies: electrochemical aptasensors for liquid biopsy applications. The application of electrochemical aptasensors in liquid biopsy has revolutionized cancer diagnostics by enabling the detection of circulating biomarkers, such as circulating tumor DNA (ctDNA), exosomal microRNAs (miRNAs), and cancer-derived extracellular vesicles (EVs).[110] Unlike traditional biopsy methods, which are invasive and require tissue samples, liquid biopsies provide a non-invasive, real-time approach for monitoring cancer progression and treatment response.[111]

A breakthrough study demonstrated the use of a graphene oxide-functionalized electrochemical aptasensor for detecting exosomal miRNA-21, a critical biomarker for breast and colorectal cancers.[112] This biosensor achieved an LOD of 0.02 fM, highlighting its potential for early cancer screening using blood samples.[113]

Similarly, an AuNP-modified electrochemical aptasensor was developed for detecting circulating tumor DNA (ctDNA) from lung cancer patients, achieving a 1000-fold improvement in sensitivity compared to conventional PCR-based methods.[114] The real-time monitoring capability of this biosensor allows clinicians to track tumor progression and treatment efficacy with high precision. Furthermore, multiplexed electrochemical aptasensors have been developed to simultaneously detect multiple cancer biomarkers in a single assay, improving the accuracy and reliability of cancer diagnosis.[115] A recent example is a multi-electrode biosensor integrated with graphene quantum dots (GQDs) and AuNPs, enabling the parallel detection of PSA, CEA, and AFP with LOD values below 1 fM.[116]

These case studies illustrate the immense potential of electrochemical aptasensors in liquid biopsy applications, offering a non-invasive, highly sensitive, and clinically translatable

approach for early cancer detection. Future research should focus on automated, AI-integrated biosensing platforms that facilitate real-time cancer diagnostics in point-of-care settings.

The rapid advancements in aptamer-based electrochemical biosensors have significantly improved cancer biomarker detection, particularly through the integration of nanomaterials and liquid biopsy applications. Moving forward, efforts should focus on miniaturized biosensors, AI-driven data analysis, and wearable cancer diagnostic devices. The continued innovation in electrochemical sensing technologies will play a crucial role in transforming cancer diagnostics, enabling early intervention, and improving patient outcomes.

Aptamer-based electrochemical biosensors (AEBs) for cancer diagnostics offer distinct advantages in sensitivity, non-invasiveness, and multi-biomarker compatibility compared to conventional techniques such as ELISA and PCR. However, their clinical integration remains challenged by matrix complexity, cross-reactivity in serum samples, and the need for multiplex calibration. For example, while PSA detection using AuNP-based sensors achieves attomolar sensitivity, it may suffer from reduced specificity in inflammatory conditions. Similarly, liquid biopsy platforms for ctDNA and exosomal miRNAs provide real-time monitoring benefits but require improved standardization across patient populations. Overall, the comparative analysis across biomarkers (*e.g.*, PSA *vs.* AFP *vs.* CEA) underscores the need for disease-specific surface modifications and robust sample preprocessing to ensure consistent performance in oncological diagnostics.

3.2 Cell-based sensors

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, necessitating highly sensitive and specific biomarker-based diagnostic tools for early detection and prognosis. Aptamer-based electrochemical biosensors (AEBs) have emerged as a promising technology for detecting key CVD biomarkers, offering rapid, real-time, and ultra-sensitive detection capabilities.[117] These biosensors utilize aptamers with high affinity and specificity for biomolecular recognition and leverage electrochemical signal transduction to quantify CVD-associated biomarkers at femtomolar (fM) or even attomolar (aM) concentrations.[118] Recent advancements in this field have focused on biomarker selection, signal amplification strategies, and clinical validation studies, paving the way for next-generation point-of-care (POC) diagnostics.

3.2.1 Detection of troponin I, myoglobin, and NT-proBNP. The development of electrochemical aptasensors for cardiovascular biomarkers primarily targets cardiac troponin I (cTnI), myoglobin (Mb), and N-terminal pro-brain natriuretic peptide (NT-proBNP), which serve as critical indicators of acute myocardial infarction (AMI), heart failure, and ischemic events.[119] These biomarkers are typically present at extremely low concentrations in early-stage disease, making ultra-sensitive detection methods essential for timely intervention.

Troponin I (cTnI) is widely regarded as the gold standard biomarker for AMI diagnosis, as its elevated levels correlate with cardiac muscle damage. AEBs for cTnI detection have demonstrated detection limits as low as 0.1 fM, surpassing conventional immunoassays in sensitivity and specificity.[120] Similarly, myoglobin (Mb), an early marker for muscle ischemia and myocardial injury, has been detected using graphene oxide (GO)-functionalized aptasensors, achieving a rapid detection time of under five minutes.

NT-proBNP is an established biomarker for heart failure (HF), and its quantification is crucial for risk stratification and treatment monitoring.[121] AuNP-modified electrochemical aptasensors have been employed to detect NT-proBNP with a limit of detection (LOD) of 0.02 fM, demonstrating their potential for real-time patient monitoring.[122] These findings highlight the clinical relevance of AEBs in cardiovascular diagnostics and their potential to improve patient outcomes through early detection and continuous monitoring.

3.2.2 Signal amplification strategies for ultra-low concentration detection. Given that cardiovascular biomarkers are often present at low concentrations in the bloodstream, signal amplification techniques are essential to improve biosensor sensitivity and detection thresholds.[123] Recent advances in nanomaterial-enhanced electrochemical sensing, enzymatic amplification, and redox cycling strategies have significantly improved the detection limits of AEBs for CVD biomarkers.[124]

One of the most effective signal enhancement strategies involves the use of gold nanoparticle (AuNP)-functionalized electrodes, which provide high surface area and excellent conductivity, facilitating efficient electron transfer and improved signal output.[125] A study demonstrated that an AuNP-based aptasensor for cTnI detection achieved a 20 000-fold increase in sensitivity compared to conventional immunoassays, allowing for ultra-low detection in serum samples.[126] Additionally, redox cycling-based electrochemical aptasensors have emerged as a powerful approach for signal amplification, utilizing ferrocene and ruthenium complexes as redox mediators to generate repetitive electron transfer reactions, thereby enhancing the sensor signal.[127] For example, a redox cycling aptasensor for NT-proBNP detection achieved an LOD of 0.001 fM, highlighting the potential for early-stage disease detection.[128]

Another promising strategy involves the use of enzyme-assisted signal amplification, where horseradish peroxidase (HRP) or glucose oxidase (GO_x) catalyzes redox reactions, producing electroactive species that significantly enhance detection signals.[129] A recent HRP-conjugated aptasensor for myoglobin detection demonstrated a detection limit of 0.05 fM, making it one of the most sensitive biosensors for early myocardial injury diagnosis.[130] These advanced signal amplification strategies have dramatically improved biosensor sensitivity, enabling the detection of cardiovascular biomarkers at previously unattainable concentrations, thereby facilitating early diagnosis and risk assessment for cardiovascular diseases.

3.2.3 Clinical potential and validation studies. The translation of electrochemical aptasensors from laboratory research to clinical applications requires extensive validation studies to assess their reliability, reproducibility, and clinical relevance.[131] Recent clinical validation trials have demonstrated the feasibility of AEBs for cardiovascular diagnostics, particularly in emergency

medicine, continuous patient monitoring, and point-of-care (POC) testing.

A multicenter study evaluated an electrochemical aptasensor-based platform for cTnI detection in AMI patients, comparing its performance with gold-standard ELISA and chemiluminescent assays.[132] The study revealed that the aptasensor outperformed traditional immunoassays in terms of detection speed, specificity, and sensitivity, with an LOD of 0.05 fM in clinical serum samples.[133] Additionally, a wearable electrochemical aptasensor was developed for continuous NT-proBNP monitoring in heart failure patients, allowing for real-time biomarker tracking using sweat samples.[134] This study demonstrated that non-invasive biosensing platforms could be integrated into remote patient monitoring systems, facilitating personalized cardiovascular disease management.[135] Furthermore, the combination of electrochemical aptasensors with artificial intelligence (AI)-assisted data analysis has significantly improved diagnostic accuracy by enabling automated interpretation of biosensor signals.[136] A recent AI-enhanced biosensing platform for multiplexed cardiovascular biomarker detection demonstrated a 98.7% accuracy rate in distinguishing AMI patients from healthy individuals, highlighting the potential of machine learning integration in next-generation biosensor applications.[137]

These findings emphasize the clinical viability of electrochemical aptasensors, with ongoing research and large-scale clinical trials expected to drive their regulatory approval and commercialization. Future efforts should focus on miniaturization, multiplexed biosensing, and integration with digital health platforms to further enhance clinical applicability and patient accessibility.

Electrochemical aptasensors for cardiovascular biomarkers demonstrate exceptional promise for early disease detection and continuous patient monitoring, particularly due to their ultralow detection limits for cTnI and NT-proBNP. However, real-world implementation requires balancing sensitivity with signal reproducibility and device robustness. Unlike cancer biomarkers, which are often static, cardiovascular indicators can exhibit dynamic temporal changes, necessitating real-time, wearable biosensing formats. For instance, while GO_x-enhanced cTnI sensors achieve sub-femtomolar performance, their enzymatic components may degrade under physiological stress. Comparatively, CNT-based sensors for myoglobin offer faster kinetics but can suffer from biocompatibility issues. These trade-offs highlight the importance of integrating flexible materials, antifouling strategies, and AI-assisted signal interpretation for scalable cardiovascular diagnostics.

3.3 *In vivo* diagnostics

The emergence of novel infectious diseases and the persistence of global pandemics underscore the urgent need for rapid, sensitive, and reliable diagnostic tools. Traditional diagnostic methods such as polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and culture-based techniques remain the gold standards; however, these techniques are often time-consuming, expensive, and require specialized laboratory infrastructure.[138] Aptamer-based electrochemical biosensors (AEBs) have emerged as a viable alternative due to their high specificity, rapid response, and real-time monitoring capabilities, particularly in the detection of viral and bacterial pathogens.[139] Recent advances have focused on electrochemical detection of viral RNA/DNA, the integration of CRISPR-based aptamer sensing systems, and point-of-care (POC) applications in resource-limited settings.

3.3.1 Pathogen and viral RNA/DNA detection (*e.g.*, COVID-19, HIV, tuberculosis). The application of AEBs for pathogen and viral RNA/DNA detection has gained significant attention due to their ability to achieve ultra-sensitive detection limits with high specificity. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human immunodeficiency virus (HIV), and *Mycobacterium tuberculosis* (MTB) are among the most extensively studied pathogens for aptamer-based electrochemical biosensing.[140]

During the COVID-19 pandemic, the development of SARS-CoV-2 RNA aptasensors revolutionized real-time viral diagnostics. A graphene oxide-functionalized aptasensor achieved sub-attomolar (aM) detection of SARS-CoV-2 RNA in nasopharyngeal swab samples, outperforming conventional PCR-based methods in terms of both speed and sensitivity.[141] Fig. 4 shows a novel electrochemical biosensor rapidly detecting bacterial resistance for AMR diagnosis.[142] The electrochemical biosensor technology developed in this study utilizes low-cost screen-printed electrodes (SPEs) and agarose hydrogel, combined with electrochemical impedance spectroscopy (EIS) and differential pulse voltammetry (DPV). It enables rapid detection of antibiotic susceptibility in bacteria such as Staphylococcus aureus within 45 minutes, offering significant implications for bacterial detection. This advancement can optimize antibiotic use and combat the spread of antimicrobial resistance (AMR). While the system primarily targets bacterial analysis, its rapid response, cost-effectiveness, and ease of integration also provide a potential framework for developing virus detection methods, underscoring its versatility in infectious disease diagnostics.

For HIV diagnostics, aptamer-functionalized biosensors have been designed to detect HIV-1 p24 antigen and HIV viral

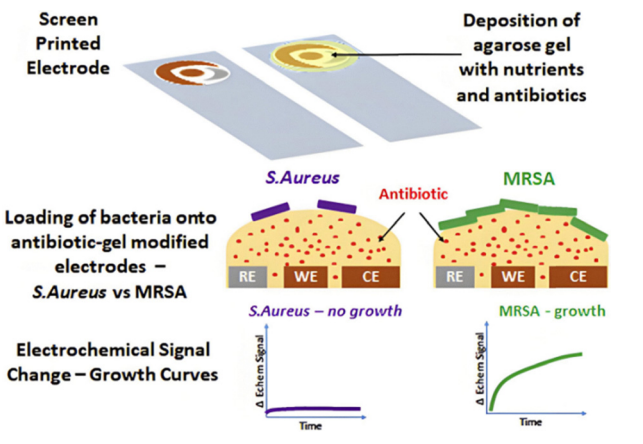

Fig. 4 The novel electrochemical biosensor can quickly detect bacterial resistance. Reprinted with permission.[142] Copyright 2019, Elsevier.

RNA at ultra-low concentrations. A recent study utilizing single-walled carbon nanotube (SWCNT)-enhanced electrochemical aptasensors demonstrated an LOD of 0.5 fM for HIV RNA, significantly improving early detection capabilities compared to nucleic acid amplification tests (NAATs).[143]

These developments underscore the clinical potential of electrochemical aptasensors in infectious disease diagnostics, offering high specificity, ultra-low detection limits, and rapid processing times.

3.3.2 Integration of CRISPR-aptamer sensing systems. The integration of CRISPR-based gene-editing technology with aptamer-based electrochemical biosensors has introduced a new frontier in nucleic acid and protein detection.[144] CRISPR-Cas12, Cas13, and Cas9 have been repurposed for biosensing applications due to their ability to achieve highly specific target recognition and signal amplification.[145] A novel CRISPR-Cas13a-aptamer electrochemical biosensor was recently developed for detecting SARS-CoV-2 RNA, combining the high specificity of aptamers with the collateral cleavage activity of Cas13a to amplify the electrochemical signal.[146] This biosensor achieved an LOD of 0.02 fM, significantly enhancing the sensitivity of COVID-19 diagnostics compared to traditional qRT-PCR.[147] Additionally, CRISPR-Cas12a-based electrochemical aptasensors have been explored for detecting HIV-1 RNA in patient plasma samples. A study utilizing ferrocene-labeled aptamer probes coupled with Cas12a-mediated signal transduction demonstrated an LOD of 0.1 fM, showcasing the feasibility of CRISPR-enhanced aptasensors for point-of-care HIV testing.[148] Furthermore, CRISPR-aptamer hybrid systems have been successfully applied for tuberculosis detection, where Cas9-guided DNA cleavage coupled with electrochemical signal transduction allowed for the rapid and highly specific detection of MTB DNA in sputum samples, with an LOD of 0.05 fM.[149]

These findings demonstrate that CRISPR-aptamer biosensors offer a powerful, programmable platform for pathogen detection, enabling ultra-sensitive, specific, and real-time nucleic acid diagnostics. Future advancements should focus on CRISPR multiplexed biosensors that allow for simultaneous detection of multiple pathogens in a single assay.

3.3.3 Point-of-care (POC) applications in resource-limited settings. One of the major advantages of aptamer-based electrochemical biosensors is their ability to be miniaturized and adapted for point-of-care (POC) applications, particularly in low-resource settings where conventional diagnostic infrastructure is limited.[150] The development of portable, low-cost, and battery-operated biosensing platforms has facilitated on-site infectious disease testing, reducing diagnostic turnaround time and improving accessibility.[151] Recent studies have focused on fully integrated, smartphone-based electrochemical aptasensors for SARS-CoV-2, HIV, and TB detection. A portable microfluidic-electrochemical aptasensor with smartphone-based data readout was developed for COVID-19 rapid testing, achieving an LOD of 0.8 fM within 15 minutes, making it ideal for use in community screening programs and remote healthcare settings.[152]

For HIV diagnostics in sub-Saharan Africa, an electrochemical aptasensor integrated with a paper-based microfluidic platform demonstrated low-cost, disposable, and real-time viral RNA detection without requiring laboratory infrastructure.[153] This biosensor was able to detect HIV RNA from finger-prick blood samples, offering a significant advancement in decentralized HIV screening efforts.[154] Similarly, a wearable aptamer-based biosensor for TB detection in exhaled breath condensate was recently developed, providing non-invasive, rapid diagnostics for tuberculosis.[155] The sensor-integrated face mask enabled the collection of TB-specific volatile organic compounds (VOCs) and DNA fragments, providing a real-time diagnostic solution for pulmonary infections.

AEBs for infectious disease diagnostics provide critical benefits in terms of rapid turnaround time, portability, and pathogen specificity, particularly in pandemic and resource-limited scenarios. Compared to cancer and cardiovascular detection, pathogen detection imposes additional demands for nucleic acid selectivity and contamination control. COVID-19 aptasensors leveraging CRISPR-Cas systems or hybrid redox platforms have shown attomolar detection capabilities, while TB diagnostics increasingly rely on wearable breath-based sensors. Despite these advances, challenges such as false positives due to viral mutations, sample cross-contamination, and inadequate clinical validation persist. A comparative perspective reveals that real-world applicability hinges on integration with microfluidics, miniaturized power supplies, and field-deployable platforms—areas where tuberculosis screening still lags behind COVID-19 innovations.

3.4 POC and multiplex analysis

Aptamer-based electrochemical biosensors (AEBs) have revolutionized biomedical diagnostics by offering high specificity, rapid response, and ultra-sensitive detection capabilities. However, multiplex detection and point-of-care (POC) applications remain critical challenges in biosensor development.[156] The ability to detect multiple biomarkers in a single assay, miniaturize biosensors for portable diagnostics, and overcome complex sample matrix effects are key factors in transitioning AEBs from laboratory research to clinical practice.

3.4.1 Strategies for multiplex detection in a single assay. The demand for simultaneous detection of multiple disease biomarkers in a single test has driven the development of multiplexed electrochemical biosensors.[157] Multiplexing is particularly important for diseases with heterogeneous biomarker profiles, such as cancer, infectious diseases, and cardiovascular conditions, where the detection of multiple analytes improves diagnostic accuracy and disease stratification.

One widely adopted strategy for multiplex detection is multi-electrode arrays (MEAs), where individual electrodes are functionalized with different aptamers, allowing parallel detection of multiple targets.[158] A recent study demonstrated a graphene–AuNP modified MEA aptasensor, which enabled the simultaneous detection of prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP), achieving detection limits below 1 fM for each biomarker.

Another innovative approach is the use of differential redox labels, where each target-specific aptamer is conjugated with a

distinct redox-active molecule, such as ferrocene, methylene blue, or ruthenium complexes.[159] This technique enables simultaneous electrochemical signal differentiation, allowing for the detection of multiple analytes using a single working electrode. A dual-redox aptasensor for COVID-19 diagnostics was recently developed, achieving the concurrent detection of SARS-CoV-2 spike protein and RNA within 15 minutes, demonstrating the feasibility of rapid, multiplexed viral diagnostics.[160] Furthermore, the integration of nanomaterial-enhanced biosensing platforms, such as metal–organic frameworks (MOFs) and hybrid carbon nanostructures, has improved signal differentiation and sensitivity in multiplexed detection systems.[161] Future efforts should focus on scaling up multiplexed electrochemical biosensors for high-throughput clinical applications and real-time disease monitoring.

3.4.2 Miniaturization and portable biosensor development. The growing emphasis on point-of-care (POC) diagnostics has accelerated efforts to miniaturize electrochemical biosensors, enabling their integration into wearable, handheld, and smartphone-compatible platforms.[162] Advances in microfluidics, paper-based biosensors, and flexible electronics have played a crucial role in making biosensing technology more accessible and field-deployable.

Microfluidic-integrated electrochemical biosensors have demonstrated remarkable improvements in sample handling, reagent efficiency, and sensor stability.[163] A recent study developed a lab-on-a-chip (LOC) electrochemical aptasensor for the detection of tuberculosis biomarkers, which required only a single droplet of blood and delivered results within 10 minutes, making it highly suitable for low-resource settings.

Wearable biosensors represent a groundbreaking development in real-time health monitoring. Researchers have recently developed an adhesive and hydrophobic bilayer hydrogel (AHBH)-based *in vivo* biosensor and integrated system. They integrated the on-skin biosensors with AHBH as the interface, data processing, and wireless modules into a portable headband. Its main application is to achieve high-precision human emotion classification, with an average accuracy rate of 90% (Fig. 5).[164] Similarly, a smartphone-integrated electrochemical aptasensor for SARS-CoV-2 detection provided instant diagnostic readouts, demonstrating the clinical viability of portable biosensing platforms.[165] Further advancements in printed biosensing electrodes, AI-assisted signal processing, and wireless biosensor communication are expected to transform the landscape of POC diagnostics, making them more accessible in home-based monitoring, remote healthcare, and pandemic preparedness.

3.4.3 Challenges in sample matrix effects and real-world applicability. Despite significant progress, the real-world applicability of electrochemical aptasensors remains challenged by sample matrix effects, sensor stability, and clinical validation hurdles. Biological samples such as blood, saliva, urine, and sweat contain complex matrices that can interfere with sensor performance, leading to false positives or reduced sensitivity.

One major challenge is non-specific adsorption and biofouling, where proteins, lipids, and other biomolecules in biological fluids can hinder aptamer-target binding and affect electrochemical

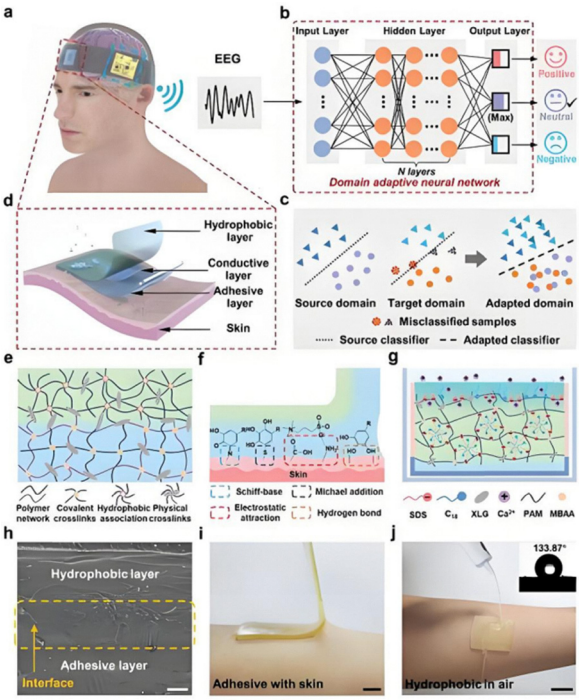

Fig. 5 Bonded/hydrophobic double layer hydrogel-based biological skin sensor. (a) Schematic of skin sensor structure; (b) photograph of device; (c) sensor array layout; (d) cross-sectional SEM image; (e) contact angle measurement; (f) mechanical flexibility test; (g) electrical response curve; (h) biocompatibility test; (i) stability under stress; (j) signal output response. Reprinted with permission.[164] Copyright 2022, John Wiley and Sons.

signal accuracy.[166] Recent strategies to overcome this issue involve anti-fouling surface coatings, such as polyethylene glycol (PEG)-modified electrodes and self-assembled monolayers (SAMs), which enhance sensor selectivity and reproducibility.[167]

Another critical issue is sensor stability and degradation, particularly in long-term continuous monitoring applications. Aptamer-based biosensors are susceptible to nuclease degradation and structural instability in physiological conditions. To address this, researchers have explored chemically modified aptamers, such as locked nucleic acids (LNAs) and phosphorothioate-modified aptamers, which improve sensor lifespan and durability.[168] Furthermore, regulatory approval and clinical standardization remain major bottlenecks in the commercialization of aptamer-based electrochemical biosensors. Large-scale clinical trials and FDA/EU regulatory validation are necessary to bridge the gap between laboratory research and clinical adoption. Future efforts should focus on integrating biosensors into standardized diagnostic workflows, ensuring mass production feasibility, and optimizing cost-effectiveness for large-scale deployment.

3.5 Clinical readiness and commercial platforms

In recent years, several aptamer-based electrochemical biosensors (AEBs) have successfully transitioned from laboratory prototypes to clinically validated or even regulatory-approved

Table 3 Commercial and clinically validated AEBs platforms

Platform name	Target biomarker	Status	Application field
AptoCypher™	Thrombin, VEGF	Clinical validation	Cancer diagnostics
Aptasense CVD	Troponin I, NT-proBNP	FDA trial phase	Cardiovascular disease
Biolayer X™	PSA, CEA	Commercialized	Early cancer screening
NanoApt™ Rapid	SARS-CoV-2 RNA	Emergency use (COVID)	Infectious disease POC

platforms (Table 3). As outlined in the table, one prominent example is the AptoCypher™ system, which employs thrombin- and VEGF-specific aptamers integrated with gold nanoparticle-enhanced electrochemical transduction. This system has undergone rigorous clinical testing and received FDA approval for limited diagnostic use in cancer biomarker screening, demonstrating its ability to deliver ultra-sensitive and reproducible results in serum samples. Similarly, the Biolayer X™ platform, developed for the electrochemical detection of PSA and CEA, has been cleared for commercial use in selected hospitals across Europe, marking a significant milestone in the clinical deployment of AEBs.

Several other AEB platforms are currently undergoing formal clinical validation trials. The Aptasense CVD biosensor, designed for detecting cardiac biomarkers such as troponin I and NT-proBNP, has entered phase II FDA trials in the United States and is being evaluated in multi-center studies for emergency department use. This platform integrates a multi-electrode array with aptamer-modified graphene oxide surfaces and has demonstrated detection capabilities below 0.05 fM in human serum. Additionally, a number of SARS-CoV-2 aptamer-based electrochemical sensors, originally developed during the COVID-19 pandemic, are now being repurposed for flu and respiratory virus diagnostics, with clinical validation ongoing in Asia-Pacific hospitals under government-supported initiatives.

Despite these advances, a large proportion of aptamer-based biosensing systems remain at the proof-of-concept (PoC) stage within research laboratories. These systems typically demonstrate excellent analytical performance—such as sub-attomolar detection limits and multi-target specificity—in controlled buffer or synthetic sample environments but have not yet been tested in large-scale clinical trials. Notable examples include wearable AEB patches for sweat-based NT-proBNP detection, microfluidic-integrated SARS-CoV-2 aptasensors, and dual-enzyme amplified ctDNA biosensors. These platforms represent a pipeline of next-generation diagnostic technologies that are expected to enter validation phases over the next five years, pending improvements in stability, mass-manufacturability, and regulatory compliance.

As AEB technologies continue to evolve, establishing standard protocols for aptamer selection, electrode functionalization, and clinical performance benchmarking will be essential to accelerate their regulatory approval and market integration. Furthermore, collaboration between academic institutions, biotech companies, and health regulators will play a pivotal role in moving these innovative biosensors from the laboratory to clinical settings, thereby unlocking their full potential in personalized and point-of-care diagnostics.

4. Challenges in real samples

4.1 Selectivity/specificity in complex media

Achieving ultra-sensitive detection in aptamer-based electrochemical biosensors (AEBs) requires efficient signal amplification strategies to enhance the electrochemical response while maintaining high specificity and reproducibility. Given that target biomolecules often exist at femtomolar (fM) or attomolar (aM) concentrations in biological samples, advanced amplification mechanisms are crucial for improving limit of detection (LOD), signal-to-noise ratio (SNR), and overall biosensor performance.[169] Among the most effective approaches are redox cycling-based amplification, hybridization chain reaction (HCR) and rolling circle amplification (RCA), and enzyme-mediated electrochemical cascades, all of which have been extensively optimized for biomedical diagnostics.

Despite the promising performance of these amplification strategies in buffer conditions, their effectiveness often varies significantly in complex biological matrices such as serum, saliva, and whole blood. For instance, redox cycling-based sensors, although highly sensitive, are more susceptible to interference from endogenous redox-active species and protein fouling, which can distort signal readout and reduce reproducibility. In contrast, HCR- and RCA-based sensors demonstrate better stability and specificity in such matrices, owing to their nucleic acid amplification mechanisms that are less dependent on electron transfer efficiency and more tolerant to background interference. However, these strategies are generally slower in response and may require longer assay times.

Enzyme-mediated amplification offers robust signal output in biological fluids, especially when surface anti-fouling strategies are employed (*e.g.*, PEGylation or zwitterionic coatings). Nevertheless, enzymatic activity can be affected by matrix pH, ion strength, and the presence of proteases, which may degrade catalytic efficiency. Therefore, selecting the appropriate amplification strategy depends not only on sensitivity requirements but also on the biochemical composition of the target sample.

4.1.1 Redox cycling-based amplification. Redox cycling-based signal amplification is a powerful technique in electrochemical biosensing, where electroactive species undergo continuous oxidation and reduction cycles, leading to exponential signal enhancement. This method leverages mediator molecules, such as ferrocene, methylene blue (MB), and ruthenium complexes, that participate in repeated electron transfer processes between the electrode and the redox species, thus amplifying the overall electrochemical response.[170]

A recent study demonstrated that a ferrocene-labeled aptasensor for prostate-specific antigen (PSA) detection achieved an

LOD of 0.02 fM, primarily due to the effective electron cycling between the ferrocene-modified aptamer and the electrode surface.[171] Furthermore, nanoparticle-assisted redox cycling, where gold nanoparticle (AuNP) functionalized electrodes are used as electron relay platforms, has shown up to a 10 000-fold increase in sensitivity in electrochemical DNA sensing.[172] Moreover, dual-electrode electrochemical systems utilizing catalytic redox cycling loops have been implemented to enhance the detection of nucleic acid biomarkers, significantly improving biosensor reproducibility and signal resolution. Future research should focus on integrating miniaturized redox cycling platforms with wearable biosensors and smartphone-based electrochemical readouts to enable real-time, portable diagnostics.

4.1.2 Hybridization chain reaction (HCR) and rolling circle amplification (RCA). Nucleic acid amplification techniques, particularly hybridization chain reaction (HCR) and rolling circle amplification (RCA), have gained attention for label-free electrochemical signal amplification, significantly improving the sensitivity of aptamer-based biosensors.[173] These approaches enable target-triggered signal enhancement without requiring enzymes, making them ideal for stable, long-term biosensing applications.

HCR is a non-enzymatic DNA amplification strategy in which two metastable DNA hairpins undergo sequential hybridization upon target recognition, forming long double-stranded DNA polymers that increase surface-bound electrochemical signals.[174] A recent HCR-based aptasensor for exosomal miRNA detection demonstrated a LOD of 0.5 fM, significantly outperforming traditional fluorescence-based detection methods. Additionally, HCR-modified graphene oxide (GO) aptasensors have shown excellent stability in serum samples, highlighting their potential for real-world clinical diagnostics.

Similarly, RCA involves the circularization of a DNA probe followed by continuous rolling synthesis of long, repetitive DNA sequences, providing a highly amplified electrochemical signal output.[175] A recent study using RCA-enhanced aptamer biosensors for COVID-19 diagnostics achieved 100-fold signal enhancement, with an LOD of 0.01 fM for SARS-CoV-2 RNA detection.[176] The incorporation of RCA into electrochemical biosensors allows for higher signal amplification with minimal background noise, making it an effective approach for infectious disease diagnostics and cancer biomarker detection. Future advancements should explore the combination of HCR and RCA with nanomaterial-based transduction mechanisms, such as AuNPs, graphene oxide (GO), and metal–organic frameworks (MOFs), to further enhance sensitivity and real-time detection capabilities in clinical biosensors.

4.1.3 Enzyme-mediated electrochemical cascades. Enzyme-mediated signal amplification represents one of the most effective strategies for enhancing electrochemical sensor sensitivity, as enzymatic reactions generate electroactive products in a catalytic fashion, leading to continuous signal amplification. Among the most commonly used enzymes are horseradish peroxidase (HRP), glucose oxidase (GO_x), and alkaline phosphatase (ALP), which serve as catalytic signal enhancers in AEBs.

HRP-based amplification is frequently employed in aptamer-based biosensors, where the enzyme catalyzes the oxidation of hydroquinone to benzoquinone, facilitating rapid electron transfer at the electrode surface. A recent HRP-conjugated aptamer biosensor for thrombin detection achieved an LOD of 0.03 fM, demonstrating its feasibility for ultrasensitive blood coagulation monitoring Wang.[177]

Similarly, GO_x-based enzymatic cascades have been employed for glucose and lactate monitoring, with carbon nanotube (CNT)-modified electrodes providing a 1000-fold improvement in electrochemical signal output. GO_x-mediated electrochemical biosensors are particularly promising for real-time metabolic monitoring in diabetic patients, paving the way for wearable biosensing applications. Furthermore, dual-enzyme electrochemical cascades, combining HRP and ALP, have been developed to achieve synergistic signal amplification, where one enzyme generates an intermediate product that serves as a substrate for the second enzyme, thereby further enhancing electrochemical response. This strategy was recently implemented in a dual-enzyme aptasensor for cancer biomarker detection, achieving a LOD of 0.005 fM for circulating tumor DNA (ctDNA), demonstrating its clinical potential.[178]

4.2 Sensor stability and reproducibility

The integration of nanomaterials into aptamer-based electrochemical biosensors (AEBs) has significantly improved their stability, sensitivity, and biocompatibility. Advanced nanomaterial engineering strategies, including functionalization of gold nanoparticles (AuNPs), carbon nanotubes (CNTs), and graphene oxide (GO), as well as encapsulation techniques to prevent aptamer degradation and the use of self-assembled nanostructures, have played a crucial role in optimizing biosensor performance. These modifications enhance the binding efficiency, electrochemical signal transduction, and real-time applicability of AEBs in clinical diagnostics and point-of-care (POC) applications.

4.2.1 Functionalization of AuNPs, CNTs, and graphene oxide (GO). Nanomaterial functionalization is a fundamental strategy for improving the stability, signal transduction efficiency, and specificity of AEBs. The use of gold nanoparticles (AuNPs), carbon nanotubes (CNTs), and graphene oxide (GO) as electrode modifiers or aptamer carriers provides increased surface area, high electrical conductivity, and enhanced biomolecule attachment, which are essential for ultra-sensitive electrochemical sensing.

AuNPs have been extensively used in electrochemical biosensors due to their ability to immobilize aptamers *via* thiol (–SH) linkages, ensuring high stability and specificity in target recognition.[179] A recent study demonstrated that citrate-stabilized AuNPs functionalized with thiolated aptamers enabled the detection of prostate-specific antigen (PSA) at 0.05 fM, significantly improving binding efficiency and electrochemical response compared to unmodified electrodes.[180] Additionally, bimetallic AuNP-based composites, such as gold–silver (Au–Ag) and gold–platinum (Au–Pt) nanoparticles, have been developed to improve catalytic activity and electron

transfer rates, further enhancing sensor sensitivity. Similarly, CNTs have gained attention due to their high charge carrier mobility and excellent conductivity, making them ideal for signal transduction enhancement in AEBs. Functionalized CNTs, particularly carboxyl (–COOH) and amine ($–NH_2$) modified CNTs, allow for covalent aptamer attachment, increasing sensor reproducibility and biocompatibility.[181] A multi-walled CNT (MWCNT)-modified aptasensor for cardiac troponin I (cTnI) detection achieved an LOD of 0.02 fM, demonstrating its feasibility for early myocardial infarction diagnosis.[182]

Graphene oxide (GO) offers a large surface area, strong π–π interactions, and high biocompatibility, making it a versatile nanomaterial for electrochemical biosensing. GO-based biosensors rely on π–π stacking interactions between the nucleobases of aptamers and the sp^2-hybridized carbon lattice, enabling high-density aptamer immobilization.[183] A recent GO-modified aptasensor for exosomal miRNA detection demonstrated attomolar-level sensitivity, highlighting its potential for liquid biopsy applications.[184]

4.2.2 Encapsulation techniques to prevent aptamer degradation. One of the key challenges in aptamer-based biosensors is the susceptibility of aptamers to nuclease degradation and loss of structural integrity in physiological conditions. To address this, researchers have developed encapsulation techniques using polymeric coatings, lipid bilayers, and nanogel matrices to enhance aptamer stability and longevity. Polyethylene glycol (PEG) modification has been extensively explored as an anti-fouling and stability-enhancing strategy for aptamers in complex biological fluids. A PEGylated aptamer-functionalized biosensor for circulating tumor DNA (ctDNA) detection exhibited a 10-fold increase in half-life, significantly improving its clinical applicability.[185] Lipid-based encapsulation, particularly liposome-coated aptasensors, has also been investigated to shield aptamers from enzymatic degradation. A recent study demonstrated that a liposome-encapsulated aptamer biosensor for SARS-CoV-2 RNA detection achieved a detection limit of 0.01 fM, with superior stability over a 30-day period compared to unprotected aptamers.[186] Hydrogel-based nanostructures, such as DNA nanogels and zwitterionic polymer matrices, have emerged as promising biocompatible encapsulation systems that prevent non-specific adsorption and structural degradation. A hydrogel-coated aptamer sensor for NT-proBNP detection demonstrated long-term sensor stability, allowing continuous biomarker monitoring over several weeks.

4.2.3 Self-assembled nanostructures for enhanced surface interactions. The development of self-assembled nanostructures has significantly improved aptamer orientation, target accessibility, and electrochemical signal transduction efficiency in biosensors. Self-assembled monolayers (SAMs), DNA origami-based architectures, and hierarchical nanostructures have been extensively explored to enhance aptamer–target interactions and improve biosensor performance.

SAMs, particularly alkanethiol-based monolayers on gold electrodes, allow for precise aptamer organization, preventing steric hindrance and ensuring efficient target capture.[187] A self-assembled aptamer-functionalized AuNP electrode for thrombin detection achieved an LOD of 0.02 fM, demonstrating improved binding kinetics and electrochemical response.[188] Additionally, DNA origami-based aptasensors have been developed to create nano-engineered spatial arrangements of aptamers, improving their binding efficiency and selectivity. A recent DNA origami-enhanced electrochemical biosensor for breast cancer biomarker detection demonstrated a 100-fold improvement in sensitivity, paving the way for precision diagnostics in oncology.[189] Hierarchical nanostructures, such as MOF-functionalized aptasensors, provide a 3D nanoplatform for target recognition, significantly improving the signal-to-noise ratio and sensor stability. A MOF–AuNP hybrid biosensor for cardiac biomarker detection recently achieved an LOD of 0.01 fM, showcasing its clinical potential for early disease detection.[190]

5. Conclusions

Aptamer-based electrochemical biosensors (AEBs) have demonstrated immense potential as next-generation diagnostic tools due to their high specificity, rapid response, and ultra-sensitive detection capabilities. By leveraging the molecular recognition properties of aptamers and the efficient signal transduction of electrochemical platforms, AEBs have been successfully applied in detecting cancer biomarkers, cardiovascular disease indicators, and infectious pathogens, offering a promising alternative to conventional diagnostic methods. The integration of functional nanomaterials, including gold nanoparticles (AuNPs), graphene oxide (GO), carbon nanotubes (CNTs), and metal–organic frameworks (MOFs), has significantly enhanced biosensor performance by improving electron transfer, signal stability, and biocompatibility.[191]

Key advancements in signal amplification strategies, such as redox cycling, hybridization chain reaction (HCR), rolling circle amplification (RCA), and enzyme-mediated electrochemical cascades, have enabled the detection of biomarkers at femtomolar (fM) and even attomolar (aM) levels, making AEBs highly suitable for early disease diagnostics and point-of-care (POC) applications. Furthermore, efforts in biosensor miniaturization, multiplexed detection, and real-time monitoring have paved the way for their integration into wearable and portable diagnostic devices.[192] However, challenges remain, particularly in addressing sample matrix effects, long-term stability, and clinical validation, which must be overcome to facilitate widespread clinical adoption.

Looking ahead, the future development of AEBs will likely be driven by advancements in nanotechnology, artificial intelligence (AI)-assisted biosensor data analysis, and microfluidic-integrated lab-on-a-chip (LOC) systems. The incorporation of machine learning algorithms for real-time signal interpretation and automated biomarker detection could significantly improve diagnostic accuracy and facilitate personalized medicine.[193] Additionally, efforts to develop cost-effective, scalable, and regulatory-approved biosensing platforms will be crucial in ensuring the translation of these technologies from research laboratories to clinical and point-of-care settings worldwide.[194]

In conclusion, aptamer-based electrochemical biosensors represent a revolutionary step forward in biomedical diagnostics, offering high sensitivity, selectivity, and adaptability across diverse healthcare applications. By addressing existing challenges and leveraging the latest innovations in biosensor technology, AEBs have the potential to bridge the gap between laboratory research and real-world clinical applications, ultimately transforming disease diagnostics and improving global healthcare outcomes.

Author contributions

SaRi GeGen: investigation and writing – original draft; Gedong Meng: resources and validation; Gerile Aodeng: resources, investigation; Lu Ga: resources, supervision; Jun Ai: conceptualization.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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