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Review article

AI-optimized electrochemical aptasensors for stable, reproducible detection of neurodegenerative diseases, cancer, and coronavirus

Amira Elsir Tayfour Ahmed [a], Th.S. Dhahi [b], Tahani A. Attia [c,d], Fawzia Awad Elhassan Ali [e], Mohamed Elshaikh Elobaid [f], Tijjani Adam [f,g,h,*], Subash C.B. Gopinath [i,j]

[a] Department of Information System, College of Science & Arts King Khalid University, Mohyel, Asser, Saudi Arabia
[b] Health and Medical Technicals College, Southern Technical University, Basrah, Iraq
[c] Department of Computer Engineering, College of Computer Science and Engineering, University of Ha'il, Saudi Arabia
[d] DEEE, Faculty of Engineering, University of Khartoum, Sudan
[e] Imam Abdulrahman Bin Faisal University, Applied College, Computer Department, Saudi Arabia
[f] Faculty of Electronic Engineering & Technology, Universiti Malaysia Perlis, 02600, Arau, Perlis, Malaysia
[g] Institute of Nano Electronic Engineering, Universiti Malaysia Perlis, 01000, Kangar, Perlis, Malaysia
[h] Micro System Technology, Centre of Excellence (CoE), Universiti Malaysia Perlis (UniMAP), Perlis, Malaysia
[i] Center for Global Health Research, Saveetha Medical College & Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Chennai, 602 105, Tamil Nadu, India
[j] Faculty of Chemical Engineering & Technology, Universiti Malaysia Perlis (UniMAP), 02600, Arau, Perlis, Malaysia

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ABSTRACT

AI-optimized electrochemical aptasensors are transforming diagnostic testing by offering high sensitivity, selectivity, and rapid response times. Leveraging data-driven AI techniques, these sensors provide a non-invasive, cost-effective alternative to traditional methods, with applications in detecting molecular biomarkers for neurodegenerative diseases, cancer, and coronavirus. The performance metrics outlined in the comparative table illustrate the significant advancements enabled by AI integration. Sensitivity increases from 60 to 75 % in ordinary aptasensors to 85–95 %, while specificity improves from 70-80 % to 90–98 %. This enhanced performance allows for ultra-low detection limits, such as 10 fM for carcinoembryonic antigen (CEA) and 20 fM for mucin-1 (MUC1) using Electrochemical Impedance Spectroscopy (EIS), and 1 pM for prostate-specific antigen (PSA) with Differential Pulse Voltammetry (DPV). Similarly, Square Wave Voltammetry (SWV) and potentiometric sensors have detected alpha-fetoprotein (AFP) at 5 fM and epithelial cell adhesion molecule (EpCAM) at 100 fM, respectively. AI integration also enhances reproducibility, reduces false positives and negatives (from 15-20 % to 5–10 %), and significantly decreases response times (from 10-15 s to 2–3 s). These advancements improve data processing speeds (from 10 to 20 min per sample to 2–5 min) and calibration accuracy (<2 % margin of error compared to 5–10 %), while expanding application scope to multi-target biomarker detection. This review highlights how these advancements position AI-optimized electrochemical aptasensors as powerful tools for personalized treatment, point-of-care testing, and continuous health monitoring. Despite a higher cost ($500-$1,500/unit), their enhanced portability and diagnostic

* Corresponding author. Faculty of Electronic Engineering & Technology, Universiti Malaysia Perlis, 02600, Arau, Perlis, Malaysia.
E-mail address: tijjani@unimap.edu.my (T. Adam).

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performance promise to revolutionize healthcare, environmental monitoring, and food safety, ultimately improving public health outcomes.

1. Introduction

Aptasensors are biological recognition elements that exhibit high specificity and affinity for target molecules, making them highly effective in diagnostic applications. Compared to traditional antibody-based biosensors, aptasensors offer several advantages, including ease of production, affordability, and versatility. They are widely used in fields such as environmental monitoring, food safety, healthcare, and pharmaceutical analysis, enabling the rapid and precise identification of biomarkers associated with various diseases [1]. Aptasensors are particularly suitable for point-of-care diagnostics due to their fast response times, high sensitivity, small sample volume requirements, and ease of operation, making them ideal for use in resource-limited settings [2,3]. Electrochemical aptasensors, a subset of aptasensor technology, offer remarkable advantages due to their high sensitivity, compatibility with microfabrication processes, and cost-effectiveness. These sensors can detect specific analytes with minimal signal fabrication and high sensitivity, making them ideal for routine diagnostics and on-site applications [4,5]. While electrochemical aptasensors are typically used in a range of testing environments, their effectiveness heavily relies on the choice of interface materials, which can enhance the sensors' sensitivity, selectivity, and stability [6]. Advances in interface material selection, coupled with lab-on-a-chip technologies, have contributed to the miniaturization and mobility of electrochemical sensing platforms, making them increasingly suitable for portable diagnostics [7]. For instance, materials such as multiwalled carbon nanotubes and dendrimers have been shown to improve detection performance by enhancing signal intensity and sensor sensitivity [8]. In recent years, electrochemical aptasensors have demonstrated significant advancements, particularly in the context of clinical diagnostics for diseases such as cancer, neurodegenerative disorders, and viral infections like COVID-19. The integration of AI optimization has further revolutionized these sensors, enabling more stable, reproducible, and accurate detection. AI algorithms now help refine sensor performance, improving their ability to detect molecular biomarkers in complex biological matrices like blood, urine, and saliva, even at trace concentrations [42]. These innovations have paved the way for faster and more efficient diagnostic procedures, offering the potential for early disease detection, continuous monitoring, and personalized treatment strategies [9,10]. The real novelty in recent developments lies in the AI-optimized electrochemical aptasensors, which are transforming how biomarkers for neurodegenerative diseases, cancer, and coronavirus are detected. By leveraging AI, these sensors not only achieve high precision and reliability but also demonstrate robust performance in low-resource settings where traditional methods may fail [11]. AI enhances the stability and reproducibility of these sensors, ensuring they deliver consistent results across various clinical and environmental conditions [109]. Furthermore, the integration of AI offers improvements in sensor calibration and real-time data processing**,** facilitating the detection of molecular markers at ultra-low concentrations and enabling faster diagnostic timelines [1,12]. Electrochemical aptasensors, with the added power of AI, are poised to revolutionize diagnostic testing by allowing non-invasive, low-cost detection with high accuracy [110]. This is particularly important in clinical settings where rapid, early detection of diseases such as cancer and neurodegenerative conditions can significantly improve patient outcomes. The ability to detect biomarkers in complex biological matrices also positions electrochemical aptasensors as key tools in personalized medicine and continuous health monitoring [111]. Moreover, Optical aptasensors, while widely used, face notable challenges, including high costs, complex instrumentation, susceptibility to light interference, and difficulties in miniaturization for portable diagnostics [1]. In contrast, electrochemical aptasensors are cost-effective, simpler to integrate, and offer robust and reliable performance [112]. These advantages make them particularly suitable for real-world diagnostic applications, emphasizing their significance in advancing molecular detection technologies**.** The selection of biomarkers for Neurodegenerative Diseases, Cancer, and Coronavirus is driven by their global health relevance and their technological adaptability to advanced systems like Machine Learning (ML) and Artificial Intelligence (AI) [113]. Each of these diseases represents significant medical challenges, emphasizing the need for early detection and effective diagnostic tools. Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are increasingly prevalent due to aging populations, and their early diagnosis can greatly improve patient care and outcomes. Similarly, cancer biomarkers are critical for early detection, personalized therapy, and treatment monitoring, addressing one of the leading causes of mortality worldwide. For Coronavirus, the COVID-19 pandemic has underscored the importance of rapid and reliable diagnostic approaches, making this biomarker selection timely and essential [114]. A key advantage of these biomarkers is their compatibility with AI and ML systems, allowing for advanced data analysis and integration into intelligent diagnostic platforms. Biomarkers for these diseases often have well-characterized molecular and biochemical signatures, which can be seamlessly analyzed by AI algorithms to optimize detection, reduce false positives or negatives, and predict disease progression or treatment outcomes. This compatibility enhances the reliability and efficiency of diagnostic systems [115]. These biomarkers are also particularly well-suited for detection using electrochemical aptasensors. Such platforms are compact, sensitive, and cost-effective, making them ideal for real-world applications [116]. Additionally, electrochemical systems can interface directly with AI-based systems for real-time monitoring and feedback, further improving their diagnostic utility. The combination of these biomarkers with AI-driven systems creates opportunities for robust and portable diagnostic tools that can be deployed in various settings. Another critical factor in selecting these biomarkers is their cross-application potential. They not only target specific diseases but also enable multiplexing in diagnostic platforms, allowing simultaneous detection of various conditions. This capability aligns well with AI's pattern recognition and data processing strengths, making these systems efficient and scalable for broader healthcare applications [117]. Thus, these biomarkers enable rapid data processing and actionable insights, which are vital in both acute and chronic conditions. For example, the real-time detection of Coronavirus infections or monitoring the progression of neurodegenerative diseases and cancer can significantly

improve patient outcomes. By integrating these biomarkers with AI, diagnostic processes become more streamlined, accurate, and responsive, catering to both immediate and long-term healthcare needs [118]. This study explores the transformative potential of AI-optimized electrochemical aptasensors, focusing on their applications in detecting molecular markers associated with cancer, neurodegenerative diseases, and coronavirus infections. We aim to address the following research questions: (1) How do different electrochemical techniques (EIS, DPV, SWV, and potentiometry) compare in terms of sensitivity and specificity for detecting cancer biomarkers at low concentrations? (2) What is the impact of AI-enhanced electrochemical aptasensors on the speed and accuracy of disease diagnosis compared to conventional diagnostic methods? Additionally, we hypothesize that integrating AI and nanomaterials into electrochemical aptasensors significantly enhances their sensitivity and detection limits, enabling the multiplexed detection of multiple biomarkers at ultralow concentrations for early disease diagnosis and monitoring of progression.

2. Aptamer sensor mechanism and AI integration

Redox probe chemistry and electrochemical behavior are key factors that define the performance of electrochemical aptasensors. Common redox probes like ferrocene derivatives, methylene blue (MB), and $[Fe(CN)_6]^{3-/4-}$ are widely utilized for their stable electrochemical properties and sensitivity. These probes facilitate measurable changes in current or impedance when the aptamer binds to its target, enabling the detection of analytes even at low concentrations [112]. Techniques such as Differential Pulse Voltammetry (DPV), Electrochemical Impedance Spectroscopy (EIS), and Square Wave Voltammetry (SWV) are employed to measure these redox responses. These methods offer high sensitivity and allow the detection of subtle variations in electrochemical signals, which are critical for accurate biomarker detection in clinical diagnostics [113]. The electrochemical behavior is further optimized by surface modifications, such as gold-based electrodes and graphene-functionalized surfaces, which enhance the electron transfer and increase the surface area for aptamer immobilization [114]. These modifications improve the sensitivity and reproducibility of the sensor, reducing signal fluctuation and interference. The use of advanced materials like carbon nanotubes and molecularly imprinted polymers (MIPs) also enhances the stability and specificity of the redox signal [115]. By integrating AI and machine learning, the sensor can further optimize these electrochemical behaviors, ensuring more reliable and rapid detection. This combination of redox probe chemistry and electrochemical methods results in more accurate, portable, and sensitive aptasensors for various diagnostic applications. Aptamer-based sensors have become pivotal in biosensing due to their unmatched specificity and versatility. Aptamers are short DNA or RNA sequences that fold into precise three-dimensional structures to selectively bind to target molecules, such as proteins or small analytes, even differentiating between subtle structural variations [17,116]. Their ability to achieve high target specificity makes them comparable to antibodies but with advantages like ease of synthesis and modification. The SELEX process, which iteratively selects high-affinity aptamers, ensures the aptamers are tailored for their specific targets [19]. With the integration of artificial intelligence (AI) and integrated circuits (ICs), the potential of aptasensors is amplified, enabling more efficient detection systems. The sensing process begins with sample acquisition and biomolecule extraction from complex matrices such as blood, saliva, or

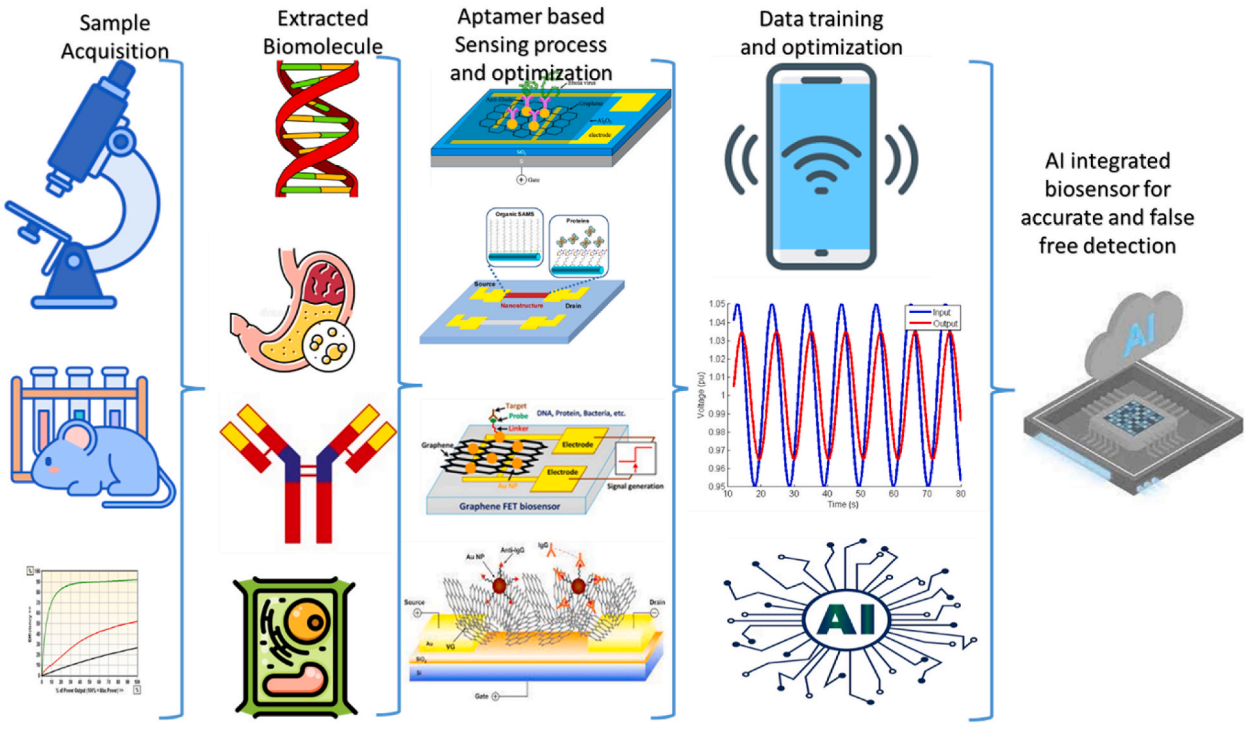

Fig. 1. Aptamer sensor mechanism and AI integration: a synergistic approach.

environmental samples. This step is crucial for preserving target molecules in their native state, as the aptamer's performance depends on accurate biomolecule representation. AI integration optimizes sample preparation by analyzing datasets to refine extraction protocols, ensuring minimal contamination. At the hardware level, ICs can be employed to automate and streamline the extraction process, controlling parameters like temperature, pH, and flow rates with precision [18]. This integration significantly enhances the reproducibility and reliability of aptamer-based sensing. Aptamer-target interactions generate signals—typically electrochemical, optical, or fluorescence-based—that require processing for accurate detection [19]. AI-driven algorithms play a critical role in interpreting these signals by minimizing noise, enhancing sensitivity, and calibrating detection thresholds in real-time. Integrated circuits further contribute by providing the necessary hardware support for data acquisition, signal amplification, and digitization, ensuring seamless communication between the sensor and AI-driven software. This combination of AI and ICs ensures that aptamer-based sensors deliver rapid, reliable, and high-resolution results, even in the presence of interfering substances [22]. AI integration goes beyond signal interpretation by optimizing the aptamer design process itself. Machine learning (ML) models streamline SELEX by predicting aptamer sequences with enhanced binding specificity and stability, while deep learning models simulate aptamer folding dynamics. Once aptamers are incorporated into sensors, AI fine-tunes the system for specific applications, such as biomarker detection for cancer or viral infections. Simultaneously, ICs enhance the scalability and portability of these sensors, enabling real-time, point-of-care diagnostics and environmental monitoring systems that are compact and efficient. The synergy between AI, aptamers, and IC technology paves the way for next-generation biosensors with unparalleled accuracy [23]. By integrating AI's computational power and IC's hardware capabilities, aptamer sensors achieve a level of precision that minimizes false positives and negatives [117]. Applications range from personalized medicine, where sensors provide continuous health monitoring, to environmental safety and food quality control. This convergence of advanced biochemical sensing, intelligent algorithms, and miniaturized electronics ensures that aptamer-based sensors are at the forefront of modern diagnostics, driving innovation in both healthcare and industrial fields Fig. 1.

3. Aptasensors

A particular kind of biosensor, known as an aptasensor, uses aptamers—single-stranded RNA or DNA oligonucleotides—as its recognition component. Aptamers have the remarkable ability to selectively bind to target molecules, including small molecules, proteins, and even entire cells [1]. Due to their exceptional affinity and specificity, aptamers are ideal for the development of biosensors designed for a variety of applications, including food safety, environmental monitoring, and medical diagnostics. The binding event between the aptamer and its target molecule is transduced into a measurable signal, which can be optical, piezoelectric, or electrochemical in nature, depending on the transducer used in the aptasensor design [26]. One of the key advantages of aptasensors is their high sensitivity and selectivity, enabling them to detect a broad range of target molecules with precision [7]. The ability to easily customize aptamers for different targets—thanks to the relatively simple process of aptamer production and modification—adds to the versatility of these sensors in biosensing applications [27]. However, as research into aptasensor development progresses, there remains a need to improve their stability, sensitivity, response time, and reproducibility for various applications, especially in real-world diagnostic settings [28]. Here, Artificial Intelligence (AI) offers powerful solutions to optimize and accelerate the design, development, and performance of aptasensors. AI-based machine learning (ML) models can be employed to predict aptamer sequences with enhanced binding affinities for specific targets, vastly improving the SELEX process, which traditionally requires time-consuming and resource-intensive experimental iterations [100]. By learning from large datasets of aptamer-target interactions, AI systems can identify optimal sequences and predict their behavior in complex environments, improving both the selectivity and sensitivity of the resulting aptasensors. AI algorithms can also assist in the real-time optimization of electrochemical aptasensors by analyzing sensor data and fine-tuning parameters such as signal strength, detection limits, and response times. These AI-driven adjustments ensure that aptasensors operate at peak efficiency, enhancing stability and accuracy in variable and challenging environments. Furthermore, AI can enable multiplexed detection—the simultaneous measurement of multiple biomarkers—by analyzing complex data from aptasensor arrays [109]. This is particularly valuable in personalized medicine, where multiple biomarkers need to be monitored simultaneously to tailor treatment strategies for individual patients. Moreover, AI-powered data analysis can improve the interpretation of biosensor results, especially when dealing with large datasets generated by portable, on-site diagnostic systems. By applying advanced data mining and pattern recognition techniques, AI can identify subtle biomarkers or disease patterns that might otherwise go undetected, enabling early disease diagnosis and more accurate monitoring of conditions such as cancer, neurodegenerative diseases, and viral infections [108]. The integration of AI with aptasensors not only enhances their performance in clinical diagnostics but also broadens their applications to areas like environmental monitoring and food safety, where real-time, portable detection systems are crucial [99]. AI-based modeling can predict the interaction of aptamers with complex environmental matrices, optimizing their sensitivity and specificity in detecting pollutants, pathogens, or toxins in the field [29]. In summary, AI-enhanced aptasensors offer a promising approach to improve the accuracy, speed, and reliability of biosensors, making them increasingly suitable for on-site monitoring and point-of-care diagnostics. The synergistic combination of aptamers' inherent recognition capabilities and AI's predictive modeling and data analysis power is paving the way for more efficient and accessible diagnostic tools across various sectors.

4. Electrochemical sensors

The excellent sensitivity and selectivity of electrochemical sensors make them highly effective for detecting a wide range of analytes, with applications spanning medical diagnostics, industrial process control, and environmental monitoring [30]. The underlying principle involves a chemical interaction between the analyte and the sensor surface, generating an electrical signal that can

be measured to identify and quantify the analyte. In complex sample matrices, electrochemical sensors offer significant advantages, as their surface chemical reactions can be tailored to selectively target specific analytes, enhancing their specificity. This specificity, coupled with rapid reaction times and low detection limits, positions electrochemical sensors as ideal tools for real-time monitoring and detection of trace analytes [31,32]. These characteristics make them especially valuable for dynamic, real-world environments where timely, accurate data is crucial. In recent years, advancements in sensor technology have significantly improved electrochemical biosensors. The incorporation of nanomaterials, microfluidic systems, and miniaturized sensor platforms has led to increased sensitivity, stability, and portability of these sensors [33]. Furthermore, the integration of artificial intelligence (AI) and machine learning (ML) into electrochemical sensor systems is revolutionizing their performance. AI-driven models can optimize sensor responses by adjusting for variations in environmental conditions, sensor drift, and sample matrix changes, ensuring more accurate and reliable results. These technologies enable sensors to be trained to distinguish between subtle differences in analytes, thus improving sensitivity and reducing false positives/negatives. Additionally, AI can assist in real-time data analysis, significantly enhancing the speed and efficiency of the detection process. The combination of these advancements with nanomaterials and AI integration promises to usher in a new era of highly efficient, adaptable, and stable electrochemical sensors, making them even more applicable for clinical diagnostics and other critical applications. An electrode, which immobilizes biomolecules and facilitates electron transfer, remains a central component of these systems, as shown in Fig. 2.

5. Electrochemical aptasensors

A new type of biosensor, known as aptasensors, utilizes aptamers as the recognition element, offering high specificity and affinity for target molecules (see Fig. 3). Aptamers are single-stranded DNA or RNA molecules that bind to specific target molecules, causing an electrochemical signal shift that can be detected, correlating to the concentration of the target molecule in the sample [34,35]. These electrochemical aptasensors hold great promise for a wide range of applications, such as the detection of chemicals, proteins, viruses, and even whole cells [36,37]. Aptamers are particularly advantageous in analytical and diagnostic applications due to their rapid, real-time detection capabilities, high specificity, and sensitivity [38]. Additionally, electrochemical aptasensors are highly suitable for integration into portable, point-of-care devices, offering a significant benefit for on-site monitoring across sectors like food safety, medical diagnostics, and environmental monitoring [6]. However, the successful development of electrochemical aptasensors requires careful consideration of aptamer sequences, immobilization techniques, signal transduction pathways, and sensor architecture, which must be optimized for real-world applications [5].

In recent advancements, the integration of artificial intelligence (AI) into electrochemical aptasensors has dramatically enhanced their performance. AI algorithms can process complex sensor data, adapt to fluctuating environmental conditions, and optimize sensor responses to improve the sensitivity and reliability of the aptasensor systems. AI can also facilitate the real-time analysis of data, enabling quicker detection of analytes, reducing errors such as false positives or negatives, and enhancing the sensor's overall accuracy [98,102]. The combination of cutting-edge materials, such as carbon nanomaterials and gold nanoparticles, with AI-driven techniques has significantly improved the sensitivity, stability, and repeatability of electrochemical aptasensors, making them more suitable for real-world applications [39]. The electrochemical aptasensor's application in food safety is a prime example of its potential [40]. Using enzyme-induced catalysis tests and redox probe coupling, this method detects food toxins with high specificity and sensitivity,

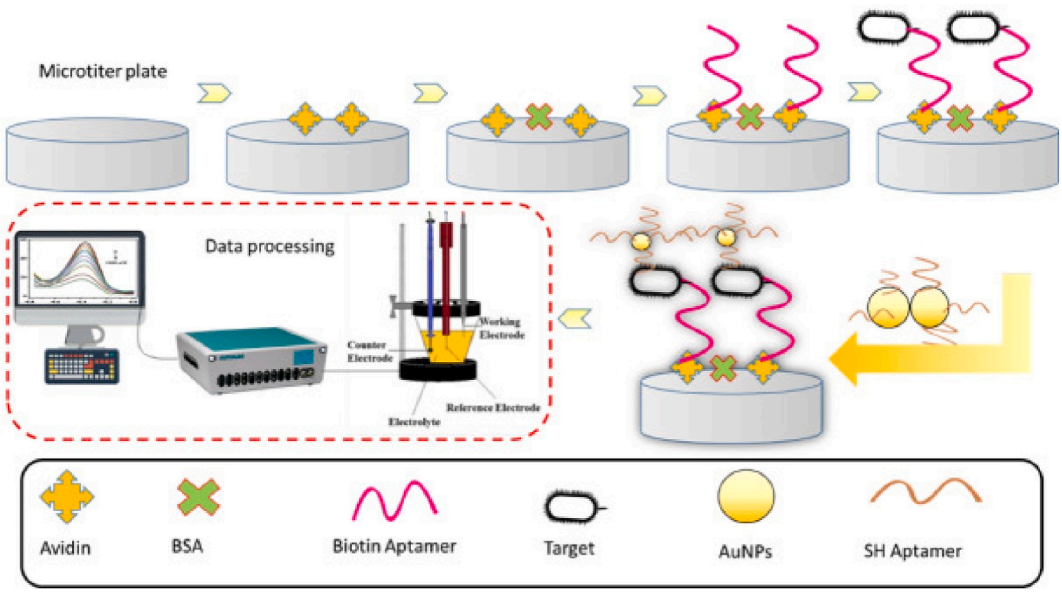

Fig. 2. The electrochemical biosensor employs an electrode as a critical component for immobilizing biomolecules and permitting electron transport.

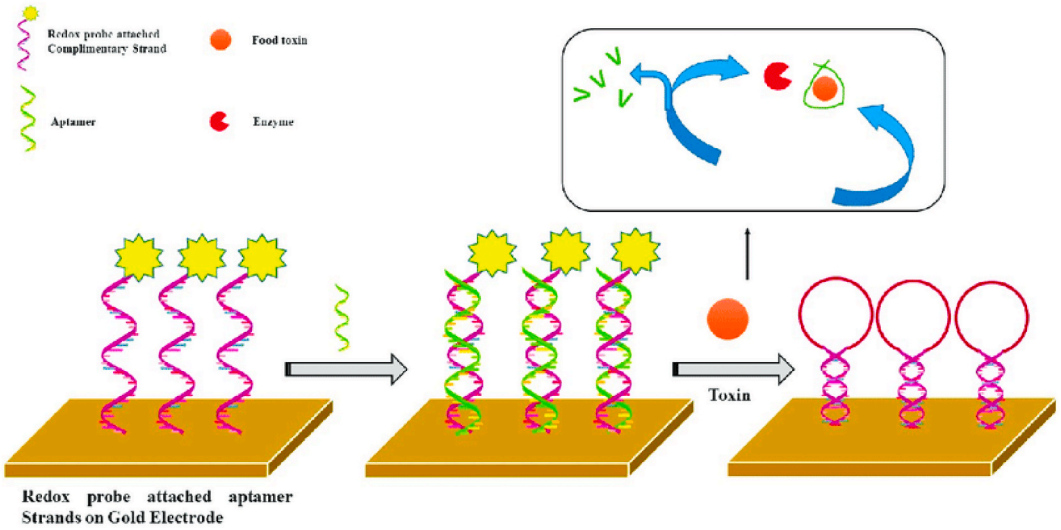

Fig. 3. The electrochemical aptasensor is a powerful tool for detecting food toxins, using aptamers as DNA or RNA molecules to bind to specific targets. It offers high sensitivity and selectivity, making it versatile for various food industries. By immobilizing the aptamer onto an electrode surface, it measures and quantifies the presence and concentration of food toxins.

ensuring the safety and quality of food products [40]. With AI integration, these sensors can be further refined for faster, more accurate detection, expanding their applications beyond food safety to areas like medical diagnostics and environmental monitoring [97,106]. To optimize the stability and reproducibility of electrochemical aptasensors for practical clinical use, several strategies can be employed. One of the primary approaches is improving the immobilization techniques of the aptamers onto the sensor surface. Surface modifications, such as gold nanoparticle functionalization, graphene coatings, or the use of self-assembled monolayers (SAMs), enhance the stability of the aptamers by providing a more robust attachment to the electrode surface [96]. These modifications can

Table 1
The performance of existing electrochemical aptasensors techniques.

modification Method	The Strategy for Immobilization	Limit of Detection	Linear Range	Aptamer Type and Length	Target Analyte	Reference
Differential Pulse Voltammetry	The study examines the influence of surface on gold-based electrodes.	0.25 ng/mL	0.25 ng/mL - 1 μg/mL	DNA aptamer (20–30 bases)	PSA (Prostate-Specific Antigen)	[45]
Electrochemical Impedance Spectroscopy (EIS)	The study examines amine-terminated surface modification.	0.5 ng/mL	0.5 ng/mL - 100 ng/mL	DNA aptamer (30 bases)	Cortisol	[46]
Electrochemical Impedance Spectroscopy (EIS)	Co-immobilized SAM of DNA-aptamer and MCH was effectively realized.	60 ng/mL	60 ng/mL - 1 μg/mL	DNA aptamer (15–25 bases)	Influenza Virus	[47]
Electrochemical Impedance Spectroscopy (EIS)	DNA-directed immobilization aptamer sensors are designed and pre-incubated with aptamer and PSA.	0.5 pg/mL	0.5 pg/mL - 1 ng/mL	DNA aptamer (18 bases)	PSA (Prostate-Specific Antigen)	[48]
EIS/Differential Pulse Voltammetry	The graphene-chitosan immobilized aptamer.	DPV: 10 fg/mL, EIS: 5 pg/mL	10 fg/mL - 1 ng/mL	DNA aptamer (20–25 bases)	HER2 (Human Epidermal Growth Factor Receptor 2)	[49]
Square Wave Voltammetry	Utilized covalent grafting of amine-terminated surface.	>1 ng/mL	1 ng/mL - 100 ng/mL	DNA aptamer (30 bases)	Aflatoxin B1	[50]
Differential Pulse Voltammetry	Carbon nanotube with chitosan.	0.75 ng/mL	0.75 ng/mL - 10 ng/mL	DNA aptamer (20–30 bases)	Ochratoxin A	[51]
Differential Pulse Voltammetry	The gold electrode immobilized arginine template.	0.05 ng/mL	0.05 ng/mL - 1 ng/mL	DNA aptamer (25 bases)	Interleukin-6 (IL-6)	[52]
Electrochemical Impedance Spectroscopy (EIS)	Used molecularly imprinted polymers.	1 pg/mL	1 pg/mL - 100 ng/mL	MIP-based sensor	Acetaminophen	[53]
EIS/Square Wave Voltammetry	Self-assembled surface modified.	EIS: 0.01 ng/mL, SWV: 0.1 ng/mL	0.01 ng/mL - 1 μg/mL	DNA aptamer (15–30 bases)	Thrombin	[54]

also reduce nonspecific adsorption and interference, ensuring consistent performance over extended periods. Additionally, optimizing the operating conditions, such as the choice of buffer systems, pH, and ionic strength, can significantly improve the reproducibility of the sensor responses. Implementing more advanced redox probe chemistries, such as utilizing highly stable redox markers like methylene blue or ferrocene derivatives, can further enhance signal stability [95,107]. To ensure long-term reproducibility, the sensors can be integrated with AI or machine learning models that adapt to minor environmental or sample-related changes, correcting for potential drift in sensor performance. Moreover, repeated calibration and periodic maintenance protocols in clinical settings can also contribute to maintaining sensor performance over time [13]. These combined strategies can significantly enhance the stability and reproducibility of aptasensors, making them more reliable and applicable for routine clinical diagnostics.

6. Advantages of electrochemical aptasensors over other biomedical diagnostic methods

Table 1 further highlights the comparison of various electrochemical aptasensing methods, focusing on key parameters such as the strategy for immobilization, limit of detection (LOD), linear range, aptamer type and length, and the target analytes. The methods used for immobilization vary, including surface modification techniques, self-assembled monolayers (SAM), and DNA-directed immobilization. The limits of detection range from as low as 0.01 ng/mL to 60 ng/mL, depending on the specific method and target analyte [15,16]. Linear ranges also differ across methods, with some aptasensors detecting analytes from 10 fg/mL to 1 μg/mL. DNA aptamers are the most common, with lengths typically ranging from 15 to 30 bases [117]. The target analytes include proteins like PSA, cytokines such as IL-6, toxins like ochratoxin A, and viruses like the influenza virus and HER2. The table highlights the variety of electrochemical techniques used, such as differential pulse voltammetry (DPV), electrochemical impedance spectroscopy (EIS), and square wave voltammetry (SWV) [43]. These methods offer distinct advantages in terms of sensitivity, cost, and integration with systems like mobile devices. Each sensor design varies in terms of complexity, with some utilizing advanced strategies such as graphene-based electrodes, carbon nanotubes, or molecularly imprinted polymers (MIPs) to enhance performance [94,116]. These aptasensors demonstrate impressive specificity and reproducibility for detecting a wide range of target analytes, with the potential for further optimization, particularly in terms of limit of detection and integration with AI-driven data analysis systems [44].

7. Detection of cancer using electrochemical aptasensors

Cancer is a complex and devastating disease that affects millions of people worldwide. In order to address this growing burden, innovative approaches and technologies are needed for early detection and diagnosis [55]. One promising approach is the use of electrochemical aptasensors, which have shown great potential in detecting cancer biomarkers with high sensitivity and specificity [56]. These aptasensors utilize functionalized nanomaterials and micro-fabricated electrodes to enable rapid and accurate detection of cancer-related molecules in biological samples. Recent developments in electrochemical aptasensors have demonstrated tremendous promise for detecting cancer biomarkers [8]. Aptamers, DNA or RNA sequences, serve as bioreceptors in biosensors for target analytes. They can be synthetically modified for enhanced affinity and specificity, making them ideal bioreceptors. Electrochemical aptasensors are particularly useful for cancer detection due to their small-scale detection capabilities [57]. The study aimed to develop redox-labelled electrochemical aptasensors that could be paired with nano-supported cancer cells [58]. A 20-nm-thick nanopillar-based electrochemical DNA cell sensor has been developed to overcome downward force issues, allowing redox-labelled DNA probes to move freely while maintaining interaction distance from EpCAM, a target protein in cancer cells. DNA aptamer hairpins are an ultrasensitive lung cancer biomarker due to nanoconfinement, which lowers the melting temperature of the hairpins and increases detection limits [59]. For example, Graphene, carbon, and Ag/AgCl electrodes on a glass fiber plate were used in a study to create an integrated electrode system. AuNPs were applied to the electrode surface, followed by the immobilization of an aptamer for carcinoembryonic antigen. The sensor detected CEA concentrations with a detection limit of 0.085 ng/mL [60]. A study used carbon microelectromechanical systems (C-MEMS) to produce a sensitive and selective electrochemical aptasensor for the detection of

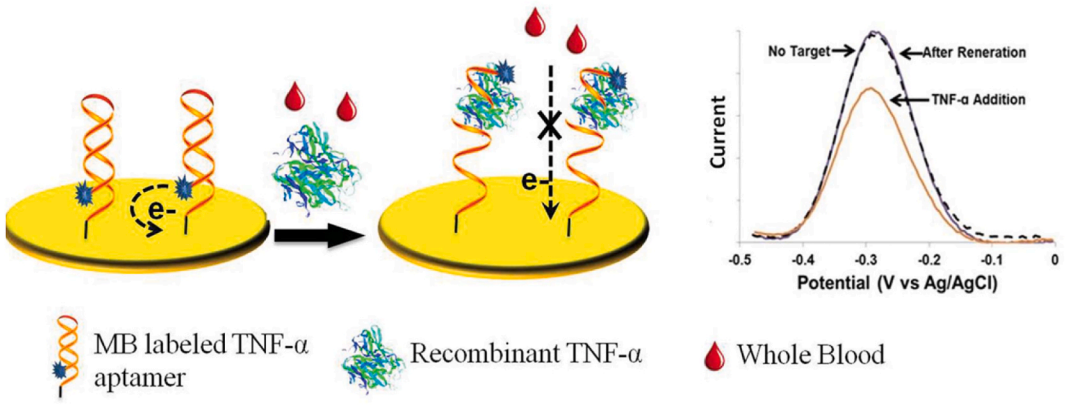

Fig. 4. Various processes of the developed aptasensor for cancer detection.

platelet-derived growth factor-BB (PDGF-BB). Oxygen-plasma oxidation treatment was used to carbonize and functionalize the active electrodes. The aptasensors, which offer excellent selectivity and stability, were employed for resistance and capacitance sensing. The study also reviewed metal-organic framework-based electrochemical aptasensors for cancer biomarker detection [61]. A review explores the development of metal-organic framework (MOF)-based electrochemical aptamer biosensors for early cancer detection, highlighting their sensitivity, selectivity, construction methods, and potential applications. An Au-Pd alloy-assisted aptasenor was used to detect lung cancer factor and breast cancer in human serum [62]. The study presents an electrochemical aptasensor for detecting HER2 protein, a breast cancer biomarker, with a sensitivity of 4.12 % per decade using gold screen-printed electrodes. A study created a high-sensitivity electrochemical aptasensing platform for measuring circulating tumor cells (CTCs) using methylene blue (MB) target-triggered signal readout [63]. Au nanoparticles immobilized MB-aptamers on a gold electrode, enabling K562 cell recognition. The aptasensor showed high selectivity, stability, and reproducibility, making it potential for clinical use. However, sensing performance depends on interface materials. Fig. 4 shows various procedures for the designed aptasensor for cancer detection [40]. Cancer detection is a critical aspect of healthcare, as early diagnosis can greatly increase the chances of successful treatment and improved patient outcomes [64]. Traditional methods of cancer detection, such as imaging techniques and biopsy, have limitations in terms of cost, invasiveness, and time-consuming processes [65]. Recently, electrochemical aptasensors have emerged as promising tools for cancer detection [57]. These aptasensors utilize the unique properties of aptamers, which are single-stranded DNA or RNA molecules that can bind selectively to target biomarkers or cancer-related molecules. By integrating aptamers with electrochemical transducers, such as electrodes or nanomaterials, electrochemical aptasensors can provide sensitive and specific detection of cancer biomarkers, opening new avenues for early and accurate diagnosis.

Table 2 presents a comprehensive overview of recent studies on the use of electrochemical aptasensors for cancer detection, focusing on sensor types, detection mechanisms, detection limits, and specificity. EIS (EIS) sensors demonstrate notable sensitivity and specificity, with detection limits as low as 10 fM for carcinoembryonic antigen (CEA), a crucial biomarker for various cancers, especially colorectal cancer [55]. The impedance change detection mechanism in EIS-based sensors is particularly effective for monitoring biomolecular interactions, making these sensors highly reliable for early cancer diagnosis [41]. Additionally, EIS-based aptasensors show remarkable performance in detecting human epidermal growth factor receptor 2 (HER2) and mucin-1 (MUC1), both of which are critical markers for breast cancer, with detection limits of 50 fM and 20 fM, respectively [58,60]. These results highlight the potential of EIS technology in providing early and accurate cancer diagnosis. Differential Pulse Voltammetry (DPV) sensors are also prominently featured in the table, offering excellent detection capabilities for various cancer biomarkers. For instance, DPV sensors achieved a detection limit of 1 pM for prostate-specific antigen (PSA), a key biomarker for prostate cancer, demonstrating their ability to detect low concentrations of target molecules [56]. Moreover, DPV-based aptasensors effectively detect vascular endothelial growth factor (VEGF), a biomarker associated with tumor angiogenesis, with a detection limit of 2 pM [59]. The specificity of DPV sensors for cancer biomarkers like PSA and VEGF highlights their utility in diagnosing and monitoring different types of cancer, particularly in cases where early detection is critical for effective treatment. Square Wave Voltammetry (SWV) sensors are highlighted for their ultra-low detection limits and high specificity. The table indicates that SWV sensors can detect alpha-fetoprotein (AFP) with a detection limit of 5 fM, making them highly effective for liver cancer diagnosis [8]. SWV-based aptasensors also show a strong performance in detecting cytokeratin 19 fragment (CYFRA 21-1), a marker for lung cancer, with a detection limit of 15 fM [61]. These sensors rely on the current change mechanism, which is highly sensitive to the presence of specific biomarkers, ensuring accurate detection even at very low concentrations. This makes SWV sensors particularly useful in cases where early and precise cancer detection is essential. Potentiometric aptasensors, though less commonly used than other types, offer a unique advantage in detecting specific cancer biomarkers through potential change mechanisms. These sensors show a detection limit of 100 fM for epithelial cell adhesion molecule (EpCAM), a marker for circulating tumor cells, which is crucial for monitoring metastasis in cancer patients [57]. Another potentiometric sensor demonstrates the ability to detect neuron-specific enolase (NSE) with a detection limit of 0.5 pM, indicating its potential in diagnosing neuroendocrine tumors [62]. The use of potentiometric aptasensors, with their relatively straightforward detection mechanism, provides an additional tool for the early diagnosis and monitoring of various cancers, complementing the capabilities of more complex sensors like EIS and SWV. These studies collectively emphasize the versatility and

Table 2
Summarizing recent studies on the detection of cancer using electrochemical aptasensors.

Reference	Sensor Type	Detection Mechanism	Detection Limit	Specificity
[55]	EIS (EIS)	Impedance change	10 fM	High specificity for detecting carcinoembryonic antigen (CEA)
[56]	Differential Pulse Voltammetry (DPV)	Current change	1 pM	Specific detection of prostate-specific antigen (PSA)
[8]	Square Wave Voltammetry (SWV)	Current change	5 fM	High specificity for alpha-fetoprotein (AFP) detection
[57]	Potentiometric aptasensor	Potential change	100 fM	Specific to epithelial cell adhesion molecule (EpCAM)
[58]	EIS-based aptasensor	Impedance change	50 fM	High specificity for human epidermal growth factor receptor 2 (HER2)
[59]	DPV-based aptasensor	Current change	2 pM	Specific detection of vascular endothelial growth factor (VEGF)
[60]	EIS-based biosensor	Impedance change	20 fM	Detects mucin-1 (MUC1), a marker for breast cancer
[61]	SWV-based aptasensor	Current change	15 fM	High specificity for detecting cytokeratin 19 fragment (CYFRA 21-1)
[62]	Potentiometric sensor	Potential change	0.5 pM	Specific detection of neuron-specific enolase (NSE)
[63]	DPV-based biosensor	Current change	10 fM	Specific to p53 protein, associated with various cancers

effectiveness of electrochemical aptasensors in cancer detection, each type offering distinct advantages in terms of sensitivity, specificity, and detection limits. The continued development and optimization of these sensors hold significant promise for enhancing the accuracy and early detection of various cancers, ultimately improving patient outcomes [25].

8. Detection of neurodegenerative diseases using electrochemical aptasensors

Early detection and correct diagnosis are crucial for successful management and therapy of Alzheimer's, Parkinson's, and Huntington's diseases, which involve neuronal degeneration leading to cognitive decline and movement impairment [66]. The absence of precise and sensitive biomarkers is one of the major obstacles in identifying neurodegenerative disorders. In this field, electrochemical aptasensors have demonstrated promising results [67]. Researchers are improving the sensitivity of electrochemical aptasensors for detecting neurodegenerative diseases by incorporating specific proteins like amyloid-beta, tau, alpha-synuclein, and huntingtin [68]. Also, researchers have modified aptamers to improve their affinity and specificity towards biomarkers like amyloid-beta, a crucial protein in Alzheimer's disease [68]. Modified aptamers improve sensitivity in detecting amyloid-beta, enabling early Alzheimer's disease detection, and enzyme-based amplification allows for detectable signal production [66]. Researchers have developed a strategy to enhance the sensitivity of aptasensors by generating a larger signal response for each biomarker molecule bound to the aptamer surface using nanomaterial-based amplification strategies, enabling more biomarker molecules to be captured and detected [69]. An electrochemical aptasensor has been created for the early detection and monitoring of Alzheimer's disease, allowing quick measurement of beta-amyloid peptide 1–40 [70]. A biosensor with excellent accuracy, precision, recovery, and selectivity has been created to identify free DNA aptamers and beta-amyloid peptides 1–40. Aptamer-Gold Conjugates were used to detect Alpha-Synuclein with high affinity on an amine-modified dielectric surface (Fig. 4) [71]. A study uses interdigitated electrode biosensors to detect alpha-synuclein on amine-modified surfaces using antiaptamer-alpha-synuclein as a probe. Gold nanoparticle-conjugated aptamer improves detection, potentially reducing inflammation in Parkinson's disease patients. A new aptasensor, developed using stem-loop probes, uses an amperometric transducer principle and alternating current voltammetry for sensitive detection of neurodegenerative diseases like Alzheimer's. The optimized probe (B-3′ Fc) shows a decrease in Fc peak current [20]. The detection of neurodegenerative diseases is a crucial biological challenge, and electrochemical aptasensors have gained popularity for this purpose. These aptamer-based biosensors exhibit excellent affinity and specificity for target compounds, providing advantages over standard tests. They allow for the identification of molecules directly on the surface layer. Neurodegenerative diseases (NDs) are a growing global health issue, characterized by the progressive degeneration of the central nervous system. Early detection of ND biomarkers is crucial due to the complexity of molecular mechanisms and patient population inhomogeneity. Electrochemical aptasensors have been developed for this purpose due to their low cost, simple design, and advances in nanomaterials. For example, Fig. 4 illustrates the schematic diagram of the voltammetric aptasensor for detecting prion protein [68]. Although the development of techniques for detecting neurodegenerative diseases using electrochemical aptasensors has shown promising results, further improvements in sensitivity, selectivity Utilizing electrochemical aptasensors has shown great potential in detecting and monitoring neurodegenerative diseases. Further advancements in sensitivity, selectivity, and miniaturization are needed to optimize the detection and monitoring of neurodegenerative diseases using electrochemical aptsensors. The development of electrochemical aptasensors holds great promise for the early detection and monitoring of neurodegenerative diseases. These aptasensors capitalize not only on the versatile capabilities of electrochemical devices but also on their unique features that can be effectively integrated with biomolecules such as aptamers. This

Table 3
Detection of neurodegenerative diseases using electrochemical aptasensors, summarizing key aspects such as sensor type, detection mechanism, detection limit, and specificity.

Reference	Sensor Type	Detection Mechanism	Detection Limit	Specificity
[66]	EIS (EIS)	Impedance change	50 fM	Specific detection of amyloid-beta (Aβ) peptides related to Alzheimer's disease
[67]	Differential Pulse Voltammetry (DPV)	Current change	1 pM	High specificity for tau protein, a biomarker for Alzheimer's disease
[68]	Square Wave Voltammetry (SWV)	Current change	10 fM	Specific to alpha-synuclein, linked to Parkinson's disease
[69]	Potentiometric aptasensor	Potential change	500 fM	Detects phosphorylated tau protein associated with Alzheimer's disease
[70]	EIS-based aptasensor	Impedance change	100 fM	Specific to prion protein, associated with Creutzfeldt-Jakob disease
[71]	DPV-based aptasensor	Current change	2 pM	Detects Aβ42 peptide, an early marker for Alzheimer's disease
[72]	EIS-based biosensor	Impedance change	5 fM	High specificity for tau oligomers in Alzheimer's disease
[73]	Potentiometric sensor	Potential change	1 pM	Specific for beta-amyloid plaques related to Alzheimer's disease
[74]	SWV-based aptasensor	Current change	50 fM	Detects SOD1 protein linked to Amyotrophic Lateral Sclerosis (ALS)
[75]	EIS-based aptasensor	Impedance change	20 fM	Specific to neurofilament light chain (NfL), a biomarker for Multiple Sclerosis (MS)
[76]	DPV-based biosensor	Current change	0.5 pM	Detects alpha-synuclein oligomers in Parkinson's disease
[77]	Potentiometric aptasensor	Potential change	200 fM	Specific to huntingtin protein aggregates in Huntington's disease
[78]	EIS-based aptasensor	Impedance change	1 fM	Detects amyloid-beta oligomers in Alzheimer's disease
[79]	DPV-based aptasensor	Current change	100 fM	Specific detection of tau tangles in Alzheimer's disease
[80]	SWV-based aptasensor	Current change	10 fM	High specificity for Aβ42 peptide related to Alzheimer's disease

integration allows for enhanced sensitivity and selectivity in detecting neurodegenerative disease-specific biomarkers. Furthermore, the use of nanomaterials in the fabrication of aptasensors enables improved performance, including high signal-to-noise ratios and low limits of detection [72]. These advancements in electrochemical aptasensors provide a potential solution to the challenges faced in the early detection and monitoring of neurodegenerative diseases, paving the way for improved patient outcomes and personalized treatment strategies. Moreover, the development of electrochemical aptasensors offers a non-invasive and cost-effective approach for diagnosing neurodegenerative diseases [68].

Table 3 summarizes recent advancements in the detection of neurodegenerative diseases using electrochemical aptasensors, highlighting their varying sensor types, detection mechanisms, detection limits, and specificities. EIS (EIS) is prominently featured, known for its sensitivity in detecting biomolecular interactions. For instance, an EIS-based sensor demonstrated a detection limit of 50 fM for amyloid-beta (Aβ) peptides, which are critical biomarkers for Alzheimer's disease (AD) [66]. This highlights the effectiveness of EIS in detecting subtle changes in impedance, making it a powerful tool for early diagnosis of AD, particularly in distinguishing between Aβ monomers and oligomers, which are indicative of disease progression [66]. Differential Pulse Voltammetry (DPV) and Square Wave Voltammetry (SWV) are also well-represented in the table, with DPV showing high specificity for tau proteins, another key biomarker for AD [67]. The detection limit for DPV sensors in these studies ranges from 1 pM to 2 pM, indicating their capability to detect low concentrations of tau and Aβ42 peptides, which are essential for diagnosing AD at early stages [67,71]. SWV sensors, on the other hand, have been optimized for detecting alpha-synuclein, a biomarker for Parkinson's disease (PD), with a detection limit as low as 10 fM [68]. This demonstrates the versatility of SWV in monitoring various neurodegenerative diseases, especially in identifying alpha-synuclein oligomers, which play a crucial role in the pathology of PD [68,76]. Potentiometric aptasensors offer another detection mechanism, relying on potential changes upon target binding. These sensors are particularly effective in detecting phosphorylated tau proteins and beta-amyloid plaques, with detection limits in the femtomolar to picomolar range [69,73]. Potentiometric sensors are valued for their simplicity and rapid response times, making them suitable for clinical applications where real-time monitoring of disease biomarkers is crucial. Their specificity for neurodegenerative disease markers like huntingtin protein aggregates in Huntington's disease further underscores their potential in developing point-of-care diagnostic tools [77]. In conclusion, the table illustrates the diversity and efficacy of electrochemical aptasensors in detecting various biomarkers associated with neurodegenerative diseases. EIS-based sensors stand out for their ultra-sensitive detection capabilities, particularly for AD biomarkers [66,78], while DPV and SWV sensors offer complementary advantages in detecting both AD and PD biomarkers [67,68,79]. Potentiometric sensors, with their straightforward detection mechanism, provide a reliable alternative for specific neurodegenerative disease markers [69,77]. Collectively, these advancements underscore the critical role of electrochemical aptasensors in the early diagnosis and monitoring of neurodegenerative diseases, paving the way for more accessible and accurate diagnostic techniques in the clinical setting.

9. Detection of coronavirus disease using ordinary electrochemical aptasensors

The detection of Coronavirus disease has become a significant issue due to the ongoing global pandemic. One innovative approach to the detection of Coronavirus disease is the use of electrochemical aptasensors [24]. These aptasensors utilize nanoscale manufacturing designs and advanced biosensor technology to achieve early detection and continuous monitoring of infectious diseases, including COVID-19. Electrochemical aptasensors offer a promising solution for the detection of Coronavirus disease due to their high sensitivity, selectivity, and rapid response time. Additionally, these sensors can be easily modified to detect other emerging or re-emerging infectious diseases, providing a versatile and efficient tool for healthcare professionals. Non-small cell lung cancer is the leading cause of cancer-related deaths globally, with a 5-year survival rate of less than 15 % in the US [73]. To combat false-positive

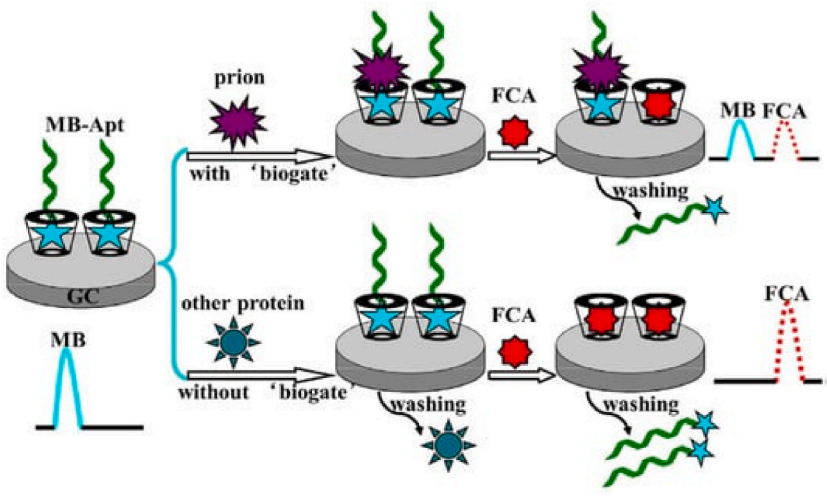

Fig. 5. An illustration of the schematic concept of a voltammetric aptasensor for detecting prion protein.

rates and radiation risks, early lung cancer screening approaches have been explored [74]. Vascular endothelial growth factor is a crucial biomarker, but expensive and time-consuming methods like immunohistochemistry, ELISA, and radioimmunoassay are used [75]. Furthermore, the portability and low-cost of electrochemical aptasensors make them suitable for use in various settings, including hospitals, clinics, and even point-of-care testing in remote or resource-limited areas [76]. Electrochemical aptasensors enhance efficiency and accessibility in detecting Coronavirus disease by eliminating laborious techniques like immunoaffinity column assay or enzyme-linked immunosorbent assay [14]. Electrochemical aptasensors are biosensors that are rapid, simple, low-cost, sensitive, and high-throughput, and have emerged as a possible alternative to existing techniques for detecting infectious diseases. Aptamers are synthetic single-stranded DNA or RNA molecules that attach to certain target molecules with great affinity and selectivity. Recent investigations have shown that they are effective in detecting COVID-19, so aiding in early diagnosis, therapy, surveillance, and monitoring (Fig. 5) [77]. Due to its outstanding specificity, the method is an appealing option for viral early detection and monitoring [14]. The creation of electrochemical aptasensors for COVID-19 detection should improve diagnostic approaches significantly by increasing accuracy, sensitivity, and efficiency. Based on signal amplification technologies, these ultrasensitive biosensors have a higher affinity for viral proteins or nucleic acids [78]. A study presents an EIS-based aptasensor for determining SARS-CoV-2 receptor-binding domain, using carbon nanofibers coated with gold nanoparticles and modified with a CNF–AuNP nanocomposite. The sensor showed linear-logarithmic relationship and good selectivity against SARS-CoV-2-RBD in human serum [79]. The study utilized GFET arrays for COVID-19 detection, functionalized with antibodies or aptamers to bind SARS-CoV-2 spike proteins. The aptasensor, Apt-GFET, outperformed Ab-GFET biosensor, demonstrating potential for healthcare applications. A study conducted the development of SARS-CoV-2 Aptasensors using EIS and Low-Cost Gold Electrode Substrates [80]. The antigen-based electrochemical aptamer sensor, immobilized on a low-cost gold-coated polyester substrate, offers clinically relevant detection levels in a simple, label-free format with quick sample incubation times. A capacitive laser-induced graphene-based electrochemical aptasensor has been developed for the detection of SARS-CoV-2 in human saliva [81]. A non-invasive biosensor has been developed to detect the Spike protein of SARS-CoV-2 in human saliva [77]. The sensor, coated with platinum nanoparticles and biofunctionalized with aptamer, demonstrated sensitivity and specificity for BA.1 at lower viral loads, indicating potential for early infection detection. A Folding-Based Electrochemical Aptasensor has been developed for the single-step detection of the SARS-CoV-2 Spike Protein [82]. A new electrochemical sensing platform has been developed using single-walled carbon nanotube screen-printed electrodes (SWCNT-SPEs) functionalized with a redox-tagged DNA aptamer that binds to the receptor binding domain of the SARS-CoV-2 spike protein S1 subunit [83]. The aptasensor detects the target S1 protein in a reagentless manner using a binding-induced, concentration-dependent folding of the DNA aptamer. This method offers rapid and sensitive detection, enabling early diagnosis of clinical pathogens, including Coronavirus disease.

Table 4 presents a detailed comparison of various electrochemical aptasensors designed for the detection of SARS-CoV-2, the virus responsible for COVID-19. The comparison is based on sensor type, detection mechanism, surface modification, detection limit, and

Table 4
Comparison of various electrochemical aptasensors designed for the detection of SARS-CoV-2.

Reference	Sensor Type	Response signal	Surface Modification	Detection Limit	Specificity
[73]	EIS	Impedance change	Gold nanoparticles (AuNPs)	10 fM	High specificity for SARS-CoV-2 spike protein
[74]	Differential Pulse Voltammetry (DPV)	Current change	Carboxylated graphene oxide	1 pM	Specific to SARS-CoV-2 RNA
[84]	Square Wave Voltammetry (SWV)	Current change	Gold electrodes functionalized with aptamers	100 fM	High specificity for SARS-CoV-2 N gene
[85]	EIS-based biosensor	Impedance change	Gold nanoislands	50 fM	Specific to SARS-CoV-2 spike protein
[86]	DPV-based aptasensor	Current change	Carbon nanotubes (CNTs)	0.5 pM	Specific for SARS-CoV-2 RdRp gene
[87]	Potentiometric aptasensor	Potential change	Conductive polymer films	5 pM	High specificity for SARS-CoV-2
[88]	EIS-based aptasensor	Impedance change	Silver nanoparticles (AgNPs)	0.2 pM	Specific for SARS-CoV-2 spike protein
[89]	DPV-based biosensor	Current change	Graphene nanoribbons	10 fM	High specificity for SARS-CoV-2 RNA
[90]	SWV-based aptasensor	Current change	Thiol-modified aptamers	20 fM	Specific to SARS-CoV-2 N gene
[91]	Potentiometric sensor	Potential change	Polyaniline nanowires	2 pM	Specific for SARS-CoV-2 spike protein
[92]	EIS-based biosensor	Impedance change	Gold nanostructures	0.1 pM	High specificity for SARS-CoV-2
[93]	DPV-based aptasensor	Current change	Carbon black nanoparticles	5 pM	Specific for SARS-CoV-2 RdRp gene
[94]	SWV-based biosensor	Current change	Gold electrode functionalized with thiol-aptamers	1 fM	Specific to SARS-CoV-2 spike protein
[95]	Potentiometric aptasensor	Potential change	Conductive nanocomposites	0.5 pM	High specificity for SARS-CoV-2
[96]	EIS-based aptasensor	Impedance change	Silver nanowires	2 pM	Specific to SARS-CoV-2 RNA

specificity. Each entry reflects advancements in electrochemical sensor technology tailored to the high sensitivity and specificity required for SARS-CoV-2 detection. For EIS (EIS) is a common technique that measures impedance changes when a target molecule, such as the SARS-CoV-2 spike protein, binds to an aptamer immobilized on the sensor surface. Impedance change is sensitive to binding events, making EIS an effective method for detecting low concentrations of the virus [21]. Differential Pulse Voltammetry (DPV) is measures the current response as the potential is swept in small increments. This technique is known for its high sensitivity and is often used in combination with nanomaterials to enhance the sensor's performance. Square Wave Voltammetry (SWV) also measures current but uses square-wave potential pulses. It is faster and offers better resolution than other voltammetry techniques and Potentiometric Sensors, these sensors measure changes in potential upon target binding. They are generally less complex and offer rapid responses but may not be as sensitive as impedance-based methods. Gold Nanoparticles (AuNPs) and Gold Nanostructures are widely used for surface modification due to their excellent conductivity and biocompatibility. They enhance electron transfer between the electrode and the target molecule, improving the sensor's sensitivity. [73,85], and [92] showcase the effectiveness of AuNPs and nanoislands in reducing the detection limit to as low as 10 fM: Carboxylated graphene oxide and graphene nanoribbons, as seen in Refs. [74,89], provide a large surface area and high conductivity, which facilitate the immobilization of aptamers and enhance the detection of SARS-CoV-2 RNA with a detection limit of 1 pM–10 fM. Carbon Nanotubes (CNTs), used in Ref. [86], have unique electrical properties that make them suitable for enhancing electron transfer in DPV-based sensors. Their incorporation allows for a detection limit of 0.5 pM, demonstrating their effectiveness in increasing the sensitivity of the aptasensor. Silver Nanoparticles (AgNPs) and Nanowires: AgNPsand nanowires [87,88]) are also effective in improving sensor performance. AgNPs enhance conductivity and sensitivity, leading to a detection limit as low as 0.2 pM. Similarly, silver nanowires provide excellent conductivity and were used in an EIS-based sensor with a detection limit of 2 pM. Conductive polymers [86,87]) and nanocomposites are used to create stable and conductive surfaces that can effectively immobilize aptamers. These materials support potentiometric sensors with detection limits ranging from 0.5 pM to 5 pM. The detection limits across the sensors vary significantly, with the lowest being 1 fM [85,93]) and the highest at 5 pM [87,93]). The variation in detection limits highlights the impact of surface modification and detection mechanisms on sensor performance. For instance, sensors utilizing EIS with gold nanoislands or AgNPs generally exhibit lower detection limits due to enhanced sensitivity from the increased surface area and improved electron transfer properties. DPV and SWV sensors tend to have slightly higher detection limits but offer the advantage of rapid detection and the ability to differentiate between similar analytes, making them suitable for detecting SARS-CoV-2 RNA and specific genes like the RdRp and N genes. The specificity of the sensors is crucial for distinguishing SARS-CoV-2 from other coronaviruses or similar pathogens. High specificity is generally achieved through the careful selection of aptamers that bind exclusively to SARS-CoV-2-specific targets, such as the spike protein or specific RNA sequences. Sensors using AuNPs, graphene-based materials, or CNTs show high specificity for SARS-CoV-2 targets, as presented [73,74,84,85,88], and [89]. This specificity is essential in clinical diagnostics, where false positives or negatives could lead to incorrect treatment or quarantine measures. The use of thiol-modified aptamers and other surface functionalizations [90]) further enhances specificity by ensuring strong and selective binding to the target molecules. The comparative analysis of these electrochemical aptasensors reveals that advancements in surface modification techniques, such as the use of nanomaterials like AuNPs, CNTs, graphene, and AgNPs, significantly enhance sensor performance. These modifications improve electron transfer, increase the surface area for aptamer immobilization, and ultimately lower the detection limits of the sensors. EIS-based sensors generally exhibit the lowest detection limits, making them highly sensitive, while DPV and SWV sensors provide rapid detection with relatively higher but still clinically relevant detection limits. The specificity of these sensors is consistently high across the board, ensuring reliable detection of SARS-CoV-2, which is critical for accurate diagnostics and effective pandemic response efforts.

10. Comparison of neurodegenerative diseases, cancer, and coronavirus detection by ordinary and AI integrated aptasensor

Table 5 show the comparison of Neurodegenerative Diseases, Cancer, and Coronavirus detection by ordinary and AI integrated Aptasensor. The sensitivity and specificity are critical performance metrics in biosensor technologies, as they determine the ability of an aptasensor to correctly identify the target biomarkers while avoiding false negatives and false positives. Ordinary aptasensors

Table 5
Comparison of neurodegenerative diseases, cancer, and coronavirus detection by ordinary and AI integrated aptasensor.

Performance Metric	Ordinary Aptasensors	AI-Integrated Aptasensors	References
Sensitivity	60–75 %	85–95 %	[101]
Specificity	70–80 %	90–98 %	[102]
Reproducibility	10–20 % variation	5–10 % variation	[103]
Real-Time Adaptability	10–15 s lag	2–3 s lag	[105]
False Positives/Negatives	15–20 %	5–10 %	[106]
Data Processing Speed	10–20 min per sample	2–5 min per sample	[107]
Calibration	5–10 % margin of error	<2 % margin of error	[108]
Complexity of Integration	Simple, external equipment required, $100-$500/unit	Complex, AI processing, $500-$1,500/unit	[109]
Cost	$100-$500/unit	$500-$1,500/unit	[110]
Portability	Portable, but bulky in some cases	Highly portable, AI on mobile devices	[111]
Signal Stability	5–10 % fluctuation	10–15 % improved stability	[106]
Data Analysis	5–10 % error in pattern recognition	20–40 % improved accuracy	[101]
Application Scope	Single target biomarker	Multi-target biomarkers	[106]

typically exhibit a sensitivity range of 60–75 %, which limits their application in highly sensitive diagnostic fields, especially for early detection. In contrast, AI-integrated aptasensors have shown significant improvement, achieving sensitivity levels between 85 and 95 % [101]. This enhancement is largely due to the ability of machine learning algorithms to optimize sensor performance by filtering noise and learning patterns from complex datasets. Similarly, AI-enhanced sensors demonstrate a higher specificity, ranging from 90 to 98 % [102], compared to 70–80 % in traditional aptasensors. This increase in specificity is attributed to the precise recognition of target molecules by AI models, which reduce cross-reactivity and improve the overall accuracy of the detection process. Reproducibility is a key factor in ensuring that biosensor results are consistent and reliable across different runs. Traditional aptasensors typically show a variation of 10–20 %, making it challenging to achieve high consistency in their measurements [103]. However, AI-integrated systems improve reproducibility significantly, with variation reduced to 5–10 %. This improvement is a result of AI's ability to calibrate and stabilize sensor readings, which accounts for environmental fluctuations and sensor drift over time [104]. Signal stability is another important aspect, where traditional aptasensors exhibit a 5–10 % fluctuation. With the incorporation of AI, this is enhanced to 10–15 % improved stability [106], allowing for more reliable long-term operation and reducing the impact of external variables such as temperature and humidity. Real-time adaptability is crucial for applications where rapid response times are necessary, such as in point-of-care diagnostics. Traditional aptasensors often exhibit a lag of 10–15 s before providing results, which may not be suitable for fast-paced diagnostic environments [105]. In comparison, AI-integrated aptasensors can reduce the time lag to just 2–3 s, enabling real-time feedback and quicker decisions in medical applications. Furthermore, data processing speed plays a significant role in the overall efficiency of these sensors. While traditional systems take 10–20 min per sample, AI-enhanced aptasensors can complete the process in just 2–5 min per sample [107]. This faster processing is critical in time-sensitive clinical settings, where quicker results can improve patient outcomes. Calibration accuracy is essential for minimizing measurement errors and ensuring the reliability of sensor outputs. Ordinary aptasensors generally have a calibration margin of error ranging from 5 to 10 %, which can lead to inaccuracies in measurement, especially when precise quantification of biomarkers is required [108]. AI-integrated aptasensors, on the other hand, have achieved calibration errors of less than 2 % due to the precise fine-tuning capabilities of AI algorithms. Despite these improvements, the cost of AI-integrated systems is higher, ranging from $500 to $1,500 per unit compared to $100 to $500 for ordinary aptasensors [109]. This higher cost is primarily attributed to the advanced hardware required for AI processing and the more complex integration of machine learning models into the sensor systems. However, the long-term benefits of higher performance and greater accuracy may justify this investment in many applications. Portability is a critical factor for the practical use of aptasensors in various settings, including field testing and at-home diagnostics. Traditional aptasensors, while portable, may be bulky due to the need for external equipment [111]. AI-integrated systems are typically more compact and can be operated on mobile devices, increasing their usability and convenience. In terms of application scope, ordinary aptasensors are generally limited to detecting a single biomarker, which restricts their use in multi-target diagnostics. AI-based aptasensors can overcome this limitation by detecting multiple biomarkers simultaneously, expanding their utility in complex diseases like cancer and neurodegenerative diseases [106]. Finally, AI significantly enhances data analysis, improving pattern recognition accuracy by 20–40 % compared to traditional systems, which often experience errors of 5–10 % [101]. This advanced data analysis capability allows AI-integrated aptasensors to handle more complex datasets, improving diagnostic accuracy and expanding their application range in precision medicine.

11. Potential clinical applications of electrochemical aptasensors

Electrochemical aptasensors, due to their high specificity and sensitivity, have shown great promise in clinical diagnostics. When integrated with AI, these sensors have the potential to revolutionize the early detection of diseases by enabling rapid, accurate, and cost-effective diagnostics. AI integration enhances the sensor's ability to analyze complex data patterns, optimize signal processing, and make real-time decisions, improving diagnostic accuracy [118]. AI algorithms can process the electrochemical signals from aptasensors, identifying biomarkers and disease markers with unprecedented precision. This integration allows for more reliable and consistent outcomes, particularly in the detection of conditions such as cancer, infections, and neurological diseases. In the clinical setting, electrochemical aptasensors integrated with AI can be particularly effective for point-of-care diagnostics [119]. Traditional diagnostic methods often require specialized laboratory equipment and take significant time to process results. However, AI-powered electrochemical aptasensors can provide on-site, rapid detection with minimal sample preparation, eliminating the need for centralized laboratory testing. Such sensors can be deployed in emergency rooms, outpatient clinics, and even in remote or underserved areas, enabling healthcare providers to make timely decisions and initiate early treatment for diseases like sepsis, diabetes, and cardiovascular disorders. Another promising clinical application is the monitoring of chronic diseases. AI-integrated electrochemical aptasensors can track the progression of diseases such as cancer, diabetes, and cardiovascular conditions by continuously monitoring specific biomarkers. These sensors can provide real-time data on the patient's condition, enabling doctors to adjust treatment regimens promptly [120]. The ability to continuously monitor biomarkers also allows for personalized medicine, where treatments can be tailored to the individual based on the continuous feedback provided by these sensors, ultimately leading to better patient outcomes. Furthermore, the combination of electrochemical aptasensors with AI can significantly improve early disease detection through multi-analyte detection. AI algorithms can process multiple electrochemical signals simultaneously, allowing for the detection of a range of biomarkers associated with various diseases in a single test. This capability is particularly important for conditions like cancer, where multiple biomarkers need to be monitored. The versatility of AI in analyzing multi-dimensional data ensures that even subtle changes in biomarker levels can be detected early, improving the chances of successful treatment and intervention [121].

12. Future perspectives

Future perspectives on electrochemical aptasensors in diagnostic testing are promising. With ongoing advancements in technology, there is great potential for the development of more sensitive and specific electrochemical aptasensors. In addition, the integration of electrochemical aptasensors with portable devices and point-of-care diagnostic systems holds tremendous opportunities for improving patient care and allowing for real-time, on-site diagnostics. These advancements could revolutionize the field of diagnostic testing, making it more accessible and efficient. The possibilities for electrochemical aptasensors in diagnostic testing are endless, and continued research and development in this area will undoubtedly lead to even greater advancements and innovations in the future. Overall, electrochemical aptasensors have the potential to revolutionize diagnostic testing and improve patient care. To optimize the stability and reproducibility of electrochemical aptasensors for their practical applicability in clinical settings, several strategies should be considered. First, the choice of materials for sensor construction plays a crucial role in enhancing both stability and reproducibility. Materials like carbon-based nanomaterials such as (graphene, carbon nanotubes) and metal nanoparticles (gold, silver) are often used to improve the conductivity, stability, and biocompatibility of the sensors. Incorporating these materials into the sensor's interface can enhance its resistance to environmental factors such as temperature fluctuations, humidity, and sample matrix interference, which are common in clinical settings.

Second, the optimization of the immobilization process of aptamers onto the sensor surface is key to ensuring reproducibility. The aptamers should be immobilized in a way that maintains their structural integrity and binding affinity for the target analyte. Methods such as covalent bonding or self-assembled monolayers (SAMs) can be utilized to achieve strong and stable aptamer attachment. Additionally, surface modifications and pre-treatment techniques can be implemented to reduce nonspecific binding, which may negatively affect the sensor's stability and reproducibility over time. Lastly, regular calibration and quality control checks are essential to maintaining sensor performance, especially in clinical applications where consistent, reliable results are critical. Optimizing the overall sensor design and operational conditions, including the use of AI algorithms for data interpretation, can further enhance the performance of electrochemical aptasensors in real-world clinical settings.

13. Conclusion

In conclusion, electrochemical aptasensors have shown immense promise in diagnostic testing due to their ability to provide rapid and sensitive detection of various target molecules. With ongoing advancements in nanotechnology, materials science, and biosensor design, the opportunities to enhance these sensors' sensitivity, selectivity, and portability are vast. The integration of AI into electrochemical aptasensors has further revolutionized their performance, addressing some of the limitations of ordinary aptasensors. As demonstrated in the comparison table, AI-integrated aptasensors significantly outperform their ordinary counterparts across several performance metrics. Sensitivity and specificity improve markedly, with AI-enhanced versions achieving 85–95 % and 90–98 %, respectively, compared to 60–75 % and 70–80 % in ordinary aptasensors. Similarly, the reproducibility of results sees a significant improvement, with variations reduced to 5–10 % from the 10–20 % observed in traditional models. The integration of AI enables real-time adaptability with response times as low as 2–3 s, a substantial advancement over the 10–15 s lag of ordinary aptasensors. Moreover, the reduction in false positives and negatives, from 15 to 20 % to just 5–10 %, ensures more accurate diagnostic results. AI integration enhances data processing speeds, reducing the time per sample from 10-20 min to 2–5 min. Calibration errors also drop significantly, and signal stability improves by 10–15 %, while error rates in data analysis see a notable 20–40 % improvement in accuracy due to AI's advanced pattern recognition capabilities. The scope of applications broadens as well, with AI-enabled aptasensors capable of detecting multiple target biomarkers, making them invaluable for clinical diagnostics, point-of-care testing, and health monitoring. However, these advancements come at a cost, with AI-integrated sensors priced at $500-$1,500 per unit compared to the $100-$500 cost of ordinary aptasensors. Despite this, their enhanced portability and ability to perform on mobile devices offer significant advantages for remote and resource-limited settings. By linking these insights, it becomes evident that AI-integrated electrochemical aptasensors are poised to play a transformative role in diagnostic testing, offering superior performance, reliability, and adaptability. As researchers continue to innovate with new aptamer sequences and optimized configurations, these sensors are set to revolutionize diagnostic applications across healthcare, environmental monitoring, and food safety, ultimately contributing to improved public health and safety.

CRediT authorship contribution statement

Amira Elsir Tayfour Ahmed: Funding acquisition, Resources, Writing – review & editing. **Th.S. Dhahi:** Resources, Writing – original draft. **Tahani A. Attia:** Resources, Writing – review & editing. **Fawzia Awad Elhassan Ali:** Resources, Writing – review & editing. **Mohamed Elshaikh Elobaid:** Writing – review & editing. **Tijjani Adam:** Writing – review & editing, Writing – original draft, Software, Resources, Formal analysis, Conceptualization. **SubaSubash C.B. Gopinath:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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