Electrochemical Readout in Lab-On-Chip Platforms: Overview of State of the Art and Future Perspectives

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Abstract. Lab-on-chip (LoC) platforms are disruptive technologies in analytical chemistry and bioengineering and are known to enable miniaturised and sensitive analysis of complex biological and chemical samples. Electrochemical detection became one of the most explored among several readout methods, hence its versatility, robustness, straightforward execution, sensitivity, and portability. Therefore, this brief review critically examines the principles, applications, and prospects of electrochemical detection in LoC technologies, highlighting its significance in advancing various fields, including clinical diagnostics, environmental monitoring, and drug discovery.

Keywords: microfluidic; in vitro; diagnostic; biomarker; analytical; medical device.

INTRODUCTION

Lab-on-chip (LoC) platforms are disruptive analytical technologies that can perform complex laboratory processes on a miniature scale [1, 2]. These platforms allow the integration of multiple functions onto a single microfluidic chip and enable rapid, sensitive, and cost-effective analysis of biological and chemical samples, making it a promising solution for a wide range of applications [3, 4]. Central to LoC technologies is a reliable detection system, which frequently uses electrochemical signal transduction and has been known to provide several benefits in contrast to other analytical methods [5, 6].

Considering electrochemical detection of analytes in LoC platforms, two main approaches are frequently described in the literature: faradaic and non-faradaic methods [7]. The former is based on redox reactions, where the analyte of interest undergoes oxidation or reduction at an electrode surface. This process generates an electrical current that is directly proportional to the concentration of the analyte [8-10]. The second method relies on thorough surface modification to allow biorecognition motifs to be anchored to a sensing substrate. The analyte's concentration is indirectly estimated by evaluating changes in the electric behaviour of the interface [11-13]. Regardless of the method, most electrodes used in electrochemical detection are typically made of conductive materials, such as carbon allotropes, platinum, or gold [14-17].

Another constituent of LoC platforms is the microfluidic system [18]. This technology offers numerous advantages over traditional wet-chemistry laboratory setups, such as reduced sample and reagent volumes, faster analysis times, portability, and cost-effectiveness [19-21]. The microfluidic system is often based on materials like glass, silicon, or polymers, containing an intricate network of microchannels and wells. These microfluidic channels serve as pathways for precise manipulation and control of fluids, such as sample introduction, mixing, reaction, and separation [22].

Integrating multiple functions on a single chip enables LoC platforms to perform complex biochemical and chemical analyses, including DNA analysis, protein assays, cell sorting, and chemical reactions [23, 24]. By automating and miniaturising these processes, LoC devices streamline workflows, reduce human error, and consume minimal amounts of reagents and samples, making them environmentally friendly [25].

Due to the benefits over standard laboratory techniques, LoC platforms are expected to be integrated into diverse fields, such as medical diagnostics, environmental monitoring, food safety, and drug development [26-28]. To all accounts, their portability and potential for point-of-care (PoC) and point-of-need (PoN) testing make them very competitive technologies for resource-limited settings and remote areas, where access to traditional laboratory facilities may be challenging [29, 30].

As research and development in microfabrication techniques continue, LoC technologies are expected to advance further, enabling the creation of sophisticated and susceptible analytical devices. These advancements will likely lead to transformative changes in various scientific and commercial sectors, bringing efficient and accessible analytical capabilities to a broader range of users [31, 32].

Therefore, consider electrochemical detection's role as a critical enabler in LoC technologies by providing real-time and label-free analysis. This review aims to delve into the underlying principles, mechanisms, and applications of electrochemical detection in the context of LoC technologies, uncovering its pivotal role in advancing multiple disciplines, including clinical diagnostics, environmental monitoring, and drug discovery [33, 34].

RESULTS AND DISCUSSION

Principles of LoC Technologies

Microfluidics and Miniaturization. Microfluidics comprises the precise manipulation of small volumes of fluids, typically in the microliter or nanoliter range, within microchannels. This miniaturisation of laboratory processes onto a chip offers numerous advantages, including reduced reagent consumption, faster analysis times, and the ability to perform high-throughput experiments [35, 36]. The unique characteristics of microfluidics enable enhanced control over sample manipulation, making it possible to integrate multiple functions seamlessly onto a single microfluidic chip.

Microfluidic platforms exhibited substantial growth in recent years, driven by advancements in materials science, microfabrication techniques, and automation. The design and fabrication of microfluidic devices have become more accessible, facilitating interdisciplinary collaboration and the translation of research into practical applications [37, 38]. These advancements have paved the way for developing LoC devices capable of handling diverse sample types, such as blood, saliva, and environmental samples, with remarkable precision and efficiency [39].

Integration of Analytical Processes. A key strength of LoC technologies is the seamless integration of multiple analytical processes onto a single chip. Sample preparation, reaction, and detection were traditionally conducted sequentially, often in separate laboratory settings. Integrating these processes onto a microfluidic chip streamlines the analytical workflow, reducing the time required for analysis and minimising the risk of contamination and errors arising from manual interventions [40].

Integrating analytical processes within LoC devices enhances analytical efficiency and allows novel assay formats by streamlining sampling and assaying operations. For example, LoC devices can combine sample preparation steps, such as cell lysis, nucleic acid extraction, and protein purification, with downstream analyses, enabling rapid and automated workflows. Such integration holds promise for many applications, from PoC diagnostics to environmental monitoring and pharmaceutical research [41].

Detection Methods in LoC Devices. While various detection methods are employed in LoC devices, electrochemical detection has emerged as a versatile technique for real-time monitoring of analytes. Electrochemical sensors and biosensors are pivotal in translating biochemical or chemical interactions into electrical signals, making them well-suited for integration into microfluidic platforms [42]. Electrochemical detection techniques, such as amperometry, potentiometry, voltammetry, and impedance spectroscopy, offer several advantages, including label-free detection, high sensitivity, and real-time monitoring capabilities [43, 44].

The versatility of electrochemical detection is reflected in its ability to detect a wide range of analytes, from small molecules to complex biomolecules like proteins and nucleic acids. Electrochemical sensors can be engineered to selectively detect specific analytes by functionalising electrode surfaces with recognition elements, such as enzymes, antibodies, or DNA aptamers [45, 46]. Moreover, electrode materials and surface modifications can be tailored to optimise sensitivity and selectivity, allowing for precise and reliable detection in various complex sample matrices.

Electrochemical Detection in LoC Technologies

Basics of Electrochemistry. Electrochemical detection in LoC technologies relies on the fundamental principles of electrochemistry, which involve the transfer of electrons between an electrode and an analyte in solution [47, 48]. The redox reactions occurring at the electrode-solution interface lead to measurable changes in current, potential, or impedance, providing valuable information about the analytes present in the sample.

The main components of an electrochemical sensor based on a three-electrode architecture are the working electrode, reference electrode, and counter electrode [49, 50]. When an electrical potential is applied between the working and reference electrodes, analytes in the sample undergo redox reactions at the working electrode surface, leading to measurable electrical signals. The magnitude of the electrical response is proportional to the concentration of the analyte, allowing for quantitative analysis [51]. On the other hand, the surface of the working electrode can be modified with biorecognition elements, such as capture antibodies. Upon the selective binding of these capture antibodies with their complementary targets, charge transfer processes may be hindered, thereby increasing the resistance to assigning transfer proportionally to the amount of the analyte bound to the capture antibodies [52].

Electrochemical detection offers several distinct advantages in LoC technologies. The label-free nature of electrochemical sensors eliminates the need for complex and costly labelling procedures, reducing the overall assay time and simplifying the experimental setup. Furthermore, electrochemical detection provides real-time monitoring capabilities, enabling dynamic analysis of biological and chemical processes, which is particularly valuable in studying time-sensitive reactions or events [53, 54].

Electrochemical Sensors and Biosensors. Electrochemical sensors and biosensors are essential for LoC devices to detect and quantify analytes in complex samples. These sensors operate, as aforementioned, by converting chemical signals from analytes into measurable electrical signals, providing rapid and sensitive detection capabilities [54, 55]. Electrochemical sensors can be classified into several types, such as immunosensors, enzymatic and non-enzymatic sensors, based on their underlying detection mechanisms [44, 46].

Electrochemical immunosensors base their detection on the use of biorecognition molecules to allow selective binding of analytes to the sensing surface. This binding leads to hindrances to charge transfer, being the change in impedance and electric current output proportional to the concentration of the analyte [52, 56]. The biorecognition molecules that can be used to craft these sensors may range from standard capture antibodies to aptamers and artificial biorecognition motifs such as molecularly imprinted polymers [57, 58]

Enzymatic biosensors utilise enzymes as recognition elements to detect target analytes selectively. The enzymatic reaction generates an electrical signal, allowing for precise detection of analytes. Enzymatic biosensors have found extensive applications in clinical diagnostics, environmental monitoring, and food safety 59,60]. For instance, glucose biosensors are widely used for monitoring blood glucose levels in diabetic patients, while biosensors targeting environmental pollutants are employed in water quality monitoring. On the other hand, numerous reports of enzymatic sensing platforms for food and drug quality control highlight the versatility of this technology [58, 61, 62].

On the other hand, non-enzymatic sensors directly interact with analytes through their inherent reactivity, eliminating the need for specific recognition elements. Non-enzymatic sensors often employ materials with unique electrochemical properties, such as metal nanoparticles or carbon nanotubes, to facilitate the detection of particular analytes. Non-enzymatic sensors have shown promise in detecting various analytes, including heavy metals, environmental toxins, pharmaceutical compounds and food contaminants[58,63].

Types of Electrochemical Detection Techniques Used in LoC

Amperometry. Amperometry is an electrochemical detection technique that measures the current generated during a redox reaction at a constant applied potential. The magnitude of the current is proportional to the concentration of the analyte, allowing for quantitative analysis. Amperometric sensors are known for their excellent sensitivity and are widely used in clinical diagnostics, environmental monitoring, and chemical analysis [41, 42].

In clinical diagnostics, amperometric sensors are commonly employed for glucose monitoring in diabetes management [46]. These sensors offer rapid and accurate measurements of glucose levels in blood or interstitial fluid, enabling patients to manage their condition effectively. Additionally, amperometric sensors find applications in environmental monitoring to detect pollutants, such as heavy metals and toxic chemicals, in water and soil samples [18, 20].

Potentiometry. Potentiometry is an electrochemical technique that measures the potential difference between the working and reference electrodes at zero current. This label-free technique provides real-time analysis of analytes and is commonly used in ion-selective electrodes (ISEs) for monitoring specific ions in solution. In LoC devices, potentiometry finds applications in pH sensing, ion monitoring, and enzymatic activity assays [52, 64].

Due to their high selectivity and sensitivity, ISEs have become valuable tools in environmental monitoring and clinical diagnostics. For instance, LoC devices with pH-sensitive ISEs can monitor changes in pH levels in environmental samples or bodily fluids, offering insights into the health of aquatic ecosystems or acid-base imbalances in patients. Moreover, enzymatic activity assays employing potentiometry can aid in diagnosing various diseases and monitoring enzymatic reactions in real-time [54].

Voltammetry. Voltammetry encompasses a group of electrochemical techniques used to study the redox behaviour of analytes. The most common types of voltammetry include cyclic voltammetry, differential pulse voltammetry, and square wave voltammetry, each with specific applications in electrochemical sensing. Voltammetry involves applying a potential sweep to the working electrode and measuring the resulting current response, providing information about the electrochemical behaviour of analytes at different potentials [52, 54, 65].

Voltammetric methods offer the advantage of qualitative and quantitative analysis, making them versatile tools for detecting various analytes. LoC devices employing voltammetry find applications in neurotransmitter detection, heavy metal analysis, and drug screening. For example, voltammetric sensors can monitor neurotransmitter release in real-time, providing critical insights into brain activity and neurological disorders. Additionally, voltammetry is employed in drug screening to assess the potency and stability of pharmaceutical compounds, facilitating the drug discovery process [46, 48, 66].

Impedance Spectroscopy. Impedance spectroscopy is an electrochemical technique that measures the impedance response of an electrode to detect analytes and assess biomolecular interactions. Impedance-based sensors are susceptible to changes in the electrical properties of the sensor surface, making them suitable for label-free detection of biomolecules and monitoring cell behaviour in cell-based assays [67, 68].

In LoC devices, impedance spectroscopy finds applications in several fields, such as cell studies, protein-protein interactions, and label-free biosensing. For instance, impedance-based biosensors can monitor the proliferation and viability of cells in real time, providing valuable data for drug development and toxicity testing. Furthermore, impedance spectroscopy has enabled label-free and sensitive detection of biomolecules, such as DNA, proteins, and antibodies, thereby offering promising opportunities for diagnostic applications and medical research [67].

Advantages of Electrochemical Detection in LoC

Sensitivity and Selectivity. Electrochemical detection provides ultrasensitive detection of analytes, even in complex matrices, while maintaining excellent selectivity. The inherent amplification of signals during redox reactions and the ability to functionalise electrode surfaces with specific recognition elements enhance the detection sensitivity, making it possible to detect analytes at low concentrations [69]. This level of sensitivity is precious in clinical diagnostics, environmental monitoring, and pharmaceutical research, where accurate measurements of trace analytes are crucial for making informed decisions [68].

Real-time Monitoring. The real-time nature of electrochemical detection is a significant advantage, enabling continuous monitoring and dynamic analysis of biological and chemical processes. This real-time capability is precious in studying time-dependent reactions, transient events, and cellular responses. LoC devices equipped with electrochemical biosensors allow researchers to gain insights into dynamic processes, providing critical data for disease diagnosis, drug development, and environmental monitoring [70-72].

Miniaturization and Portability. One of the most significant advantages of LoC technologies with electrochemical detection is their miniaturisation and portability. These devices drastically reduce the size and weight of analytical systems by integrating complex laboratory functions onto a single microfluidic chip. The portability of LoC devices offers several benefits, including on-site analysis in remote or resource-limited settings, PoC testing at the patient's bedside, and the ability to conduct field studies with minimal infrastructure requirements [20, 25]. The reduced size also contributes to cost savings and efficient use of resources, making LoC technologies with electrochemical detection accessible to a broader range of users.

Reduced Sample and Reagent Consumption. LoC devices with electrochemical detection significantly reduce sample and reagent requirements, contributing to cost savings and environmental sustainability. Integrating multiple analytical steps onto a single chip reduces the required reagent volume, making it feasible to perform assays with small sample volumes, especially in clinical diagnostics and pharmaceutical research. The reduced reagent consumption also lowers the generation of hazardous waste, promoting eco-friendly and sustainable analytical practices [69].

Integration with Sample Preparation Steps. Electrochemical detection integrates with sample preparation steps, enabling a streamlined and automated workflow. The integration of sample preparation, such as cell lysis, nucleic acid extraction, and protein purification, simplifies the assay process, reduces manual handling steps, and minimises the risk of contamination, enhancing the reproducibility of results. Combining sample preparation and electrochemical detection is advantageous in PoC testing and high-throughput screening applications, where rapid and reliable results are essential [37].

Applications of LoC Technologies with Electrochemical Detection

Clinical Diagnostics. LoC devices with electrochemical detection significantly advance clinical diagnostics, particularly in PoC testing, biomarker detection, and infectious disease diagnosis. The ability to detect disease-specific biomarkers in bodily fluids with high sensitivity and specificity holds promise for early disease detection, enabling timely interventions and personalised treatment strategies [73].

PoC Testing (POCT). Electrochemical detection's rapid and sensitive nature allows on-site testing, enabling timely and accurate clinical decision-making. In remote or resource-limited settings, LoC devices with electrochemical sensors can offer diagnostics capabilities that were once only available in well-equipped laboratories. POCT is particularly valuable in underserved regions and during emergencies, as it allows immediate medical assessment and intervention [73, 74].

Detection of Biomarkers. Electrochemical biosensors have shown promise in detecting disease-specific biomarkers, facilitating early diagnosis and personalised treatment strategies. Biomarker detection using electrochemical sensors has applications in cancer diagnostics, cardiovascular disease monitoring, and infectious disease detection. The ability to detect multiple biomarkers simultaneously using multiplexed assays enhances the diagnostic power and accuracy of LoC technologies in clinical settings.

Infectious Disease Diagnosis. Electrochemical detection offers a robust platform for rapidly identifying infectious pathogens, critical in managing outbreaks and preventing transmission. LoC devices with electrochemical biosensors have been developed to detect viruses, bacteria, and parasites, enabling timely diagnosis and efficient disease surveillance. The rapid and accurate identification of infectious agents is essential for implementing effective control measures and containing outbreaks [76, 77].

Environmental Monitoring. LoC technologies with electrochemical detection provide cost-effective and real-time solutions for monitoring environmental pollutants, water quality, air pollution, and soil contaminants. These miniaturised devices with electrochemical sensors can be deployed remotely, continuously monitoring critical environmental parameters and providing valuable ecological assessment and management data. LoC devices' portability and real-time capability make them ideal tools for monitoring environmental changes and studying ecological dynamics in various ecosystems [78, 79].

Drug Discovery and Pharmaceutical Research. Electrochemical detection in LoC devices accelerates drug discovery efforts, enabling high-throughput screening, pharmacokinetic studies, and pharmaceutical quality control. Electrochemical assays can assess drug potency, toxicity, and metabolic stability, aiding in identifying potential drug candidates and optimising drug formulations. The ability to rapidly evaluate drug candidates' activity and safety profiles using LoC devices with electrochemical detection expedites drug development. It reduces costs associated with traditional drug screening methods [80, 81].

Challenges and Limitations

Sensitivity and Signal-to-Noise Ratio. Despite the outstanding sensitivity of electrochemical detection, challenges related to the signal-to-noise ratio persist. Background noise from electronic circuitry and interference from other species in the sample matrix can impact the accuracy and reliability of measurements. Researchers are actively exploring novel signal processing algorithms and electrode modifications to enhance the signal-to-noise ratio and improve the detection limits of LoC devices with electrochemical detection [82, 83].

Biofouling and Surface Modifications. Minimising biofouling and enhancing electrode stability are critical to improving the longevity and reproducibility of sensors. In complex biological samples, such as blood or tissue extracts, biomolecules can adsorb onto the electrode surface, reducing sensor performance. Researchers are investigating surface coatings and bio-passivation strategies to mitigate biofouling effects, prolonging the sensor lifespan and maintaining accurate measurements over extended periods [84, 85].

Standardisation and Reproducibility. Adopting LoC devices with electrochemical detection in real-world applications requires the establishment of standardised protocols and quality control measures. Variability in sensor fabrication, surface functionalisation, and experimental conditions can affect assay results, necessitating rigorous quality assurance and robust validation procedures. Developing standardised guidelines will ensure the reproducibility and comparability of results across different laboratories and applications[86].

Integration and Scalability. Integrating multiple functions onto a microfluidic chip requires interdisciplinary collaboration and advanced engineering expertise. The complexity of integrating diverse components, such as microfluidic channels, electrodes, and electronic circuits, necessitates seamless coordination between experts from different fields to ensure reliable and efficient LoC devices. Additionally, scaling up production for commercial applications poses challenges related to cost-effectiveness and mass production [30].

Cost and Accessibility. The cost of manufacturing LoC devices with electrochemical detection remains significant, particularly for widespread adoption in resource-limited settings. While advancements in microfabrication and mass production techniques have contributed to cost reduction, efforts are ongoing to make LoC technologies more affordable and accessible to a broader user base. Initiatives aimed at resource-sharing, open-source designs, and collaborative research can further promote the accessibility of LoC technologies with electrochemical detection [78, 87].

Future Perspectives

Nanomaterials and Enhanced Sensing Performance. Integrating nanomaterials into electrochemical sensors holds great promise for improving sensitivity, selectivity, and overall performance. Nanomaterials, such as carbon nanotubes, graphene, and metal nanoparticles, offer unique properties that enhance the sensors' surface area, electrical conductivity, and biorecognition capabilities. Researchers are exploring novel nanomaterial-based sensors to achieve higher sensitivity and enable the detection of analytes at even lower concentrations, expanding the potential applications of LoC devices with electrochemical detection [87, 88].

Development of Multiplexed Assays. Advancements in multiplexed assays will enable the simultaneous detection of multiple analytes, significantly enhancing the scope of LoC technologies. Multiplexed assays allow for measuring multiple biomarkers or chemical species in a single sample, providing comprehensive information for disease diagnosis, drug screening, and environmental monitoring. Integrating multiplexed assays with LoC devices will streamline analytical workflows and reduce the overall assay time, improving efficiency and throughput [89, 90].

LoC for Personalized Medicine. The integration of electrochemical detection with personalised medicine holds transformative potential for healthcare. Personalised medicine optimises patient care by considering individual genetic, environmental, and lifestyle factors. LoC devices with electrochemical sensors can contribute to personalised medicine by enabling rapid and precise diagnostics, predicting drug responses, and monitoring disease progression. The ability to perform fast and on-demand diagnostics using LoC technologies will facilitate tailored treatment strategies, optimising patient outcomes and reducing healthcare costs [91, 92].

Autonomous and Self-Powered Devices. Developing self-powered LoC devices will enhance portability and simplify operation, expanding their applications in resource-limited settings. Integrating energy harvesting technologies, such as solar cells or micro-scale fuel cells, can provide the necessary power for LoC devices, eliminating the need for external power sources and making them more self-reliant. Autonomous LoC devices offer exciting opportunities for PoC testing in remote regions and during emergencies, as they do not depend on external power infrastructure[93,94].

Advancements in Data Analysis and Interpretation. Innovations in data analysis and interpretation algorithms will facilitate real-time analysis and decision-making in LoC technologies. As the complexity and volume of data generated by LoC devices increase, advanced data analysis tools, including machine learning and artificial intelligence [95], will be crucial in extracting meaningful insights and automating decision-making processes. Researchers are developing algorithms to efficiently process and interpret data from LoC devices, enabling rapid and accurate decision-making in various applications [96, 97].

CONCLUSIONS

The integration of electrochemical detection in LoC technologies has emerged as a powerful analytical tool, revolutionising various fields, including healthcare, environmental monitoring, and pharmaceutical research. Despite challenges, the continuous efforts in research and development are steadily overcoming limitations, paving the way for a future where LoC technologies with electrochemical detection will drive advancements in analytical science and contribute to improving global health and environmental sustainability.

The versatility, sensitivity, and portability of electrochemical detection make it an indispensable component in the advancement of LoC technologies, offering exciting prospects for transforming diagnostics, personalised medicine, and environmental monitoring in the future. As interdisciplinary collaborations continue to flourish, and with sustained investment in research and infrastructure, the full potential of LoC technologies with electrochemical detection can be realised, opening new frontiers in analytical science and benefiting society. The ongoing advancements in nanomaterials, multiplexed assays, personalised medicine, and autonomous devices will shape the future of LoC technologies, empowering researchers, clinicians, and environmental scientists with innovative tools for tackling pressing global challenges.

Conflict of Interest

The authors declare that there is no conflict of interest.

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