Journal of Neonatal Surgery
ISSN(Online):2226-0439
Vol.14 , Issue 33s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

A Review On Perspectives Of Electrochemical Sensors In Next-Generation Healthcare

Dr.Yasodha T[1*], Dr.Menaka T[2], Vijayalakshmi M.S[3] , Sangeetha A[4*]

[1]Professor, Department of Biotechnology, Madha Engineering College,Chennai,India

[2]Assistant Professor, Department of Electrical and Communication Engineering, Peri Institute of Technology,Chennai, India

[3]Assistant Professor, Department of Pharmaceutical Technology, Sri Muthukumaran Institute of Technology,Chennai, India

[4]Assistant Professor, Department of Biomedical Engineering, Madha Engineering College, Kundrathur,Chennai

[4*]btmbty@gmail.com

[1]0000-0003-0473-0783, [2]0000-0001-6527-2013, [3]0009-0006-5892-2480 and [4]0009-0005-9028-6181

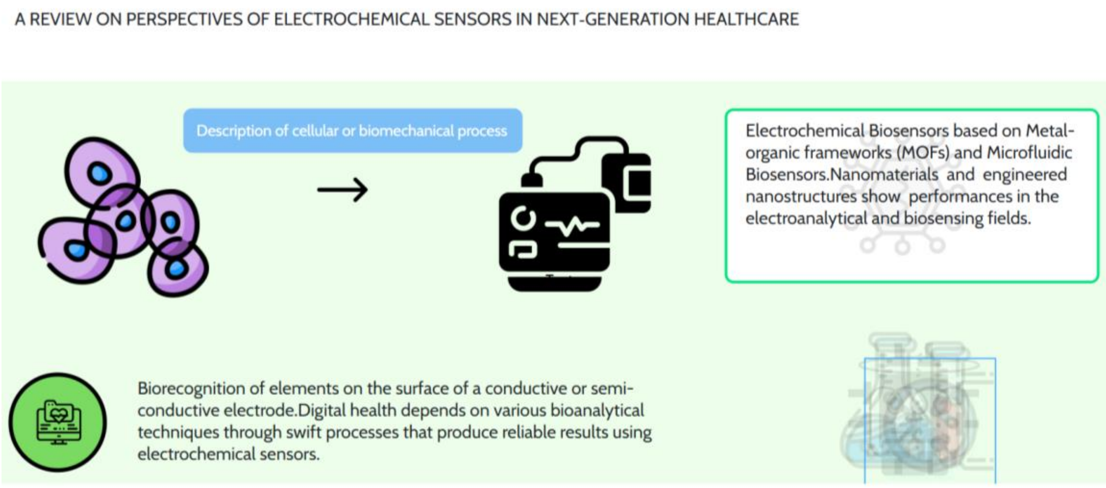
.Cite this paper as: Dr.Yasodha T, Dr.Menaka T,Vijayalakshmi M.S , Sangeetha A (2025) A Review On Perspectives Of Electrochemical Sensors In Next-Generation Healthcare. Journal of Neonatal Surgery, 14, (33s) 644-653

ABSTRACT

Impacts of sensors have increasing demand in various fields such asagriculture,environment,healthcare,medicine and pharmacology. Electrochemical approaches as a sole platform or integrated with metal organic frameworks/nanomaterials provide promising technologies due to their simplicity, high sensitivity and specificity. Electrochemical sensors have paved the way for emerging novel technologies in early stage diagnosis of diseases through its related biomarkers and biochemicals.Hence our primary focus is to review novel technologies for the early-stage detection and diagnosis of diseases (cancer,cardiovascular and diabetes) related biomarkers such as alpha-fetoprotein, hemin, glucose, uric acid,hydrogen peroxide and nicotine. Our review aims to provide insights of integrated electrochemical sensors with metal organic frameworks (MOF), nanomaterials and microfluidics. The new era of digital health depends on various bioanalytical techniques through swift processes that produce reliable results.Hence this paper outlines and summarize the advancements in electrochemical approach that are applicable in healthcare and medicine...

Keywords: Electrochemical sensors ,nano/MOFsensors,microfluidics,immunoassay, biomarkers for diseases

INTRODUCTION



Recent developments in the healthcare and pharmaceutical industries increase awareness among burgeoning population about the diagnosis and treatments of various diseases.Hence to save time and earlier diagnosis of diseases there is a need to develp rapid, sensitive and user-friendly methods.One such swift advancement and demand in the market is analytical devices. Designing and functioning of these analytical devices depend on electrochemical sensors.

Bioanalytical techniques involved electrochemical sensors used for detecting infectious pathogens based on immunosensors, electrochemical nanobiosensors, electrochemical cell biosensors, and electrochemical aptasensors to sense the bioanalytes.[1,2,3,4].

This Review focuses on recent advances in electrochemical sensors and biosensors based on nanomaterials, MOF composites , immunosensors and microfluidic biosensors . Furthermore the designing of electrochemical sensors and biosensors leads to advancements in biomedical and healthcare industries. The electrochemical sensors is used to detect biomarkers including glucose, dopamine, lactic acid, L-tryptophan, uric and ascorbic acids, H2O2, and nicotine.[5,6,7].

The analytical potential of electrochemical biosensors in voltametric, amperometric , impedimetric and microfludic technology provide attractive impacts due to their noteworthy features of being easily used ,reliable results and cost effectiveness. Studies on the determination of biomolecules with accurate results related to diabetes, cancer and viral/bacterial diseases encompass electrochemical analytical devices [8,9,10].

Bio/chemical sensing properties of electrochemical sensors turn them unique due to their high porosity and adsorption capability,excellent electrical conductivity and electrocatalytic activity.Electrochemical sensors are classified based on measurement types and bioanalytical detection techniques involved the following electrochemical biosensors :

1.1. Voltammetric

Cyclic voltammetry (CV): This electrochemical method used in voltammetric sensors, where the electrode potential is linearly scanned in a repeated cycle over time. It records the current in terms of potential and applied step by step or continuously to obtain a voltammogram. The results of cyclic voltammograms provide information about the redox behavior, kinetics, and electrochemical properties of the substances in the solution.

1.2. Amperometric

Chronoamperometry : CA measures the current over time when a fixed potential is applied to an electrode in a solution, providing information about reaction kinetics, electrode behavior, and electrochemical species. Electrical signals such as current, voltage, impedance, and potential are proportional to the concentration of the target analyte. It has preferred for detecting infectious agents, play vital roles in the development of electrochemical biosensors and provide accurate quantitative analysis[11,12].

1.3. Impedimetric

Impedimetric biosensors are the electrochemical devices applied widely for healthcare diagnostics enable its potential in wound monitoring and early disease diagnostics viz., SARS-CoV-2, pathogenic avian influenza DNA and other complex biological fluids[13,14,15].

Electrochemical impedance spectroscopy (EIS) is a highly promising tool for the analysis of blood. The electrical properties of plasma and blood cells provide fundamental insights into the health status of patients. In this study, a small chamber with two planar electrodes placed at the bottom is used for sensitive detection of blood hematocrit, sedimentation and dielectric properties of plasma and erythrocytes. The changes in the blood impedance spectrum were measured at frequencies between 40 Hz and 110 MHz for a few hours[16,17,18].

Bio-impedance measurement is a medical application used to analyze body composition, pulmonary edema, respiration rate, BMI, body temperature and lungs composition[19,20].Different potential value at different frequency was applied and current is measured. An efficient spectrometer using AD5933 with Bluetooth connectivity helps to develop portable and wearable sensors.

Affinity towards swift analytical processes leads to advancements in the treatments,early diagnosis of diseases/pathogens. Interdisciplinary impedance technology provides sensing multiplex analytes through label free, non-destructive detection methods at very low level with automated approach [21,22].

Our review provides an insight into the electrochemical sensors as analytical devices and its advancements in biomedical and healthcare industries. The designing of electrochemical sensors and biosensors leads to innovative technologies in the integrated fields such as microfluidics, nanocomposites applied to health care and biomedical industries [23,24,25].

Recent developments in the healthcare and pharmaceutical industries increase awareness among burgeoning population about the diagnosis and treatments of various diseases.Hence to save time and earlier diagnosis of diseases there is a need to develp rapid, sensitive, selective, and user-friendly methods.One such swift advancement and demand in the market is analytical devices capable to resolve large number of analytical problems and challenges in the medical and pharmacological domains [26,27,28].

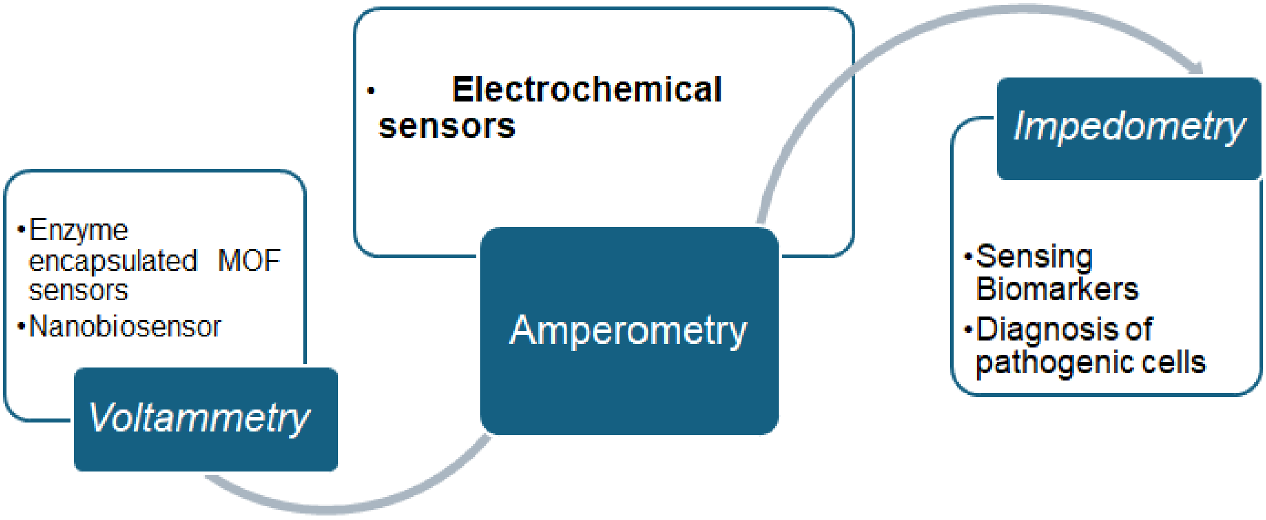


Figure 1. Electrochemical sensors and integrated applications

Electrochemical sensors as analytical devices to detect the analytical molecules from biological fluids for disease diagnosis. The molecules/biomarkers associated with diseases such as neurodegenerative, Alzheimer's and Parkinson's diseases, metabolic, infectious diseases, cancer can be detected swiftly and the earlier diagnosis decides the further treatment [29,30,31].

At present scenario accurate diagnosis of diseases and treatment by saving time and cost depends on the analytical devices.For such advancements electrochemical sensors paved the way in digital health and telemedicine. To increase the performance of the developed electrochemical sensors, electrode modification with hybrid materials, including nanomaterials, MOFs, and their combinations as a common approach and serum/blood and urine have been analyzed as biological fluids[32,10].

2. MULTIPLEXED EC ANALYSIS AND DIAGNOSIS OF DISEASES/ PATHOGENS/BIOMARKERS

Electroanalysis towards detection of biomolecules and pathogens is gained much importance in past few decades. Enzymatic and non enzymatic sensors widely used due to their high selectivity and sensitivity towards biofluids that have been widely used for determining the presence of hydrogen peroxide, glucose, and uric acid.Some of the pathogens and biochemicals were detected by electrochemical biosensors are listed below with references (Table-1). Biorecognition/ sensing strategies of elements involves device specificity and targeting bio analytes will enable these platforms to promote to real time clinical diagnosis.

In pharmacological contexts, hemin is typically formulated with human albumin prior to administration by a medical professional, to reduce the risk of inflammation of a vein in the legs and to stabilize the compound allowed to circulate in free-form. A hemin functionalized graphene sheet was prepared via the noncovalent assembly of hemin on nitrogen-doped graphene.

Nitric oxide functions as a signaling molecule, facilitating communication between adjacent cells and exerting regulatory effects on various biological redox processes. hemin/ luminol/H2O2-based chemiluminescence reaction was proposed as a method for the instantaneous measurement of NO in diverse biological solutions. Researchers[33,34,35] investigated a hemin/H_2O_2/luminol reaction for accurately detecting NO in various solutions. Hemin's interference with NO/peroxynitrite$^-$ modulated the propagated signal due to hemin, the NO levels in solution were estimated by amperometric detection This electrocatalytic reduction-based strategy provided potential for the design of the ultrasensitive detection method with noteworthy promise for clinical investigations such as cancer application[36].

Table-1.EC Analysis of Biomolecules and Pathogens

S.No	Bioanalytes/Pathogens/Biomolecules	References
1	Hydrogen peroxide	[28,31]
2	Glucose	[34,35]
3	Glutathione	[36]

4	Cholesterol	[37,38]
5	Uric acid	[21]
6	Nitric oxide	[39]
7	Albumin and creatinine	[40]
8	Hemin	[41,42]
9	*Escherichia coli*	[23,27]
10	*Coxiella burnetii*	[43,44,45]
11	Gram-negative bacteria	[46]
12	*Staphylococcus aureus*	[47]
13	*Streptococcus pneumonia*	[48]
14	*Entamoeba histolytica*	[49,50]

For clinical diagnostics multiplexed electrochemical devices were designed. Advanced electrochemical methods of detecting multiple proteins from human samples like serum, saliva, tissue, and urine are applied to the diagnosis and therapeutics. Multiplexed immunosensors with multi-labelled and multi-spot assay were demonstrated by these immunosensors were prepared with an array electrode for the simultaneous detection of different cancer biomarkers for carcinoma. Researchers experimented multiplexed electrochemical immunoassay of biomarkers using metal sulfide quantum dot nanolabels. [57,63].

2.ELECTROCHEMICAL IMMUNOSENSORS

There are three components of electrochemical sensors : an identification probe, a power converter, and a data analyzer. The identification materials on the electrode surface by chemical or physical methods. The target molecules on the surface of the electrode are captured through intermolecular-specific recognition. The signals are converted into electrical signals, such as current, voltage and impedance, etc.

Due to their simple operation, economy, convenient detection, high sensitivity, and fast response, electrochemical biosensors have been widely used in biomedicine, food engineering, environmental monitoring, and other fields.

Electrochemical sensors simultaneously detect multiple targets in complex biological samples with reliability, portability, low cost, selectivity and sensitivity. Hence, the integration of electrochemical immunoassays provide great potential for clinical diagnostics. The aim of immobilization is to sustain the catalytic activity to enable their repeated and continuous use. In electrochemical biosensors, immobilized enzymes are used for the biorecognition of elements on the surface of a conductive or semi-conductive electrode. Immobilization refers to the process of attaching enzymes or microorganisms to organic or inorganic carriers using physical and/or chemical methods.[51].

When the target analyte interacts with the biorecognition element, it triggers a physical or chemical reaction that generates an electrical signal. The biorecognition element acts as a molecular recognition component that selectively binds to the target analyte. This binding event leads to a change in the sensor's electrical properties, which can be measured using various electrochemical techniques [52].

The electrical properties of erythrocyte cytoplasm and membranes from the impedance spectrum of the blood samples reveal β- and δ-dispersions. It is found that the electrical properties of membranes significantly influenced the blood impedance at various frequencies [53,54].

3.ELECTROCHEMICAL BIOSENSORS BASED ON NANOMATERIALS

The integration of bioanalytical elements with electronic elements to develop electrochemical sensors and biosensors implemented since 1960s.Various electrochemical devices, such as amperometric sensors, electrochemical impedance sensors, and electrochemical luminescence sensors as well as photoelectrochemical sensors, provide wide applications in the detection of chemical and biological targets in terms of electrochemical change of electrode interfaces [55,56].

With remarkable achievements in nanotechnology and nanoscience, nanomaterial-based electrochemical signal amplifications have great potential of improving both sensitivity and selectivity for electrochemical sensors and biosensors. Nanomaterials such as nanowires, nanotubes, nanopores, nanowells and engineered nanostructures show performances in the electroanalytical and biosensing fields.[58].

The electrode materials play a vital role in the construction of high-performance electrochemical for detecting target molecules through various analytical principles. Furthermore, these electrode materials synergically involve in catalytic activity,conductivity and biocompatibility to accelerate the signal transduction. Preparation of carbon nanospheres based multiplexed electrochemical immunosensors utilised immobilized signal probes to sense biomolecules , secondary antibodies and alpha-fetoprotein (AFP) [57,5,10].

Functional nanomaterials amplify biorecognition with specific designed signal tags leads to highly sensitive biosensing. Significantly, extensive research on the construction of functional nanoelectrode materials, coupled with numerous electrochemical methods, is advancing the wide application of electrochemical devices [48].

Walcarius et al. 2013 [60] highlighted the recent advances of nano-objects and nanoengineered and/or nanostructured materials for the rational design of biofunctionalized electrodes and related (bio)sensing systems. Immobilized nanocomposite matrices integrated with the functionalised biomolecules contribute to the improvement of bioelectrode performance in terms of sensitivity and specificity.

With different kinds of nanoparticles (NPs), paper-based microfluidic biosensor devices have shown a great potential in the enhancement of sensitivity and specificity of disease diagnosis in developing countries. $Cu_3SO_4(OH)_2$ nanosheet arrays, e $Cu(OH)_2$ hierarchical nanoarrays, and (f) CuHHTP hierarchical nanoarrays of biomolecules like proteins, lipids, and DNA, contributing to several diseases, including cardiovascular diseases, neurodegenerative disorders, and cancer [33-37;45-51].

4. ELECTROCHEMICAL BIOSENSORS BASED ON METAL-ORGANIC FRAMEWORKS (MOFS)

Metal Organic Framework composites-based electrochemical sensors provide remarkable impact due to their extensive specific surface area, tunable pore sizes, exceptional catalytic performance, and abundant active sites. MOF-based EC sensing systems utilised widely in medical diagnostics for diseases such as diabetes, neurodegenerative , cardiovascular disorders, cancer and provide promising results[58-62]. MOF-based electrochemical (EC) detecters sense the key biomarkers in various bioanalytes including glucose, dopamine, uric and ascorbic acids, hydrogen peroxide and nicotine.

Pathogenic microorganisms such as protozoans, fungi, prions, viruses, and bacteria in the human body .Foodborne pathogens can enter the body via several ways of infection that affect the human health are listed in Table-1.

5. MICROFLUIDIC BIOSENSORS

Traditional detection technologies rely on large detection equipment and complex operation processes which are limited in the development of miniaturization and high sensitivity. Microfluidics provides a new solution for related technical breakthroughs: The micrometer scale of the microfluidic platform enhances the scalability of the devices and meets the requirements for sensor and system miniaturization. Microfluidics technology has gained substantial attention among researchers and scientists, especially in electrochemistry and biochemistry studies, for imitating the traditional benchmark laboratory instruments on a miniaturized chip-based system [51,52,53].

Furthermore, the potential of microfluidics relies on its patterned design to capable of constructing multi-channel structures.This enhances the capability of the multiplexity and swift operation of the detection systems. Microfluidics biosensing can enhance the selectivity, specificity, and detection time of the system by adjusting the flow rate, channel geometry, etc [54].

Microfluidics is applied in various domains such as biomedical, electrochemical, pharmaceutical and clinical fields due to the advantages like minimum sample volume, fast response, precision, multiplex operation, and rapid assessment. These properties convey significant resources to electrochemical and biochemical facets.

Research in microfluidics has made noteworthy advancements over the recent decades and has grown in popularity because of the vital characteristic benefits such as portability, versatile design, minimal reagents, the potential for simultaneous process, and easy connection to a smartphone for data access and storage on the cloud. Microfluidic biosensors are miniature lab-on-a-chip devices using tiny channels to precisely control fluids for rapid, sensitive, and automated healthcare diagnostics, enabling early disease detection, personalized medicine, and point-of-care testing (POCT) with minimal sample/reagent use [63-67]. They detect biomarkers (proteins, DNA, cells) in body fluids (blood, saliva, sweat) using nanotechnology and optical/electrical signals, supporting cancer liquid biopsies, pathogen detection, and continuous monitoring via wearables and smartphone integration, offering cost-effective, portable, and convenient health analysis [75].

To detect the target analytes, the paper-based microfluidic platforms must be integrated with sensing materials such as reagents (chemicals, enzymes, antibodies) or electrochemical sensors to provide detectable signals such as color and electrical current[68-72]. These sensing materials can be stored directly by physical absorption in the matrix of the paper and chemically immobilization on the f ibrous paper while electrochemical sensors can be patterned on the surface of the paper [73,74].

The amperometric nitric oxide (NO) microfluidic sensors exhibit noteworthy analytical performance in phosphate buffered saline. The analytical performance of the device was investigated in simulated wound fluid and whole blood. The results showed that the sensor is able to measure NO in complicated biological samples which demonstrated the feasibility of clinical applications. Detection sensitivity of 1.4 pA nM^{-1} was demonstrated along with the limit of detection (LOD) of 840 pM [39].

CONCLUSION

Electrochemical sensors based analytical devices for assessing bioanalytes to diagnose diseases for its specific biomarkers, determining the course of the disease and to treat according to the stages and monitoring the recurrence of the disease.. In this review, the current status of electrochemical sensors developed and applied for the determination of molecules associated with diseases such as neurodegenerative, metabolic, infectious diseases, cancer and clinically important pathogenic bacteria are summarized.Development of a novel electrochemical interface along with functional materials and enzyme immobilization plays a critical role for the rational design and construction of bioelectronic devices.Future and scope in this field directs further research towards telemedicines and combating the outbreaks of infectious diseases of population of diverse regions of the world.

DECLARATIONS

Availability of data and materials

All publicly available datasets used in the studies reviewed in this review are described in this article.

Competing interests

The authors declare that they have no competing interests.

FUNDING

Not applicable.

Authors' contributions

TY contributed to writing concept,original drafts, writing-review and editing, visualization, and conceptualization; **TM** contributed to writing original drafts and validation; **MSV** and

AS contributed to writing-review and editing and validation

ACKNOWLEDGEMENT

Authors are thankful to their managements for providing the computational resources.

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