1.1 Introduction

In the past, doctors were only seen by people when they were ill in order to receive diagnosis and treatment. The last few decades have been marked by a notable improvement in the quality of our lives, which has encouraged more frequent and routine check-ups to be sought. By patients, early diagnosis and treatment of illnesses can have their suffering and national healthcare costs lessened, particularly for chronic diseases like diabetes and cardiovascular disease, which are the world's leading causes of death and disability. Traditionally, this diagnosis has been depended upon by intricate, costly, and time-consuming laboratory apparatus, which conducts medical tests on samples (such as blood and tissue) obtained invasively from the human body in centralized institutions. An aging population, the rise in births, the prevalence of chronic conditions, and the requirements of sports and military personnel have significantly increased the demand for healthcare services these days. In response to this growing need, individuals and the health sector alike have turned towards health self-monitoring as a crucial means for managing health and, more specifically, treating diseases. This approach relies on the ability to track individuals physiological and biochemical data remotely, catering to the need for dispersed healthcare monitoring.

Acknowledging this need, the scientific community and industry sectors have actively developed a variety of home-based sensors and biosensors designed for point-of-care (PoC) diagnostics. Among these innovations, electrochemical and biosensors have set themselves apart as the leading solutions in home-based health monitoring systems. Their dominance in this space can be attributed to their simplicity, affordability, mobility, and quick response time, making them an appealing choice for consumers looking for efficient and reliable health monitoring options [1,2]. By providing individuals with the tools to monitor their health conditions from the comfort of their homes, these technologies offer a significant advantage. They empower people to take an active role in their health management, potentially leading to early detection of diseases and timely intervention. This is especially crucial for populations like the elderly, individuals with chronic conditions, or those in professions with high physical demands, such as athletes and military personnel, where continuous health monitoring is paramount.

Moreover, the development and widespread adoption of these innovative diagnostic tools represent a significant step forward in the healthcare industry. It not only underscores the importance of individual health autonomy but also highlights the potential for technological advancements to revolutionize the way we approach healthcare. By enabling remote and timely health monitoring, these technologies are paving the way for a more proactive, preventative, and personalized healthcare paradigm [3].

1.2 Sensors

A sensor is a device or instrument that detects or measures physical, chemical, biological, or environmental changes and converts them into measurable signals or data. Sensors are essential components of various systems and applications, including industrial processes, environmental monitoring, healthcare diagnostics, and consumer electronics [4,5]. Schematic diagram for components of sensor is shown in **figure 1.1**.

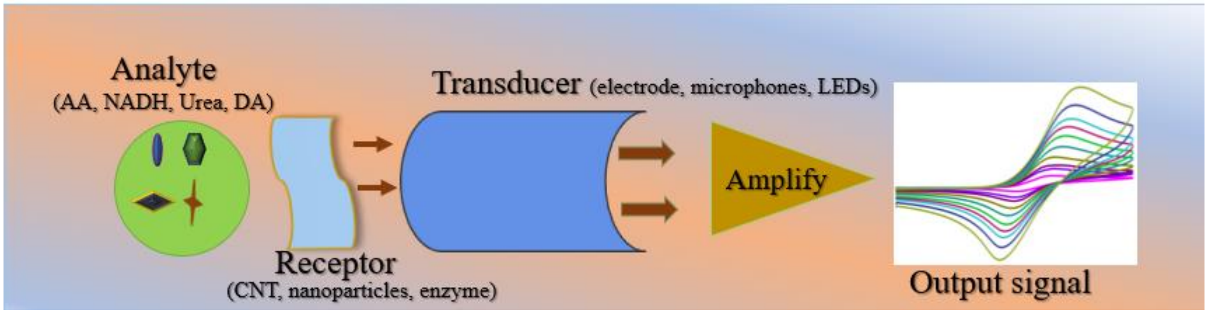


Figure 1.1 Schematic representation of the electrochemical sensor.

Many areas have come to rely on quantitative and qualitative analysis, including environmental monitoring, food quality control, forensic science, and biological diagnostics. A healthy existence depends on their content in the human body. An accurate and selective analytical approach is necessary to maintain a balanced and sufficient amount of biomolecules. The combination of a biological component and a transducer to construct what we today call a biosensor was first realized in the 1960's [6,7].

Biosensors are analytical devices that incorporate a biological recognition system to detect and quantify specific analytes in a sample. The interaction between the analyte and the recognition element produces a measurable signal, such as a change in electrical conductivity, optical properties, or mass, which is then correlated with the concentration of the analyte. They utilize transducers to do this. The transducer, which is a detecting device, is responsible for transmitting signals from the recognition component to the electronic circuit [8,9]. Numerous fields are increasingly using biosensors, including healthcare, the food business, environmental monitoring, and countless more. They are very important in environmental monitoring for tasks including estimating levels of harmful chemicals, heavy metals, phenolic compounds, and pesticides [10]. Urea, blood glucose, ascorbic acid, cholesterol, and lactate levels may be detected and quantified with the use of biosensors in the medical field. They may be used to check the microbiological contamination of food items, the perishability of meat, and much more in the food sector. There has been explosive growth in biosensing methods that integrate disciplines as diverse as chemistry, biology, biochemistry, physics, electronics, and computer science [11].

Depending on the analyte of interest and depending on under what circumstances, it will be measured, different demands will be put on the monitoring system in terms of linear concentration range, response time and measurement frequency. Many sensing methods are used for the quantitative and qualitative identification of analytes, including surface-enhanced Raman scattering (SERS), fluorimetry detection, bacterial bioreporters, electrochemical sensing, and others [12,13].

1.3 Classification of sensors

1.3.1 Based on transducers

A transducer is a component of a sensor that converts one form of energy or signal into another. In the context of sensors, a transducer typically converts a physical, chemical, or biological input into an electrical signal that can be measured and analyzed.

Sensors are broadly categorized into optical, electrochemical, electronic, thermal, and gravimetric sensors based on their operating principle and transducers.

1.3.1.1 Optical sensor

Optical sensors detect optical signals generated by reactions between receptors and analytes, facilitating real-time, label-free detection. They sense changes in absorption, reflection, transmission, or refraction caused by recognition events. Optical sensors can be label-free or label-based, with direct analyte-receptor interaction in the former and indirect signal generation (e.g., fluorescence, colorimetry) in the latter. They offer superior sensitivity, cost-effectiveness, small size, and operational simplicity compared to conventional techniques. Optical sensors find applications in biomedical research, pharmaceuticals, environmental monitoring, healthcare, security, and military [14].

1.3.1.2 Colorimetric sensors

Colorimetric sensors offer promise for detecting various substances due to their simple fabrication, low cost, quick detection, high selectivity, sensitivity, and easy naked-eye sensing.

They are particularly valuable for onsite detection of clinically important molecules in regions with limited resources. Noble metal nanoparticles, especially gold nanoparticles (GNPs), have been extensively used in colorimetric sensors due to their biocompatibility and ability to induce color changes through aggregation or re-dispersion phenomena. These changes, affecting inter-particle plasmon coupling, result in color transitions (e.g., red-to-blue or purple, or purple-to-red). This technology has the potential to significantly impact health management in resource-constrained regions by providing accessible diagnostic solutions without the need for sophisticated instrumentation [15].

1.3.1.3 Electrochemical Biosensors

The electrochemical biosensors constitute a major category of the biosensor technology where the mode of transduction for chemical sensing is based on the electrochemical processes. Potentiometry, amperometry, impedance spectroscopy, and conductometry are well known electrochemical processes which involve the measurement of potential, current, charge transfer resistance, and conductance of the cell. Based on this mode of measurements, the electrochemical biosensors are categorized as potentiometric biosensors, amperometric biosensors, impedimetric biosensors, and conductometric biosensors that are discussed below. Classic methods for identifying biomarkers, such as gas chromatography, high-performance liquid chromatography, and enzyme-linked immunosorbent assay, tend to be expensive, slow, and require specialized equipment and skilled operators. In contrast, electrochemical sensing provides a more affordable, simple, and quick approach for detecting biomarkers [16,17].

1.3.1.4 Potentiometric biosensors

Potentiometry involves measuring the potential of an electrochemical cell under static conditions, making it a valuable quantitative analytical approach. Unlike methods reliant on current flow, potentiometry operates with minimal or no current passing through the cell, ensuring the analyte composition remains unchanged during determination.

A typical potentiometry system consists of two half-cells. The cell's potential is calculated using the equation $E_{cell} = E_c – E_a$, where E_c and E_a are the potentials for the redox reactions at the cathode and anode, respectively. The selectivity of potentiometric systems for determining cations, anions, or biomaterials depends on the membrane material used in potentiometric sensor fabrication [18]. Potentiometric sensors, such as those for urea, uric acid, and glucose, are widely available in the market. Due to their versatility, there is a promising future for biomaterial measuring kits in the market [19]. The measurement of proteins [20], neurotransmitters [21–23], tiny molecules [24], and toxins [25] has been made possible by more recent developments in this field.

Ion-selective electrode (ISE)-based potentiometry has long been utilized as a low-cost, traditional method that can convert portable kits. Potentiometric sensors offer several benefits, including fast response times, a wide dynamic range, ease of use, portability, quick modification, and low costs [26,27]. In light of the above information, the special properties of potentiometric membrane sensors, and the high level of accuracy with which biomarkers can be used to evaluate the health status of an organism, it appears that the development of biomarkers using potentiometric techniques and measuring biological compounds could be a quick and easy way to determine the best course of action to treat individuals suffering from chronic diseases [28,29].

1.3.1.5 Amperometric biosensor

Amperometric biosensors are among the most popular, numerous, and commercially successful devices in the field of biomolecular electronics. These biosensors are significant because they paved the way for the emergence of the cutting-edge discipline of analytical biotechnology. Clark initiated research in the field of biosensors, particularly in amperometric transducers, with his study on the oxygen electrode published in 1956 [30]. The working principle of an amperometric biosensor involves measuring the electrical current produced by a redox reaction between a biological recognition element (such as an enzyme or antibody) and its target analyte. This recognition element is immobilized on an electrode surface. When the target analyte interacts with the recognition element, it triggers a biochemical reaction that results in the transfer of electrons to or from the electrode. This electron transfer generates a measurable electrical current, which is proportional to the concentration of the target analyte in the sample. By monitoring this current, the concentration of the analyte can be determined. A new amperometric DA sensor has been developed by Li, B. et al. using the PEDOT/ssDNA biocomposite, which was created using an easy one-step electrochemical deposition method [31].

1.3.1.6 Conductometric biosensors

The working principle of a conductometric biosensor involves measuring changes in the electrical conductivity of a solution due to interactions between a biological recognition element and its target analyte. Typically, the biosensor consists of two electrodes immersed in a solution containing the recognition element immobilized on a substrate. When the target analyte binds to the recognition element, it induces a change in the conductivity of the solution. This change could be due to the alteration of ions, pH, or other chemical properties of the solution caused by the biochemical reaction between the recognition element and the analyte. By monitoring the electrical conductivity of the solution using the electrodes, the concentration of the analyte can be determined. The magnitude of the conductivity change is proportional to the concentration of the analyte present in the sample. Therefore, conductometric biosensors provide a means to detect and quantify specific analytes in a sample based on their effects on the electrical conductivity of the solution.

1.3.1.7 Impedimetric biosensors

EIS, or electrochemical impedance spectroscopy, is a sensitive method for analyzing the interfacial characteristics associated with biorecognition events, such as enzyme-catalyzed reactions or biomolecular recognition events of particular binding proteins, lectins, receptors, nucleic acids, whole cells, antibodies, or substances related to antibodies, occurring at the modified surface. When the target analyte in a sample bind to the recognition element on the biosensor surface, it causes a change in the impedance of the system. This change is often due to the alteration in the dielectric properties, the charge distribution, or the conductivity of the medium around the biosensor surface.

Electrochemical impedance spectroscopy (EIS) integrates the examination of resistive and capacitive characteristics of materials, achieved by applying a small amplitude sinusoidal excitation signal to perturb a system at equilibrium [32]. The detection of these impedance changes is typically done by applying a small AC voltage to the biosensor and measuring the resulting current. The frequency-dependent impedance spectrum of an electrochemical system can be visualized using Nyquist or Bode plots.

Nyquist plots typically feature a semicircular region on the axis followed by a linear segment. The semicircle in the higher frequency range indicates the electron-transfer-limited process, while the straight line in the low-frequency range corresponds to the diffusion-limited process. This spectrum is useful for determining the kinetics of electron transfer and the diffusional properties [33].

Equivalent circuit models serve as valuable tools for interpreting impedance spectra, facilitating the characterization, analysis, and study of coatings, batteries, fuel cells, and corrosion phenomena. This technique is also widely applied in investigating electrode kinetics, conducting polymers, semiconductors, sensors, animal and plant tissues, and various other materials [34,35].

1.3.2 Based on Receptors

A molecule or materials designed to specifically recognize and bind to a particular analyte is termed a receptors/bioreceptor.

Sensors are classified based on receptors and interactions. Biosensors are categorized as affinity and catalytic. Catalytic biosensors use enzymes, tissues, microorganisms, or whole cells, generating a new product upon analyte interaction. Affinity biosensors use cell receptors, antibodies, or nucleic acids, with no new product formed. Receptors include ions, nucleic acids, cells, enzymes, antibodies, nanomaterials, quantum dots, and biomimetic materials. This categorization helps in understanding the principles of biorecognition and the diverse range of biosensor applications.

1.3.2.1 Nanomaterials as receptors

Nanomaterials have emerged as a significant category of receptors in sensor development, driven by advancements in nanoscience and nanotechnology. They offer a high surface-to-volume ratio, facilitating analyte immobilization in a small volume. Immobilization methods include adsorption, covalent interaction, and entrapment. Graphene, gold nanoparticles, carbon nanotubes, silver nanoparticles, graphene oxide, quantum dots, and polymer nanoparticles are extensively studied nanomaterials. Nanomaterial-modified sensors can exhibit high sensitivity, especially when their size matches that of the analytes (e.g., biomolecules, DNA, pathogens, antibodies, metal ions). Combining natural receptors with nanomaterials enhances sensitivity and selectivity, enabling the detection of target molecules like odorants, tastants, dopamine, hormones, and other compounds [36,37].

1.3.2.2 Enzyme as receptor

Enzymes, as biocatalysts, accelerate biological reactions with high selectivity. Enzyme-based sensors rely on enzyme-substrate binding and catalytic properties. Recognition mechanisms include monitoring enzyme changes, enzyme inhibition or activation by analytes, and analyte metabolization by enzymes. Despite their specificity, enzyme structures are sensitive to environmental factors, limiting stability and adaptability. Challenges include chemical inhibitors, ionic strength, pH, and temperature effects on catalytic activity, particularly at high temperatures (>60°C). Glucose and urea sensors are common examples. Ondes et al. developed a potentiometric urea biosensor with 0.77 µM detection limit and 30 s response time, while Cordeiro et al. proposed W-Au-based glucose biosensors for brain glucose monitoring [38,39]. Introduction of nanoparticles enhances enzyme sensor applications. Enzymes are typically attached to optical and electrochemical transducers using immobilization techniques such as covalent attachment, adsorption, and entrapment. These methods enable the fabrication of biosensors with improved performance and versatility [37].

1.4 Parameters of a sensor

The important parameters of sensor are discussed as follows

1.4.1 Sensitivity

Sensitivity refers to the ability of the sensor to detect small changes in analyte concentration. It is typically expressed as the change in signal per unit change in analyte concentration (e.g., current change per unit concentration change). It can be determined using the calibration curve's slope.

1.4.2 Linear range and Linearity

The linear range of an electrochemical sensor refers to the concentration range over which its response is directly proportional to the analyte concentration, ensuring accurate quantification, while linearity describes how well the sensor response aligns with a straight line within this range, indicating consistent and predictable behavior.

1.4.3 Limit of detection (LOD)

The limit of detection is the lowest concentration or smallest amount of analyte that can be reliably detected by a sensor. It is determined as the signal corresponding to a specified low concentration above the background signal, typically three times the standard deviation of the background signal. $\mathrm{LOD} = \frac{\mathbf{3\,S}}{\mathbf{m}}$ where, S is the standard deviation, and m is the slope of the calibration curve.

1.4.4 Limit of quantification (LOQ)

The limit of quantification is the lowest concentration of analyte that can be accurately quantified by the sensor, typically defined as the concentration corresponding to a signal-to-noise ratio of 10:1.

1.4.5 Selectivity

Selectivity refers to the sensor's ability to respond specifically to the target analyte in the presence of other interfering substances. High selectivity reduces false positive or negative results.

1.4.6 Response Time

Response time is the time taken by the sensor to reach a stable response after exposure to a change in analyte concentration. A fast response time is important for real-time monitoring applications.

1.4.7 Stability

Stability refers to the sensor's ability to maintain its performance over time. It includes factors such as drift, repeatability, and long-term reliability of the sensor's response.

1.4.8 Accuracy and Precision

Accuracy refers to the closeness of the sensor's measured value to the true value of the analyte concentration, while precision is the degree of repeatability of the sensor's measurements under identical conditions, typically expressed as the standard deviation of replicate measurements.

These parameters are crucial for evaluating and optimizing the performance of electrochemical sensors for various applications [8,40–42].

1.5 Electroactive mediators

Electroactive mediators are molecules that are used to facilitate electron transfer between the analyte and the electrode surface in electrochemical sensing. These mediators can undergo reversible redox reactions, which allows them to shuttle electrons between the analyte and the electrode, enhancing the sensitivity and selectivity of the sensor.

Some common electroactive mediators used in electrochemical sensing include:

1.5.1 Methylene blue: Methylene blue is a redox-active dye that is often used as a mediator in electrochemical sensors due to its reversible redox behavior and stability [43].

1.5.2 Quinones: Quinones, such as benzoquinone and anthraquinone, are commonly used as mediators in electrochemical sensors due to their ability to undergo reversible redox reactions [44].

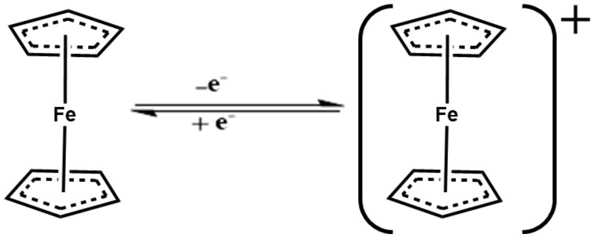
1.5.3 Tetrathiafulvalene (TTF) derivatives: TTF derivatives are electron-rich molecules that can act as mediators in electrochemical sensors, facilitating electron transfer between the analyte and the electrode [45].

1.5.4 Ferrocene derivatives: Ferrocene and its derivatives are widely used as mediators due to their well-defined redox properties and high stability.

Ferrocene and its derivatives have emerged as pivotal elements in the development of electrochemical sensors, due to their remarkable electrochemical properties and stability [46]. The incorporation of ferrocene moieties into sensing platforms enables the facile and reversible redox process, which is fundamental in achieving high sensitivity and specificity in the detection of various analytes. These compounds often facilitate electron transfer processes, enhancing the electrochemical signal in the presence of the target substance, thereby allowing for the detection of even trace amounts. Moreover, the structural versatility of ferrocene derivatives permits the tailor-made design of sensors, whereby specific functional groups can be introduced to selectively interact with a wide range of biological and environmental targets. Consequently, integrating ferrocene and its derivatives, i.e., Fcmc and Dmfc, into electrochemical sensors represents a significant advancement in analytical chemistry, offering promising applications in medical diagnostics, environmental monitoring, and food safety assessment.

1.5.4.1 Properties and Electrochemical application

Since its discovery in 1951, Ferrocene has been the focal point of extensive research [47]. The molecule's chemical characteristics are remarkable due to its sandwich structure, which involves d-π interactions between the Fe (II) core and the cyclopentadienyl (Cp) moieties. The most distinctive feature of ferrocene is its capability to undergo reversible oxidation to ferrocenium ion. This is facilitated by the fact that ferrocene possesses a lower oxidation potential, enabling it to lose an electron and form two stable redox states, Fe (II) and Fe (III) for Fc and Fc^+, respectively [48,49].



This unique characteristic of ferrocene makes it highly valuable as an internal standard in electrochemical studies. The compound ferrocene is of interest to everyone due to its notable attributes such as low biotoxicity [50], heat and photochemical stability [51], commercial availability, and resilience or stability in aerobic and wet environments.

Ferrocene and its derivatives exhibit a broad spectrum of chemical and physical properties that make them highly versatile and applicable across various fields such as sensor technology, materials science, and catalysis. These compounds have been extensively studied for their unique electrochemical characteristics, which were thoroughly assessed using cyclic voltammetry (CV). This analytical method allowed for the detailed evaluation of the electrochemical behavior of different ferrocene derivatives, including ferrocene monocarboxylic acid (Fcmc) and dimethyl ferrocene (Dmfc). The focus of this analysis was on determining the redox potentials between the ferric (Fe^{+III}) and ferrous (Fe^{+II}) stages of these compounds, as well as assessing their capability for electrochemical reversibility. For the purposes of these investigations, ferrocene itself was employed as a benchmark mediator, providing a standard against which the performance of its derivatives could be measured. This comprehensive approach not only highlights the potential of ferrocene and its derivatives in various applications but also contributes to a deeper understanding of their electrochemical properties.

1.6 Chemical modifications of the electrodes surface

The efficiency of a developed sensing electrode is generally measured based on its selectivity and sensitivity towards the determination of the target molecule. Electrode surface modification is a widely accepted technique to boost the selectivity and sensitivity of the electrocatalytic determination methods. Carbon nanotubes (CNT), MWCNT, carbon nanospheres, and graphene are among the carbon-based electrode surface modifiers. These carbon- based catalytic support systems are found to raise the electro-active surface area of the electrode with more stability and conductivity. Similarly conducting polymer modifications using polyaniline, polypyrrole, polythiophene and so on can improve the physicochemical properties of the substrate electrode [52,53]. Non-carbon- based surface modifiers such as metal and metal oxide nanoparticles can also improve the electron transfer kinetics between the electrode analyte interface.

1.6.1 Metal/Metal oxide nanoparticles and their bimetallic composite

Nowadays metal and metal oxide and their bimetallic composite have taken a significant role in the fabrication of electrochemical sensors. They are capable of enhancing the electrocatalytic activity of the sensor towards the target molecule and aid in the miniaturization of the sensing device. The unique properties of the nanomaterials improve the sensitivity, selectivity, and reproducibility of the sensing electrode and provide a more durable and economical sensing substrate. Recently various hybrid systems involving metal and metal oxide nanoparticles have achieved huge significance in the electrochemical sensing of biomolecules [54]. Nanoparticles can increase the electro-active surface of the substrate electrode, thereby increasing the conductivity and electrocatalytic activity of the sensor device [55,56]. Furthermore, the electrocatalytic performance of the sensor can be upgraded by using bimetallic composites.

1.6.2 Carbon materials

Carbon, especially in the form of nanomaterials like carbon nanotubes (CNTs), and graphene is widely used in electrochemical sensors due to its unique properties. These materials enhance reactivity of biomolecules, promote electron transfer in proteins, and offer high sensitivity. Synthetic diamonds are also promising for biosensors and bio interfaces due to their inertness and biocompatibility [57–59].

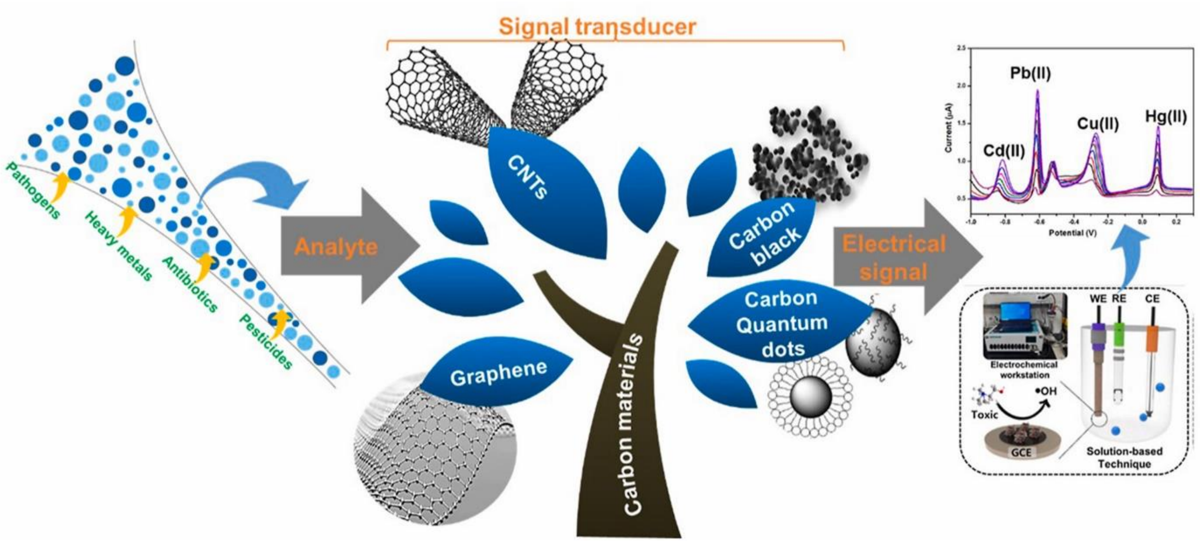


Figure 1.2 Various carbon materials used in electrochemical sensing [60]

Graphene has brought a significant revolutionary change in the present science and technology due to its extra-ordinary electrical, mechanical, thermal and optical properties. It is a carbon layer of graphitic structure in a honeycomb-like lattice. The hexagonally arranged carbon atoms of sp^2 hybridization can have different forms such as zero dimensional fullerenes, rolled one dimensional carbon nanotubes, and stacked three-dimensional graphite [61,62]. Graphene is a very strong material even though it is so thin and on the nanometer scale. The high electrical conductivity of graphene gave a significant role in electrochemical analytical studies. In graphene, van der waal's force of attraction plays a major role between the different layers of covalently bonded carbon atoms and C-C bond length is found to be 0.142 nm [63]. The unique structural features of graphene results in several amazing properties such as good carrier mobility, optical transparency, brilliant thermal - electrical conductivity and high specific surface area (SSA) [64]. The zero-band gap semiconductor- graphene consists of bonding π orbitals as valance band and anti-bonding π^* orbitals as the conduction bands. Graphene exhibits a very good electron flow which is observed to be better than in copper. Since it provides a high SSA, graphene shows significant electrochemical reaction responses compared to other carbon forms. Achieving faster electron transfer between the electrode and the analyte, a low detection limit, a wide linear response range, good stability and reproducibility, and increased sensitivity and selectivity of the electrochemical sensor is fundamentally dependent on the modification of these electrodes with suitable nanostructured materials. Over the past few decades, there has been a development of various modification materials, with multi-walled carbon nanotubes (MWCNTs), which were developed in 1991, finding wide applications in lab-on-chip sensors, drug delivery vehicles, and energy storage devices. Unlike graphene, MWCNTs form a network structure on the electrode surface, facilitating electron transfer and offering more binding sites [65–69].

The literature survey demonstrates that electrochemical analysis is consistently less complex, more flexible, accurate, and provides rapid results. Electrochemical sensing has recently made a significant impact across various research fields, particularly in the analysis of biomolecules. This is due to its cost-effectiveness and the ability to apply a wide range of modifications.

1.7 Advantages of employing nanomaterial-modified electrodes in electrochemical sensing

Several instrumental techniques, such as ICP-OES or spectrometers, for example, chromatography, potentiometry, and fluorometry, are made available for the determination of environmentally hazardous species. However, it is found that most of these techniques necessitate the use of a colorimetric probe, a redox dye indicator, etc., and they are characterized by being time-consuming, costly, or requiring a sophisticated instrumentation work-up [70,71]. In earlier times, electrodes that were modified with enzymes and heavy molecular mass conductive polymers were being utilized for the electrosensing of analytes. However, the major drawbacks associated with the utilization of such modified electrodes have been encountered, which include several problems as follows:

- Very careful pre-treatment of the enzyme is required, as it is highly sensitive to factors such as temperature, pH, and the local environment, among others.
- the pre-treatment process of enzymes is executed with utmost care. It involves meticulously controlling and monitoring environmental parameters such as temperature, pH, etc to preserve the enzyme's active state, thereby ensuring its effectiveness in subsequent applications.
- Enzymes, due to their high molecular masses, can lead to electrode fouling and increased solution resistance, ultimately reducing sensitivity.

The fragility of enzyme-based modified electrodes poses challenges for storage and stability. However, advancements in hybrid nanomaterial-modified electrodes have mitigated these concerns to a significant extent. Electrochemical methods have garnered interest due to their simplicity, affordability, rapidness, and high sensitivity in analyte detection. Utilizing nanomaterials offers several benefits for electrochemical detection, including enhanced stability and sensitivity. Overall, nanomaterial-modified electrodes represent a promising approach for improving the practicality and effectiveness of electrochemical sensing.

The technological advancement harnesses the unique properties of nanomaterials, such as increased surface area and enhanced electrical conductivity, to significantly improve the sensitivity and specificity of sensors. The incorporation of nanomaterials into the sensor design not only facilitates the early detection of disease biomarkers in non-invasive or minimally invasive samples but also supports the real-time tracking of disease progression or response to treatment.

Moreover, the application of nanomaterial-modified sensors extends beyond the scope of disease management. It also includes environmental monitoring, where such sensors can detect toxins or pathogens in water and air, and industrial applications, where they play a pivotal role in quality control and safety assurance processes [72,73].

Nanoparticles exhibit unique catalytic activity due to their quantum-scale dimensions, differing from their bulk counterparts. Micro/nano electrode ensembles offer advantages over conventional electrodes, including increased mass transport, reduced solution resistance influence, less electrode fouling, and improved detection limits. Noble nanomaterials like palladium, gold, and silver are commonly used to functionalize electrodes for electrochemical sensing. Monitoring electrochemical sensing in aqueous electrolytes requires safe potential regions to prevent solvent decomposition and gas evolution.

1.8 Significance of Some Biologically Important Molecules

The concentration of biomarkers such as NADH, dopamine, glucose, ascorbic acid, Na^+, and H^+ in body fluids is crucial for assessing an individual's health and bodily functions. These biomarkers serve as key indicators of various physiological and biochemical processes, providing valuable insights into a person's overall health status. Some of few are discussed here.

1.8.1 Ascorbic acid

Ascorbic acid (AA, vitamin C), being one of the most important biomolecules, has been shown to play critical roles in a range of physiological and pathological processes. These roles include acting as an anti-scurvy agent, providing neuroprotection in brain injuries/dysfunctions, modulating neurological functions, and promoting stem cell differentiation [74].

Unsaturated lactones like ascorbic acid have antioxidant properties. In both the plant and animal realms, it is extensively dispersed. The anterior pituitary lobe, leukocytes, animal organs, liver, and several fresh fruit juices are among the important sources of it. Through hydrogen atom transfer, it functions as a free radical scavenger in biological systems and is an enzyme cofactor for the production of several physiologically significant compounds, including collagen, catecholamine, myelin, and neuroendocrine peptides [75]. A high level of oxidative stress in human metabolism has been connected to diabetes, cancer, and liver disease. This same oxidative stress has also been associated to the concentration of AA. According to research, a daily intake of slightly less than 10 mg of AA is all that is required to avoid scurvy and preserve the tissues' ability to repair. Lipid peroxidation, cytotoxicity via H_2O_2 production, DNA damage, and mutagenesis are just a few of the many harmful processes it may accelerate. In order to prevent healthy persons from losing 3–4% of their body store, the daily intake of AA must match the quantity expelled by oxidation. So, in order to absorb about 60 mg/day, AA would be required. The needs for AA are considerable in premature newborns and neonates. Humans with high needs during pregnancy, breastfeeding, antimicrobial treatment, and hemodialysis must take AA dosages of 60–2000 mg/day in order to eradicate vitamin C deficiency. Developing facile analytical methods for selective and reliable measurement of ascorbic acid (AA) is crucial. Electrochemical approaches are ideal due to their high sensitivity, low cost, and miniaturization potential. Unfortunately, despite AA being electrochemically active, it is hindered by its sluggish electron-transfer kinetics and severe fouling of the electrode [76–78].

1.8.2 Dopamine

Dopamine (DA), a crucial neurotransmitter in the brain, was discovered by Arvid Carlsson in 1957. It plays a significant role in various physiological functions, including cardiovascular, central nervous, endocrine, and renal systems. DA influences attention, learning, memory, movement, mood, behaviour, and mental cognition. Imbalances in DA levels can lead to depression, addiction, schizophrenia, Alzheimer's, and Parkinson's diseases [79]. Elevated DA levels can cause cardiotoxicity, leading to heart failure, hypertension, and increased heart rate. The concentration of DA varies in different human biofluids, with levels around 5 nM in urine and cerebrospinal fluid and less than 0.13 nM in human blood. Parkinson's disease affects approximately 10 million people globally, resulting from the depletion of dopaminergic neurons in the substantia nigra of the brain, leading to tremors, bradykinesia, dementia, and impaired speech. Substance abuse, including alcohol, nicotine, cocaine, and heroin, can inhibit dopamine transport and reuptake, leading to increased levels and higher rates of depression and mental illness [80].

The design and fabrication of diagnostic tools for reliable, swift, and quantitative detection of changes in dopamine concentration in real samples, such as cerebrospinal fluid and human serum, are crucial for understanding its role in normal and abnormal biological processes. Despite its importance, accurately detecting dopamine in complex biological samples with enhanced sensitivity and selectivity using advanced point-of-care diagnostic devices remains challenging processes [81].

Electrochemical detection is a promising approach for dopamine detection due to its electroactivity and ease of oxidation. However, the accuracy and sensitivity of electrochemical detection methods depend on the electrode material used [82–84]. Recent advancements in biosensing devices based on nanostructured materials offer efficient platforms for dopamine detection, but many are limited to prototype stages. Further research and development are needed to improve the accuracy, sensitivity, and practicality of these devices for widespread use in clinical settings.

1.8.3 Dihydronicotinamide adenine dinucleotide

1,4-Dihydronicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide (NAD^+) are essential cofactors that carry charges and play pivotal roles in central metabolic pathways, including oxidative phosphorylation, the tricarboxylic acid cycle, and glycolysis. They also contribute to protecting cells from oxidation, cell signaling, and DNA repair processes [85,86]. The structure of this coenzyme is based on two nucleotides derived from adenine and nicotinamide. NADH also plays a crucial role in producing and stimulating neurotransmitters like dopamine, serotonin, and noradrenaline, enhancing muscular movement and mental attention. The NAD^+/NADH couple is involved in over 300 enzyme reactions catalyzed by dehydrogenases. Deficiency of NADH can lead to energy scarcity, resulting in symptoms such as tiredness, depression, attention deficit, muscle pain, and Alzheimer's [87]. Quantifying these compounds is vital for studying redox biological processes and detecting various enzyme substrates.

Electrochemical oxidation of NADH has been extensively studied for various bio electrochemical applications such as biosensors, biofuel cells, and bioreactors. However, direct oxidation of NADH on conventional solid electrodes requires a high overpotential due to its large activation energy. This process often leads to fouling of the electrode surface from coupled side reactions and accumulation of oxidation products, resulting in low sensitivity. Research efforts have focused on reducing the oxidation overpotential of NADH and improving electron transfer by employing modified sensing surfaces [88–90].

1.9 Aim and scope of the work

The aim and scope of the present study involves the fabrication of the mediated electrochemical biosensors for the electrocatalytic determination of the selected different biomolecules. The following are the main objectives of the work.

- To synthesis metals nanoparticles and modified carbon paste electrode (CPE) for electrochemical sensing of various biomolecules.
- To analyze the materials using various techniques, including XRD, XPS, AFM, SEM, and TEM, to characterize their properties.
- To optimize the experimental parameters, including pH, scan rate, and number of cycles, essential for electroanalytical investigations such as amperometry, differential

pulse voltammetry, electrochemical impedance spectroscopy and cyclic voltammetry techniques for the chosen biomolecules.

- To confirm the suitability of the developed electrochemical sensors for detecting specific biomolecules (such as ascorbic acid, NADH, and dopamine) in real samples.

Additionally, the sub-objectives listed below are the focus of our thesis:

- Synthesis of Palladium nanoparticles and its characterization. Further, fabrication of a voltammetric sensor for the ascorbic acid determination.
- Synthesis of Co-NC/Pd nanocomposite and its characterization. Further, fabrication of modified CPE for the voltammetric determination of NADH.
- Synthesis of Ni-Pd nanoparticles decorated on f-MWCNT and its characterization. Further fabrication of modified CPE for the voltammetric detection of dopamine.

The study presented here deals with the development and evaluation of biosensor systems for the sensing and detecting of some biomolecules (using mediators and nanomaterials). This research study involves electrochemical modifications of CPE using different electrode modifiers such as f-MWCNT, Pd, Co NC/Pd and Ni-Pd nanoparticles which improve the electrocatalytic activity of the modified electrodes towards the target biomolecules. Results on these programmes are reported in the present thesis.

1.10 References

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