

Review

Electrochemical Sensors and Their Applications: A Review

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Abstract: The world of sensors is diverse and is advancing at a rapid pace due to the fact of its high demand and constant technological improvements. Electrochemical sensors provide a low-cost and convenient solution for the detection of variable analytes and are widely utilized in agriculture, food, and oil industries as well as in environmental and biomedical applications. The popularity of electrochemical sensing stems from two main advantages: the variability of the reporting signals, such as the voltage, current, overall power output, or electrochemical impedance, and the low theoretical detection limits that originate from the differences in the Faradaic and nonFaradaic currents. This review article attempts to cover the latest advances and applications of electrochemical sensors in different industries. The role of nanomaterials in electrochemical sensor research and advancements is also examined. We believe the information presented here will encourage further efforts on the understanding and progress of electrochemical sensors.

Keywords: electrochemical sensor; electrodes; biosensor; potentiometric sensor; amperometric sensor; nanosensors; conductometric sensor



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1. Introduction

A chemical sensor is defined by the IUPAC [1] as “a device that converts chemical data, ranging from the concentration of a single sample component to complete composition analysis, into an analytically usable signal”. For the most part, a chemical sensor is constituted of two essential functional units: a receptor and a physicochemical transducer. The receptors are variable and can range from activated or doped surfaces to complex (macro)molecules that create highly specific interactions with the analyte (Figure 1).

If the receptor is of biological origin (e.g., DNA, antibodies, and enzymes), the device is referred to as a biosensor. The receptor interacts with the analyte, converting the recognition event into a predetermined output signal. One of the primary requirements of sensors is to maintain a high degree of specificity for the intended analyte in the presence of potentially interfering chemical species to avoid false-positive outcomes. Another critical component of sensors is the transducer, which is responsible for converting the signal created by the receptor–analyte interaction into a readable value. Thus, both chemical and biosensors can be classified into catalytic or affinity-based devices. Whereas catalytic sensors utilize catalytic activity to generate the signal, as in the case of enzymatic, DNAzyme, or functionalized surfaces that can perform redox reactions under certain conditions, affinity-based devices rely on highly specific interactions between the receptor and analyte, e.g., using the specific affinity of nucleic acids (i.e., ssDNA and aptamers), antibodies–antigens, or host–guest interactions. The monitoring of the recognition events can be performed using several methods (e.g., optical, gravimetric, or electrochemical) depending on the type of transducer utilized [2].

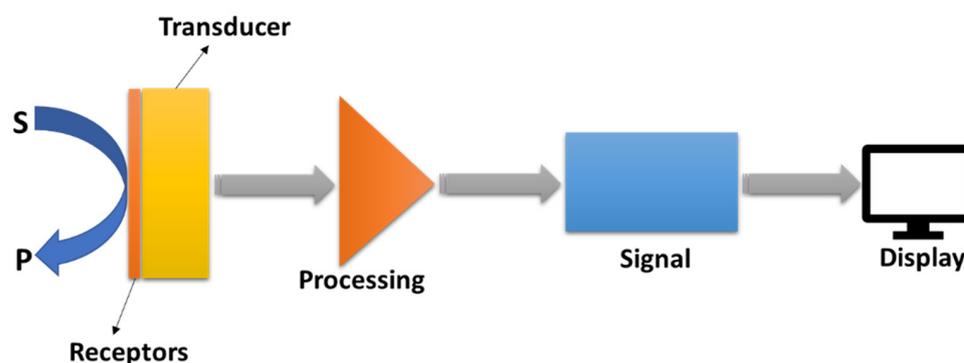


Figure 1. A schematic diagram illustrating the major components of a standard sensor. Adapted with permission from Shetti, N.P.; Nayak, D.S.; Reddy, K.R.; Aminabhvi, T.M. Graphene–Clay–Based Hybrid Nanostructures for Electrochemical Sensors and Biosensors. In Graphene-Based Electrochemical Sensors for Biomolecules; Elsevier, 2019; pp. 235–274, ISBN 9780128153949, Reference [3].

Being the market leaders, electrochemical sensors are, by far, the most frequently employed type of sensor due to the fact of their advantages associated with low detection limits, as low as picomoles, rapidness, and the low-cost equipment utilized for sensing. Electrochemical sensors come in a variety of form factors ranging from the top-bench to fully integrated wearable devices [3]. The utility of a chemical sensor is to deliver accurate real-time information regarding the chemical composition of its surroundings. In an ideal scenario, such a device would be able to respond constantly and reversibly without interfering with the sample. In such devices, a biological or chemical identification layer is coated on a transduction element. In electrochemical sensors, the analytical information is taken from the electrical signal produced by the interaction of the target analyte and the recognition layer. Various electrochemical devices can be employed for environmental monitoring depending on the nature of the analyte, the character of the sample matrix, and the sensitivity or selectivity requirements. The bulk of these devices fall into several categories such as amperometric and potentiometric electrochemical sensors (depending on the device's nature) [4,5]. Electroactive species that are involved in chemical or biological identification are detected using amperometric sensors.

2. Types of Electrochemical Sensors

Electrochemical sensors can be classified into several categories including amperometric, potentiometric, impedimetric, photoelectrochemical, and electrogenerated chemiluminescence. For potentiometric sensors, as a result of specific sensor–analyte interactions, a local Nernstian equilibrium is formed at the sensor interface, when no current is allowed to flow in the system giving information about the analyte's concentration. Amperometric sensors employ a voltage placed between a reference and working electrodes to initiate electrochemical oxidation or reduction, measuring the resulting current as a quantitative indicator of the analyte's concentration, according to the Cottrell equation:

$$i = \frac{nFAc_j^0 \sqrt{D_j}}{\sqrt{\pi t}}$$

where:

i = Current (in ampere);

n = Number of electrons;

F = Faraday constant (96,485 C/mol);

A = Area of the (planar) electrode in cm^2 ;

c_j^0 = Initial concentration of the reducible analyte $\{\displaystyle j\}$ in mol/cm^3 ;

D_j = Diffusion coefficient for species $\{\displaystyle j\}$ in cm^2/s ;

t = time in seconds.

Conductometric sensors, frequently referred to as impedimetric sensors, on the other hand, measure changes in the surface impedance to detect and quantify analyte-specific recognition events on the electrode. The extraordinary success of electrochemical sensor research, and its growing influence on analytical chemistry, make it difficult to address all of the achievements within the scope of this review and, therefore, we aimed to demonstrate the variability in the field, rather than deep immersion into a certain type of electrochemical sensor. Table 1 lists the different analytes, types of biosensors, and electrochemical measurement techniques [6].

Table 1. Biosensor receptors and electrochemical measurement methods.

Analytes	Receptor/Chemical Recognition System	Measurement Approach	Reference
Ions	Permselective, ion-conductive inorganic crystals, or biological ionophores	Potentiometric	[7]
Dissolved gases, vapors	enzyme(s)	Amperometric or potentiometric	[8]
Antibody/antigen	Inert metal, antibody, receptor	Amperometric, potentiometric, or conductometric	[9]
Various proteins and low-molecular weight substrates	Antigen/antibody oligonucleotide duplex, aptamer enzyme-labeled	Amperometric or potentiometric	[10]
	Specific ligands		

2.1. Potentiometric Sensors

Due to the fact of their simplicity and low cost, since the early 1930s, potentiometric sensors have been the most extensively used practical sensors. Potentiometric devices can be classified into three categories:

1. Ion-selective electrodes (ISEs);
2. Coated-wire electrodes (CWEs);
3. Field-effect transistors (FETs).

The type and content of the membrane material play a significant role in constructing an electrode that is selective to a single species. The research in this sector has paved the way for a variety of applications involving an almost infinite number of analytes, with the only restriction being the membrane matrix's dopant and ionophore composition. ISEs may be classified into three categories based on the type of the membrane: glass electrodes, liquid electrodes, and solid electrodes. Over two dozen ISEs are commercially available from companies, such as Corning, Orion, Radiometer, Beckman, and Hitachi, and they are widely used for the analysis of organic ions and anionic or cationic species in a variety of effluents, in the oil industry and in the manufacturing process and monitoring of drugs, using response membrane electrodes specifically designed for this purpose [11–13]. Wearable device technology paired with potentiometric ion sensors based on an all-solid-state concept offers significant potential in the tracking of physical status during athletic performance along with clinical medicine via sweat analysis [14].

pH electrodes have been the most extensively used potentiometric device for several decades and are the most widely used potentiometric device overall. A thin ion-sensitive glass membrane is used to create glass electrodes, which are the most common type and are available in a variety of forms and sizes. Nonetheless, additional types of potentiometric sensors that utilize organic polymers (e.g., polymethylene blue) or redox-active molecules (e.g., ferrocenes and quinones) can be used to detect pH in addition to those described above. Additionally, it has been reported that glass electrodes for monovalent cations, such as sodium, lithium [15,16], ammonium, and potassium sensors, can be employed [17]. These electrodes are composed of novel glass compositions. The use of glass membrane electrodes to determine pH solutions has proven highly effective; however, it is now

confined to aqueous measurements. It is essential to make corrections when determining the concentration of hydrogen ions in nonaqueous liquids [18].

2.2. Amperometric Sensors

Amperometric measurements are frequently used as an analytical method of high accuracy and sensitivity in which the applied voltage serves as a driving force for electrocatalytic redox reactions that generate electrical currents proportional to the concentration of the analyte. A controlled-potential system is required for the fundamental instrumentation, and the electrochemical cell is composed of two electrodes submerged in an electrolyte of an appropriate composition. A more sophisticated and common design is the employment of a three-electrode cell, with one of the electrodes functioning as a reference electrode [19]. However, whereas a working electrode is defined as the electrode where the reaction of interest occurs, a reference electrode (such as Ag/AgCl or Hg/Hg₂Cl₂) is defined as the one that maintains a constant potential when compared to a working electrode [20]. As an auxiliary electrode, an inert conducting substance (e.g., platinum or graphite) is often employed. In controlled-potential studies, a supporting electrolyte is necessary to prevent electromigration effects, lowering the resistance of the solution and maintaining the ionic strength constant. Theoretical considerations, as well as practical approaches, have been well described [21,22].

2.3. Impedimetric Sensors

One strategy is to stimulate the cell with a small-magnitude alternating potential and then see how the system responds in a steady state. This strategy has many benefits. The most significant ones are the ability to perform sensitive measurements using an experiment because the response may be permanently steady and can thus be averaged over a long period of time, the capability to treat the response theoretically using generalized linear current-potential characteristics, and measurement over a broad time or frequency range [6]. Polymers, either by themselves or in combination with a conductor, are also often utilized. For example, polypyrrole is capable of detecting volatile amines and when doped with ClO₄⁻ and tosylate, it can be used as an NH₃ sensor [23].

In Table 2, examples of electrochemical transducers that are often employed for measurements (i.e., potentiometric, impedimetric, and amperometric) are reported as well as instances of analytes that have been measured [24].

Table 2. Types of electrochemical transducers for various kinds of sensors along with the analytes they measure.

Measurement Category	Transducer	Transducer Analyte	Reference
Potentiometric	Ion-selective electrode (ISE), glass electrode, gas electrode, metal electrode	K ⁺ , Cl ⁻ , Ca ²⁺ , F ⁻ , H ⁺ , Na ⁺ , CO ₂ , NH ₃ redox species	[25]
Amperometric	Carbon electrode, chemically modified electrodes (CMEs)	O ₂ , sugars, alcohols, phenols, oligonucleotides	[26]
Conductometric	Interdigitated electrodes, metal electrode	Urea, charged species, oligonucleotides	[27]

3. Electrochemical Sensor Applications

Electrochemical sensors have long been desirable for the investigation of biological, environmental, industrial, and pharmacological species, not only for their long-term dependability, high sensitivity, and accuracy but also for their low cost, speed, and ease of downsizing. For more than two decades, numerous nanomaterials with extraordinary characteristics, such as metals, conductive polymers, metal oxides, and metal–organic and carbon-based nanomaterial frameworks, have been included in electrochemical assays to

promote analytical performance. This modification allows for increasing the loading capacity through the use of recognition molecules, such as enzymes, antibodies, and aptamers, as well as bioinspired receptors, which can capture targets specifically and effectively, thereby increasing the specificity of the electrochemical sensors. This is closely related to the aim of providing strong electrocatalytic activity for certain electrochemical processes. Additionally, by altering the surface shape and structure, it is possible to increase both the electrical conductivity and surface area, which should enhance the sensitivity of these tests. Electrochemical sensors have gained popularity recently owing to new applications such as single-molecule sensing, in vivo analysis, wearables, and point-of-care diagnostics [28].

Electrochemical sensors have a number of advantages, including their high sensitivity, which enables low LODs and LOQs; their rapid analytical response, which makes them ideal for flow analysis and alert systems; their simplicity, which allows for a virtually limitless variety of geometries, electrode materials, and configurations; their ease of use (simple and low-cost equipment, the ability to be integrated as a detection module in a variety of analytical systems).

Biosensors are interesting analytical instruments for environmental and biological investigations, because they have the following additional advantages:

- i. Quick data collection;
- ii. Detection of the important substrate is frequently accomplished without previous separation;
- iii. A sensitivity that can reach ng/mL;
- iv. Good selectivity and, occasionally, even specificity;
- v. A high benefit/cost ratio and easy usage [29–31].

Biosensors are composed of three major components:

- Biocomponents or systems of biological detection: Biocomponents include enzymes, antibodies, other similar binding molecules, DNA probes, live cells, and organelles;
- Transducers: Converts the signal generated by the analyte's interaction with the biocomponent into a quantifiable electrical signal;
- A signal processing system: It turns the measured signal into a form that is accessible and readable.

3.1. Biomolecule Electrochemical Detection

Biomolecules of a small size (e.g., hormones, nucleic acids, and enzymes) are detected based on their physiological and biological roles, which include transferring regulating biological activity, genetic information, and catalyzing cellular processes [32–34]. Nonetheless, creating biomolecule-sensing technology continues to be a difficult task [35]. Biomolecular methods, such as Western blot, polymerase chain reaction (PCR), and gel electrophoresis, have been developed for the analysis of biomolecules [36]. Despite their precision, they are limited by constraints such as large reagent needs, laboriousness, and long-time requirements [37].

Various studies on electrochemical approaches for identifying biomolecules as an early diagnostic tool have been published [38–40]. Mohan et al. [41] developed an integrated electrochemical biosensor that could detect biomarkers in urine. This may help improve the effectiveness of clinical disease management and indicates that pathogen identification in combination with quantitative detection of lactoferrin can provide important information for the diagnosis of urinary tract infections (Figure 2).

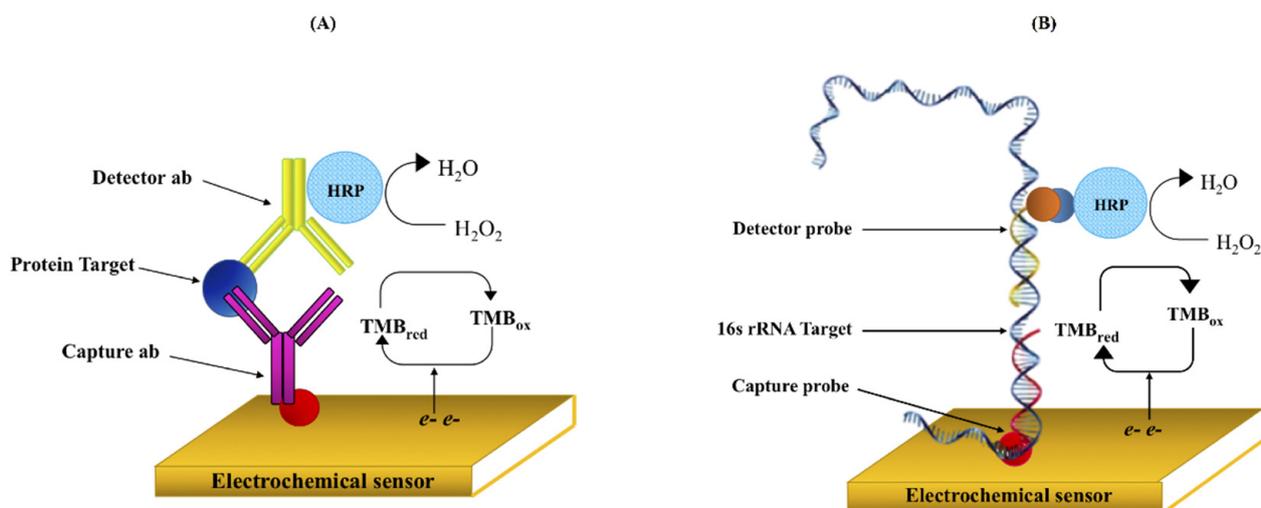


Figure 2. Urine-based diagnostics for the electrochemical biosensor detection of nucleic acids and proteins: (A) scheme for pathogen identification based on sandwich hybridization between bacterial 16S rRNA and capture and detector oligonucleotide probes; (B) sandwich detection using capture and detection antibodies. The schematic diagrams of the immunoassay based on host urinary proteins were adapted from Mohan, R.; Mach, K.E.; Bercovici, M.; Pan, Y.; Dhulipala, L.; Wong, P.K.; Liao, J.C. Clinical Validation of Integrated Nucleic Acid and Protein Detection on an Electrochemical Biosensor Array for Urinary Tract Infection Diagnosis. PLoS One 2011, Reference [41].

3.1.1. Electrochemical Biosensing for Viral Infections

Electrochemical biosensors are robust, easy to use, portable, and inexpensive analytical systems that can operate in turbid media and provide highly sensitive readouts [42]. DNA and RNA electrochemistry have been utilized to diagnose viral illnesses such as hepatitis E, coronavirus, HIV, influenza virus, bacterium, malaria, and Zika virus [43–47] (Figure 3).

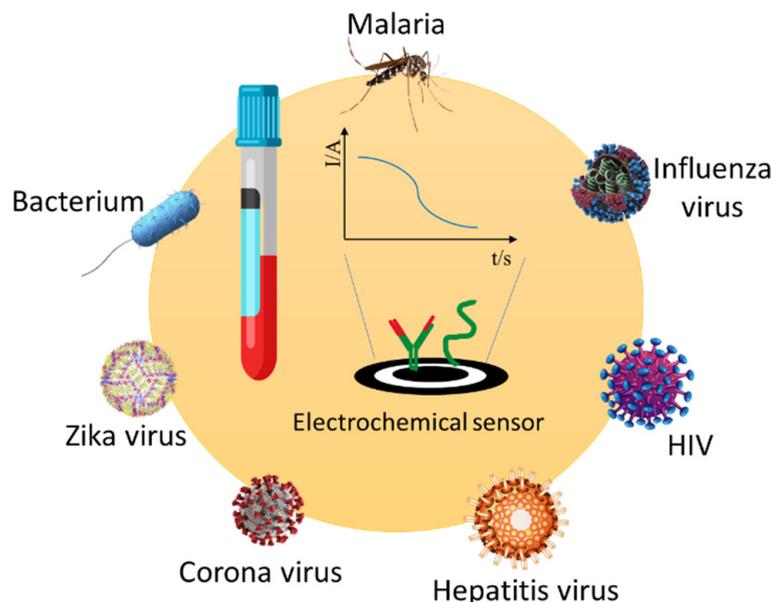


Figure 3. Schematic representation of the electrochemical sensor for the diagnosis of viral and tropical diseases.

Aptamers are short, single-stranded oligonucleotides (i.e., DNA or RNA) that range in size from 10 to 100 nucleotides. They are created using the SELEX method [48], which stands for the systematic evolution of ligands by exponential enrichment. By monitoring the change in the current response or electrical resistivities from the redox interaction

between the targets and the aptamers attached on the electrode surface of the sensor, the electrochemical aptasensor determines the concentration of the interested targets [49].

Another example is the use of electrochemical techniques for detecting enzymes and hormones to monitor for pregnancy-related disease and cancer [50,51]. In comparison to traditional procedures, such as Western blot and PCR, in terms of the time and cost, an electrochemical approach is a preferable option [52]. Nevertheless, its effectiveness is dependent on the conductivity characteristics of the sensing surface [53,54]. Electrochemical performance with complex samples necessitates preventing signal overlapping due to the fact of interference.

Table 3 summarizes the typical electrochemical-sensing technologies for nucleic acids, enzymes, and hormones [55].

Table 3. Electronic biosensor systems for the detection of biomolecules.

Target	Substrate	Immobilization Process	Detection Methods	Reference
DNA	Screen-printed electrode	Au nanoparticles/TFO probe/methylene blue/target DNA (ssDNA or dsDNA)	Cyclic voltammetry (CV)/square wave voltammetry (SWV)	[56]
DNA	Platinum electrode	MoS ₂ -polyaniline/ssDNA/methylene blue (MB)	CV/differential pulse voltammetry (DPV)	[57]
Thrombin	Glassy-carbon electrode	Graphene oxide/MNP-TBA1 (magnetic nanoparticle thrombin-binding aptamer)/HAP-TBA2 (hydroxyapatite-TBA2)	CV/SWV	[58]
Thrombin	Au electrode	Thiol-group/aptamer/tetra-ferrocene	DPV/electrochemical impedance spectroscopy (EIS)	[59]
MMP-2	Au electrode	Selenium/peptide/Na ₂ MoO ₄ /ssDNA	CV/EIS	[60]
MMP-9	Au electrode	L-cysteine/EDC/NHS/peptide/MB	CV	[61]
Estrogen (ER alpha)	Screen-printed electrode	5'-thiol-modified DNA aptamer/Tris-(2-carboxyethyl) phosphine hydrochloride	DPV	[62]
Estrogen (17-β Estradiol)	Au electrode	6-mercapto-1-hexanol (MCH)/aptamer-graphene	DPV/EIS	[63]
Human chorionic gonadotropin (hCG)	Glassy-carbon electrode	Carbon nano-onions (CNOs)/gold nanoparticles (AuNPs)/polyethylene glycol (PEG)	CV/SWV	[64]

3.1.2. Electrochemical Sensors: Recognition of the SARS-CoV-2 Virus

Coronavirus (COVID-19), a pandemic that has killed many people, is on the rise again, and has spread all over the world, causing many global health problems [65,66]. Though new ways of detecting COVID-19 are being worked on all the time, there is still a need for new ways to detect COVID-19 early and ensure its monitoring. RT-PCR tests have been widely used because they can be life-saving diagnostic tools. However, because of their multiple steps, time-consuming process, need for highly skilled people, and high costs, these tests may not be good for monitoring many different samples at the same time. Over the last few years, electrochemical-sensor-based techniques have been used to detect SARS-CoV-2. These methods are fast and cheap as well as sensitive and specific. Neither a serological or RT-PCR assay nor the electrochemical detection of SARS-CoV-2 by sensors/biosensors is the best way to identify COVID-19. However, these methods can be used together [67–69]. There is a lot of hope that electrochemical sensors and biosensors can help improve point-of-care tests for the deadly SARS-CoV-2 virus.

Yakoh et al. [70] developed an electrochemical paper-based analytical device (ePAD), which was used in the detection of SARS-CoV-2 immunoglobulins (i.e., IgG and IgM) and specifically targeted SARS-CoV-2 antibodies. Antibodies can interfere with the redox conversion of [Fe(CN)₆]^{3/4} or create immunocomplexes, hence, decreasing the current

response [71]. The sensing mechanism of the ePAD is due to the interruption of the redox conversion caused by the development of a complex between the captured immunoglobulins produced in response to COVID-19 infection in people and immobilized SARS-CoV-2 spiking protein. This procedure was examined for cross-reactivity [72] with anti-Epstein-Barr virus (anti-EBV), anti-hepatitis B surface antigen (anti-HBsAg), anti-hepatitis C virus (anti-HCV), anti-Rubella, and anti-cytomegalovirus (anti-CMV), but no cross-reactivity was observed [73].

3.2. Enzyme-Based Electrosensor Applications

Enzymes are organic catalytic molecules created by living organisms. They accelerate biological processes by decreasing activation energy, and they can accelerate the conversion of substrates to products in cellular metabolism by a factor of at least 10 million [74]. Enzyme-mediated substrate conversion is very specific. Numerous enzymes are selective for a single substrate, whereas another type of enzyme can affect multiple structurally similar substrates. In order to begin an enzyme-catalyzed reaction, the enzyme must form a complex with its substrate. Enzymes are unaltered by the processes they catalyze and are recyclable and effective in minute quantities. Equally, the enzyme catalyzes either the forward or reverse process [75].

Enzymatic activity monitoring is in great demand. For measuring enzymatic activity, many analytical techniques have been reported, e.g., mass spectrometry [76], spectrophotometry, Raman spectroscopy, and electrochemical techniques. Because of their ease of use, cheap cost, and speed, electrochemical procedures are favored over other analytical techniques [77], which may need sophisticated pretreatment, filtering, and a knowledgeable operator. Enzymatic sensors are created by immobilizing an enzyme on an electrode and then used to determine the concentration of the matching substrate. The primary distinction between enzyme-based biosensors is the immobilization technique and the mediator used [78].

In a recent study, the authors constructed an amperometric Glc biosensor with Gox immobilized on MWCNTs, as the biorecognition element, and RuO₂ acting as the mediator. To boost the sensor's stability, the enzyme was coated with a Nafion[®] membrane. The designed sensor was used to determine the concentrations of hydrogen peroxide and glycol. The developed sensor was employed as an electroanalytical technique for studying the inhibition of the enzyme's function, and the influence of the heavy metal cations (i.e., Cd²⁺, Hg²⁺, and Ag⁺) on the activity of the Gox enzyme was examined [78].

3.3. Ion-Selective Electrodes (ISEs): Application in Medicine

Clinical chemistry, namely, the determination of physiologically relevant electrolytes in physiological fluids, continues to be the predominant application sector for ISEs [79], with billions of regular ISE measurements conducted worldwide each year [80]. The International Federation of Clinical Chemistry (IFCC) has certified sensors for pH and ionized calcium, potassium, and sodium for use in commercially available clinical analyzers [81]. Additionally, magnesium, chloride, and lithium ions are commonly identified by matching ISEs in blood plasma, urine, and hemodialysis solutions [82], among other locations. Sensors for the characterization of physiologically significant polyions (i.e., heparin and protamine), phosphates [83], dissolved carbon dioxide, and other blood analytes have been extensively studied over the years and are on the verge of displacing less reliable and/or inconvenient analytical techniques for blood analysis. In comparison to conventional analytical techniques, ISEs respond to ion activity rather than the concentration, which makes them particularly interesting for clinical applications, because ion activity is typically connected with health issues. While the majority of ISEs are utilized *in vitro*, the ability to take measurements *in vivo* and continually use implanted sensors might prove a helpful diagnostic tool for physicians. Sensors must meet two strict requirements: first, they must cause the least amount of disruption to the *in vivo* environment, which can be problematic due to the injuries and inflammation frequently caused by implanted sensors, as well as

the leaching of sensing materials; second, they must be immune to the environment, with the effects of cell adhesion, protein adsorption, and extraction of lipophilic species on a sensor. Nonetheless, microfabricated sensor arrays have been used to successfully detect electrolytes in situ in rabbit muscles [84].

Pharmaceutical analysis is another area in which ISEs excel [85]. ISEs have been used to identify a wide variety of pharmaceuticals in pharmaceutical formulations and manufacturing processes. Drugs and their metabolites can be quantified in actual bodily fluids. Though ISEs are not frequently employed in pharmaceutical chemistry at the moment, they offer significant promise, as seen by the development of a number of ISE applications in recent years [86–89]. The majority of drug-selective electrodes are ion exchange based and take advantage of the frequently high lipophilicity of drugs and metabolites [90].

3.4. Biosensors' Distinct Characteristics in Health Services

Diabetes prevalence and diabetes patients' use of biosensors are significant contributors to worldwide business profitability. Rapid and preventive diabetes detection is becoming increasingly popular. Biosensor developments have made it possible to detect blood glucose in the presence of various intervening substances throughout a wide temperature range. Using ZnO nanorods to detect glucose is a low-cost, safe, accurate, rapid, and safe method [91]. The sensitivity and accuracy of biosensors within a minute sample volume are improving, and they are now widely employed in the diabetes domain, with significant market demand projected in the coming years. Portable electronic gadgets are an important part of the overall healthcare system because of their high capacity for monitoring, therapy, diagnosis, fitness, and well-being. They will increase preventative measures and obtain a better perspective of their well-being by combining therapeutic technologies accessible in hospitals and emergency care centers.

Technological advances and the increasing use of biosensors in a several number of applications are driving the market (Figure 4) [92]. People's lives have been enhanced by wearable biosensors [93,94].

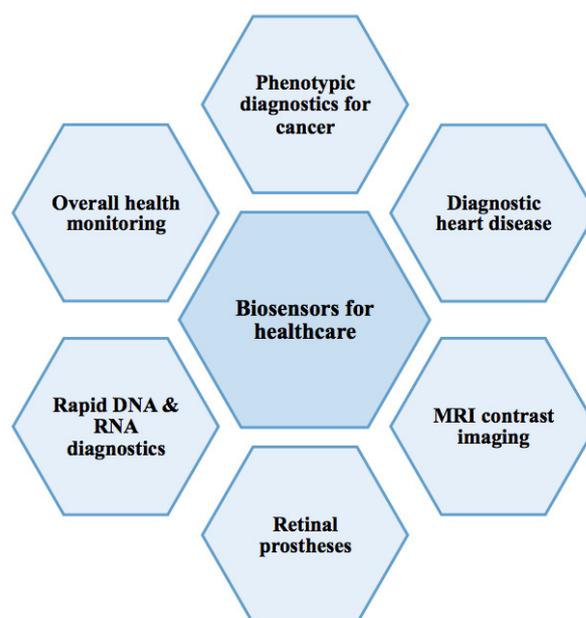


Figure 4. Biosensors' typical functions in healthcare services.

3.5. Electrochemical Sensors: Environmental Applications

Electroanalytical chemistry has the potential to be a game-changer in terms of environmental protection. Electrochemical sensors and detectors, in particular, are tempting for on-site monitoring of priority pollutants and other environmental requirements. Such technology may meet a lot of the needs for on-site environmental analysis. Such capabilities

have already tremendously aided decentralized clinical analysis (Figure 5). Electrochemical sensors for pollution management are still in the early phases of development, despite their tremendous potential for environmental monitoring [95].

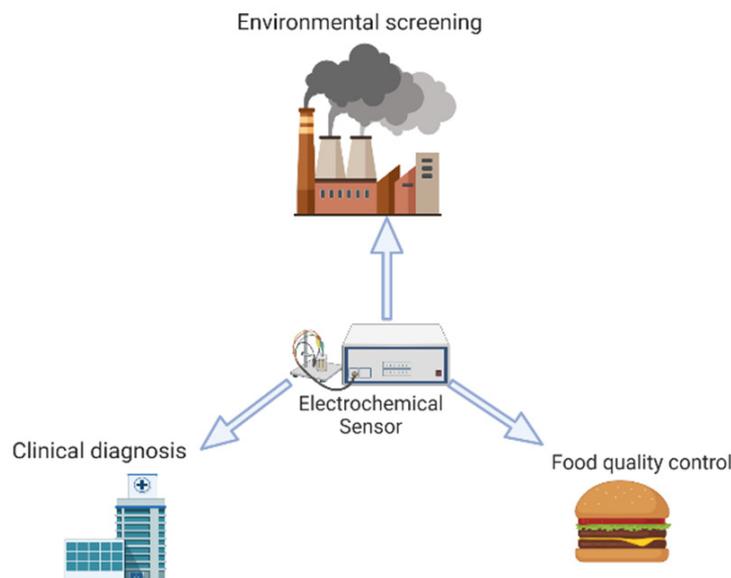


Figure 5. Schematic depiction of the application of electrochemical sensors.

The identification of inorganic ions, metal cations, organic chemicals, and biomolecules is possible using the trace electroanalytical method, known as electrochemical stripping analysis (ESA). It is based on a step where the target analyte(s) or a compound of the target is preconcentrated on an appropriate working electrode. The remaining accumulated analyte is then removed using an electroanalytical method [96]. Electrochemical stripping analysis has long been acknowledged as a highly effective method for determining trace metal concentrations [6,96–100]. Its extraordinary sensitivity is a result of the “built-in” accumulation process, which preconcentrates the target metals onto the working electrode. Electrochemical devices’ intrinsic miniaturization and low power needs meet a large number of criteria for on-site and in situ hazardous metals measurements. Due to the fact of its sensitivity to both low metal concentrations and the chemical form of metals in solution, stripping analysis is ideally suited for speciation research. Recent technological advancements have overcome past barriers to such field uses. As a result of these advancements, significant attention is currently being paid to decentralized electrochemical testing for trace metals. Additionally, nonelectrolytic (adsorptive) accumulation strategies have been devised to broaden the scope of stripping analysis to include trace metals that cannot be electrodeposited. Strip analysis is a two-step process. Typically, the first, or deposition phase, comprises the electrolytic deposition of a small number of metal ions in solution onto the mercury electrode to preconcentrate the metals. Following the preconcentration process, the stripping (measurement) step is performed, which entails the dissolving (stripping) of the deposit. Stripping analysis can be performed in a variety of ways, depending on the nature of the deposition and measuring stages [95]. In potentiometric sensors, the analytical data are obtained by converting the recognition process into a potential signal that is proportional (logarithmically) to the concentration (activity) of species created or consumed during the recognition event. Such devices rely on the use of ion-selective electrodes to obtain the potential signal [101]. In Table 4, examples of environmental analyses using electrochemical sensors and biosensors are listed.

Table 4. Environmental analyses using electrochemical sensors and biosensors.

Analyte	Recognition	Recognition Element	Detection Method	Reference
Uranium	Preconcentration	Nafion	Voltammetry	[102]
Peroxides	Biocatalysis	Peroxidase	Amperometry	[103,104]
Pesticides	Enzyme inhibition	Acetylcholinesterase choline oxidase	Amperometry	[103,104]
Hydrazines	Electrocatalysis	Ruthenium catalyst	Amperometry	[105]
Lead	Ion recognition	Macrocyclic ionophore	Potentiometry	[106]
Mercury	Preconcentration	Crown ether	Voltammetry	[107]
Nickel	Preconcentration	Dimethylglyoxime	Voltammetry	[108]
Cyanide	Enzyme inhibition	Tyrosinase	Amperometry	[109]
Nitrite	Preconcentration	Aliquat 336 ion exchanger	Voltammetry	[110]
Nitrosamines	Electrocatalysis	Ruthenium catalyst	Amperometry	[111]
Phenol	Biocatalysis	Tyrosinase	Amperometry	[112,113]
Sulfite	Biocatalysis	Sulfite oxidase	Amperometry	[114]
Benzene	Modulated-microbial activity	Whole-cell	Amperometry	[115]

3.6. Recent Uses of Carbon-Based Nanosensors in Pharmaceutical Analysis

Carbon-based nanosensors have seen a lot of use in pharmacological analysis in recent years as well as in real-world applications such as tablets and human serum. Cheemalapati et al. [116] used multiwalled carbon nanotubes on a glassy-carbon electrode to establish an electroanalytical measurement of anxiolytic buspirone hydrochloride. They employed MWCNTs were synthesized in dimethylformamide and had lengths of 0.1–10 μm . The linear range was determined using cyclic voltammetry, differential pulse voltammetry, and amperometry. Baytak and Aslanoglu [117] used a glassy-carbon electrode to make a nanosensor containing multiwalled carbon nanotubes and indium-tin oxide nanoparticles to determine the beta-adrenergic agonist metaproterenol. In pills and urine, the differential pulse voltammetric technique was used, which had a linear range of 1.2×10^{-8} M. Kutluay and Aslanoglu [118] employed MWCNTs functionalized with nickel nanoparticles to determine Bromhexine, a mucolytic medication.

3.7. Electrochemical Sensors: Design of Analytical Kits

Electrochemical techniques have been demonstrated to offer more benefits over other analytical methods due to the fact of their mobility and inexpensive cost. The majority of large firms have used this sort of analytical technology due to the fact of its rapid and selective analysis. Electroanalytical sensors are projected to be the next generation of analytical systems due to the fact of their ease of operation and great variety. As a result, several scientists and researchers have concentrated their efforts on developing and fabricating electroanalytical sensors with excellent selectivity and sensitivity for a variety of chemicals including pharmaceuticals, food, and environmental toxins. In a recent review paper, Karimi-Maleh et al. [119] discussed the mechanism and several applications of DNA, enzymatic, and electrocatalytic techniques for electroanalytical evaluation of medicinal, food, and environmental chemicals. In Table 5, a summary of the several types of electrochemical sensors and their applications in a variety of fields is presented. The interaction of DNA with analytes, particularly the intercalation reaction, is a highly helpful technique for determining anticancer medicines. Anticancer medicines deactivate the guanine and adenine bases and alter the oxidation base signals utilized for drug analysis. On the other hand, due to the selective interaction between the enzyme and the analyte, enzymatic biosensors may be utilized as selective analytical instruments.

Table 5. Electrochemical sensor types and its relevance in diverse disciplines.

Class of Sensor	Electrode(s) Type	Application	Industry	Reference
Novel Cell-Based	Tungsten Disulfide Nanosheets/Hydroxylated Carbon Nanotube Nanocomposites	Environmental Toxicity Monitoring	Environment	[120]
Molecular Imprinted	Multiwalled Carbon Nanotubes	Determination of Trace Enrofloxacin in Marine Environment Samples	Environment	[121]
CeO ₂ Nanostructured	Graphite Sensors Modified by Cerium Oxide Nanoparticles (Cpe-CeO ₂ Nps)	Detecting Diethylstilbestrol (DES) and 17β-Estradiol (E2) in Environmental Samples	Environment	[122]
Nonenzymatic	Zinc/Zinc Oxide Core–Shell Nanostructures	Determination of Hydroquinone	Medical	[123]
Novel Sandwich-Type Biosensor	Magnetic Covalent Organic Framework/Pillararene Heterosupramolecular Nanocomposites	Human Norovirus (HuNOV) Detection	Medical	[124]
Disposable	PtNi Alloy Nanoparticles	Monitoring of H ₂ S Released by Human Breast Cancer Cells	Medical	[125]
RT-LAMP	Screen-Printed Electrodes	Detect N and Orf1Ab Genes of the SARS-CoV-2 Genome	Medical	[126]
Dual Functional	Macroscopic Polyaniline (PANI)	Detection of pH and Lactate in Sweat of the Human Body	Medical	[127]
Molecularly Imprinted Polymer (Mip)-Based	Nano Gold-Doped Poly O-Phenylenediamine (Poly-O-Pd) Film	Rapid and Ultrasensitive Cortisol Detection	Medical	[128]
Implantable Tri-Anchored Methylene Blue-Based pH	Chip-Based Ag/AgCl Reference Electrode	Real-Time Intratumoral Tissue pH Detection	Medical	[129]
Capsaicin	Bimetallic Metal–Organic Framework Nanocage	Rapid Detection of Capsaicin	Food	[130]
Ultrasensitive	Glassy-Carbon Electrode (GCE)	Determination of Rutin Antioxidants in Mandarin and Kiwi Samples	Food	[131]
Amplified	Graphene Oxide (RGO) Paper Electrode Composed of Silver Nanoparticles	Detection of Sudan I in Chili Powder	Food	[132]
Laser-Enabled Flexible	Flexible Graphene Electrodes (FGEs)	Fast Food Security Detection (Real-Time On-Site Identification of Chloramphenicol, Clenbuterol, and Ractopamine in Meat)	Food	[133]

4. Role of Nanomaterials in Electrochemical Sensors

Over the past years, nanotechnology has gained a lot of traction in the sensor industry. It is considered that the employment of such technologies, as well as the usage of nano-sized materials, has a positive impact on sensor performance. Nanomaterials have been discovered to offer a variety of unique and intriguing physical and chemical characteristics [131,134]. In recent decades, low-dimensional nanometer-sized materials and systems have established a new field of study in condensed-matter physics. In addition to the aforementioned categories of materials, there are a variety of materials of various sorts that may be used to create nanosensors. Carbon is known as a one-of-a-kind element because of its numerous uses. Carbon is a fascinating element that exists in a variety of forms including graphite, diamond, fullerenes, and graphene. Some of the most significant and recent advances, made possible by the use of carbon-based nanostructures in nanotechnology for chemical and biological sensor creation as well as their use in the pharmaceutical and biomedical fields, have been reviewed in previous studies [135–139].

Recent advances in nanomaterials' unique physicochemical features have been extremely successful in improving biosensors, and the potential for enhancing desirable molecular interaction has boosted the diagnostic sensitivity of these biosensors [140,141].

In the majority of reported biosensors, nanocomposites are used to increase the sensitivity, selectivity, and repeatability. Nanocomposites are solid materials composed of numerous phase domains with nanoscale features in at least one of them. The distinct and intriguing features of nanocomposites have attracted interest in recent years. Nanocomposites have several benefits in the manufacturing of sensors including a high surface-to-volume ratio, reactive capacity, biocompatibility, and high adsorption [142,143]. Nanocomposites are accountable for electrochemical reaction catalysis, biomolecule immobilization, biomolecule labeling, and electron transfer rate increase [144,145]. Conducting polymers, nanofibers, graphene, carbon nanotubes (CNTs), metal–organic frameworks (MOFs) [146], and nanoparticles (Nps) [147] are the most common nanocomposites [148] utilized to change the electrode surface [149–151]. Due to the fact of their evenly distributed metal centers, MOFs can be used as electrocatalysts for CO₂ reduction reactions (CO₂RR) [152].

Figure 6 shows the principle of an electrochemical sensor based on carbon nanomaterials for detecting biomarkers of metabolic diseases [153].

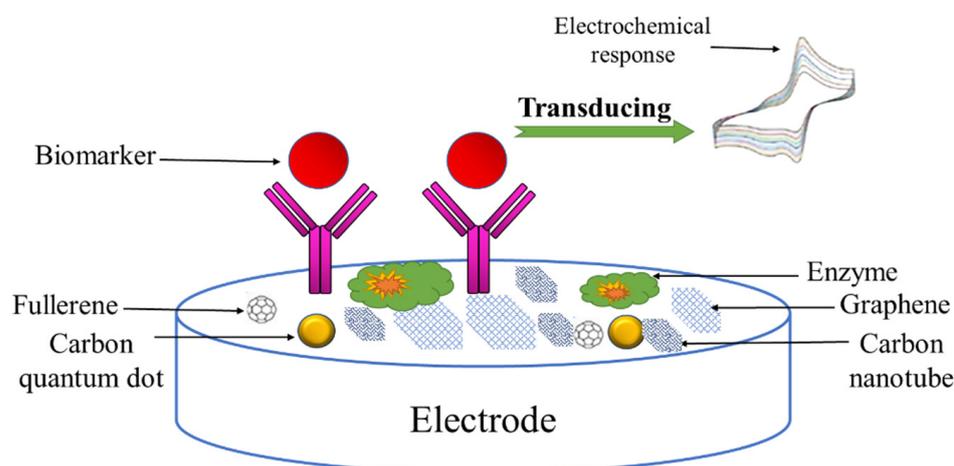


Figure 6. Schematic diagram of an electrochemical biosensor based on nanomaterials.

4.1. Carbon Nanotubes

Due to the fact of their tiny size and favorable electrochemical characteristics, carbon nanotubes have sparked great interest in electrochemistry. The great majority of research to date has employed carbon nanotube ensembles on nanostructure macroscopic electrodes, either randomly distributed nanotubes or aligned carbon nanotubes [154]. Carbon nanotubes (CNTs) are allotropes of elongated fullerenes with a modest average diameter of 100 nm. Due to the large surface area (l/d ratio), a superb platform for the efficient transport of active chemical, biological, or biochemical components is accessible. Carbon nanotubes are classified primarily according to their shape and size, as carbon nanotubes are classified primarily according to their shape and size as single-walled carbon nanotubes (SWCNTs) or multiwalled carbon nanotubes (MWCNTs). Carbon nanotube-based sensors for the detection of paracetamol and hesperidin have been developed [155–157]. The variable surface morphology of carbon materials permits a variety of surface functionalities for the development of highly efficient electrochemical sensors with long-term stability [158]. The conductivity of the tubes is critical for their involvement in electrochemistry as a result of their electrical characteristics. MWNTs are considered to be metallic conductors, which is an extremely desirable feature for an electrode.

4.2. Graphene in Sensors

Dresselhaus et al. [159] established graphene as the most commonly utilized nanomaterial for a range of applications [160–165]. The enormous specific area of graphene

encourages high quantities of biomolecules to be loaded onto [166] the detecting base, resulting in high detection sensitivity. Electrons may easily pass between the graphene surface and biomolecules due to the fact of its tiny bandgap and good conductivity. Highly pure graphene, with no contaminants, and its derivative materials are harmless in character and cost effective due to the fact of their superb uniform surfaces.

Graphene's large sensing surface area increases the loading of specific chemical species, such as proteins and enzymes, either by passive adsorption or chemical cross-linking to the analyte's active groups [167]. The conductivity of graphene varies depending on the production or treatment method used. The electrical conductivity of graphene is 60 times that of SWCNTs, with particulate graphene having a reported electroconductivity of 64 mS/cm [168] compared to graphene's 108 mS/cm [169]. The graphene family is being utilized to create and enhance electrocatalysis for increasing biomolecule loading and increasing the surface area.

4.3. Electrosensing Using Gold Nanoparticles

In electrosensing, gold nanoparticles are commonly utilized. The current tendency is to use "green" chemistry to photosynthesize gold nanoparticles (Phyto-AuNPs). Because Phyto-AuNPs are physiologically and catalytically stable, active, and biocompatible, they have a wide range of uses, including tactile and wearable (bio)sensors [170]. Because of their unique visual, physical, and electrochemical features, gold nanoparticles stand out [171]. To produce gold nanoparticles, a range of physical and chemical processes are utilized. Chemical synthesis, in comparison to physical synthesis, is extremely straightforward, labor saving, and economical. Chemicals and solvents, as well as reaction byproducts, can, nevertheless, be harmful to both people and the environment [172,173]. Recently, alternative techniques for nanoparticle production have evolved, which are based on a "green" chemical approach. The term "green" refers to reducing the use of hazardous chemicals and increasing the use of organic materials such as plants, for instance, the use of plant extracts (phytosynthesis) as reducing, stabilizing, and capping agents. The "green" approach is an efficient and environmentally beneficial way of creating gold nanoparticles [174]. The primary advantages of phytosynthesis include simplicity, environmental safety, a high synthesis rate, an absence of extra reagents, and the possibility of large-scale nanoparticle production [174–176].

The unique properties of phytosynthesized gold nanoparticles (Phyto-AuNPs) include their high catalytic activity in the degradation of organic dyes [172,177] and their anticancer [178], antioxidant [179], and antibacterial activity [180] as well as their biocompatibility and low cytotoxicity [175]. These properties make Phyto-AuNPs extremely attractive for biomedical applications such as diagnostic studies, theranostics, cell imaging, and protein as well as drug and photodynamic therapy and gene delivery [175,181].

Glassy-carbon electrodes are often used in sensors, and adding gold nanoparticles to glassy-carbon electrodes makes them more stable and sensitive electrochemically. Using a layer-by-layer method, gold nanoparticles and methylene blue were combined to create laminated films on a glassy-carbon electrode that could detect human chorionic gonadotropin (HCG). Due to the large area of the nanoparticles that can be used to load anti-HCG, this immunosensor could be used to measure the amount of HCG in blood or urine samples. Jena et al. [182] came up with the idea of using gold nanoparticles to make a sensor that can measure the amount of polyionic drugs such as protamine and heparin.

Nanosensors have advanced rapidly in recent decades, and they now play an increasingly important role in pharmaceutical and therapeutic applications where measurements in technology and science are critical. In recent years, the use of nanomaterials in the design of electrochemical nanosensors has piqued attention. Because of the improved chemical and physical characteristics resulting from discrete nanoelectrode devices or alterations of the surface of electrodes with nanomaterials, these devices offer an appealing choice for improving the present electroanalytical techniques in the pharmaceutical field [183–188].

5. Future Aspects

Research on electrochemical sensors is a promising area. It must be acknowledged that selection continues to be at the center of most of the problems in this area. However, electrochemical sensors' quick analytical speed and capacity to detect exceedingly minute amounts without significantly damaging the sample remain highly desirable characteristics when direct detection in undamaged samples is attainable [175].

In the future, biosensor approaches may lead to the creation of a cell-friendly analyte for precision medical diagnostics and point-of-care testing. The development of electrochemical sensors has significantly advanced biological research. Sensitivity, selectivity, and processing speed are further benefits, all of which will help future industries. As a result, rapid, nondestructive, and adjustable electrochemical sensors may be used in sophisticated big systems for disease detection and quality standards of stem-cell-based products.

Recent advances in this sector include the use of arrays to monitor a broad variety of inorganic and organic contaminants as well as the development of various biological recognition materials, microelectronic industrial advancements, and micro- and disposable sensors. Additionally, flow-injection systems and online systems have been designed for monitoring a variety of contaminants. Recent advancements in the field of nanomaterials have also enhanced sensors' features. Using sensor arrays to build multianalyte detection systems might be useful not only for pollution management but also for therapeutic and diagnostic monitoring.

6. Conclusions

This review summarizes the latest advancements in electrochemical sensors designed to identify minute biomolecules (DNA, enzymes, hormones, etc.) and to keep track of a variety of inorganic and organic pollutants updated electrochemically. The introduction of new sensors made from various chemical or biological sensing materials is ongoing. Furthermore, the development of incredibly small, reproducible, and affordable (disposable) sensor devices is made possible by mass production technology, which is ideal for the microelectronics industry. These devices are combined with lightweight, user-friendly microprocessor-based instrumentation. Other breakthroughs in selective and stable identification elements, such as "smart" sensors and remote electrodes, molecular devices, multiparameter sensor arrays or micromachining, and nanotechnology, will undoubtedly have a significant influence on pollution management. Electrochemical sensors are a further development in biological research. In addition, there are advantages in the future industry in terms of sensitivity, selectivity, and processing time. Electrochemical methods are fast, accurate, and nondestructive tools for analyzing a wide range of targeted targets. Functional peptides, aptamers, and nanomaterials (for example, carbon nanotubes, graphene, graphene derivatives, metal nanoparticles, and gold nanoparticles) have been used to increase sensitivity. The interaction of the target with a particular probe or composite produces a detectable read signal during the electrochemical measurement.

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