Review

Electrochemical Sensors Based on Organic Conjugated Polymers

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Abstract: Organic conjugated polymers (conducting polymers) have emerged as potential candidates for electrochemical sensors. Due to their straightforward preparation methods, unique properties, and stability in air, conducting polymers have been applied to energy storage, electrochemical devices, memory devices, chemical sensors, and electrocatalysts. Conducting polymers are also known to be compatible with biological molecules in a neutral aqueous solution. Thus, these are extensively used in the fabrication of accurate, fast, and inexpensive devices, such as biosensors and chemical sensors in the medical diagnostic laboratories. Conducting polymer-based electrochemical sensors and biosensors play an important role in the improvement of public health and environment because rapid detection, high sensitivity, small size, and specificity are achievable for environmental monitoring and clinical diagnostics. In this review, we summarized the recent advances in conducting polymer-based electrochemical sensors, which covers chemical sensors (potentiometric, voltammetric, amperometric) and biosensors (enzyme based biosensors, immunosensors, DNA sensors).

1. Introduction
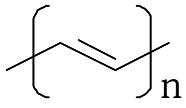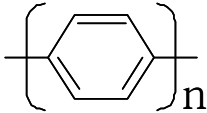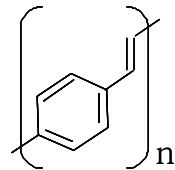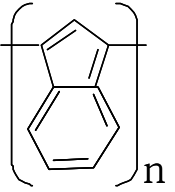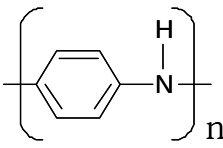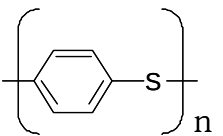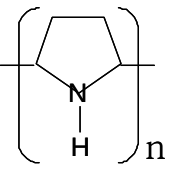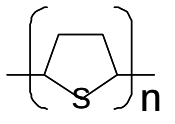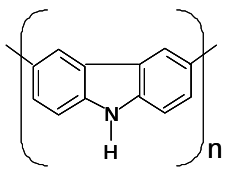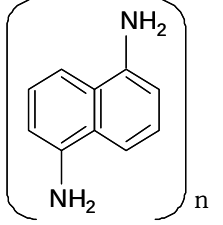
Organic conjugated polymer (conducting polymers) [1-3] are mainly organic compounds that have an extended π-orbital system, through which electrons can move from one end of the polymer to the other. The conducting polymers are known to have considerable flexibility in chemical structures that can be modified. By chemical modeling and synthesis, it is possible to modulate the required electronic and mechanical properties of conducting polymers. Common classes [3] of organic conductive polymers include poly(acetylene)s, poly(pyrrole)s, poly(thiophene)s, poly(terthiophene)s, poly(aniline)s, poly(fluorine)s, poly(3-alkylthiophene)s, polytetrathiafulvalenes, polynapthalenes, poly(p-phenylene sulfide), poly(para-phenylene vinylene)s etc.. Diverse applications of these conducting polymers have been studied [3]. Of many desirable properties for the application of these conducting polymers in various practical devices, polymer stability is one of the most important criteria. The growths and stabilities of poly(aniline)s [4, 5], poly(pyrrole)s [6, 7], and poly(azulene)s [8] have been studied. Poly(thiophene)s possess excellent thermal and environmental stability, solubility, processibility, and high conductivity when doped, which makes it an important class of conducting polymers [9,10]. Table 1 shows the chemical structures of common conducting polymers and their respective conductivity. Except these common conducting polymers, some analogous conducting polymers have also been reported [1-3]. Conducting polymers can be reversibly doped and undoped using electrochemical techniques accompanied by significant changes in conductivity [11]. The electrical conductivity of conducting polymers changes over several orders of magnitude in response to change in pH, applied potentials, or their environments [12]. Grafting of organometallics to the backbone of the conducting polymer can also tune their physical properties [13-16].

Many types of analytical applications of the conducting polymers have been reported since their discovery. These compounds have useful applications in the development of chemical sensors. During the last two decades, conducting polymers have emerged as one of the most interesting materials for the fabrication of electrochemical sensors [2]. The great advantage of conducting polymer based sensors over other available techniques is that the conducting polymers have the potential to exhibit improved response properties and are sensitive to small perturbations. Earlier inert polymers were being used only to provide mechanical strength to the membranes but conductive polymers improve the sensitivity of the sensors due to their electrical conductivity or charge transport properties.

Conducting polymers are also known for their ability to be compatible with biological molecules in neutral aqueous solutions [17]. Moreover, the polymer itself can be modified to bind biomolecules to a biosensor [18]. Another advantage of conducting polymers is that the electrochemical synthesis allows direct deposition of a polymer film on the electrode substrate followed by biomolecules immobilization [19]. It is thus possible to control the spatial distribution of the immobilized enzymes, the film thickness, and modulation of enzyme activity. Conducting polymers can act as an electron promoter. Moreover, conducting polymers can be deposited over defined areas of electrodes. The unique properties of conducting polymers have been exploited for the fabrication of electrochemical sensors and biosensors [2-3].
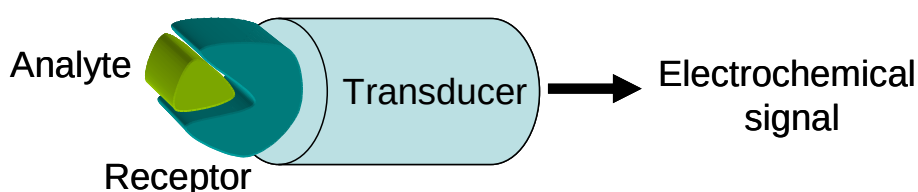
Amongst many analytical techniques available, the development of chemical sensors has made significant strides in the last two decades. The rapidly growing applications of chemical sensors reflect

Table 1. Names, structures, and conductivities of some common conducting polymers.

Conducting Polymer	Structure	Conductivity (S/cm)
Polyacetylene		1000
Polyparaphenylene		100 – 500
Polyparaphenylene vinylene		3
Polyazulene		0.1
Polyaniline		1 – 100
Polyparaphenylene sulfide		1 – 100
Polypyrrole		40 – 100
Polythiophene		10 – 100
Polycarbazole		10 – 100
Polydiaminonaphthalene		10^{-3}

the extent to which analytical chemists require these devices for cheap, accurate, convenient and quick analysis of various samples. Chemical sensors are miniaturized analytical devices, which can deliver real-time and on-line information about the presence of specific compounds or ions in complex samples. Usually an analyte recognition process takes place followed by the conversion of chemical information into an electrical or optical signal (Figure 1). It converts the activity of a specific ion in a solution into an electrical potential [20].

Figure 1. Schematic presentation of an electrochemical sensor.

A number of instrumental techniques such as UV-visible and infrared spectrophotometry, atomic absorption spectrophotometry, flame photometry, fluorometry, mass spectrometry and chromatography etc. are available at the disposal of analytical chemists. Generally these methods provide reproducible results with high sensitivity and good selectivity. However, all these analytical techniques require sophisticated instruments and chemical manipulation of sample before measurement which may be time consuming and inconvenient. The chemical sensors have no such requirements. These provide accurate, reproducible, fast and often selective determination of various chemical species. Not only this, the technique could be non-destructive, adaptable to small sample volumes and to on-line monitoring due to these merits. The utility of chemical sensors is being increasingly realized in medicinal, environmental, agricultural, and industrial fields.

2. Electrochemical Sensors

2.1. Classification of electrochemical techniques

Generally electrochemical methods are based on the transformation of chemical information into an analytically useful signal. Any sensor used in electroanalytical determination contains two basic functional units; one receptor part, which transforms the chemical information into a form of energy and one transducer part which transforms the energy, bearing chemical information, into a useful signal. A broad range of electrochemical techniques can be used for this purpose. Some of the most commonly used, are described below:

Voltammetry: Voltammetry refers to the measurement of current resulting from the application of potential. It utilizes three or two electrode electrochemical cell systems. The use of the three electrodes (working, auxiliary, and reference) along with the potentiostat allows accurate application of potential

functions and the measurement of the resultant current. The electrode potential is ramped linearly to a more negative potential, and is then ramped in reverse back to the starting voltage. The forward scan produces a current peak for any analytes that can be reduced through the range of the potential scan. The current will increase as the potential reaches the reduction potential of the analyte, but then declines as the concentration of the analyte is depleted close to the electrode surface. As the applied potential is reversed, it will reach a potential that will re-oxidize the product formed in the first reduction reaction, and produce a current of reverse polarity from the forward scan. This oxidation peak will usually have a similar shape to the reduction peak. The potential difference between the reduction and oxidation peaks is theoretically 59 mV for a reversible reaction. In practice, the difference is typically 70-100 mV. Larger differences, or nonsymmetric reduction and oxidation peaks are an indication of a nonreversible reaction.

Amperometry: Basically in amperometry, a uniform potential is applied and the change in current is monitored as a function of time. The determination of the concentration of a material in a sample is carried out by measuring the current passing through a cell containing the solution. During amperometric assays the potential of the indicator electrode is adjusted to a value on the plateau of the voltammetric wave. The current that flows between the indicator electrode and a second electrode in the solution is measured and related to the concentration of the analyte.

Potentiometry: Potentiometry is based on the measurement of a potential under no current flow. The measured potential may then be used to determine the analytical concentration of some components of the analyte gas or solution. The signal is measured as the potential difference between the indicator electrode (ion-selective electrode, redox electrode, metal-metal oxide electrode) and the reference electrode. The potential that develops in the electrochemical cell is the result of the free energy change that would occur if the chemical phenomena were to proceed until the equilibrium condition has been satisfied. This concept is typically introduced in quantitative analysis courses in relation to electrochemical cells. For these electrochemical cells, the potential difference between the cathodic potential and the anodic potential is the potential of the electrochemical cell which can be calculated by using the Nernst equation. Physical phenomena which do not involve explicit redox reactions, however whose initial conditions have a non-zero free energy, also will generate a potential. An example of this would be ion concentration gradients across a semi-permeable membrane. This can also be potentiometric phenomena, and is the basis of measurements that use ion-selective electrodes. The following equation is generally used to determine the concentration of the analyte in test solutions: E_{mem}= Constant – RT/z_i F ln a_i, where z_i and a_i are the charge and the activity of the ion of interest respectively.

Impedometry: The approach is to perturb the cell with an alternating potential in small magnitude and to observe the way in which the system follows the perturbation at steady state. Many advantages attribute to these techniques. The most important includes a) an experimental ability to make sensitive measurements because the response may be indefinitely steady and can therefore be averaged over a long term, b) an ability to treat the response theoretically by linearized current-potential characteristics and c) measurement over a wide time or frequency range (10^4 to 10^{-6} s or 10^{-4} to 10^6 Hz). Since this usually works close to equilibrium, one often does not require detailed knowledge about the behavior

of the current-potential curve over great ranges of over potential. This advantage leads to important simplifications in treating kinetics and diffusion.

Conductometry: The capability of the analyte to conduct an electrical current is monitored. From Ohm's law (E = IR) it is apparent that the electric current (I) is inversely proportional to the resistance (R), where E represents potential difference. The inverse of the resistance is the conductance (G = 1/R). In conductometry, the electrical conductivity of a sample is used to determine the components and their concentration. However, conductivity measurements are difficult due to the variable ionic background of the samples and relatively small conductivity changes that are observed in such high ionic strength solutions.

2.2. Conducting polymer-based electrochemical sensors

A humidity sensor using chemically synthesized poly (1,5-diaminonaphthalene) doped with carbon has been reported by Shim et al. [21]. It is very useful to design miniaturized devices. They have also reported a terthiophene carboxylic acid polymer film based sensor modified with a copper complex of 1,5-diaminonaphthalene for the estimation of oxygen content of an aqueous solution [22]. Ivaska et al [23] have reported a Ca^{2+}-selective polyaniline based membrane consisting polyaniline, bis[4-(1,1,3,3-tetramethylbutyl)phenyl]phosphoric acid, and dioctyl phenylphosphonate. A polypyrrole based potassium microsensor containing polypyrrole in plasticized polyvinyl chloride membranes, has also been reported by Zachara et al. [24]. A ternary hybrid system glass/polypyrrole/Pt has been reported by Berthold et al [25]. They have used it as solid inner contact for an all-solid-state pH glass electrode. Polypyrrole with chloride or nitrate doping was coated chemically onto pH-sensitive silicate glasses with high lithium content. The sensor showed favourable properties for pH sensor applications. Electropolymerized poly(1-aminoanthracene) films on platinum electrodes have been tested as a pH sensor by Bulhose et al. [26]. The electrodes showed a wide Nernstian response in the 1–12 pH range. Potentiometric Ag^+ sensors have been prepared by galvanostatic electropolymerization of 3,4-ethylenedioxythiophene on glassy carbon electrodes [27]. All-solid-state potassium-selective electrodes with plasticizer-free membranes have been fabricated by incorporation of valinomycin as the ionophore and potassium tetrakis [3,5-bis(trifluoromethyl)phenyl] borate as the lipophilic additive in a semiconducting conjugated polymer matrix of poly(3-octylthiophene) [28]. A thiophene derivative, (4-benzeno-15-crown-5 ether)-thiophene-3-methylene-amine monomers on Au(III) surfaces has been reported to promote ordered polymerization to form polymer nanoparticles or clusters by which the size of the polymer nanoparticles could be controlled electrochemically. The resulting sensor exhibited the selective response towards potassium ion with a detection limit of 4×10^{-5} M [29], which showed a little low detection limit. Electropolymerization of polypyrrole in the presence of Eriochrome Blue-Black B as the counter anion has been reported to generate selective recognition for silver ions in the concentration range of 1×10^{-8} to 1×10^{-1} M Ag^+, with a detection limit of 6×10^{-9} M [30]. Electrochemical properties of poly (3,4-ethylenedioxythiophene) doped with hexacyanoferrate (II, III) ions have been studied in the presence of Cu^{2+} ions. Binding of Cu^{2+} ions in the conducting polymer layer results in analyte ions flux into the transducer phase and a lower detection limit of 10^{-7} M Cu^{2+} was achieved [31]. Temsamani et al [32] have developed a mercury ion sensor by electropolymerization of 3-methylthiophene on the surface of a bare sonogel–carbon

electrode. This electrode shows a detection limit of 1.4×10^{-3} mg l^{-1} Hg(II). Shim et al [33] have reported a electrochemically polymerized 3'-(4-formyl-3-hydroxy-1-phenyl)-5,2':5',2"- terthiophene film on a Pt electrode which shows selective response towards Al(III) ions in the concncentration range of 5.0×10^{-8} - 7.0×10^{-10} M, and the detection limit was 5.0×10^{-10} M and 3.0×10^{-11} M using the linear sweep voltammetry and differential pulse voltammetry, respectively. Polyaminopyridines have also been used for the selective determination of Ag$^+$ was also reported by the same group [34]. A sensitive electrochemical method for simultaneous determination of Pb (II), Cu (II), and Hg (II) ions using electropolymerized 3',4'-diamino-2,2';5',2"-terthiophene on a glassy carbon electrode, followed by the reaction with ethylenediaminetetraacetic acid (EDTA) has also been reported by Shim et al. [35]. The detection limits are approximately 6.0×10^{-10}, 2.0×10^{-10}, and 5.0×10^{-10} M, for Pb (II), Cu (II), and Hg (II) ions, respectively. They have also reported an EDTA-bonded conducting polymer 3',4'-diamino-2,2';5',2''-terthiophene modified electrode exhibiting the selective electrochemical response towards various trace metal ions namely, Cu(II), Hg(II), Pb(II), Co(II), Ni(II), Fe(II), Cd(II), and Zn(II) at the different pHs using square wave voltammetry from 0.1 M to 10.0 M for Co(II), Ni(II), Cd(II), Fe(II), and Zn(II) and 5.0×10^{-10} M to 2.0×10^{-8} M for Cu(II), Hg(II), and Pb(II) after 10 min of preconcentration [36]. The detection limits are 1.0×10^{-10} M, 3.0×10^{-10} M, 4.0×10^{-10} M, 5.0×10^{-8} M, 6.0×10^{-8} M, 6.5×10^{-8} M, 8.0×10^{-8} M, and 9.0×10^{-8} M for Cu(II), Hg(II), Pb(II), Co(II), Ni(II), Cd(II), Fe(II), and Zn(II), respectively. An all-solid-state hydrogen-ion-selective electrode has been fabricated by the same research group using the polymer hybrid membrane composed of Tecoflex polyurethane, polyvinyl chloride, and silicon rubber, which were casted on a carbon rod [37]. This sensor exhibited a long lifetime and high sensitivity for the H$^+$ ion. Poly (1,8-diaminonaphthalene)-modified electrode has been developed for the determination of the Se(IV) ion in an aqueous medium and investigated with anodic stripping voltammetry without pre-treating the sample and by using cyclic voltammetry [38]. The detection limit employing the anodic stripping differential pulse voltammetry was 9.0×10^{-9} M for Se (IV). An all-solid-state calcium-selective electrode has been constructed with poly(pyrrole) solid-contact doped with calcium complexing ligand Tiron [39]. The good potentiometric response of this sensor was linear in the concentration range between 10^{-4} to 10^{-9} M with a slope close to Nernstian and detection limit equal to $10^{-9.6}$ M. Polypyrrole derivatized at the 3-position with dimethoxybenzyl and dihydroxybenzyl functionalities has been used to develop a pH sensor [40]. Anodic coupling of 5,5'-bis(3,4-(ethylenedioxy)thien-2-yl)-2,2'-bipyridine has been reported to produce a polymer film that able to coordinate protons and divalent transition metal ions (Fe^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+}) with corresponding spectral and redox changes [41]. Dordick et al have reported a sensor array for Fe^{3+}, Cu^{2+}, Co^{2+}, and Ni^{2+} consisting of 15 phenolic homopolymers and copolymers generated from phenolic monomers by peroxidase-catalyzed oxidative polymerization [42]. This work is interesting because the different metal ions have different binding capabilities with heteropolymers. Therefore, this property can be utilized to prepare a wide variety of sensors with commercially available phenols. Potentiometric Ag$^+$ sensors have been prepared by galvanostatic electropolymerization of 3,4-ethylenedioxythiophene and pyrrole on glassy carbon electrodes by using sulfonated calixarenes as doping ions [43].

Fabregas et al. [44] have reported a nitrate ion selective electrode by using sulfonated poly(ether ether ketone), an ion conducting polymer, as a polymeric matrix. Poly(3,4-ethylenedioxythiophene)

doped with chloride electrodeposited on the glassy carbon substrate resulted in a chloride selective sensor exhibiting lower hysteresis in the calibration plot [45]. Although this sensor exhibited a narrow working concentration range but it showed a higher selectivity over the commercially available electrodes. A nano-particle comprised poly-5,2′:5′,2″-terthiophene-3′-carboxylic acid (nano-conducting polymer) layers on a glassy carbon electrode has showed good response for phosphate ion determination with a detection limit of 3.0×10^{-7} M [46]. Electrochemically coated films of overoxidized polypyrrole directed single-walled carbon nanotubes onto glassy carbon electrode have been reported, which exhibited excellent electrocatalytic properties for nitrite, ascorbic acid, dopamine, and uric acid [47]. A perchlorate ion (ClO_4^-) sensor based on doped poly(3,4-ethylenedioxythiophene) films has been reported by Harmon et al [48]. This conducting polymer is extreamly stable in oxidized state and also the prepared sensor could exhibit a longer life time of more than 8 months, which is higher than the analogous sensors. Platinum electrodes modified with a cellulose acetate membrane or with poly(1,8-diaminonaphthalene) film have been used for the rapid amperometric detection of nitrite and nitrate ions in water [49]. This is a reagentless method. Although it has a short life time of less than 12 weeks but it is almost free from interferences. A potentiometric sensor for sulfide ion based on electrochemically deposited film of poly(3-methylthiophene) and poly(dibenzo-18-crown-6) onto an alloy substrate has been reported by Bishop et al [50]. An NO sensor based on a carbon fiber microelectrode modified by a poly(N-methylpyrrole) incorporating $[(H_2O)Fe^{III}PW_{11}O_{39}]^{4-}$ sublayer and coated by a Nafion external layer has been reported [51]. This sensor was based on the NO oxidation and differential normal pulse voltammetry was employed for the quantification of NO. It had a sensitivity of 2.65 ± 0.15 nAμM^{-1}. All-solid-state chloride-selective electrodes with plasticizer-free membranes have been prepared by incorporation of tridodecylmethylammonium chloride in a semiconducting conjugated polymer matrix of poly(3-octylthiophene) [52]. Electrochemically deposited polypyrrole films on glassy carbon electrode from aqueous solutions of different sodium salts (F⁻, Cl⁻, NO⁻, HSO⁻) have also been prepared [53]. The electrochemical behavior of such electrodes was studied by cyclic voltammetry. These doped films exhibited selective behavior for the corresponding anions.
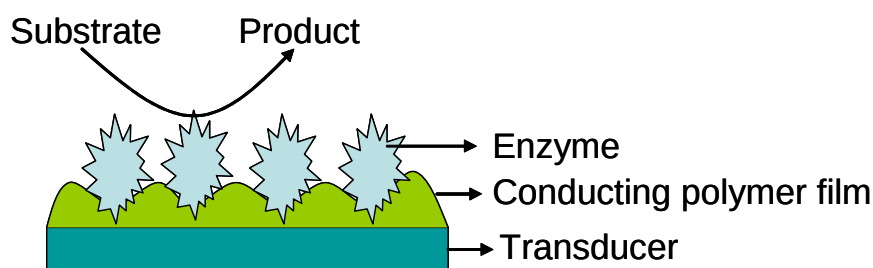
An ammonia sensor has been developed by using an amino-silane (($CH_3O)_3$-Si-$(CH_2)_3NH(CH_2)_2$-NH_2) self-assembled monolayer, employed as artificial seeds for chemical polymerization of polyaniline [54]. This sensor exhibited a detection limit of 2.99×10^{-5} M but at low concentrations of ammonia, response time was very slow. Polyaniline-(acrylonitrile-butadiene-styrene) composite film has also been reported as a sensor material for aqueous ammonia [55]. Poly (*p*-aminobenzene sulfonic acid) films doped with flavins (flavin adenine dinucleotide, flavin mononucleotide, riboflavin) composite modified glassy carbon electrode have been used to detect NADH and NAD$^+$ electrochemically [56]. The preparation of poly-(3-methylthiophene)-multi-walled carbon nanotubes hybrid composite electrodes has been reported for amperometric NADH detection with a detection limit of 1.7×10^{-7} M [57]. Polypyrrole modified with ferrocene by direct incorporation during polymerization so as to increase its sensitivity, has been used for carbon monoxide gas sensor applications [58]. Electorpolymerized poly (5-amino-1-naphthol) on polypyrrole showed a linear response for ammonia in the concentration range from 0 to 1.2×10^{-4} M [59]. Nafion and cellulose acetate films were coated on poly (pyrrole) films to avoid the interference from other anionic species,

such as ascorbate, urate, etc. Copper ions complexed in terthiophene carboxylic acid (TTCA) polymer film exhibited an enhanced anodic current for acetaminophen oxidation when compared to polymer coated and bare glassy carbon electrodes in human blood and buffer media [60]. The calibration range obtained using cyclic voltammetry was between 2.0×10^{-5} and 5.0×10^{-3} M.

2.2. Conducting polymer-based electrochemical biosensors

The control of diseases is essential to improve the quality of our lives, which is greatly dependent on diagnosis by monitoring various biochemical compounds in the body fluid. The diagnosis of a disease by measuring the constituents in body fluids first took place in the middle ages. For example, diabetes mellitus was then diagnosed by tasting the sweetness of urine [61]. Nowadays, many biochemical compounds, such as salts, sugars, proteins, hormones, DNA etc. are analyzed to assist in diagnosis and to assess disease. The monitoring of the biochemical compounds in the body fluid requires typical analytical methods for biochemical test, experts to run the tests, and time for performing clinical tests. Since the levels of various compounds in a body system are directly related to some diseases, it is possible to monitor the progress of diseases by monitoring the concentration of these compounds. Thus, continuous, fast, and sensitive monitoring is required to measure the body fluid concentration efficiently. In this context, electrochemical biosensor is a promising analytical method for sensitive and selective detection of biomolecules [62-66]. The unique property of conducting polymers along with the possibility to entrap enzymes during electrochemical polymerization has been exploited for the fabrication of amperometric biosensors [67-70]. This review concentrates on giving examples of conducting polymer based electrochemical biosensors, which have been carried out in our lab in the last five years and in other laboratories. For more detailed descriptions of the fundamental aspects of biosensors and their applications, many excellent books and reviews are available, and are suggested for further reading [62-72].

Figure 2. Schematic presentation of a biosensor.

Most biosensors described in literature use an enzyme as biological recognition element (Figure 2). The first biosensor, known as the "enzyme electrode" was demonstrated by Clark and Lyons in 1962 for the determination of glucose [73]. Amperometric enzymatic biosensors for choline [74] and glutamate [75] have been fabricated by the covalent immobilization of choline oxidase and glutamate oxidase enzymes onto the poly-5,2$'$:5$'$,2$''$-terthiophene-3$'$-carboxylic acid, poly-TTCA (poly-CP) layers on a glassy carbon electrode. The electrochemically prepared conducting polymer layer oxidized the enzymatically generated H_2O_2 at a lower potential and was the basis of detection of choline and
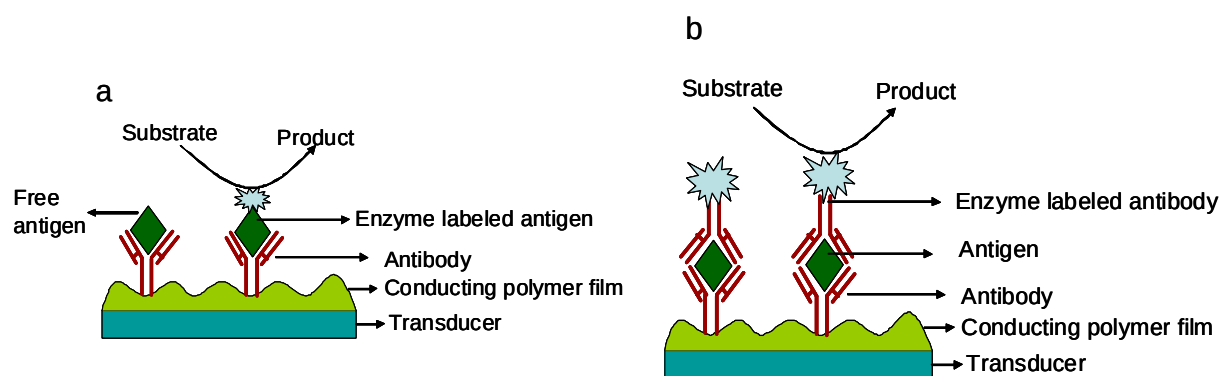
glutamate. The biosensors showed good selectivity towards other interfering anions. A xanthine biosensor has been fabricated by the covalent immobilization of xanthine oxidase (XO) onto a functionalized conducting polymer (Poly-5, 2': 5', 2"-terthiophine-3-carboxylic acid), poly-TTCA through the formation of amide bond between carboxylic acid groups of poly-TTCA and amine groups of enzyme [76]. The linear dynamic ranges of anodic and cathodic detections of xanthine were between 5.0×10^{-6} - 1.0×10^{-4} M and 5.0×10^{-7} to 1.0×10^{-4} M, respectively. The detection limits were determined to be 1.0×10^{-6} M and 9.0×10^{-8} M with anodic and cathodic processes, respectively. The applicability of the biosensor was tested by detecting xanthine in blood serum and urine real samples. A biosensor based on cytochrome c3 (Cyt c3) has been introduced to detect and quantify superoxide radical ($O_2^{\cdot -}$). Cyt c3 isolated from the sulfate-reducing bacterium (Desulfovibrio vulgaris Miyazaki F. strain), and its mutant were immobilized onto a conducting polymer (polyTTCA) coated electrode by covalent bonding [77]. A potential application of the Cyt c3 modified electrode was evaluated by monitoring the bioelectrocatalytic response towards the $O_2^{\cdot -}$. The hydrodynamic range of 0.2-2.7 $\times 10^{-6}$ M and the detection limit of 5.0×10^{-8} M were obtained. In an other work, Cyt c has been immobilized onto lipid bonded conducting polymer (poly(3,4-diamino-2,2:5,2-terthiophene) (polyDATT) layers of model biomembrane for the fabrication of another $O_2^{\cdot -}$ biosensor [78]. The detection limit was determined as 40 ± 9 nM. The potential use of hydrazine has been examined for the catalytic reduction of enzymically generated H_2O_2 in a biosensor system by covalently co-immobilizing hydrazine and glucose oxidase (GOx) onto polyTTCA [79]. The performance of the hydrazine-GOx based glucose sensor was compared with an HRP-based glucose sensor. A linear calibration plot was obtained in the concentration range between 0.1 and 15.0 mM, and the detection limit was determined to be 40.0 ± 7.0 μM. A simple and fast method for electrochemical detection of amplified fragments by the polymerize chain reaction (PCR) has been successfully developed using capillary electrophoresis (CE) in a microfluidic device with a screen-printed carbon electrode (SPCE) modified with a conducting polymer, poly-5,2'-5',2"-terthiophene-3'-carboxylic acid (polyTTCA) [80]. The sensitivity of the assay was 18.74 pA/(pg/μL) with a detection limit of 584.31 ± 1.3 fg/μL. An electrochemical method has been developed for analyzing PCR amplification through the detection of inorganic phosphates (P_i) [81]. This method coupled a microchip to conducting polymer nanoparticle comprising of poly-TTCA/pyruvate oxidase (PyOx) modified microbiosensor. The sensitivity of the analysis was 0.59 ± 0.01 nA/cycle with a regression coefficient of 0.971.

A novel amperometric biosensor based on horseradish peroxidase/polypyrrole (PPy) deposited onto the surface of ferrocenecraboxylic acid functionalized sol–gel derived composite carbon electrode for the detection of H_2O_2 has been reported [82]. The detection limit was determined to be 5×10^{-5} M and the biosensor retained 90% of the initial sensitivity after 1 week when stored at 4°C. The biosensor has a fast response and a relative large linear range making it suitable for the detection of H_2O_2. The pH effect on the co-electropolymerization of glucose oxidase and polypyrrole (PP) on the characteristics of glucose oxidase/PP biosensor has been studied [83]. The linearity of this glucose biosensor was between 0 to 10 mM, sensitivity was 7 nAmM^{-1}, and long-term usability was about 2 weeks. Although the linear range is not so wide, the biosensor exhibited high sensitivity. The electropolymerized polyaniline, poly (*o*-toluidine), and poly (anilinie-cotoluidine) films have been used for the fabrication of glucose biosensors [84]. Electrochemical co-entrapment of glucose oxidase and *p*-benzoquinone

into the polypyrrole matrix for the fabrication of a glucose biosensor has been reported by Seker and Becerik [85]. The *p*-benzoquinone was used as an electron transfer mediator between glucose oxidase and the electrode. Ramanavicius et al. have prepared polypyrrole film in the presence of glucose oxidase from *Pencillum vitale*, glucose, and oxygen revealing that optimal conditions of glucose oxidase activity (pH 6.0) are similar to pyrrole polymerization reaction (pH 6.5) [86]. The influence of electrolyte nature and its concentration on the kinetics of electropolymerization of 1,2-diaminobenzene (1,2-DMB) has been studied [87]. Prussian blue (PB) dispersed nanostructured 1,2-DMB was used to fabricate glucose, choline, lysine, lactate, ethanol, and glycerol-3-phosphate biosensors by immobilizing respective enzymes. The glucose biosensor had a detection limit of 1.0×10^{-5} M, long-term stability (about 3 months), and a wide linear range. A PB dispersed nanostructured 1,2-DMB film improved the sensitivity and stability of a glucose biosensor. Glucose oxidase-based ultra micro-electrodes fabricated via sonication and deposition of polysiloxane coating onto the working glucose oxidase/polyaniline electrode coated with insulating diaminobenzene has been reported for the improved response [88]. Arslan et al. have fabricated a polysiloxane/polypyrrole/ tyrosinase electrode by entrapment of tyrosinase in conducting matrix by electrochemical copolymerization for determining the phenolic content of green and black tea [89]. An amperomteric tyrosinase biosensor based on conducting poly (3,4-ethylenedioxythiophene) (PEDOT) has been reported for the estimation of herbicides and phenolic compounds [90]. The detection limits for monophenol and di-phenol ranged from 5×10^{-9} M to 0.5×10^{-6} M, and for diuron and attrazine were found to be 2.14×10^{-6} M and 4.6×10^{-6} M, respectively. Although this biosensor can detect various phenolic compounds but the selectivity is a major problem of this biosensor. Boyukbayram et al. have made a comparative study of immobilization methods of tyrosinase (Tyr) on electrolpoymerized conducting and non-conducting polymers for application to the detection of dichlorvos organaophosphorous insecticide [91]. Jiang et al. have demonstrated that incorporation of polyvinylalcohol (PVA) onto a polymer film caused higher sensitivity than that of pure PPy sensor [92]. Kan et al. have reported stronger affinity between uricase and polyaniline prepared by template process resulting in the increased stability of this polyaniline–uricase biosensor [93]. Haccoun et al. have fabricated a reagentless lactate biosensor using electro-copolymerized copolymer film of poly(5-hydroxy-1,4-naphthoquinone-co-5-hydroxy-3-acetic acid-1,4-naphthoquinone) [94]. These studies showed that the presence of interferences like acetaminophen, glycine, and ascorbic acid does not influence the response of this mediated (quinine group) copolymer electrode. However, this biosensor can be used for the determination of l-lactate up to 1 mM. Bartlett et al. have reported that poly(aniline)–poly(anion) composites films can be utilized for electrochemical oxidation of NADH at around 50 mV *vs.* SCE at pH 7 [95]. The low oxidation potential of NADH has implications towards the technical development of microelectrodes, biofuel cells, and amperometric biosensors. Lactate oxidase (LOD) and lactate dehydrogenase (LDH) have been co-immobilized on electrochemically prepared polyaniline (PANI) films by physical adsorption technique for the fabrication of a lactate biosensor [96]. Asberg and Inganas have cross-linked horseradish peroxidase in highly conducting poly (3,4-ethylene dioxy thiophene) (PEDOT)/ (polystyrene sulphonate) (PSS) dispersion using poly-4-vinylpyridine for estimation of hydrogen peroxide [97]. Grennam et al. have shown that horseradish peroxidase immobilized screen-printed electrodes based on chemically polymerized polyaniline/polyvinylsulphonate films can be used for the mass production of biosensors

[98]. Morrin et al. have electrochemically applied nanoparticulate polyaniline (PANI) doped with dodecylbenzenesulphonic acid (DBSA) to glassy carbon electrode surface for physical adsorption of horseradish peroxidase [99]. Jia et al. have fabricated horseradish peroxidase (HRP)-based H_2O_2 biosensor by self-assembling gold nanoparticles to a thiol-containing sol–gel network of 3-mercaptaopropyltrimethoxysilane (MPS) [100]. Ngmana et al. have immobilized horseradish peroxidase poly (2-methsulphonated polyaniline- 5-sulphonic acid)/l-lysine composite [101]. The correlation coefficient and detection limit of the amperometric HRP biosensor were determined to be 0.9966 and 0.01 mM of H_2O_2, respectively. Mathebe et al. have electrostatically immobilized horseradish peroxidase on the surface of polyaniline film electrochemically deposited onto platinum disc electrode [102]. The correlation coefficient and linear range of the polyaniline/peroxidase based biosensor were found to be 0.995 and 2.5×10^{-4} to 5×10^{-3} M, respectively. Brahim et al. have developed a 2-hydroxyethyl methacrylate/ polypyrrole system containing glucose oxidase, cholesterol oxidase, and galactose oxidase [103]. The observed stability of nine months for this system indicates that this biosensor could be subcutaneously used to monitor glucose, cholesterol, and galactose. Ivanov et al. have used glassy carbon electrodes modified with polyaniline for the immobilization of cholinesterase using cross-linking technique [104]. Cosnier et al. have demonstrated that the immobilized thionine in the poly (dicarbazole-*N*-hydroxysuccinimide) resulted in the improved sensitivity and the maximum current of catechol of the polyphenol oxidase based biosensor [105]. Langer et al. have immobilized choline oxidase in nanostructured polyaniline layers of controlled nano and micro porosity for the estimation of choline in food [106]. The choline oxidase based polyaniline biosensor was stable for about 30 days. The nanostructured polyaniline layers improve the sensor performance and stability. Qu et al. have also reported an amperomteric biosensor for detection of choline based on a polyaniline multilayer film and a layer-by-layer assembled functionalized carbon

Figure 3. Configuration of a (a) competitive and (b) non-competitive immunosensor principles using immobilized antibody on to a conducting polymer film.

nanotube [107]. Layer by layer assembly of carbon nanotubes increased the sensitivity of the biosensor.

Electrochemical immunosensors (Figure 3) combine the analytical power of electrochemical techniques with the specificity of biological recognition process. For a more detail understanding on the immunosensor, many excellent books and reviews are available and suggested for further reading [108-112]. Shim et al. reported a disposable and mediatorless immnunosensor based on a conducting
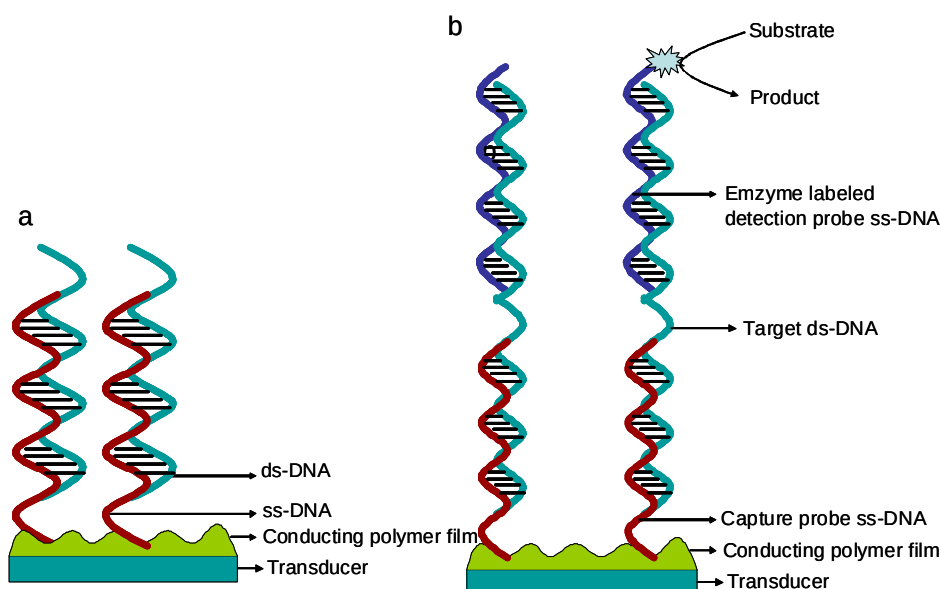
polymer coated screen-printed carbon electrode developed using a separation-free homogeneous technique for the detection of rabbit IgG as a model analyte [113]. In another work, a simple and direct immunosensor for the determination of carp (*carassius auratus*) vitellogenin (Vtg), a female specific protein, has been proposed based on an antibody captured conducting polymer coated electrode [114]. A disposable amperometric immunosensor has been studied for the rapid detection of carp (*carassius auratus*) vitellogenin (Vtg) [115]. To develop a general method for the detection of histidine-tagged protein, the interactions of the histidine epitope tag of MutH and MutL proteins with the epitope specific monoclonal anti-His$_6$ antibody has been monitored by a label-free direct method using impedance spectroscopy [116]. Label-free detection of bisphenol A based on impedance measurement was achieved with an impedimetric immunosensor [117]. The immunosensor was fabricated by the covalent bond formation between a polyclonal antibody and a carboxylic acid group functionalized onto a nano-particle comprised conducting polymer. Under optimized conditions, the linear dynamic range of BPA detection was 1-100 ng/mL. The detection limit of bisphenol A was 0.3 ± 0.07 ng/mL. The proposed immunosensor was applied to a human serum sample and the BPA concentration was determined by the standard addition method.

A label free and reagentless immunosensor based on direct incorporation of antibodies into conducting polymer films at the surface of the screen-printed electrode (SPE) using ac impedimetric electrochemical interrogation has been reported [118]. It has been demonstrated that the real component of the impedimetric response acts as a dominant component of Ac impedimetric response of anti BSA loaded conducting polypyrrole (PPy) film on its exposure to the different concentration of BSA. BSA could be detected with a linear response from 0 to 1.136×10^{-6} M. The nature of the observed faradic response current has arisen due to antibody–antigen interaction. The use of SPE may have an advantageous for miniaturization of this immunosensor. Ramanaviciene and Ramanavicius have discussed the use of conducting polymer thin films for application as electrochemical affinity sensors with the emphasis on design and applications of novel immunosensors [119]. They have briefly discussed the biological active component for the creation of polypyrrole based immunosensors. Gooding et al. have fabricated the glassy carbon electrode modified with anti-rabbit IgG antibody entrapped in an electrodeposited polypyrrole membrane for label free amperometric detection of rabbit IgG antigen in flow injection system [120]. Zhang et al. have fabricated a low-cost label-free amperometric immunosensor based on anti-rubella serum immobilized onto nano-Au/poly-*o*-phenyldiamine doped with Prussian blue for the detection of rubella vaccine [121]. Tahir et al. have described the characteristics of polyaniline compounds in different protonic acid for application to diarrhea virus detection based on polyclonal and monoclonal BVDV antibodies [122]. They have proven that polyaniline with perchloric acid show highest conductivity in pH 6.6 and the sensitivity of the biosensor ranged from 103 to 104 cell culture infective dose (CCDI) mL^{-1}. Lillie et al. fabricated simple immunosensor formats by polymerizing pyrrole loaded with avidin or antibody to luteinising harmone (LH) on a gold inter-digited electrode and demonstrated that impedance spectroscopy can be used to detect LH between 1 and 800 IU L^{-1} [123]. Farace et al. have developed a reagentless immunosensor for the detection of luteinising hormone based on antibody entrapped in a conducting polypyrrole matrix using impedance spectroscopy [124].

Electrochemical methods for DNA hybridization detection (Figure 4) have many advantages that are very fast to detect and can be directly applied to a portable DNA sensor. Shim et al. reported an electrochemical method to directly detect DNA hybridization developed on the basis of a conductive polymer, which was polymerized on the glassy carbon electrode with a terthiophene monomer having a carboxyl group [125]. Detection of protein-DNA interaction with a conducting polymer based DNA probe has also been carried out [126]. A sensitive electrochemical assay of DNA and proteins employing electrocatalytic reduction of hydrogen peroxide by labeled hydrazine on the probe immobilized surfaces was developed [127]. The method utilizes a conducting polymer, poly-5, 2':5', 2"-terthiophene-3'-carboxylic acid (polyTTCA), covalently linked to the dendrimer (DEN) and hydrazine. The linear dynamic ranges for the electrocatalytic detection of DNA and proteins, extending from 1.0 fM to 10 μM and 10 fg/mL to 10 ng/mL, were observed along with the detection limits of 450 aM (2700 DNA mols. in a 10-μL sample) and 4.0 fg/mL, respectively.

The electrochemically prepared conducting polypyrrole/polyvinyl sulphonate films have been used to immobilize *calf thymus* DNA [128] for the fabrication of a DNA biosensor, which can detect DNA hybridization. The application of conducting poly (thiophen-3-yl-acetic acid 1,3-dioxo-1,3-dihydro-isoindol-2-ylester) (PTAE) to DNA hybridization electrochemical sensor has also been reported [129]. This sensor has a sensitivity of 0.62 A/nM and detection limit as 1 nM of target oligonucleotides (ODN). Youssufi and Makrouf have prepared conducting polypyrrole substituted with ferrocenyl groups as DNA electrochemical sensor [130]. This sensor had a detection limit of less than 1.0×10^{-12} M of DNA. Poly (aniline-aniline boronic acid) wires on ds-DNA templates have been fabricated [131],

Figure 4. Schematics of (a) Direct and (b) detection of DNA hybridization.

which had redox functions at neutral pH solutions. The direct electrical contact between biocatalyst and the electrode was achieved through these wires. A preliminary study showed that glucose oxidase might be similarly contacted with negatively charged polyelectrolyte templates like polystyrene sulphonate. A biosensor based on polyaniline intercalated graphite oxide nanocomposite (PAI/GO) for monitoring DNA hybridization has been reported [132]. Zhu et al. have developed a novel and

sensitive electrochemical DNA biosensor based on electrochemically fabricated polyaniline nanowire and methylene blue for detection of DNA hybridization [133]. Single stranded DNA has been immobilized on self-assembling polymer based on polyallyamine modified with thioctic acid for hybridization assays [134]. Lori et al. has developed a conducting polymer surface by doping *N*-nitriloacetic acid (NTA) into the electropolymerized polyvinylsulphonate doped polyaniline (PANI/PVS) at a screen printed carbon electrode for the immobilization of *his*-tagged biomolecules [135]. The resulting NTA-PANI-/PVS film was shown to have interesting electrochemical properties. The electrosynthesis of conducting copolymer using pyrrole and pyrrole-oligonucleotide (ODN) at platinum disc electrode has been reported [136]. Cadmium sulphide (CdS) nanoparticles were incorporated into the polymer film for the improvement of the sensitivity. Electrochemical impedance spectroscopy can be used to visualize charge transfer through conducting polypyrrole films loaded with oligonucleotides probes formed on the carbon nanotube modified electrodes as a basis for reagent less protocol [137]. This technique has several advantages such as high selectivity and reduced reaction time without the use of mediators or fluorescent materials for complementary and mismatched target sequences.

3. Conclusions

Conducting polymers are now widely used in the design of electrochemical biosensors. Conductive polymers improve the sensitivity and selectivity of electrochemical sensors and biosensors due to their electrical conductivity or charge transport properties. Conducting polymers can be electrochemically grown on very small size of electrode, thus allowing for in vivo monitoring of biomolecules. Biomolecules, such as enzyme, antibody, DNA, aptamer etc. can be immobilized onto conducting polymers without any loss of activity, which makes conducting polymers biocompatible with biological molecules in neutral aqueous solutions. Conducting polymers can act as an electron promoter. Moreover, conducting polymers can be deposited over defined areas of electrodes. The unique properties of conducting polymers have been exploited for the fabrication of electrochemical sensors and biosensors.

Acknowledgements

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