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Electroanalytical Sensor Technology

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1. Introduction

The subject of electrochemical sensors is broad, spanning many aspects of physical and analytical chemistry, materials science, biochemistry, solid-state physics, device fabrication, electrical engineering, and even statistical analysis. Thus, the field of electrochemical sensors cannot be dealt with holistically in a single chapter. Here, we will focus on electrochemical sensor technology from an analytical perspective, where the rigours of sensor behaviour will be discussed as they relate to the quality of the quantitative information that can be derived. The definition of analytical chemistry was given by the Federation of European Chemical Societies (FECS) in 1993 [1] and adopted by IUPAC:

“develops and applies methods, instruments and strategies to obtain information on the composition and nature of matter in space and time, as well as on the value of these measurements, i.e., their uncertainty, validation, and/or traceability to fundamental standards.”

Electroanalytical chemistry, also known as electroanalysis, lies at the interface between analytical science and electrochemistry. It is concerned with the development, characterisation and application of chemical analysis methods employing electrochemical phenomena. It has major significance in modern analytical science, enabling measurements of the smallest chemical species, right up to the macromolecules of importance in modern biology. The history of electrochemical sensors starts basically with the development of the glass electrode by Cremer in 1906 [2]. Haber and his student Klemensiewicz took up the idea in 1909 and made the basis for analytical applications [3]. The former wanted to introduce the device as “Haber electrode” causing protests of Cremer. The latter should be given full appreciation of the invention of the glass electrode though Haber dominates the literature [4]. Today, the electrochemical sensor plays an essential analytical role in the fields of environmental conservation and monitoring, disaster and disease prevention, and industrial analysis. A typical chemical sensor is a device that transforms chemical

information in a selective and reversible way, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal. A huge research effort has taken place over the several years to achieve electrochemical sensors with attractive qualities including rapid response, low cost, miniaturisable, superior sensitivity and selectivity, and appropriate detection limits. Approximately 2000 peer-reviewed papers concerning electrochemical sensors were published in 2011 according to Thomson Reuters Web of Knowledge® showing the considerable research effort underway in this field.

In the highly diverse field of chemical (and biochemical) sensing, the sensor is governed by both the aspect of the environment it is measuring and the matrix in which it is in. As well as sensors that use electrochemistry as the type of energy transfer that they detect, optical [5], thermal [6] and mass-based [7] sensors are also well-developed. From an analytical perspective, electrochemistry is appealing as it directly converts chemical information into an electrical signal with remarkable detectability, experimental simplicity and low cost. There is no need for sophisticated instrumentation, e.g., optics. A very attractive feature of electrochemistry is that it depends on a surface phenomenon, not an optical path length, and thus sample volumes can be very small, lending itself to miniaturisation.

The interest in electrochemical sensors continues unabated today, stimulated by the wide range of potential applications. Their impact is most clearly illustrated in the widespread use of electrochemical sensors seen in daily life, where they continue to meet the expanding need for rapid, simple and economic methods of determination of numerous analytes [8-10]. Through the refinement of existing sensing technologies along with the development of innovative functional sensor materials including nano- and biological materials [11-14], improved data analysis [15], and sensor fabrication and miniaturisation [16-18], opportunities for the construction of new generation sensors with much improved performances are emerging. Two branches of electrochemical sensors are developing: sensors with increased specificity and sensors capable of simultaneous/multiplex determination. In both of these branches, the ability to operate in complex biological matrixes will remain critical, forcing researchers to solve problems of biocompatibility and stability [19]. As such, the analytical and physical properties that must be considered when developing (and commercialising) chemical and biological sensors include (but are not limited to):

- Cost
- Miniaturisation
- Sensitivity
- Sensor reproducibility
- Selectivity/Specificity
- Multi-analyte detection
- Stability

Few sensors, if any, exhibit optimal characteristics for all properties. For example, for *in vivo* application, due to the complex environment of these measurements, sensing selectivity becomes critical and a trade-off between selectivity and other parameters such as cost or

response time is needed [20]. When developing electrochemical sensors, some properties can be prioritised over others depending on final application. An electrocatalytic hydrogen peroxide sensor with a low milli-molar (mM) detection range may, for example, have application in waste water or industrial applications. However, in order to be viable for application in clinical diagnostics, it would demand a sensitivity several orders of magnitude lower.

Following an overview of the standard sensing technologies and a brief introduction to biosensors, this chapter will review chemical and biological sensors under the criteria listed above, discussing the latest research developments in these areas published in the peer-review literature in the last three years. We will focus on all the facets of electroanalytical sensing technology with particular emphasis on the impact of nanotechnology and nanomaterials, microfabrication and biotechnology on the field to date.

2. Electrochemical sensing principles

Depending on the exact mode of signal transduction, electrochemical sensors can use a range of modes of detection such as potentiometric, voltammetric and conductimetric. Each principle requires a specific design of the electrochemical cell. Potentiometric sensors are very attractive for field operations because of their high selectivity, simplicity and low cost. They are, however, less sensitive and often slower than their voltammetric counterparts. In the past, potentiometric devices have been most widely used, but there is an increasing amount of research being carried out on amperometric sensors that has tipped this balance. There are also sensors relying simply on conductivity changes of ions, but there is a far larger group of sensors, which work on resistivity and impedance, such as chemiresistors and capacitive sensors. As the underlying operating principle for conductimetric sensors is usually not an electrochemical reaction or property, they should be classified as electrical chemical sensors rather than as electrochemical ones. While most electrochemical techniques for sensing analytes of interest are based on the changes in potential or current, Shan *et al.* [21] have developed a completely novel method for performing electrochemical measurements. In their work, they report a method for imaging local electrochemical current using the optical signal of the electrode surface generated from a surface plasmon resonance (SPR). The electrochemical current image is based on the fact that the current density can be easily calculated from the local SPR signal. The authors demonstrated this concept by imaging traces of TNT on a fingerprint on a gold substrate.

More detailed theoretical discussions on potentiometric, voltammetric and conductimetric measurements are available in this and many other textbooks [22-24] and so will not be discussed in detail here.

2.1. Potentiometric sensors

In potentiometric sensors, the analytical information is obtained by converting the recognition process into a potential signal, which is logarithmically proportional to the

concentration (activity) of species generated or consumed in the recognition event. The Nernst equation logarithmically relates the measured electrode potential, E , to the relative activities of the redox species of interest:

$$E = E^0 + \frac{RT}{nF} \ln \frac{a^O}{a^R} \quad (1)$$

Where E^0 is the standard electrode potential (quoted relative to the idealised Standard Hydrogen Electrode, SHE) and a^O and a^R are the activities of the oxidised and reduced species, R is the universal gas constant; T is the absolute temperature; F is the Faraday constant; n is the number of moles of electrons exchanged in the electrochemical reaction.

The most representative potentiometric sensor is the ion selective electrode (ISE)[25]. The ISE uses an indicator electrode which selectively measures the activity of a particular analyte ion. An ion-selective membrane, placed at the tip of the electrode, is designed to yield a potential signal that is selective for the target ion. This potential signal is generated by a charge separation at the interface between the ion-selective membrane and the solution due to selective partitioning of the ionic species between these two phases. The response is measured under conditions of essentially zero current. The response of the indicator electrode should be fast, reversible and governed by the Nernst equation.

In classical ISEs, the arrangement is symmetrical [26] which means that the membrane separates two solutions, the test solution and the inner solution with a constant concentration of ionic species. The electrical contact to an ISE is provided by a reference electrode (usually Ag/AgCl) in contact with the internal solution that contains chloride ions at constant concentration. The measured ISE potential is the sum of the two reference electrode potentials, the membrane potential constituted by boundary potentials at each membrane/solution interface, and a possible diffusion potential which may be caused by an ion concentration gradient within the ion-selective membrane phase.

ISEs with solid inner contacts are considered to be asymmetrical [26]. Taking into consideration that potentials generated at each membrane interface are included in the overall sensor signal response it is clear that to obtain a solid-contact ISE with a stable electrode potential, a fast and thermodynamically reversible ion-to-electron transduction in the solid state is required without any contribution from parasitic side reactions. Solid-contact potentiometric ion-selective electrodes have nowadays similar performance characteristics to conventional inner-solution ion-selective electrodes and offer new and advantageous technical possibilities such as miniaturization to the μm scale, cost-effective fabrication, no need for maintenance, flexibility, and multiple shape configurations. Among the electroactive materials available today, conducting polymers have emerged as a promising ion-to-electron transducers for solid-contact ISEs [25, 27, 28]. In this type of solid-contact ISE, the conducting polymer is coated with a conventional ion-selective membrane, and the ion-selectivity is determined mainly by the ion-selective membrane. For example, potentiometric sensors based on a glassy carbon electrode covered with polyaniline and various thiocalix[4]arene ionophores have been developed and applied for the successful determination of Ag^+ ions [29]. Other configurations for solid-contact ISEs recently reported

involve the use of carbon cloth coated with a conventional plasticized PVC-based K(+)-selective membrane [30], carbon nanotubes (CNTs) drop-coated with a K⁺-selective polyacrylic membrane [31], PVC-based molecularly imprinted polymers [32] and graphene coated with an ionophore-doped polymeric membrane [33].

ISEs are been combined with semiconductor field effect transistor (FET) technology to give ion-selective FETs, where the gate has been replaced by an ion-selective membrane. ISFETs with bare gate insulator (silicon oxide, silicon nitride, aluminium oxide, etc.) show intrinsic pH-sensitivity due to electrochemical equilibrium between protonated oxide surface and protons in the solution. To obtain sensitivity to other ions a polymeric membrane containing some ionophore is deposited. The advantages of ISFETs include small size and rugged construction, making it a useful sensing technology for environmental and industrial analysis.

Light addressable potentiometric sensors (LAPS) [34, 35] is another type of field-effect transducer that are used as potentiometric chemical sensors which has gained reasonable popularity. Their principle of operation is quite similar to that of ISFETs in which the drain-source current in a space charge region at the semiconductor/insulator interface depends on the applied gate potential. Illumination by light source with modulated intensity generates an AC photocurrent that depends on the applied potential. Like ISFET sensors, ion-selective membranes of various types may be deposited onto the insulator surface to give the required ion sensitivity [26].

2.2. Voltammetric sensors

Voltammetry provides an electroanalytical method, the premise of which is that current is linearly dependent upon the concentration of the electroactive species (analyte) involved in a chemical or biological recognition process (at a scanned or fixed potential). Voltammetry implies a varying voltage. Cyclic voltammetry, squarewave and stripping voltammetry are some of the more common techniques. Amperometry is strictly a sub-class of voltammetry in which the electrode is held at constant potentials for various lengths of time. The distinction between amperometry and voltammetry is mostly historic as there was a time when it was difficult to switch between "holding" and "scanning" a potential. This function is trivial for modern potentiostats, and today there is little distinction between the techniques which either "hold", "scan", or do both during a single experiment. The recent review by Gupta *et al.* [36] focuses on the various applications of voltammetry to pharmaceutical analysis from 2001 to 2010.

Stripping analysis is one of the most sensitive voltammetric methods [37, 38]. Such techniques enjoy the advantages that there is no need for derivatization and that these methods are less sensitive to matrix effects than other analytical techniques. It is mostly used for trace analysis of heavy metals for environmental analysis [39, 40]. Cathodic or anodic stripping voltammetry have also been used for a highly sensitive determination of nucleobases, nucleosides, nucleotides or acid-hydrolyzed NAs, based on formation of sparingly soluble complexes of the NA constituents with electrochemically generated mercury or copper(I) ions [41].

In amperometry, the working electrode is held at a constant potential while the current is monitored. The current is then related to the concentration of the analyte present. This sensing method is commonly employed in both biosensors and immunosensors, which will be discussed further later. The first amperometric sensor was the oxygen electrode developed by L.C. Clark [42]. Oxygen entering the system through a gas-permeable membrane is reduced to water at a noble metal cathode. Clark also described the first glucose biosensors in 1962, using his oxygen electrode to determine the depletion of oxygen by the action of glucose oxidase on glucose [43]. Today, about 50 years on, Hu *et al.* [44] reported an oxygen sensor based on an inkjet printed nanoporous gold electrode array on cellulose membranes using ionic liquid as electrolyte. The sensor looks like a piece of paper but possesses high sensitivity for O₂ in a linear range from 0.054 to 0.177 v/v %. Hydrogen peroxide sensors as well as non-enzymatic glucose sensors are of particular interest in the field of amperometric sensors [20].

The development of all voltammetric techniques has been based predominantly on the use of mercury, carbonaceous materials and noble metals as working electrodes. However, toxicity of mercury, inconvenience in working with liquid hanging drop electrodes, and a limited range of potentials for mercury for anodic reactions has essentially eliminated mercury from this list. Carbon-based working electrode materials include all allotropic forms of carbons - graphite, glassy carbon, amorphous carbon, fullerenes, nanotubes, and are all used as important electrode materials in electroanalytical chemistry. Over the past five decades, carbon paste, i.e., a mixture of carbon (graphite) powder and a binder (pasting liquid), has arguably become one of the most popular carbon electrode materials used for sensors given that carbon pastes can readily be screen-printed for the mass-production of electrodes. Screen-printing is a thick-film process, which has been used for many years in artistic applications and, more recently, for the production of miniature, robust and cheap electronic circuits. During the early 1980s, the process was adapted for the production of carbon-paste-based amperometric biosensors which had a huge impact on biosensor commercialisation. The majority of most successful electrochemical sensors, including the blood glucose biosensor strip, to date, employ a screen-printed carbon-paste as the working electrode [45, 46].

The use of new materials, especially nanomaterials, has become an increased area of research in electrochemical sensors. The incorporation of these nanomaterials in conjunction with one another to form novel composites is particularly interesting, as many of these materials have been found to have synergistic effects. Zhong *et al.* [47] reported a non-enzymatic hydrogen peroxide amperometric sensor based on a glassy carbon electrode modified with an MWCNT/polyaniline composite film and platinum nanoparticles. The composite films have a large specific surface, high redox electrochemical activity and good environmental stability. Due to the synergistic catalytic activity between MWCNTs-PANI nanocomposites and Pt nanoparticles, the fabricated non-enzyme amperometric sensor displayed a high sensitive detection of H₂O₂. CNTs were also used by Guo *et al.* [48] who developed a sensitive amperometric sensor for tryptophan by modifying a glassy carbon (GC) electrode with gold nanoparticle decorated CNTs. The nanocomposite material

demonstrated synergistic enhancement for the electrocatalytic activity toward the oxidation of tryptophan.

2.3. Conductimetric and impedimetric sensors

Conductimetric sensors are based on the measurement of electrolyte conductivity, which varies when the cell is exposed to different environments. The sensing effect is based on the change of the number of mobile charge carriers in the electrolyte. If the electrodes are prevented from polarizing, the electrolyte shows ohmic behaviour. Conductivity measurements are generally performed with an AC supply. The conductivity is a linear function of the ion concentration; therefore, it can be used for sensor applications. Ventura *et al.* [49] have reported a paper-based conductivity sensor for hydrogen. Palladium nanoparticles were attached onto a covalently cross-linked CNT paper. Depending on the design of the sensor, p-type or n-type conduction was observed as the resistance of the paper was measured under exposure to hydrogen gas. This paper demonstrates a simply designed, flexible gas sensor, highlighting the next stage in the development of functional nanotube paper. Another format reported was an electrospun nylon 6,6 nanofiber containing an ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate) was electrospun and found to behave as an effective, reversible chemiresistor for detecting organic vapours, highlighting another route to a simple, flexible gas conductivity sensor [50]. Conductivity measurements in general, are non-specific for a given ion type. Also, the polarization and the limiting current operation mode need to be avoided as these can damage the electrode interface. Thus, a small amplitude alternating bias can be used for sensor measurements with frequencies where the capacitive coupling is still not determining the impedance measurement. This was used for the sensing of ammonia on polyaniline-modified interdigitated arrays to prevent polarisation of the polyaniline [51].

Impedance-based sensors have a similar design as mixed potential type sensors. Instead of measuring the voltage, a sinusoidal voltage is applied and the resulting current is measured. Impedance is then calculated as the ratio of voltage to current in the frequency domain. By using small amplitude sine wave perturbation, linearity in electrochemical systems can be assumed, allowing frequency analysis. An excellent review of the use of impedance for the sensing of gases has recently been published by Rheaume & Pisano [52].

The use of impedance/capacitance has also been used to detect the antibody/antigen complex formation which has application in electrochemical immunosensors. This phenomena was first reported in 1998 when upon formation of an Ab/Ag complex on the surface of the electrode, the increase in dielectric layer thickness caused changes in capacitance proportional to the size and the concentration of antibodies [53]. Impedance changes between electrode surfaces and a surrounding solution upon a binding event can be transduced into an electrical signal using a frequency response analyser. There are several theories as to how this binding event affects changes in real and imaginary components of the system, although it is difficult to identify the origin of these changes. One theory hypothesises that binding of larger antigens forms a resistive barrier, causing the impedance to increase whilst binding of smaller antigens can

facilitate a charge transfer and lower impedance [54]. Future work must establish the origin of this impedance change, whether from increases in surface density or perhaps from conformational changes that modify charge transfer across the sensor interface. Recent examples of impedance-based immunosensors include a silicon nitride (Si_3N_4) surface with covalently bound anti-human serum albumin (anti-HSA) [55]. Electrochemical impedance spectroscopy (EIS), measurements for the specific detection of HSA proteins where a detection limit of 10^{-14} M were achieved. This is one of a handful of papers that have generated EIS measurement on insulating surfaces. Mostly impedimetric immunosensors are based on conducting materials. Chemically modified graphene (CMG), immobilised on a printed electrode was demonstrated as a disposable platform for the attachment of anti-IgG (anti-Immunoglobulin) [56]. The principle of detection lies in the changes in impedance spectra of a bulk solution-based redox probe (10 mM $\text{K}_4[\text{Fe}(\text{CN})_6]/\text{K}_3[\text{Fe}(\text{CN})_6]$) after the attachment of IgG to the immobilized anti-IgG. The immunosensor was optimised and it was found that thermally reduced graphene oxide has the best performance in terms of sensitivity when compared to other CMG materials.

3. Biosensors

Biosensors aim to utilise the power of electrochemical techniques for biological processes by quantitatively producing an electrical signal that relates to the concentration of a biological analyte. The relatively low cost and rapid response of these sensors make them useful in a variety of fields including healthcare, environmental monitoring, and biological analysis among others [19]. Biosensors use biomolecules as recognition elements which must be immobilised (or coupled) to the transducer. The transducer is the electrode (or set of electrodes) in the case of the electrochemical sensor. The specificity and selectivity that a biosensor provides is attributed to this immobilised biological recognition element. Biocatalytic and bioaffinity recognition elements are the two classes of molecules employed. Enzymes, which are biocatalytic recognition elements are the best known and studied. Recent development has focused on improving the immobilization and stability of the enzymes [57, 58]. Enzymes immobilized to nanosized scaffolds such as spheres, fibres and tubes have all recently been reported [59-61]. The premise of using nanoscale structures for immobilization is to reduce diffusion limitations and maximize the functional surface area to increase enzyme loading. In addition, the physical characteristics of nanoparticles such as enhanced diffusion and particle mobility can impact inherent catalytic activity of attached enzymes [62]. Increased enzyme stability at these surfaces is also widely reported. A novel platform based on buckypaper (which is a thin membrane of CNT networks) was reported using glucose oxidase as the model enzyme. A biocompatible mediator-free biosensor was studied and the potential effect of the buckypaper on the stability of the biosensor was assessed. The results showed that the biosensor had a considerable functional lifetime of over 80 days [58]. Greatly enhanced electrochemistry of the enzyme can be observed by the use of nanoparticles, due to the ability of the nanoparticles to reduce the distance between the redox centre of the enzyme and the electrode. Willner's group has contributed significantly to this area by taking the approach of reconstituting apo-proteins on cofactor-modified electrodes as a general strategy to electrically contact redox enzymes with electrodes [63, 64].

A recent news article in Nature Chemistry [65] points to the major Achilles heel of enzyme-based sensors. To measure glucose, enzymes such as glucose oxidase, hexokinase, or glucose dehydrogenase can be coupled to reactions that generate a signal. But such an analytical set-up can be used only if analogous enzymes are available for the analyte of interest. They identify a paper by Lu & Xiang [66] that overcomes this severe limitation where a method (Figure 1) for expanding the principle of the glucose meter to detect other analytes is reported. Instead of measuring the analyte directly, their strategy aims to produce glucose in quantities proportional to the amount of the analyte of interest. The approach uses magnetic microbeads coated with an enzyme (invertase) that is conjugated to either DNA aptamers or DNAzymes. These DNA oligomers can be selected from huge libraries of random DNA sequences, based on their binding to an analyte of choice. When the target binds to the aptamer or DNAzyme, invertase is released into the solution. After magnetic separation of microbeads, the invertase hydrolyses sucrose into glucose, which can then be quantified using a conventional glucose meter. Lu and Xiang demonstrate the measurement of four different classes of non-glucose analytes: a small molecule (cocaine), a nucleoside (adenosine), a protein (interferon-gamma) and a metal ion (uranium).

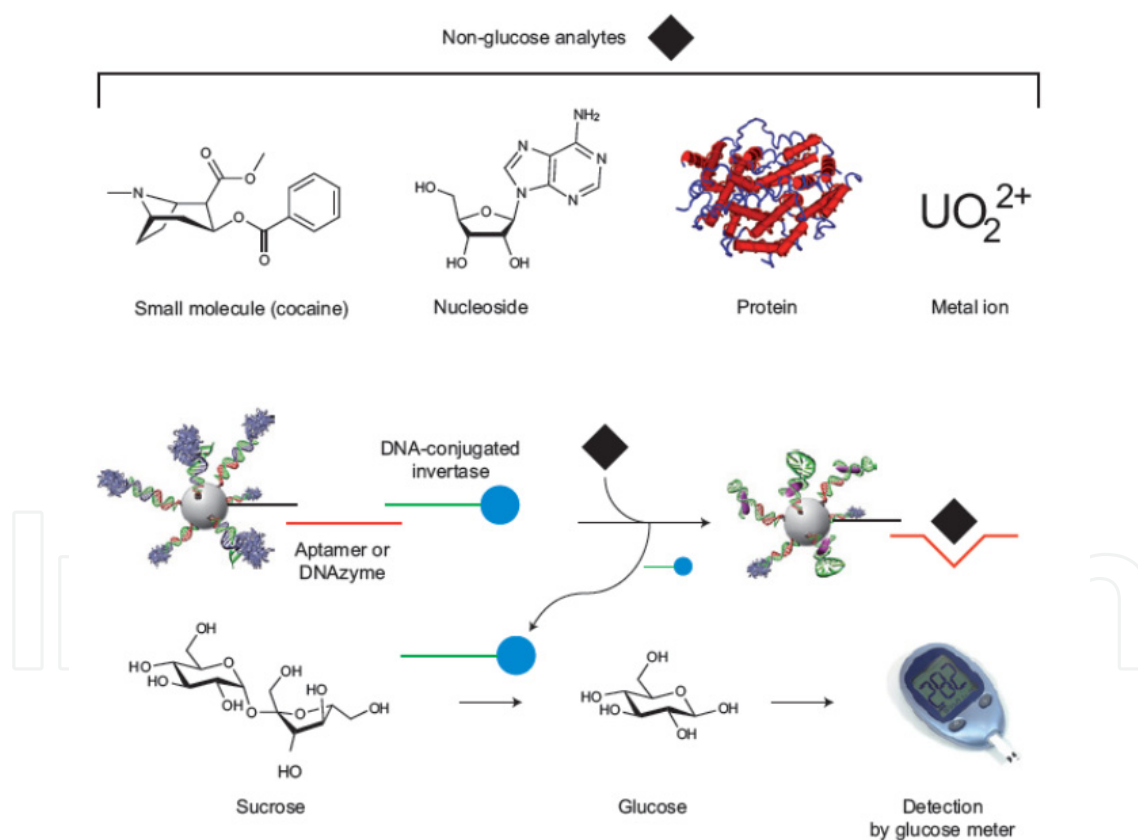


Figure 1. Sensing a variety of analytes using a glucose meter. Aptamers or DNAzymes that bind a wide range of analytes can be selected from huge libraries of random DNA sequences. When the analyte binds to its aptamer, invertase is released. Sucrose is then converted to glucose in proportion to the original analyte and can be detected using a standard glucose meter. Reprinted by permission from Macmillan Publishers Ltd: [Nature Chemistry] (Sia SK and Chin CD, Analytical Chemistry: Sweet Solution to Sensing, Nature Chemistry, 3: 659-660.), copyright (2011).

The second class of bioaffinity recognition elements such as antibodies and DNA are also widely used in biosensing. Immunosensors, which perform immunoassays based on antigen and antibody recognition, have become vital for the determination of biochemical targets relating to health concerns spanning from cancer antigens [67] to pathogens [68]. Some of the most significant advances include development of immunosensors for the continuous monitoring of analytes, point of care (PoC) devices, with lower unit costs, automation, reusability and ease of use [8]. A continual concern with immunosensor development is the capability to sensitively detect relevant immunological compounds without compromising the bioactivity of the immunoactive species on the electrode. Stabilisation of sensor constructs was achieved by using polylysine films into which anti-biotin molecules were immobilised [69]. Cross-linking prevents conformational change and unfolding of the antibodies allowing markedly enhanced sensitivity when compared with similar constructs, longer storage times and higher resistance to extremes of pH and temperature. Many researchers have increasingly utilized nanomaterials to support the immunoactive agents while simultaneously enhancing the electrochemical and analytical capabilities of the electrode [70, 71]. A triple signal amplification strategy was designed by Lin *et al.* [17] for the ultrasensitive immunosensing of a cancer biomarker, carcinoembryonic antigen (CEA). This strategy was achieved using graphene for accelerating electron transfer, poly(styrene-co-acrylic acid) microbead (PSA) carried Au nanoparticles (NPs) as tracing tags to label signal antibody and Au NPs induced silver deposition for anodic stripping analysis. An *in situ* synthesis of Au NPs led to the loading of numerous Au NPs on the PSA surface and convenient labelling of the tag to the secondary Ab. With the sandwich-type immunoreaction, the anchored Au NPs further induced the chemical deposition of silver for electrochemical stripping analysis of target antigen. The triple signal amplification greatly enhanced the sensitivity for biomarker detection. A detection limit as low as to 0.12 pg/mL was reported. The immunosensor exhibited good stability and acceptable reproducibility and accuracy, indicating potential applications in clinical diagnostics.

In recent years there has been increasing interest in finding new molecules that are able to mimic antibodies and replace them for therapeutic purposes and for bioanalytical applications. Antibodies are difficult and expensive to manufacture and are produced *in vivo*, by immunizing animals. Different molecules are currently being studied as alternatives to antibodies for bioanalytical applications; among these are nucleic acid aptamers. One of the main advantages of nucleic acid aptamers compared with antibodies is their *in vitro* selection procedure and their chemical synthesis. These manufacturing procedures do not depend on a particular analyte (possibility of using toxins, and molecules that do not elicit a good immune response) and enable the use of non-physiological conditions (including extremely high or low temperature and pH), do not require animals and cell lines, and are cost-effective. Most of the electrochemical detection principles described for other bioaffinity assays are applicable to electrochemical aptamer-based biosensors, or aptasensors. Label-free modes are based on the change in electrode surface behaviour after formation of the aptamer–target complex (usually monitored by electrochemical impedance spectroscopy [19, 72] or by use of a FET [73]).

4. Physical and analytical properties of electroanalytical sensors

4.1. Cost

Electrochemical sensors provide a low cost analytical tool. Furthermore, the ability to produce electrochemical sensors in large numbers at a low cost is a major requirement for many applications. For instance, for commercial sensors aimed at the medical self-testing and smart packaging markets, single-shot use has many advantages as it immediately overcomes issues with cross-contamination and integrating sensors into disposable packaging. Thus, the ability to mass manufacture sensors, with minimal production costs facilitates the potential of sensors as low-cost disposable platforms.

The current state-of-the-art in sensor manufacturing is the commercial glucose test strip which is produced in volumes of billions annually. Given the volumes being manufactured, the cost per sensor is a fraction of a cent. The manufacturing technology that has been exploited so successfully for this is screen-printing [46]. Screen-printing is a thick-film process, which has been used for many years in artistic applications and, more recently, for the production of miniature, robust and cheap electronic circuits. During the early 1980s, the process was adapted for the production of amperometric biosensors which had a huge impact on biosensor commercialisation. The majority of most successful electrochemically based devices, including the blood glucose biosensor strip, to date, have used screen-printing as the manufacturing tool [74]. Another type of low-cost printing is also being adopted for sensor fabrication is inkjet [44, 75, 76]. It has the required levels of flexibility, resolution and scale-up required for sensor production. It remains to be seen however if it is adopted by the electrochemical sensor community. Crooks research group recently reported a paper-based electrochemical sensing platform with integral battery and electrochromic read-out [77] (Figure 2). The platform is fabricated based on paper fluidics and uses a Prussian blue spot electrodeposited on an indium-doped tin oxide thin film as the electrochromic indicator. Although this is not a printed platform, the concept of using screen- and/or inkjet-printing to mass produce such a sensor could be easily envisaged. It is likely however, that a combination of print and possibly non-print methods (e.g., photolithography) will be adopted in the future in order to produce systems comprising not only the sensor component, but also the display, power and circuitry components in order to build highly sophisticated, low-cost autonomous systems [45].

4.2. Miniaturisation

Through the reduction in size of both the functionally critical components of sensing devices and the sensors themselves, miniaturisation offers a range of distinct advantages to the analyst, including the reduction of:

- transport times and volumes
- dead volumes
- sample preparation
- reagent consumption
- energy consumption
- time expenditure and monetary cost.

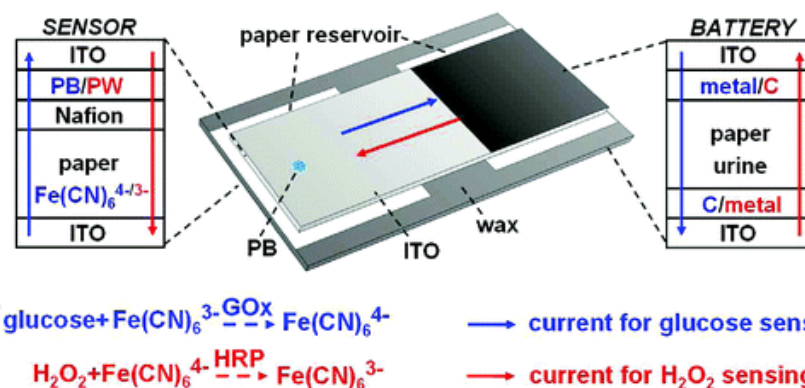


Figure 2. Drawing illustrating the operational principles of a paper-based electrochemical sensing platform with integral battery and electrochromic read-out. The device consists of two parts: a sensor section and an Al/air battery section, which are separated by a wax barrier. For glucose detection, the paper reservoir of the sensor section is preloaded with dried GOx and $\text{Fe}(\text{CN})_6^{3-}$. The catalytic oxidation of glucose by GOx results in conversion of $\text{Fe}(\text{CN})_6^{3-}$ to $\text{Fe}(\text{CN})_6^{4-}$. $\text{Fe}(\text{CN})_6^{4-}$ is then oxidized back to $\text{Fe}(\text{CN})_6^{3-}$ on the lower ITO electrode, which results in reduction of PB to colorless PW on the upper ITO electrode. The H_2O_2 sensor operation is similar, except that HRP catalyzes the oxidation of $\text{Fe}(\text{CN})_6^{4-}$ to $\text{Fe}(\text{CN})_6^{3-}$ in the presence of H_2O_2 . The resulting $\text{Fe}(\text{CN})_6^{3-}$ is then reduced at the lower ITO electrode, while PW is oxidized to PB at the upper ITO electrode. The battery section of the device drives the electrochemical reactions in the sensor section [77]. Reprinted with permission from (Liu H and Crooks RM, Paper - Based Electrochemical Sensing Platform with Integral Battery and Electrochromic Read-Out, *Analytical Chemistry*, 84: 2528-2532). Copyright (2012) American Chemical Society.

This coupled with improved portability has resulted in miniaturisation becoming a major driving force in sensor research, prompting not only the scaling down of established sensing devices [78], but also the development and application of novel sensing materials [79, 80] in a variety of sensors. At present the majority of electrochemical sensor development is application orientated which has resulted in the extreme miniaturisation of sensing devices. This is in a large way due to the concurrent advances in nanotechnology which has allowed the fabrication of novel sensors possessing signal transduction mechanisms that exploit the unique physical phenomena of the nanoscale [81]. These sensors may utilise, for example, the spectroscopy of plasmonic nanoparticles, the deflection of cantilevers and the conductivity of nanowires [81, 82].

The focus of this section will be on the development of novel sensors produced through novel fabrication techniques, which show comparable or improved sensing performance with conventional sensors while also highlighting improvements in the ideal sensor features listed in the chapter's introduction. Success in terms of the improved selectivity and stability of miniaturised potentiometric sensors will be further discussed in following sections.

The impact miniaturisation is having on the field of electrochemical research is most readily visualised when we consider the development of biosensors, specifically those that are commercially available, the most prominent of which is the glucose sensor. In his review *Electrochemical Glucose Biosensors*, Wang, describes in detail the refinement of the original glucose sensor fabricated by Clark and Lyons in 1962, to today's commercially available disposable electrodes with portable personal readout devices to the potential, continuous non-invasive *in vivo* real time monitoring [83].

Continuing the theme of non-invasive *in vivo* monitoring, Wang also describes the development of a miniaturised flow cell amperometric sensor, which could be inserted into a subject's tear duct. The screen printed microflow detector was first shown to possess the ability to detect catecholamine neurotransmitters norepinephrine and dopamine with the rolled microsensor giving a rapid and sensitive response to trace levels of the two neurotransmitters (approx. 165 nM norepinephrine and 530 nM dopamine). Further functionalization of the sensor by the addition of a carbon working electrode coated with a film containing glucose oxidase, allowed the sensitive detection (8 μ M) of glucose [84].

Wang's group also depict their work with screen printed electrode (SPE) as sensors. Screen printing is a technique that offers a variety of advantages including low-cost mass production, minimal sample volume and low cross-contamination [85]. Au SPEs, coated with a ternary monolayer interface, containing hexanedithiol (HDT), SHCP a thiolated capture probe, and 6-mercapto-1-hexanol (MCH) were shown to offer direct, sensitive detection of nucleic acid hybridization in serum and urine. Modification of the sensing layer further improved the sensor's sensitivity with a 10-fold improvement in the signal-to-noise ratio for a 1 nM target DNA compared to common SHCP/MCH binary interfaces. The SPEs also allowed direct quantification of the target DNA down to 25 pM and 100 pM in undiluted serum and urine samples, respectively. These SPEs possessed good anti-fouling properties after extended exposure to raw human serum and urine samples, showing good potential as low cost nucleic acid sensors [86].

In another account Wang *et al.* outline their development of wearable SPEs for the voltammetric detection of trace heavy metal contaminants (copper linear detection from 10 - 90 ppb with a limit of detection (LOD) of 13 ppb) and nitro - aromatic explosives (detection range of 100 - 900 ppb of TNT with a LOD of 42 ppb) in seawater [87]. The modification of SPEs by inkjet printing is further illustrated by a number of other groups including Sriprachubwong *et al.* [88] who describe how the graphene-PEDOT:PSS modified SPEs electrochemical activity to H_2O_2 , nicotinamide adenine dinucleotide (NADH) and $\text{K}_4\text{Fe}(\text{CN})_6$ is significantly enhanced, in comparison to unmodified SPEs.

Microelectrodes are another popular means of miniaturisation as they exhibit increased temporal resolution and current densities, with reduced ohmic drop and charging currents, and high Faradaic to capacitive current ratios. However individually their current output is often overshadowed by electrochemical noise. To counteract this, microelectrode arrays are fabricated, improving sensitivity and facilitating lower detection limits in comparison to macroelectrodes [89]. Thus microelectrodes are one of the most obvious successes in sensor miniaturisation because they are small, able to operate in low sample volumes and with portable instrumentation systems. This has resulted in a significant volume of research into the working mechanism of microelectrodes particularly as they do not experience an ohmic drop during their operation [90-92].

Although the continuous improvement of microfabrication techniques has enabled researchers to fabricate ultramicroelectrodes of increasingly diminutive size [93] it is through the incorporation of novel materials that the greatest advances in sensor

development are seen. For example, Dumitrescu *et al.* describe the fabrication of ultramicroelectrodes composed of networks of single-walled CNTs using lithography. The resulting electrodes exhibited low background current and decreased double layer charging in comparison to macroelectrodes, which coupled with their low surface area and capacitance resulted in fast response times in comparison to metal ultramicroelectrodes making them suitable for a variety of applications [94]. Similarly other groups report the application of printed electrodes in environmental and biological analysis [95, 96]

The work of Banks *et al.* highlights the advantages of miniaturised SPEs over conventional carbon electrodes, specifically in terms of cost and time efficiency. SPEs have been shown to possess a greater ease of use, scale of economies and are disposable in nature, requiring reduced volumes of the analyte (μl). This gives them a significant advantage over conventional (solid) carbon electrodes and other fabrication approaches (such as lithography) in sensing applications. The incorporation of nanomaterials to improve electron transfer processes, selectivity and sensitivity will only further enhance the field of electrochemical sensors pushing towards smaller and well-defined geometries in formats such as screen printed microelectrode arrays and 'lab on a chip' approaches with the overall ethos of simpler, cheaper, disposable, scalable and ease of use [85].

It follows that the application of interdigitated electrode arrays (IDAs) can also be exploited to further miniaturise sensing systems often through the incorporation of nanocomposites, Liu *et al.* [97] describes the detection of volatile sulphur compounds (associated with a variety of ailments [98-100]) in a subject's breath exhalations. The authors report that the fabricated PANI/AuNPs sensor electrodes exhibited a good response to both H_2S (1.0 ppm) and CH_3SH (1.5 ppm) gases and that in comparison with other sensors, these novel IDA electrodes possess a greater selectivity and sensitivity while also being low cost. IDAs were also the basis of a humidity sensor developed by Cassidy *et al.* [101] where an Ag polymer nanocomposite was shown to give linear detection over a range of 10 – 60 % relative humidity (RH), the resulting sensor was found to be reversible and repeatable with minimal hysteresis.

The design and fabrication of electrochemical sensors remains a vibrant area of research with the miniaturization of electrodes continuing down to the nano regime, allowing the routine measurement of fast electron kinetics at diminutive analyte concentrations. The use of nanomaterials in sensor design continues to increase enabling significant improvements in the analytical performance and utility of biosensors.

4.3. Sensitivity

The sensitivity of a sensor is defined as the slope of the analytical calibration curve for a given analyte. A sensor is sensitive when a small change in analyte concentration causes a large change in the response. Within the linear range of response, the sensitivity is a well-defined value. Improvements in sensitivity of sensors have always been of paramount interest [102]. Immunoassays based on specific antigen-antibody recognition, is a promising

approach for selective and sensitive analysis. Electrochemical immunosensors, which combine specific immunoreactions with electrochemical transduction, have attracted growing attention in recent years. They have many advantages including simple instrumentation and operation, high sensitivity and selectivity, and wide linear range. Since enzyme labels provide great signal amplification in the assay and also a large number of antibody–enzyme or antigen–enzyme conjugates are commercially available, the majority of electrochemical immunoassays are based on the use of specific enzyme/substrate couples [103-105]. Sensitivities of ng/ml can routinely be achieved in enzyme-based electrochemical immunosensors. Many interesting signal amplification strategies have been adopted to further improve sensitivity of these sensors [106-108]. For example, an immunosensor with a detection limit of 1.0 pg/mL was developed for Interleukin-6 (IL-6) based on a dual amplification mechanism resulting from Au nanoparticles (AuNP)-poly-dopamine (PDOP) as the sensor platform and multienzyme-antibody functionalized AuNP-PDOP CNT. Nonenzymatic immunosensors have also been reported to be able to achieve very low detection limits. Pichetsumthorn *et al.* [102] reported a nonenzymatic impedimetric biosensor for the small molecule atrazine. They used nanoporous alumina membranes and interfaced them with a printed circuit board. The assay achieved non-faradic detection, i.e. the transfer of charge between the biomolecule and the electrode is mediated without the use of a redox probe. The limit of detection was in the fg/mL regime with a dynamic range of detection spanning from 10 fg/mL to 1 ng/mL. Such high sensitivity was attributed to the confinement of the small molecules in the nanopores of the alumina membranes which resulted in an amplification of the impedance signal measured due to the modulation of the electrical double layer. Another highly sensitive, nonenzymatic electrochemical immunosensor [109] was constructed using a graphene platform combined with mesoporous PtRu alloy as a label for signal amplification. A low detection limit of 9.63 pg/mL using a sandwich-type assay approach for microcystin-LR (MC-LR) was reported. Again, this approach does not rely on enzymes or electrochemical redox mediators to function, but rather on the strong catalytic action of NP-PtRu alloys upon H₂O₂. Anodic stripping voltammetry (ASV) is a highly sensitive method for the analysis of trace concentrations of electroactive species in solution. Detection limits for metal ions at sub-ppb concentrations have been reported. ASV detection of metal nanoparticle labels have been used in both immunosensors [110] and DNA sensors [111]. Au nanoparticles are the most frequently used among all the metal nanoparticle labels available. Recently, Shen & Zhang reported a sensitive immunosensor using ASV for the detection of hepatitis B surface antigen (HBsA) based on copper-enhanced Au nanoparticle labels [112]. A linear range of 0.1–1500 ng/mL with a detection limit of 87 pg/mL was reported which was based on the determination of Cu by ASV.

In the past few years, many efforts have been devoted to improve the sensitivity of metal oxide gas sensors [13]. Sakai *et al.* found that the porous structure of the sensing film played a critical role in the performance of the sensor because it dictated the rate of gas diffusion [113]. Indeed, several groups have found that the particle size of the metal oxide heavily affected the sensitivity of sensor [114, 115]. Although many methods have been reported to

synthesize nanoparticles of metal oxides, often they are not stable and may easily aggregate. Besides, nanoparticles may be compactly sintered together during the high temperature film coating process, rendering them nonporous, which is a disadvantage for gas diffusion through them. If porous nanostructures are used as gas sensing materials, the gas sensing properties will be much improved. On the basis of this, nanostructures with many kinds of shapes such as porous nanowires, porous nanotubes and porous nanospheres have been reported to have excellent gas sensitivity properties. A nanocomposite of SnO₂ and multi-walled carbon nanotubes (MWCNT) [116] was exploited to detect persistent organic pollutants (POPs) which possess stable chemical properties and are ordinarily difficult to detect with metal oxides [116]. The ultrasensitive detection of aldrin and dichlorodiphenyltrichloroethane (DDT) was carried out using the nanocomposite of small SnO₂ particles and MWCNTs. The nanocomposite showed a very attractive improved sensitivity compared with a conventional SnO₂ sensor. A LOD of 0.5 ng was achieved for aldrin and DDT, which was attributed to the highly porous 3D structured SnO₂/MWCNT nanocomposites (which enhances gas diffusion).

4.4. Selectivity

Selectivity is defined as the ability of a sensor to detect one specific species even in the presence of a number of other chemical species or interferents. All electrochemical sensors exhibit a high degree of selectivity. This section will discuss recent research to develop highly selective electrochemical sensors and efforts to improve the selectivity of existing sensors through the incorporation enhanced sensing membranes. This section is divided in two parts focusing first on potentiometric and then voltammetric and amperometric sensors.

4.4.1. Potentiometric sensors

As discussed earlier, there are several basic types of potentiometric devices including ISEs, FETs [117, 118]. The ISE is the most representative potentiometric sensor; recently there has been a marked increase in the demand for miniaturised ISEs as interest in the biological application of potentiometric sensors. Recent advances in nanoscale potentiometry were discussed by Bakker and Pretsch with the authors discussing the nature and role of interfacial films on both sides of the ion-selective membrane and summarising the improved general performance of the nano-electrodes in terms of detection limits, biocompatibility, and sensor stability [119]. The application of conducting polymers in potentiometric sensing is discussed widely throughout the literature [120-123] with Faridbod *et al.* [124] reporting the use of conducting polymer-based ISEs to over 60 inorganic ions.

Ultimately the development of new means of ion recognition continues to be the main focus of ISE research, with researchers discussing the synthesis of a range of ionophores targeting silver [125, 126], lead [127] and cobalt [128] among others. In each instance improved selectivity is reported coupled with favourable LODs. Buhlmann's group having reported

the success of highly fluorinated liquid phases as sensing materials, detailing the design of numerous ion-selective sensors which incorporate fluorinated membranes [129-131].

Throughout sensor research as a whole, the area with the greatest level of continued consistent development is that which exploits nanomaterials and their novel properties, illustrated by the rapidly growing number of publications in this area. This phenomenon is most evident in the area of electrochemical sensors. Within the field of potentiometric sensors and specifically the design of contacts for all solid state sensors, the potential of nanomaterials such as CNTs and fullerenes has been rigorously examined. Rius *et al.* [132-135] described the development of many sensors based on SW- and/or MW- CNT sensors, including an all-solid-state potassium ion-selective membrane electrode and a perchlorate selective membrane electrode using a MWCNT-derived solid contact.

Recent advancements in the field of potentiometric sensors and especially in terms of ISEs have seen a significant focus on the development and fabrication of sensing membranes particularly in terms of their composition, where the incorporation of CNTs and unique ionophores in both carbon paste electrodes and polyvinylchloride (PVC)-based membranes. Carbon pastes utility as the basis of a sensing membrane is becoming increasingly clear, with the development of a number of sensors incorporating MWCNTs and specific ionophores [136-138].

Trace analysis has always been a strength of electrochemical detection. At present the detection of copper ions has become a priority of industry as many biochemical processes carried out in industrial settings depend on the presence of copper ions. Copper can displace metal ions *in vivo* and the potential of sensing techniques to determine the concentration of copper in a sample are both costly and time-consuming, prompting the fabrication of selective sensors by a number of groups [16, 139, 140]. For example, Petkovic *et al.* [140] discuss the development of a novel Cu^{2+} ISE using a PVC matrix containing N,N',N'',N'''-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane as the ionophore. A simple construction method affords a cost-effective, rapid measurement of copper in a mixed solution with EDTA. With the additional benefits of a superior working pH range and longer sensor lifetime coupled with a comparable measurement signal in comparison with commercial sensors.

Improved composition of ISE membranes has enhanced the response time for ionic sensing and as detailed above, PVC [140] has proven to be suitable for ISE construction as it allows for ease of construction and improved lifetime/robustness of the sensing matrix. PVC containing ISEs have been utilised in range of industrial studies including medical research and water contamination experiments [137, 141-144]. PVC membranes containing ISEs, have also demonstrated potential as anion selective electrodes. For example, Alvarez-Romero *et al.* [145] discuss the successful development of a graphite-based composite containing epoxy resin, doped with chloride ion doped polypyrrole, as a chloride ion selective electrode. Zahran *et al.* [146] report a novel PVC-based sensor that exhibit selectivity toward halides (chloride and bromine specifically). Similarly Kang *et al* [147] describe the fabrication and characterisation of a PVC based Sc^{3+} octaethylporphyrin composite fluoride selective

electrode this is significant as fluoride selective sensors allow for rapid detection of toxic organic fluorophosphates, which can contaminate drinking water.

The sensing of uncharged molecules is a constant challenge for researchers as they are not influenced by ionophores traditionally used to sense anionic or cationic species. The use of molecularly imprinted polymers (MIPs) has been greatly increasing in ISEs [148-151]. For example, Liang *et al.* [148] report the use of a polymeric membrane ISE to detect neutral molecules, utilising a MIP, as the sensing element and an indicator ion that is similar in structure to the targeted neutral species. The sensing protocol incorporated two stages: accumulation of neutral species in the membrane phase followed by the removal of the indicator ion and potential measurement with the ISE. The sensing device was shown to be both selective and sensitive.

The potential of potentiometric sensors is becoming increasingly apparent in biomedical research with potentiometric sensors playing greater roles in pharmaceutical development, disease screening, and disease research. PVC plays a major role in membrane fabrication for ISEs showing great versatility in terms of the variety of species sensed. Kumar *et al.* [152] present a sensor capable of selective determination of domperidone, a clinically useful pharmaceutical for a wide variety of stomach ailments. Typically the pharmaceutical's concentration is measured using a combination of analytical techniques. The authors were able to accomplish this through the use of two separate sensors, made of a PVC membrane and a carbon plate, with the electroactive ion pair domperidonephosphotungstic.

Other groups have also reported the successful fabrication of potentiometric sensors for both drug and biological detection [153-155].

4.4.2. Voltammetric sensors

Voltammetry, or more specifically amperometry is a powerful, potentially highly selective analytical technique [156]. Carbon-based electrodes are widely used in voltammetric studies because of their low cost, availability, stability and processability. This has resulted in the availability of a variety of carbon-based electrodes including GC, carbon paste (CP), polycrystalline boron doped diamond (pBDD), CNTs, and most recently graphene. Carbon-based sensors are easily modified via casting, electrodeposition, functionalisation etc. to impart selectivity. For example coupling nanostructures with high surface area with stripping voltammetry greatly enhances specificity. CNTs are ideal materials for incorporation into electrochemical sensors due to their high surface area, high aspect ratio, and enhanced catalytic properties. This is illustrated by the work of Xu and colleagues who developed a GC electrode modified with a nafion/bismuth/MWCNTs composite film capable of the sensitive detection Pb^{2+} and Cd^{2+} (LODs of 25 and 40 ppt respectively) [157]. The nanocomposite allowed the sensor to exploit bismuth's wide potential window and insensitivity to O_2 , as well as the MWCNTs enhanced adsorptive capabilities and high surface area. The authors also noted that there was no interference exhibited by a significant number of anions, with a 500-fold mass ratio of SCN^- , Cl^- , F^- , PO_4^{3-} , SO_4^{2-} , NO_3^- for example showing no influence on the sensing films signal response for $Pb(II)$ and $Cd(II)$.

Again much of sensor research is driven by a focus on a final application, with the demand for improved and continuous environmental monitoring driving a significant portion of sensor development. For example Zima *et al* report the use of numerous CPEs that incorporate nanotube or nanoparticles and are modified both chemically and biologically for the detection of various organic molecules such as pharmaceuticals and environmental pollutants. Within this work the authors describe how the performance of these sensors is enhanced, for example, a Tyrosinase modified CPE detected Cysteine with a LOD of 1 - 8 μ M with no interference from Ascorbic acid and Uric acid, similarly a CPE modified with Glucose oxidase and gold nanoparticles showed no effects in the presence these common interferents [158].

The incorporation of nanomaterials in the fabrication and development of biosensors has resulted in their improved selectivity. This is particularly evident when considering sensors for the detection of neurotransmitters such as dopamine. Shang and colleagues described the fabrication of a dopamine selective, boron-doped diamond (BDD) electrode [159]. The electrodes sensitivity (LOD of 5 nM) and selectivity was augmented by the anionic nature of the dopant, sulfobutylether-cyclodextrin, which pre-concentrated the dopamine and excluded common anionic interferences like ascorbic acid and uric acid. Yan *et al.* produced a 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of dopamine, sensor, through the functionalising of SWCNTs that were adsorbed with cyclophane (a DOPAC recognition element) on to a GC electrode [160]. The sensor demonstrated a significant selectivity to DOPAC as the SWNT transducer coupled with a cyclophane recognition element exhibited a stronger binding affinity for DOPAC over both Ascorbic acid and Dopamine.

The incorporation of bio- materials [161, 162] into electrochemical sensors enables a level of selectivity that is comparable to that seen in nature, with the majority of advancements in biosensors due to the immobilization of a biological material (and hence it's physiochemical properties to an electrode's surface electrode [163, 164]. Mimicking nature selectivity has been attempted with the use of molecularly imprinted polymers but so far has not rivalled the selectivity of biomolecules such as antibodies, nucleic acids, aptamers, etc.

4.5. Multi-analyte detection

Simultaneous detection of multiple analytes is a highly desirable feature of any sensor. Current research is endeavouring to exploit the capability of voltammetric analysis to sensitively, selectively rapidly differentiate between numerous compounds. This is particularly evident in recent developments in biosensors. Recent research highlights the interest in simultaneously quantifying physiologically relevant compounds such as uric acid, ascorbic acid and/or catecholamines [165-167]. A large body of literature describes the production of a variety of sensors with multi-analyte sensing capabilities, exploiting a variety of nanomaterials including CNTs [168-170], individual nanoparticles [171] and polymer nanocomposites [172, 173]

The electronic nose or tongue is an analytical instrument comprising an array of chemical sensors with partial specificity or cross-sensitivity to different components of a mixture/compound, and an appropriate method of pattern recognition and/or multivariate calibration for the data processing. They can quantitatively differentiate between the composition of complex liquids/gases. Such sensors have a number of applications in various industrial areas including the pharmaceutical industry and the food and beverage sector [174], where they can be used to analyse flavour ageing in beverages, quantify bitterness of dissolved compounds, quantify taste masking efficiency of formulations [175] (e.g. tablets, syrups, capsules), analyse medicines stability in terms of taste. Electronic tongue/noses are increasingly studied due to their industrial capabilities coupled with their fast and relatively cheap methodology [176]. For example, Pigani and colleagues detail their development of a poly(3,4 - ethylenedioxythiophene) modified electrode that could be incorporated into an electronic tongue. The sensor was utilised in the blind analysis of red wines, (a sample set of 144 red wines of different origin and variety) for classification and calibration purposes. Treating the data obtained from voltammetric measurements using partial least squares analysis allowed the authors to both correlate the calibration procedure results with those from traditional analytical methods and develop classification models for the wines, based on quantitative parameters and qualitative information such as the origin and variety. The sensor may also be used for quality control as it can rapidly identify samples that failed to meet threshold limits for SO₂, colour intensity and total polyphenols.

Similar studies by Gutierrez *et al.* [177, 178] in which the authors developed a sensing system for the classification and characterisation of both red and white wines. The sensor consisted of six ISFET sensors, a conductivity sensor, a redox potential sensor, two amperometric electrodes, a gold microelectrode and a microelectrode for sensing electrochemical oxygen demand. The system was shown to be capable of distinguishing between samples according to their grape and even geographical origin the authors also demonstrated the system's ability to differentiate between the mono - varietal samples and their mixtures further emphasise the extent of development sensing has undergone in the last decade and its expanding potential for multiple applications in a variety of industries will only encourage further development of multi-analyte sensing devices.

4.6. Stability

The most desirable sensors are those that retain their characteristics when tested or used under varying conditions and environments, i.e. are those which can function in a myriad of harsh conditions. Where nanomaterials are encompassed in the sensor fabrication, the resulting nanocomposites possess enhanced physical and chemical properties when compared to their constituent components depending on the chemical nature of each component and how they interact. This interaction depends strongly on characteristics of each component, i.e. interface, size, shape and structure. In extreme cases, where there is no or little interaction between the components, the composites' properties should be equivalent to a simple sum of the properties of the individual elements. In cases where the

interaction between the constituents is strong, the properties of the composite system can differ substantially from the simple sum of the properties of the individual components. The characteristics of the individual components are lost and new features arise as a result of the strong interaction [166].

Chik and Xu [179] have described a fabrication method that not only allows the addition of a variety of materials, including metals, semiconductors, and CNTs to an anodised aluminium oxide porous membrane but also, through tuning of the synthesis parameters, controls the nanomaterials morphology. This enabled the authors to engineer the physical properties of the composite by determining the shape, size, composition and doping of the nanostructures, as well as new properties produced by their interaction with the matrix itself. Some of these properties and functions were not intrinsic to the individual nano-elements but were due to the collective behaviour of the nanostructures within the membrane. The novel nanocomposite platform described potentially offers a wide range of applications in various fields including electronics, optics, mechanics, and biotechnologies.

Shi *et al.* [180], summarise a range of chemical sensors that apply the optical principles of nanomaterials for the detection of multiple chemical and biochemical analytes. These include colorimetric biosensors based on gold nanoparticles, gas sensing semi-conductors which exhibit changes to their optical transmittance when exposed to gases such as NO, and CO and optical humidity sensors based on changes in cobalt oxide films' absorbance in the visible wavelength. In this review the authors also report the development of a SrCO₃ nanoparticle based ethanol sensor which displayed exceptional durability during a 100 hour reaction with 2000 ppm ethanol at 380 °C.

Chemiresistor sensors have many potential applications, including environmental monitoring [183]. However these sensors can become unstable in extreme environments. The preparation of a nanocomposite can counteract the existing weaknesses of conventional sensors by combining the strengths of nanoparticles with the composite material [184]. This is clearly illustrated in the application of nanocomposites in humidity sensing techniques. Humidity sensing materials can be grouped into two types; ceramics and polymers both possess good chemical and thermal stability, environmental adaptability and a wide range of working temperatures.

Often the sensing mechanisms these materials employ are their surface electrical conductivity or the dielectric constant, which are affected by the adsorption of water vapour. Polymer-based humidity sensing materials possess some advantages in comparison to ceramics; including a higher sensitivity, decreased humidity hysteresis, low cost, flexibility and easy processability [180]. For example, Wang *et al.* [185] describe the improved humidity sensing capability and stability seen by combining nano BaTiO₃ with acrylic resin as a nanocomposite humidity sensor. The authors determined that the electrical properties of the sensor, including resistance versus relative humidity, humidity hysteresis, response recovery time and long term stability of the composite sensor were better than that of a sensor composed just of the nano BaTiO₃. Similar research has led to multiple reports on

chemical polymerisation and electrochemical techniques for the preparation of polymer nanocomposites for gas and humidity sensor applications [186-188].

Similarly the stability of biosensor may be significantly enhanced through the incorporation of nanomaterials [189, 190]. For example, Gopalan *et al.* fabricated an electrochemical biosensor-based on a multi-component composite comprising of MWNT, silica, Nafion and PANI. This blend of these materials within the sensing composite resulted in excellent electrocatalytic activity, sensitivity and stability. Silica gave the composite mechanical stability due to its rigid 3D porous structure and the inclusion of the MWCNTs was also benefited the sensors mechanical rigidity. Moreover the incorporation of Nafion minimised the brittleness of the pure sol-gel derived silica and enhanced the sensor's long-term stability. The authors utilised this organic-inorganic nanocomposite as a glucose biosensor possessing enhanced stability over time. The sensor displayed a reproducible current response (R.S.D. < 2.2%) for 10 measurements. The stability of the Nafion-silica/MWNT-g-PANI/GOx biosensor was determined by storing the biosensor at 4 °C in PBS (pH 7) for 20 days and monitoring the response current daily for 1.0 mM of glucose at +0.20 V. The biosensor retained its 93% current response after 20 days by loading GOx within the nanocomposite [191].

Similarly Guell and co-workers [192] detail a study of the differing characteristics of three carbon-based electrodes: GC, pBDD, and CNTs. The authors determined that "pristine" CNT networks exhibited background current densities that were 2 orders of magnitude lower than GC and 20 times lower than pBDD for the detection of serotonin, however pBDD electrodes underwent significantly less fouling (minimised by optimisation of the potential range) than the CNTs electrode and exhibited superior stability which is often attributed to the H-surface termination of as-grown pBDD electrodes.

Apetrei *et al.* compared CPEs prepared with graphite, carbon microspheres, or MWCNTs. The electrodes made using carbon microspheres were the most stable (giving consistent results for successive measurement of catechol, with a relative standard deviation of just 3.2%) and gave the best performances in terms of kinetics. Their work also demonstrated that an array combining the three electrode types could discriminate between a number of anti-oxidants depending on their chemical structure and reactivity [193].

Strategies for enhancing the stability of electrochemical sensors continue as advances already made result in the application of sensors in a variety of environments previously considered excessively harsh, e.g. extreme temperatures [194], both high and low pH [195]. Analytical chemists have overcome such challenges by both incorporating biomolecules into sensor platforms and exploiting the desirable properties of novel materials with nanotechnology allowing the development of a variety of disposable and long-life sensors.

5. In summary

Electrochemical sensors have a long and rich history in the field of analytical chemistry contributing to multiple industries. The impact of electrochemical sensors is clearly

illustrated by their multiple every day applications and the sheer number of commercially available sensors available. This is evident especially in the field of potentiometric sensors where the further development of ISEs remains the mainstay of recent research. The enhancement of such devices sensing abilities in terms of sensitivity, selectivity, and stability through the incorporation of both novel ionophores into sensor membranes and strategies including analyte preconcentration and background subtraction has allowed the effective detection of cations, anions, and neutral species in challenging environments (conditions with high concentrations of background analytes and biological milieu).

As the demand for sensitive, rapid, and selective determination of analytes continues to grow, so too does the utility of electrochemical sensors. Unlike their spectroscopic and chromatographic counterparts, they are readily adapted for the detection of a wide range of analytes and may be incorporated into robust, portable and/or miniaturised devices while remaining relatively inexpensive.

Despite their ubiquitous presence, electrochemical sensors remain a dynamic field of research especially when coupled with the continued expansion of nanoscience and nanotechnology. Nanomaterials already have extensive applications in electrochemical sensors systems with a significant potential for future development. This is primarily due to the unique and attractive properties that nanoparticles and nanostructures exhibit, the exploitation of which allows the development of electroanalytical systems exhibiting similarly attractive analytical behaviours. A wide variety of metallic and organic nanomaterials have been used to fabricate a diverse range of electrochemical sensing systems, based on their special physical, chemical and even biological properties. Further development of electroanalytical sensor technology, with the discovery and subsequent exploitation of novel properties of nanomaterials will only result in the further evolution of electrochemical sensing platforms.

The majority of modern electrochemical sensor development focuses on the incorporation of both microfabrication and nanofabrication to design sensors of a smaller size and hence lower power demands, of lower cost, and improved portability. The miniaturisation of electrodes continuing down to the nano regime has allowed measurements of fast electron kinetics at very low analyte concentrations. The demand for increasingly low detection levels has been met with the production of arrays. The incorporation of nanostructures has augmented the electrode reactive surface area even with less material used in the physical electrode allowing greater signal to noise ratio for a given analyte.

The development of sensors for the measurement of neurotransmitters is a major trend emerging in voltammetric sensor research, with the sensitivity and selectivity of such sensors being greatly improved due to the development of both measurement techniques and electrode materials. A recent shift in focus from glucose analysis to other physiologically analytes, has driven biosensor development, with DNA hybridization and immunological recognition being the basis of a significant portion of new electrochemical detectors. Again the application of nanomaterials has enabled significant improvements in the analytical performance and utility of biosensors.

In conclusion, the field of electrochemical sensors continues to grow and develop new applications at pace. The incorporation and interaction of unique materials, both nano and biological, remains the focus of a significant portion of research. This will likely continue as the production of sensors with increased specificity and sensors capable of simultaneous determinations with the ability to operate in complex matrixes remains the long term focus of sensor research.

Abbreviations

2-diisopropylaminoethanethiol	DIPAET
Alternating Current	AC
Boron - Doped Diamond	BDD
Carbon Nanotube	CNT
Carbon Paste Electrode	CPE
Coated Wire Electrodes	CWES
Deoxyribonucleic Acid	DNA
Electrochemical Impedance Spectroscopy	EIS
Ethylenediaminetetraacetic acid	EDTA
Femtograms	fg
Glassy Carbon	GC
Glutathione	GSH
Hepatitis B surface Antigen	HBsA
Human Serum Albumin	HSA
Indium Tin Oxide	ITO
Ion Selective Electrode	ISE
Light Addressable Potentiometric Sensors	LAPS
Localised Surface Plasmon Resonance	LSPR
Methyl dopa	MDA
Millilitres	ml
Molecularly Imprinted Polymers	MIPs
Nanograms	ng
National Nanotechnology Initiative	NNI
Nicotinamide Adenine Dinucleotide	NADH
Parts per Billion	ppb
Persistent Organic Pollutants	POPs
Poly(3,4-ethylenedioxythiophene)	PEDOT
Poly(styrene-co-acrylic Acid)	PSA
Polyaniline	PANI
Poly-Dopamine	PDOP
Prussian Blue	PB
Quantum Dots	QDs
Room Temperature Ionic Liquids	RTIL
Single Walled Carbon Nanotube	SWCNT
Standard Hydrogen Electrode	SHE

Three Dimensional	3D
3,4-dihydroxyphenylacetic acid	DOPAC
Anodic stripping voltammetry	ASV
Carcinoembryonic Antigen	CEA
Carbon Nanotube Epoxy Composite Electrodes	CNTECE
Chemically Modified Graphene	CMG
Cyclic Voltammetry	CV
Dichlorodiphenyltrichloroethane	DDT
Electrospun Carbon Nanofiber – Modified Carbon Paste Electrode	ECF-CPE
Federation of European Chemical Societies	FECS
Field Effect Transistor	FET
Glucose Oxidase	GOD
Graphene Nanoribbon	GNR
Hexanedithiol	HDT
Immunoglobulin G	IgG
International Union of Pure and Applied Chemistry	IUPAC
Ion Selective Field Effect Transistor	ISFET
Limit of Detection	LOD
Mercapto-1Hexanol	MCH
Microcystin-LR	MC-LR
milli-molar	mM
Multi Walled Carbon Nanotube	MWCNT
Nanoparticles	NPs
Nitrate Reductase	NR
Nuclear Fast Red	NFR
Parts per Million	ppm
Point of Care	PoC
Poly(3,4-ethylenedioxythiophene) : Poly(styrenesulfonic Acid)	PEDOT:PSS
Poly(styrenesulfonic Acid)	PSS
Polycrystalline Boron Doped Diamond	pBDD
Polyvinyl chloride	PVC
Prussian White	PW
Relative Humidity	RH
Screen Printed Electrode	SPE
Specific Thiolated Capture Probe	SHCP
Surface Plasmon Resonance	SPR
Trinitrotoluene	TNT

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