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Electrochemical stripping analysis

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Abstract

Electrochemical stripping analysis (ESA) is a trace electroanalytical technique for the determination of metal cations, inorganic ions, organic compounds and biomolecules. It is based on a pre-concentration step of the target analyte(s), or a compound of the target, on a suitable working electrode. This is followed by a stripping step of the accumulated analyte using an electroanalytical technique. Advantages of ESA include high sensitivity and low limits of detection, multi-analyte capability, low cost of instrumentation and consumables, low power requirements, potential for on-site analysis, speciation capability and scope for indirect biosensing. This Primer covers fundamental aspects of ESA and discusses methods of pre-concentration and stripping, instrumentation, types of working electrodes and sensors, guidelines for method optimization, typical applications, data interpretation and interferences, and method limitations and workarounds. Finally, the current trends and future prospects of ESA are highlighted.

Electrochemical stripping analysis (ESA) is a family of electroanalytical techniques mainly applicable to the quantitative determination of metal cations, inorganic anions, organic compounds and biomolecules. It is used in fields where trace or ultra-trace quantification is required. For example, one of the main applications of ESA is to monitor and speciate heavy metals in environmental samples[1–3.] Other important applications involve pharmaceutical analysis, food analysis, clinical chemistry and forensics[4–6]. The term 'electrochemical stripping analysis' refers to a group of electroanalytical methods, where the analysis is performed in a two-step process[7]. The initial pre-concentration step involves pre-concentration (accumulation) of the analytes or their compounds onto a suitable working electrode. During the second stripping step, the analyte is quantified using an appropriate electroanalytical technique[8–12.] The pre-concentration step differentiates ESA from other electroanalytical methods because it enriches the working electrode with the target analyte(s) or a compound of the target(s). Therefore, the analyte concentration on the working electrode surface is much higher than its concentration in the original sample. As the subsequent electrochemical quantification step monitors the accumulated analyte, high sensitivity and low limits of detection can be achieved[13,14].

Other advantages of ESA include multi-analyte capability, low cost of instrumentation and consumables, low power requirements, potential for on-site analysis, speciation capability and scope for indirect biosensing.

ESA traces its roots back to the 1930s with Christian Zbinden's experiments. Zbinden exhaustively electrolysed a dilute Cu2+ solution with copper deposition on a platinum electrode. He then reversed the polarity of the two electrodes, dissolving the copper metal at constant current, and measured the charge required to dissolve the copper deposit. The amount of copper was then calculated using the Faraday law[15]. However, Geoffrey Barker can be considered the inventor of modern stripping techniques when, in a landmark paper, he formulated the complete concept of stripping techniques at a mercury drop electrode[16]. The evolution of ESA and associated important advances in the field[17] are summarized in Fig. 1. Different ESA variants have been developed, depending on the pre-concentration method and subsequent electrochemical quantification used. Pre-concentration can be performed by various approaches, including the following[7,11,12]: reduction or oxidation of the analyte on a suitable working electrode; adsorption of the analyte or its compound on a suitable working electrode; chemical reaction of the analyte with the working electrode material or the oxidized form of the working electrode; extraction of the analyte within the working electrode material; ion-exchange reaction of the analyte with an exchanger attached on the working electrode; and ion transfer of the analyte between two immiscible electrolytes. The most widely used pre-concentration methods are schematically described in Fig. 2a and involve either electroreduction or adsorption. Electroreduction occurs by electrolysis of metal cations at solid, mercury or green metal — such as bismuth, tin or antimony — working electrodes[18,19] (Fig. 2a(i)). The metal cations are reduced to the corresponding metals, forming a deposit on the solid electrode, or an amalgam with a mercury electrode or an alloy with green metal electrodes. Organic compounds or metal complexes can be adsorbed at different types of working electrodes[20,21] (Fig. 2a(ii)). To induce adsorption of analytes on the electrodes, metal cations are usually converted into complexes with organic ligands possessing surface-active properties, whereas many organic compounds are inherently surface-active and adsorb spontaneously on the working electrode.

The amount of analyte, or its compound, that accumulates on the electrode determines the sensitivity of detection. Normally, pre-concentration is performed under conditions which promote efficient pre-concentration and selective attachment or binding of the analyte to the working electrode. For example, desirable pre-concentration conditions may involve long deposition times, convective mass transfer of the analyte to the working electrode surface or favourable potential of the working electrode.

In the stripping step, the pre-concentrated analyte undergoes a redox reaction, which can be exploited for quantification (Fig. 2b). In the case of electrolytic pre-concentration of metal cations, stripping involves oxidation of the accumulated metals back into solution as metal cations. For adsorbed species, stripping involves reduction or oxidation of the accumulated organic compound, or reduction of the accumulated metal complexes. The method used to perform the stripping step and record the electrochemical response is critical and depends on the specific application (Fig. 2c). Electrochemical quantification is normally performed by voltammetry or (chrono-)potentiometry. The relevant stripping modes are termed stripping voltammetry and potentiometric stripping analysis (PSA), or stripping (chrono-)potentiometry, respectively.

This Primer focuses on the instrumentation and electrodes used in ESA, typical applications of ESA in various fields, guidelines for method optimization and method limitations. The Primer does not cover more specialized topics such as less common pre-concentration methods, chemically modified electrodes with selective ligands and theoretical aspects of ESA. Experimentation

Instrumentation

ESA uses simple and inexpensive instrumentation of small size, low power requirements and no need for maintenance. This is a distinct advantage over competing techniques, such as atomic spectrometry, which rely on laboratory-based instrumentation. The principle of the modern three-electrode potentiostat — comprising a working electrode, a reference electrode and a counter electrode — was described in 1942 (ref.22) and the vast majority of ESA applications still use a similar set-up23. In this configuration, the potential of the working electrode is controlled or measured with respect to the reference electrode and current flows exclusively between the working electrode and the counter electrode (Fig. 3Aa). Today, ESA experiments are conducted with multipurpose instruments commercialized by different manufacturers that control the pre-concentration conditions — time and potential — and can implement the selected stripping technique, such as different variants of stripping voltammetry and PSA, under computer control[24]. These instruments can accommodate different types of working, counter and reference electrodes depending on the application of interest. They usually provide additional input/output lines to trigger external ancillary equipment, such as stirrers and pumps. In addition to conventional benchtop electrochemical workstations, portable battery-powered and handheld instruments capable of conducting ESA are now available. This has enabled on-site or point-of-care stripping measurements to be performed in conjunction with integrated electrochemical sensors[2,25]. For multiplexed experiments, multi-potentiostats are available that can control either several working electrodes, which share common reference and counter electrodes[26], or many independent three-electrode cells[27]. In many cases, ESA experiments are conducted using instruments fabricated in-house and controlled by proprietary software[28,29]. Paper-based instruments are also possible[30]. FIGURE 3Ab–d illustrates schematics of a conventional benchtop three-electrode set-up using a batch cell, an online configuration featuring a three-electrode flow-through cell and a typical portable instrument with an integrated three-electrode sensor.

Types of working electrodes

The working electrode represents the most important component of an electrochemical cell. The general criteria for an ideal working electrode include minimal non- faradaic (or capacitive) contributions, wide polarization potential window, low cost, mechanical stability, ease of machining or forming into different shapes, reproducible surface morphology, low toxicity, resistance to fouling and high electron transfer rate. Additional criteria for the selection, design or fabrication of a suitable working electrode are analyte- specific. They are mainly associated with the desired analyte pre-concentration mechanism on the electrode surface, issues of sensitivity, selectivity and the preferred antifouling properties. Solid electrodes made of various forms of carbon — such as glassy carbon and boron- doped diamond — and inert metals — such as platinum — are commercially available in the form of discs or wires. Such electrodes have some limitations as working electrodes[31]. They require careful pretreatment, polishing, conditioning and cleaning. Additionally, deposits formed during the accumulation step are not uniform and intermetallic compound formation is common. As a result, their applications in ESA are limited.

Carbon paste electrodes (CPEs) are made in- house by mixing graphite and a hydrophobic binding liquid, such as paraffin or silicone. The accumulation on CPEs is often based on a synergistic adsorptive/extractive mechanism, in which the hydrophobic binder in the paste serves as an extraction medium. Therefore, these electrodes are very useful for the determination of many less polar organic compounds by ESA[32]. Mercury working electrodes have traditionally been used for ESA of metals and organics. Liquid mercury has many favourable attributes as an electrode material. For example, it is available at high purity; has adsorptive properties, which are useful in adsorptive accumulation; has a high hydrogen reduction overpotential; the drop can be reproduced with high precision; a new surface is available for each measurement; and mercury forms amalgams with many metals. These properties facilitate the accumulation and stripping steps, while minimizing the formation of intermetallic compounds. For many years, the hanging mercury drop electrode (HMDE) —which consists of a drop of mercury suspended at the end of a capillary filled with mercury — has dominated ESA[17]. It is commercialized by several manufacturers under different names, such as the HMDE or the multimode electrode. The mercury film electrodes, which consist of a thin layer of mercury deposited on a conductive substrate[33], can be easily prepared in the laboratory and provide even lower limits of detection than the HMDE[34,35].

A family of more environmentally friendly sensors are the various amalgam electrodes, which are fabricated by ex situ amalgamation of mercury with gold, silver or copper[36,37], as it has been shown that the amount of mercury released from these sensors is negligible[38]. However, the use of mercury is discouraged owing to current and future health and environmental concerns, alongside respective legislation to address these issues[38]. A major requirement for alternative electrode materials is a sufficiently high hydrogen reduction overpotential that would enable efficient operation even in acidified samples. Over the past two decades, non- toxic green metals — antimony, tin and, in particular, bismuth — have been increasingly applied as working electrode materials. They display an attractive performance in ESA and compare favourably with that of mercury- based electrodes[39,40]. These working electrodes can be fabricated by machining bulk metal rods. Alternatively, a thin film of the green metal can be electrodeposited on a conductive support, such a boron- doped diamond[41], glassy carbon[42], carbon paste[43] and various metals[31], either simultaneously with the target metals (in situ deposition*)* or in a separate solution (ex situ deposition). Another fabrication method is to modify an electrode with metal precursor compounds — oxides or salts — that are converted into the green metal during analysis[39,40].

Gold working electrodes in the form of wires, rods or gold thin films are commercially available and widely used for mercury, arsenic and selenium detection by ESA as there is a strong interaction of these elements with a gold surface[44]. Gold electrodes can also be used for the monitoring of other trace metals45. Screen- printed electrodes (SPEs) are fabricated by squeezing the chosen conductive printing ink on an insulating substrate through a screen mesh template[46]. The printing material is normally a graphite- containing ink; however, gold, platinum and silver SPEs can be produced by using graphite ink loaded with these metals. SPE devices are becoming increasingly popular for ESA as screen printing offers versatility in terms of electrode design, potential for integration and miniaturization, choice of materials and scope for mass production of low- cost, disposable and highly reproducible sensors[47–49]. Importantly, this manufacturing approach enables the construction of integrated three-electrode sensors that do not require external reference and counter electrodes and can operate even with drop- sized samples. SPEs are produced by, or can be ordered to individual specifications from, many companies. However, they can also be manufactured in- house using standard screen- printing equipment.

Other, more specialized laboratory- based fabrication and microfabrication approaches can produce fully integrated sensing devices for ESA. These methods include microengineering[50–53], injection moulding[54] and 3D printing[55,56]. In addition, different flow- through cells[57,58], fluidic or microfluidic platforms[59,60] and three- electrode paper- based fluidic devices[61,62] have been reported for ESA. Microelectrodes, with active dimensions of a few to a few tens of micrometres, or ultra- electrodes and nano- electrodes, with active dimensions of less than 100 nm, offer numerous advantages compared with macro- electrodes. These advantages include enhanced mass transport, reduced ohmic drop, low parasitic capacitive currents and scope for miniaturization.

Several types of microelectrodes have been used in ESA[63,64.] Their main drawback is the low signal due to their small size, which makes measurements sensitive to extraneous noise. This problem can be addressed by using arrays of interconnected microelectrodes arranged in a geometrical pattern. This enables current amplification proportional to the number of the elements in the array[65]. Single microelectrodes or arrays can be made of carbon, platinum, gold, iridium, boron- doped diamond and alloys. They are usually modified with mercury, bismuth and gold films, plus antifouling coatings, such as agar and Nafion. Single microelectrodes can be fabricated in- house or purchased, but the fabrication of microlectrode arrays requires access to specialized microengineering manufacturing facilities. Working electrodes modified with polymers[66], metal nanomaterials and micro materials[42,67–69] and metal oxides[69] extend the sensing applicability in ESA. The modification step aims to enhance the detection sensitivity or selectivity and to improve the robustness of the relevant sensors, through protection from matrix effects or stabilization of the sensing layer. However, these types of modified sensors are not available off the shelf and fabrication in the laboratory requires the development of proprietary modification methods and skilled personnel.

Pre- concentration variables

In ESA, the sensitivity critically depends on the amount of analyte accumulated on the surface of the electrode during pre- concentration. This is mainly defined by the rate of mass transport to the electrode, the deposition time and the deposition potential. Longer pre- concentration times enhance the sensitivity, but lead to an undesirable increase in analysis times. This can be addressed by more efficient mass transfer of the analyte to the surface of the working electrodes during the pre-concentration step. Normally, this is achieved by forced convection, for example mechanical stirring of the solution using a magnetic stirring bar or rotation of the electrode. However, in addition to these conventional methods, some unconventional techniques have been developed to enhance mass transfer, such as the application of vibrations, ultrasound, microwaves, magnetic fields or heating of the working electrode[70,71]. Finally, in many cases pre- concentration is performed in flow- through electrochemical cells under flow conditions that promote mass transport to the electrode surface[57]. For methods involving electrolytic pre- concentration of metals, the deposition potential should be more negative than the reduction potentials of the target metal(s). However, a very negative pre-concentration potential may cause excessive hydrogen evolution, which could interfere with the deposition process. On the other hand, it was recently shown that ultra- cathodic deposition beyond the point of hydrogen evolution can, under some circumstances, yield substantial enhancement in sensitivity[72,73.] For methods involving adsorptive pre- concentration, the efficiency of adsorption depends on the hydrophobicity, molecular structure and charge of the target adsorbate, as well as the potential, which defines the charge, of the electrode[74]. Therefore, the optimum pre- concentration potential is often determined experimentally.

Stripping step

The stripping step can be implemented by various means, normally different variants of stripping voltammetry and PSA. It must be noted that the pre- concentration step is similar in both voltammetric and (chrono-)potentiometric stripping methods. As a result, the relevant pre- concentration parameters are the same. In stripping voltammetry methods, the potential of the working electrode is scanned with respect to time in a linear fashion or using a pulsed modulated waveform[19,75] (Fig. 2c(i)). Depending on the potential scan direction, the relevant techniques are termed anodic stripping voltammetry (ASV) and cathodic stripping voltammetry (CSV). As the potential of the working electrode reaches the redox potential of an accumulated species, a redox semi- reaction occurs giving rise to a faradaic current, which is recorded as a peak- shaped response in the voltammogram. Pulsed voltammetric waveforms — such as differential pulse or square wave — are preferable to a linear scan waveform because they can discriminate against the parasitic capacitive current resulting in lower limits of detection[75,76]. The differential pulse waveform discriminates well against the capacitive current but is limited to relatively low scan rates. By contrast, the square wave modulation combines higher scan rates with efficient discrimination against the capacitive current, but can lead to low sensitivity in the case of electrochemically irreversible stripping reactions[77]. The different parameters of the scanning waveform, such as scan speed, pulse amplitude, pulse duration and pulse frequency, affect the features of the voltammogram, including peak height, peak width and background characteristics. Usually, these parameters are optimized experimentally.

In PSA, the accumulated species is oxidized using a chemical oxidant. Alternatively, the accumulated species is oxidized or reduced using a current of appropriate polarity. This variant of PSA is sometimes referred to as constant current PSA or constant current stripping (chrono-)potentiometry[78,79] (Fig. 2c(ii)). The potential of the working electrode is monitored with respect to time and the differential $\Delta t/\Delta E$ is recorded as a peak- shaped response in the potentiogram. In stripping (chrono-) potentiometry, which exploits a chemical species such as dissolved O2 as an oxidizing agent, the supply of oxidant to the electrode surface defines the sensitivity of detection and should remain as constant as possible. In constant current stripping chrono- potentiometry, the oxidizing or reducing current is user- defined and determines the sensitivity of detection. The choice of stripping technique depends on the application of interest. However, it is generally acknowledged that PSA with chemical oxidation of the accumulated species is more tolerant to adsorption effects caused by organic matter in many samples[80]. It is also suitable for low ionic strength and low conductivity solutions[78] and unaffected by capacitive contributions. Consequently, it may be preferable to stripping voltammetry in the case of slow electrochemical kinetics[81], but is more sensitive to variations in hydrodynamic conditions[82]. Only scarce data exist regarding the relative sensitivity achieved with each stripping technique. A recent study summarizing the literature on iron and copper determination by PSA and stripping voltammetry concluded that no clear advantage of either technique could be documented[83].

Sample preparation and optimization

Some liquid samples with a simple matrix, for example tap water, can be analysed without pretreatment. However, many liquid samples and most solid samples — including beverages, pharmaceuticals, fuels, food, and environmental and clinical material — require sample treatment in order to release the target analytes, convert them into quantifiable species and eliminate matrix interferents. Sample treatment ranges from simple UV irradiation for organic matter removal to more complex procedures, such as microwave or acid digestion, dry ashing or ultrasound- assisted extractions[3,4]. Sample processing prior to ESA must ensure that the sample is well buffered at the optimal pH for analysis. In environmental and biological samples, heavy metals are found as free hydrated cations, as complexes with organic ligands (humic and fulvic acids) and inorganic anions (Cl−, SO4 2−) or adsorbed on colloidal matter[84–86]. As the pH of the sample decreases, metals are released from their bound form as free metal cations, leading to an enhanced stripping response[19,87]. For many organic compounds, the pH determines their speciation and charge. This, in turn, determines their adsorptive properties and the potential at which they are stripped. Local pH changes at the electrode surface during electrodeposition should also be considered. For instance, highly negative working electrode potentials can cause a local pH increase, which can lead to the formation of hydroxides or metal oxides on the surface of the working electrode. Consequently, appropriate buffers are usually added to the sample, which additionally increase the solution conductivity. An elegant method to acidify the sample without the addition of chemicals has been recently proposed and is based on the in situ local electrochemical production of protons using a protonator electrode[88]. Finally, dissolved oxygen may cause oxidation of the accumulated species and, in this case, deoxygenation is recommended by purging with an inert gas, such as nitrogen or argon; an alternative approach involves the use of an electrochemical bult- in oxygen filter[89].

For method optimization in ESA, the different instrumental parameters — deposition time, deposition potential, mass transfer conditions, stripping method and relevant variables — and chemical conditions — sample pH, electrolyte type and concentration — should be judiciously selected to achieve optimum sensitivity and selectivity. The majority of reported methods are based on univariate optimization, where the parameters are singly optimized one after the other. However, chemometric optimization techniques have been reported that involve simultaneous intentional variations of the experimental conditions under a predetermined protocol[90–93.]These optimization strategies are faster and take account of possible interactions between the various parameters. The main variables that determine the signal in ESA are schematically illustrated in Fig. 3B.

The response in ESA is visualized as a voltammogram or potentiogram, where the presence of analytes is observed in the shape of peaks. Prior to quantification, stripping peaks should be assigned to the corresponding chemical species. This is particularly important in metal analysis because different oxidation states or complexed forms, such as free metal and labile or inert complexes, will result in peaks with different peak potential and height[85,94]. In stripping voltammetry, peak current values are usually considered as the analytical parameter, although the use of peak area is preferable for voltammograms with an intricate baseline or non- Gaussian peak shape (Fig. 4A). If (chrono-)PSA is considered, the area under the peak- shaped response is recommended as the analytical parameter[95,96] (Fig. 4A). The quality of the results of an analytical determination is directly related to the accuracy with which peak currents and peak areas are measured, alongside the suitability of the selected calibration method. In this context, the appropriate baseline subtraction method is of great relevance. Different algorithms for baseline subtraction have been proposed[97–99] and the software of modern electrochemical instruments includes integrated routines to perform this task. Figure 4B illustrates how appropriate definition of the baseline affects the current to be measured — the same is applicable for peak areas — using ASV as an example. It must be pointed out that direct subtraction of a blank signal is not usually considered owing to the difficulty of reproducing the matrix of the sample. Therefore, the use of analysis tools provided by electrochemical software is the preferred way considered for measurements. If the obtained voltammograms are largely affected by background current or instrumental noise, preprocessing is recommended before peak integration. Preprocessing can range from derivative signal transformation[100] and function fitting[101] to digital smoothing[102]. This data treatment can be directly performed with the software provided by the instrument, or undertaken externally using different algorithms[103–107]. However, excessive preprocessing can introduce artefacts in data analysis. For example, the effect of overcorrection in stripping signals is demonstrated in Fig. 4C. Quantitative information is obtained by using an appropriate calibration method. Establishing a correct calibration procedure is essential to prevent systematic errors and matrix effects. Depending on the application, calibration can be carried out using univariate or multivariate methods with standard solutions[108–112]. The principle of univariate calibration with a calibration curve prepared using external standards is illustrated in Fig. 4Da and is based on the establishment of a relationship between the signal and the concentration of an individual analyte. By contrast, in multivariate calibration methods, whole sets of voltammograms are mathematically treated to deduce the concentration of one or more analytes[113]. In cases where matrix effects are significant, the calibration method must be able to correct for the presence of matrix interference. To this end, although calibration with matrix- matched standard solutions can be used[114], the method of standard additions or modified standard additions is preferable because it is simpler, faster and does not require matrix- matched standard solutions[115,116]. The standard additions method involves adding small volumes of a concentrated standard solution of the analyte(s) directly into the sample, as illustrated in Fig. 4Db. Additionally, internal standards can correct for signal variability in consecutive measurements. This is achieved by using the ratio of the target compound signal to the internal standard signal as the analytical parameter[117–119]. In external calibration methods, the linear calibration curve should bracket the expected analyte concentration in the sample and include at least 5, and preferably more, calibration points to improve the precision. In the case of standard additions, the signals due to the native analyte and after the standard additions should be within the linear range of the method[120] The vast majority of commercial electrochemical workstations are offered bundled with proprietary user interfaces, including control, data collection, signal processing, data evaluation and display. This has the advantage of significantly reducing the processing time required for routine analysis.

Method validation includes the derivation of key parameters — linearity, limits of detection and quantification, precision, accuracy and ruggedness — calculated in the manner recommended by regulatory authorities[121–123]. Applications ESA has long been considered a powerful tool for the determination of trace metals, organics and metal–organic compounds in a wide range of samples[11–13,79,124–126]. Its advantages include low limits of detection, good selectivity and the capacity to simultaneously detect several elements. Despite the fact that a direct comparison between ESA and competing trace metal analysis techniques is application- dependent, the applicability, precision and sensitivity of ESA are considered comparable with those of modern atomic spectrometry and mass spectrometry approaches, but at a small fraction of their cost[127–131]. However, ESA outperforms these approaches for on- site and online monitoring applications owing to portable instrumentation and availability of disposable sensors. For instance, low- cost portable ASV analysers have been found to match the performance of advanced spectroscopic approaches for the determination of lead in water and blood[132,133]. ESA is also the preferred approach for analysis of samples containing high concentrations of inorganic salts, such as seawater, and redox or chemical speciation studies of some metal ions and their complexes. In addition, ESA, unlike atomic spectrometry methodologies, is applicable to many organic compounds and biomolecules. The sensitivity, selectivity, linear range and limit of detection of ESA techniques in routine applications are dependent on numerous parameters. These include the composition of the sample analysed, the type and concentration of the supporting electrolyte, and the instrumental parameters.

Instrumental variables include the type of working electrode, the analyte pre- concentration time and potential and the stripping step mode. The lowest detection limits achieved by the most popular ESA techniques range from 10^{-10} to 10^{-11} mol l^{-1} (ref.40). Typical applications include the determination of metals and organic compounds in various samples. For example, samples may be environmental, such as natural water, sediments, soil, fly ashes, minerals and airborne articulate matter. Alternatively, they could be industrial, from industrial fluids and waste, metals, alloys, gasoline, oils, ceramics and pigments. Other applications deal with biological, biochemical and clinical material originating from plants, hormones, nucleic acids, organs, body fluids and tissues. Additional sample types include food-related material, for example foodstuff, wines and juices, pharmaceuticals in both formulations and antibiotics or samples in forensics, for instance drugs in body fluids, gun powder residues and explosives.

Trace metals and metalloids

ASV has been widely used for the simultaneous measurement of heavy metal content — in particular copper, lead, cadmium and zinc — in water samples and other media, including blood and body fluids. The range of metals that can be quantified by different ESA techniques is presented in Fig. 5. For example, the lead concentration in blood can be determined on- site using commercially available portable ASV- based analysers[134]. This enables a lead exposure assessment of children[135], lead miners and smelters[133] and wild animals[136,137]. New ASV procedures continue to be developed and applied for determination of copper, lead, cadmium or zinc using new sensors, configurations and procedures[19,39,40,57,138–140]. ASV has also been exploited for the quantification of other metals forming alloys, notably for the detection of mercury or arsenic, using gold working electrodes[141,142]. Alongside ASV, researchers have developed methods involving adsorptive pre- concentration, for example adsorptive stripping voltammetry (AdSV) and PSA with adsorptive pre- concentration, for the detection of metal cations that form complexes with certain ligands[143]. Such adsorptive accumulation of metal complexes expands the scope of ESA towards important metals — such as iron, nickel, cobalt, uranium, vanadium and molybdenum — that cannot be readily pre- concentrated by electrolysis.

These procedures have mostly been applied to the analysis of sea and inland water samples for trace elements that are toxic or essential for aquatic organisms[141,144–146]. To increase the sensitivity of adsorptive procedures it is possible to exploit efficient adsorptive accumulation of the electroactive species, combined with catalytic reactions. During these processes, analytes induce cyclic or non-cyclic catalytic reactions in the vicinity of the working electrode surface[147–151]. The dual amplification induced by such adsorptive- catalytic methods enables the sensitivity to be enhanced by one or two orders of magnitude. This allows inorganic ion detection, for example of molybdenum, cobalt and platinum, at concentrations as low as 10^{-12}–10^{-13} mol l^{-1}. The proper selection of ligand and catalytic agent plays a significant role in achieving extremely high sensitivity in catalytic adsorptive stripping methods.

Water samples are analysed in the laboratory or on- site using automated flow systems[57,141,152–154]. These automatic analysers have been used to couple ESA with continuous flow analysis, flow injection analysis and sequential injection analysis[57,140]. Various flow cells with miniaturized electrodes obtained by thin- film deposition on chips and photolithography, along with portable instrumentation, can be used in stripping flow systems. This facilitates on- site procedures, reduces the time of analysis, facilitates sample handling and eliminates oxygen interference[57,140]. The application of submersible voltammetric probes has also been reported for in situ monitoring of metal pollutants in water and to evaluate their depth profiles[154–156]. Additionally, protocols have been developed for remote monitoring of mercury traces[157] or nickel and uranium[152,158] in seawater and inland water. ESA can also be applied to monitor industrial processes. This is particularly useful for procedures involving highly concentrated media in the zinc industry (Case study 1), metal plating, batteries and energy storage technologies or in the electrolysis of brine. For example, traces of elements such as cobalt, nickel, iron, manganese, titanium, molybdenum and chromium were determined offline and online in brine using AdSV or catalytic adsorptive stripping voltammetry (CAdSV)[159,160].

Different ESA methods have been applied to determine metals and metalloids in various food samples, including animal tissues, fruit and vegetables, dairy products, sugar, beverages and juices[4]. A prerequisite for this is the preliminary removal of the sample matrix, which can complicate quantification of heavy metals and metalloids at trace and ultra- trace concentrations. Careful decomposition of the sample is necessary to eliminate organic matter. This ensures quantitative retention of the analytes and coverts them into a form suitable for ESA quantification. Other fields where ESA is invaluable are forensic analysis, for example for gunshot residue detection[161], fuel quality control[162], battery research and energy applications[163] and pharmaceuticals6. Notably, multi- element methods can quantify several target metals at the same working electrode in a single run[45,164], or at devices with spatially separated working electrodes with each electrode dedicated to a single target metal[165]. An example of multi- element ASV analysis in a single run is illustrated in Fig. 6a, which shows the voltammogram in a sample containing zinc, cadmium, indium, lead and bismuth. ESA methods may be applied for the speciation of trace metals, including labile and inert fractions of metals, redox species and covalently bound species. The considerable potential of ESA methods in speciation studies has been documented in numerous reviews that present various procedures exploiting conventional and modern approaches to metal speciation by means of ESA[79,94,141,166–170].

ASV allows differentiation of electrochemically inert and labile fractions of metal in water media. The latter include free and reversible complexed metal ions capable of reduction and accumulation at the electrode surface[166,167]. This is achieved via the proper selection of solution pH, supporting electrolyte and deposition potential and, if necessary, the addition of a complexing ligand. An interesting example of mercury speciation by means of ASV with a gold film electrode is the quantification of methylmercury in the presence of inorganic mercury[171]. The addition of a diethylenetriaminepentaacetic acid (DTPA) complexing ligand to a solution containing both species results in transformation of Hg+ to the electrochemically inactive Hg–DTPA complex. This occurs at the potential where methylmercury undergoes reduction to the metallic state and enables selective determination of CH_3Hg^+. AdSV and PSA with adsorptive pre- concentration uses the competition of substances naturally present in water samples and the added ligand during complex formation with metal ions. This occurs in the time between ligand addition and the adsorption equilibrium[141]. By titrating the sample with the selected metal and monitoring the concentration of labile metal, it is possible to calculate the complexing capacity or the amount of metal bound by the dissolved organic material[172].

ASV and AdSV are highly suitable for investigating redox speciation of metals in environmental media. This is because either one species is electrochemically inactive within the applied potential range or one of the investigated oxidation states of a given metal selectively forms an electrochemically inactive complex. ESA techniques have been successfully used to detect couples such as Cr(VI)/Cr(III), Fe(III)/Fe(II), Tl(III/I), V(V/IV), Mn(IV/II), U(VI/V), As(V/III), Se(VI/IV), Sn(IV/II) and Sb(V/III). AdSV and CAdSV methods have found wide applications for chromium speciation in various environmental samples[145,150]. The past two decades of research have seen the application of not just mercury electrodes but also environmentally friendly sensors such as silver amalgam[173–175] and various types of bismuth film electrodes[176–180]. A CAdSV procedure to monitor chromium traces using a submersible electrochemical probe and dialysis membrane that prevents electrode fouling has also been described[156].

Case study 1. One spectacular example of how ESA can be applied for on- site monitoring of an industrial process is the determination of trace metal contaminants in a zinc plant electrolyte during purification[181]. The concentrated zinc sulfate solution used to produce electrolytic zinc is obtained by leaching zinc ores with sulfuric acid and contains some impurities. The contaminant concentration needs to be reduced to an acceptable level before the electrolyte is placed in the electrolytic tanks. If this is not done, the electrolyte will reduce the current efficiency of the electrolytic process and, subsequently, damage the metallic zinc end product. Atomic spectrometry techniques are not viable for monitoring the purification process. By contrast, solutions containing high concentrations of zinc with high ionic strength are ideal media for analytical investigation with ESA. To control the purification processes, Bond's team elaborated several original online procedures with a HMDE working electrode. These procedures can be used to perform simultaneous ASV quantification of cadmium, lead, antimony and copper. They can also be used for simultaneous detection of nickel and cobalt via AdSV with dimethyldioxime, or for extremely sensitive and selective AdSV determination of cobalt in the presence of α- benzildioxime as a ligand and nitrite as a catalytic agent[182,183]. The last of these procedures has an additional advantage, as it does not require the matrix exchange procedure. When ASV is combined with AdSV with chloroanilic acid as a ligand, it is possible to detect total antimony and perform a speciation study of Sb(V) and Sb(III). Other elements are determined offline, for example germanium using AdSV with pyrocatechol violet and total arsenic by means of CSV. Specially designed on- stream voltammetric analysers allow automation of numerous stages of determination, data acquisition and the transfer of data to a central computer, all of which enable increased control of the process. The interference caused by the extremely high excess of zinc is eliminated using a bottom- drain flow- through cell that facilitates matrix exchange.

Case study 2. The CAdSV method with DTPA and nitrate is among the most useful techniques, as it enables the differentiation of Cr(VI), non- reactive and reactive Cr(III) in solution. The procedure is based on the formation of a Cr(III)–DTPA complex, which adsorbs on the electrode surface and then reduces to the Cr(II) complex. This is immediately reoxidized in the presence of nitrate, regenerating the complex with Cr(III). These reduction/oxidation processes repeat multiple times in a catalytic cycle[150,184,185]. The combined adsorptive/catalytic effects enhance the sensitivity and decrease the limit of quantification for chromium down to concentrations of approximately 10^{-11} mol l^{-1}. The CAdSV signal is also dependent on the chemical forms of the Cr(III) species that form complexes with DTPA[186–190]. Complexes formed by non- labile Cr(III) ions with organic ligands found in natural waters are voltammetrically inactive in the presence of DTPA and nitrate ions. Hydrated Cr(III) ions originally present in the solution form stable complexes with DTPA. After about 30–40 min at ambient temperature, slow structural changes make these complexes unresponsive to CAdSV. This process becomes increasingly rapid if the temperature is increased to around 40 °C, or when certain aminopolycarboxylic acids such as nitrilotriacetic acid (NTA), ethylenediaminetetraacetic acid (EDTA) or diaminocyclohexanetetraacetic acid (DCTA) are added to the sample[191]. Instantaneous Cr(III) ions, which appear at the surface of the working electrode upon reduction of Cr(VI) to Cr(III), form complexes with DTPA. These complexes adsorb to the electrode surface and are catalytically active in the presence of nitrate ions, providing an enhanced CAdSV response. These differences in behaviour of the Cr(VI) and Cr(III) species enabled the design of speciation studies. Total chromium may be quantified with the same CAdSV procedure after oxidation of the Cr(III) species to Cr(VI) via UV irradiation of the samples. Numerous CAdSV procedures using DTPA and nitrate have been applied for the speciation of chromium in various materials. After combining the CAdSV method with tangential ultrafiltration of river water samples, it was possible to evaluate the distribution of Cr(VI) and Cr(III) in the solution and the isolated colloidal fraction. From this, the total chromium in the particulate could be derived[190].

Organic compounds

Trace levels of many organic compounds with electroactive groups can also be detected by means of ESA[192–194]. The accumulation of target organic compounds can proceed according to different protocols[20,21]. These rely on electrolytic pre- concentration, including formation of insoluble compounds with the electrode material, and non- electrolytic pre- concentration, which may involve adsorption at open- circuit potential, adsorption at an applied potential, extraction- based accumulation, ion pair formation and ion exchange. Most analytical protocols for determining organic compounds involve adsorptive accumulation of the analyte. Such analytes include the active ingredients of various pharmaceuticals, organometallic compounds, pesticides and herbicides, food colourants, explosives and emerging contaminants, for example acrylamide[195], carcinogens[194] and cannabis[196]. ESA is typically conducted in aqueous solutions[5,21], but can also be performed in non-aqueous media such as acetonitrile with tetrabutylammonium salts for the determination of explosive materials, for example TNT[197]. Macromolecules, such as proteins and nucleic acids, can also accumulate on the electrode surface and are determined via PSA and CSV[198,199]. Organic compounds can also be determined using a vast array of working electrodes[32,63,200–203]. The selection of working electrode and the instrumental and chemical conditions are paramount and the instrumental and chemical conditions are paramount for maximizing the amount of adsorbate on the working electrode surface. An example is illustrated in Fig. 6b for the determination of caffeine by AdSV, which demonstrates the drastic signal enhancement afforded by modifying a SPE with Nafion and graphene[204].

Case study 3. An example of an organic substance determined via ESA is thiomersal, an organometallic compound with preservative and antimicrobial properties that is used in topical medications, cosmetics and vaccines. The R1- S- Hg- R2 group of thiomersal can produce signals specific to both reduction and oxidation. The reduction- specific response can be recorded at the HMDE or renewable Ag(Hg) film electrode and is well developed and highly sensitive[205,206]. The oxidation specific signals of thiomersal observed at positive potentials can be recorded with carbon electrodes, such as the CPE and the CPE modified by addition of La2O3. La2O3 facilitates charge transfer and improves sensitivity to the oxidation of thiomersal. The La2O3/CPE electrode enabled thiomersal to be quantified in vaccines and pharmaceutical dose samples[207]. In addition, a carbon SPE coated with chitosan can also be used to determine thiomersal[208].

Biosensing

Over the past decade, ESA has found wide applicability in the bioaffinity sensing of proteins, cells and DNA[209–211]. One of the most common biosensing methods is the sandwich approach illustrated in Fig. 6c. First, a capture biomolecule with affinity to the target is immobilized on the working electrode surface. Then, the modified electrode is put in contact with the sample and the target is selectively attached to the capture biomolecule. A reported probe with affinity to the target biomolecule, labelled with metal — silver, copper or gold — nanoparticles or metal- based quantum dots — usually nanocrystals composed of CdS or PbS — is introduced and selectively binds with the target, forming a sandwich structure. Finally, the metal labels are dissolved and converted into the respective cations, which are quantified by ESA. As each biomolecular probe can accommodate a large number of quantifiable labels, very low limits of detection (in the range of femtomoles per litre) can be achieved. Additionally, multiplexed detection of several target biomolecules is possible using different metal-based nano- labels with different stripping peak potentials[212]. Reproducibility and data deposition

Reproducibility aspects are related to analyte losses or contamination[213], control of the instrumental parameters, the fabrication process itself and chemical issues, such as the formation of intermetallic compounds or the fouling of electrode surface. From an analytical point of view, repeatability and reproducibility are considered as the within- run precision and between- run precision of a method, respectively. Both are related with random errors and are expressed as a percentage relative standard deviation[214]. For ESA measurements, repeatability refers to repetitive measurements using a single device, whereas reproducibility refers to measurements performed with different devices[215,216]. Control of instrumental parameters related to both the pre- concentration/deposition step and stripping step is fundamental to obtain reproducible results[217,218]. In the former, control of deposition time and potential should be accompanied by accurate control of the mass transport. This is because hydrodynamics determines the pre- concentration efficiency. On the other hand, factors that affect the stripping step should be carefully controlled, such as the magnitude of the oxidizing current or the concentration of oxidant in stripping potentiometry[78]. The replacement of simple bare electrodes — for example mercury, platinum or carbon — by modified electrodes also introduces additional sources of uncertainty. Fouling is the accumulation of unwanted material on the electrode surface. It is caused by adsorption of molecules from the sample solution or products of the electroanalytical process. They inhibit the direct electron transfer process and affect both the repeatability and durability of an electrode. To minimize this problem, different strategies have been effectively applied. Among them, the inclusion of a cleaning or conditioning step prior to the measurement can be useful if products of the electroanalytical reaction are retained on the electrode. Another strategy considers the inclusion of a protective layer or permselective barrier on the electrode to prevent the fouling agent reaching the electrode[219]. Then, reproducibility in between electrodes will be affected by the manufacturing process. The more modification steps introduced into the device, the greater the variability. This issue can be partially addressed by using electrodes manufactured by inherently precise high- throughput approaches, such as screen- printing and microengineering methods.

The sample matrix also affects reproducibility. It influences the background current, whereas the sample might contain species that interact with the electrode or affect the analyte response. The pH and concentration of the complexing agent in adsorptive pre- concentration of trace metals should be carefully controlled. The target metals may form intermetallic compounds with co- deposited metals or with the electrode material —usually mercury or bismuth — causing a decrease, shift or distortion of the signals[19]. Some authors point out that PSA minimizes these problems owing to the nature of the stripping step, in which the evolution of a potential is considered[78]. In some cases, where the aim is to minimize uncontrolled variability, the use of internal standard calibration procedures could be recommended instead of more common and extended external calibration plots or standard addition calibration methods[220].

Limitations and optimizations

Range of species detectable by ESA

A prerequisite for detection of an analyte by ESA is the ability of the analyte itself, or a compound of the analyte, to pre- concentrate on a suitable working electrode. This requirement narrows the range of analytes that can be detected by ESA with respect to other voltammetric techniques as there are many organic and inorganic species that do not lend themselves to deposition. Another general limitation is that the target, or its compound, must be electrochemically active. This limitation can be overcome by the use of ion- transfer stripping voltammetry between two immiscible electrolytes (aqueous and organic), which is applicable to the detection of many ionic species that do not possess redox properties (for example, oligopeptides, neurotransmitters, vitamins and polysaccharides)[63]. The target analyte is transferred from the aqueous to the organic phase and is accumulated close to the interface by modulating the potential difference between the two immiscible phases. During the stripping step, the analyte is transferred back from the organic phase to the aqueous phase by scanning the potential while the current resulting from the transfer of the ionic analyte is measured.

Sample contamination

As ESA is a trace analytical technique, the accuracy of the results is strongly dependent on the degree of sample contamination[19,221,222]. Contamination may stem from impurities in reagents or containers, and from the ambient environment during sampling or sample treatment. The principles of Good

Laboratory Practice should be observed during handling and storage of samples. Laboratory conditions should be carefully controlled to avoid contamination by dust and airborne particulates. Reagents and water of the highest possible purity should be used. Many samples, such as seawater, contain sufficient conductivity to allow analysis without the addition of a supporting electrolyte, whereas use of microelectrodes alleviates the need for a supporting electrolyte in many samples[223]. The use of closed flow systems minimizes the risk of contamination from environmental sources[57]. To avoid metal leaching from and adsorption on laboratory containers, polyethylene, rather than glass, vessels and cells should be used and cleaned thoroughly with acid.

Electrode conditioning and regeneration

The condition of the electrode surface is very important in ESA. In this respect, use of the HMDE or the single- use type of electrode, such as screen- printed sensors[224], is advantageous as a new, clean surface is available for each stripping cycle. For solid reusable electrodes, remains of accumulated species or redox species deposits generated during the stripping step can alter the electrode response or contribute to carry- over phenomena. Therefore, some form of conditioning or cleaning after the stripping step is necessary to return the electrode to its initial condition. Cleaning can be either mechanical or electrochemical[225]. Mechanical cleaning involves polishing the electrode with an abrasive material. This approach is not practical for field sensors that are intended to be left in an environment for a long time period. Renewable in situ electrodes have been developed. One example is the silver liquid amalgam film electrode. This is based on cyclic renovation of the electrode surface, achieved prior to each measurement by coating a silver wire with a fresh liquid amalgam film[226]. A second example is the bismuth bulk electrode. This electrode has a sensor body partly filled with the internal electrolyte solution. Before each measurement, the electrode is cleaned and activated[227]. Electrochemical cleaning, which involves cycling the potential or holding the potential at a judiciously selected predetermined value for a defined period of time, can be used to condition the electrode surface[225,228].

Formation of intermetallic compounds

In many samples, several metal cations are likely to be present in a wide concentration range. Intermetallic compounds can form as a result of alloying with the electrode or with other metals present in the solution during the deposition process. Compared with when the metal is deposited alone, intermetallics can exhibit completely different stripping behaviour. A typical example is the formation of an intermetallic copper–zinc compound. This results in suppression of the zinc peak, and appearance of the copper–zinc intermetallic stripping peak, which is in close proximity to the copper stripping peak. As the intermetallic and copper peaks severely overlap, the effect is a virtual enhancement of the copper peak[229]. Various methodologies have been applied to prevent the formation of intermetallics. To this end, the selection of a suitable working electrode is critical. On solid electrodes, intermetallic compounds are more severe than on mercury or bismuth electrodes because the different metals are more likely to interact with each other. In addition, at solid electrodes, electrodeposited metals often give rise to more than one peak due to the formation of deposits with different stripping potentials, known as underpotential deposition. This phenomenon complicates the analytical signal interpretation[31,230]. Figure 7a illustrates a case study where a copper–lead intermetallic compound is formed, resulting in drastic changes of the lead peak and the appearance of a spurious peak arising from the copper–lead stripping. In the case of mercury and bismuth electrodes where the target metals are dissolved to form amalgams and alloys, respectively, interactions between the pre- concentrated metals and intermetallics are less likely to form. Careful choice of the supporting electrolyte[231], deposition potential and time can be used to address the effect of intermetallic compounds[232]. Another approach is preferential formation of an alternative intermetallic compound. For example, the formation of the copper–zinc intermetallic compound, which complicates the determination of

Zn(II), can be prevented by adding Ga(II) to the sample. This forms a more stable gallium–copper intermetallic, thereby releasing zinc. This method of adding a third element can be successfully used to minimize several other intermetallic interferences[233]. Finally, the application of neural networks[234,235] and support vector regression methods[236] have been reported to address the effect of intermetallic compounds.

Overlapping stripping peaks

Overlapping stripping peaks can result from two or more metals depositing independently, not as an intermetallic compounds but by stripping at similar potentials, for example cadmium and thallium, cadmium and indium or copper and bismuth. This makes quantification difficult. The degree of overlap depends on many factors, such as the electrode material, the solution matrix, the relative concentrations of the metals and the deposition potential. Prior to ESA analysis, interfering metals can be removed by using a pretreatment processes, such as ion- exchange resins[237,238]. Some approaches used to improve resolution between adjacent peaks include a suitable working electrode[222], control of the chemistry[239] and application of different chemometric approaches, for example curve fitting[240], fast Hartley transform deconvolution[241], multicomponent analysis[242], independent component analysis[243] and neural networks[244,245]. Figure 7b illustrates the separation of overlapped indium and cadmium peaks by using a chemical approach (changing the supporting electrolyte) and a chemometric approach of peak fitting.

Surface- active compounds

Organic matter in many environmental and biological samples — such as proteins, fats, cells and surfactants — can block or foul the surface of the electrode[246,247]. In most cases, a gradual decrease, or even complete suppression, of the stripping signal results from electrode fouling by organic materials. The effects of organic matter are particularly critical in methods involving adsorptive accumulation owing to competition with the analyte for sites on the electrode surface. Different schemes have been developed to alleviate matrix effects due to surface- active compounds. These include the use of sample decomposition with acids4, addition of fumed silica that preferentially adsorbs these compounds[248], use of permselective coatings such as Nafion[249,250], pretreatment of the sample with exchange resins[251] and UV irradiation to destroy organic matter[145].

Outlook

Ninety years have passed since Zbinden reported the use of stripping analysis for detecting metal ions in 1931, demonstrating the new concept for determination of copper[15]. Over the past six decades there has been tremendous progress in the fundamental and practical aspects of ESA, including new stripping principles and electrode materials. During the 1980s, introduction of alternative, non-electrolytic, adsorptive accumulation schemes expanded the scope of ESA towards additional trace metals, as well as organic compounds of biological and environmental significance. These advances greatly increased the range and power of ESA, allowing trace measurements to be performed rapidly, reliably and inexpensively. Gradually, ESA is moving away from traditional centralized laboratory-based measurements to decentralized field and home testing, with diverse applications ranging from continuous remote sensing to single- use measurements. Bulky instruments and electrochemical cells based on toxic mercury drop electrodes are being replaced with handheld analysers and disposable printed strip electrodes[252]. Significant developments in electrochemical sensing approaches, along with advances in microelectronic technology, have led to the introduction of remote and wearable ESA platforms. Over the next decade, these sensors, connected to smartphones in a wireless mode, are expected to accelerate the realization of decentralized environmental and clinical testing of toxic metals and organic compounds of biological significance. Such future use of ESA sensors is expected to bring new opportunities for the monitoring of water quality, for example home- based drinking water testing kits for toxic heavy metals such as lead and cadmium. These rapid changes are facilitated by the development of wearable electrochemical sensors. Already, such developments have brought a major paradigm shift in electroanalytical chemistry[253]. On- body ESA systems are expected to offer continuous monitoring of trace metals in sweat, tears, interstitial fluids and saliva. Proof- of- principle demonstration of such capabilities include a non- invasive epidermal sensor to monitor zinc in sweat[254] and an electrochemical sensor screen printed on underwater garments to monitor copper in seawater[255]. These applications require the use of flexible electrodes on textiles and accessories integrated with conformal electronic circuitry and displays. Forensic applications, for example assays of gunshot residues, will rely on stretchable gloves for swipe- and-detect measurements of antimony or lead[256]. Networks of in situ submersible ESA sensor arrays, remote probes and autonomous boats with ESA capabilities provide continuous remote monitoring of water resources for detecting sudden metal discharges[156,257–259]. Remarkably, ESA has been used widely for in situ field operations since the mid-1970s, particularly during oceanographic shipboard missions[260]. Another area attracting increasing attention is miniaturized and microfluidic devices. Microfluidic systems can process small sample quantities in channels from tens to hundreds of micrometres in size. Microfluidic devices can incorporate important experimental steps into a single device. These steps include sample preparation, separation, reaction and detection. Consequently, use of microfluidic devices can reduce transport, processing and labour expenses. This makes them an ideal choice for chemical assays in developing countries or resource- limited environments. By contrast, paper- based analytical devices enable fluidic manipulation of samples and reagents within hydrophilic channels delimited by hydrophobic barriers on paper substrates. Paper- based analytical devices provide a convenient way to perform ESA for point- of care or on- site applications in a cost-effective manner. They achieve this by taking advantage of the many favourable attributes of paper as a platform: low cost, wide availability, flexibility, capillary action, biodegradability and low weight. Several microfluidic devices and electrochemical paper- based analytical devices have been reported for ESA of metals and metalloids in various samples[165,261–263.] Current ESA assays offer the unique ability to detect up to four or five trace metals simultaneously, down to remarkably low (sub- nanomolar and sub- picomolar) detection limits using compact, low- powered, inexpensive instrumentation. Despite such impressive capabilities and tremendous progress, the widespread use and commercial activity of ESA are hindered by its limited scope for big- scale, multiplexed analysis and the different sample pretreatments required to address matrix effects. Continued multidisciplinary efforts between electrochemists, analytical chemists, electrical engineers, biologists, material scientists, statisticians, biologists and medical practitioners are expected to address existing gaps towards the next generation of smaller, faster and better ESA systems. These collaborative efforts will result in new advanced electrode materials and innovative ESA approaches (capable of measuring rapidly over a dozen trace elements in ultrasmall microlitre samples), and powerful new analytical capabilities that will accelerate new and novel applications in new frontiers (for example, under the skin and within our cells). A growing use of ESA is expected for investigation of metal nanoparticles and their application as electrochemical labels for diverse bioaffinity assays[264]. Such progress and vision will allow ESA to retain its place as one of the most powerful tools for trace analysis.

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Author contributions

Introduction (A.E. and D.S.); Experimentation (C.E.B. and R.D.C.); Results (C.A. and C.P.- R.); Applications (A.B. and A.K.); Reproducibility and data deposition (C.A. and C.P.- R.); Limitations and optimizations (A.E. and D.S.); Outlook (J.W.); overview of the Primer (A.E., C.A., C.E.B., A.B., R.D.C., A.K., C.P.- R., D.S. and J.W.).

Competing interests

The authors declare no competing interests.

Fig. 1 Historical evolution of ESA**.** ESA, electrochemical stripping analysis; PSA, potentiometric stripping analysis.

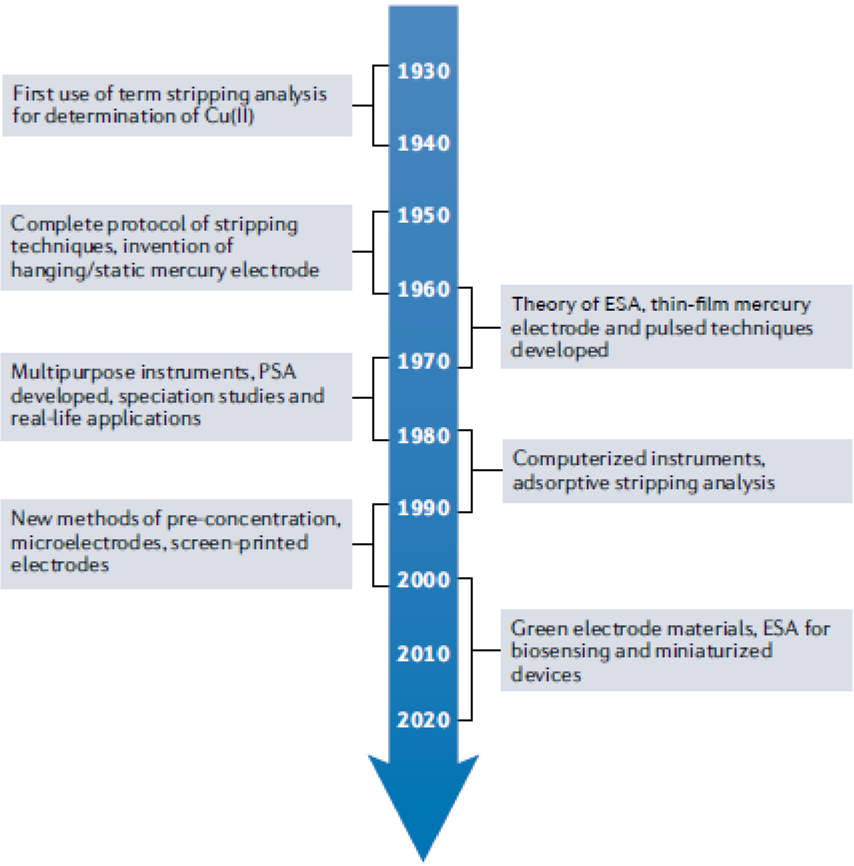

Fig. 2 The principle of ESA. a | Methods of pre-concentration in electrochemical stripping analysis (ESA). In electrolytical methods (part i), metal cations are reduced and accumulated on the working electrode as metals. In adsorptive methods (part ii), metal cations (after conversion to surface-active complexes with organic ligands) and organic compounds are adsorbed on the working electrode. b | Stripping mechanisms involving oxidation or reduction of the accumulated analyte. c | Stripping methods in ESA. Stripping voltammetry (part i) involves stripping of the analyte using a potential scan of the working electrode while a voltammogram (potential versus time) is recorded. Potentiometric stripping analysis (PSA) (part ii) involves stripping of the analyte using a constant current or a chemical agent and a potentiogram (derivative of time versus potential) is recorded.

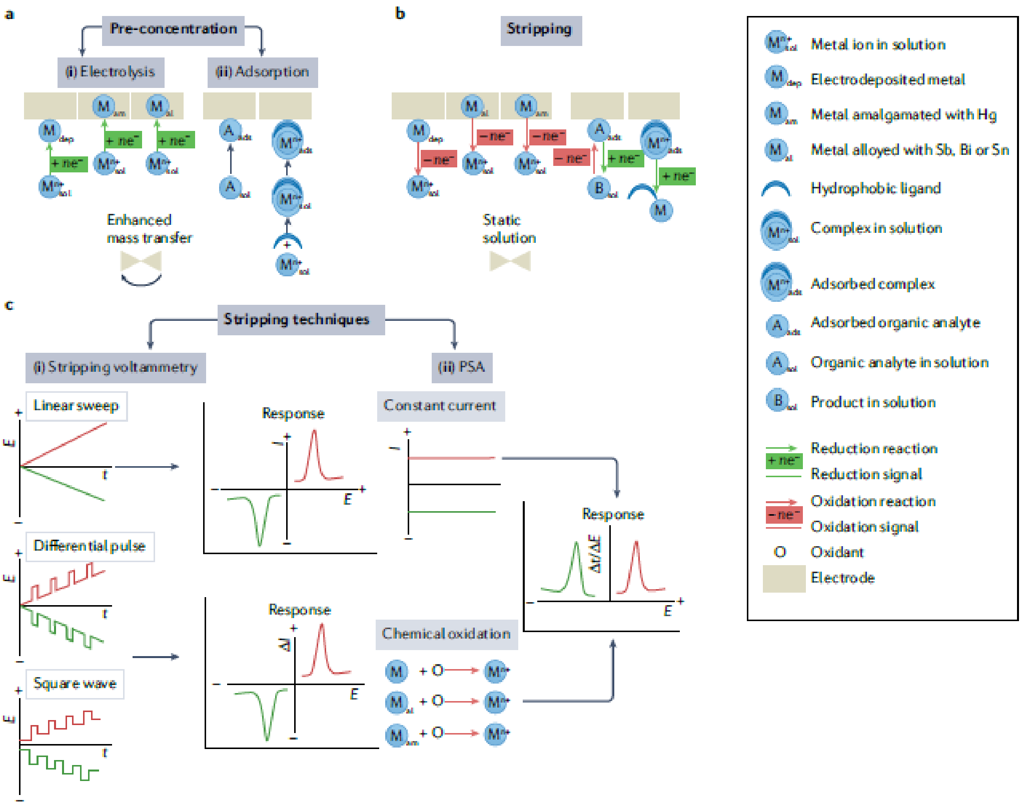

Fig. 3 Experimental set-ups and main variables in ESA. A | Functionality of a three-electrode configuration in electro-chemical stripping analysis (ESA), where V is a voltmeter, A is an ammeter, E is potential of the working electrode with respect to the reference electrode and i is current that flows between the counter and working electrodes (part Aa). Schematics of different experimental set-ups in ESA: laboratory benchtop potentiostat with a batch cell (part Ab), labora-tory benchtop potentiostat with a flow-through cell (part Ac) and portable potentiostat equipped with a three-electrode sensor (part Ad). B | Variables that affect the signal in ESA.

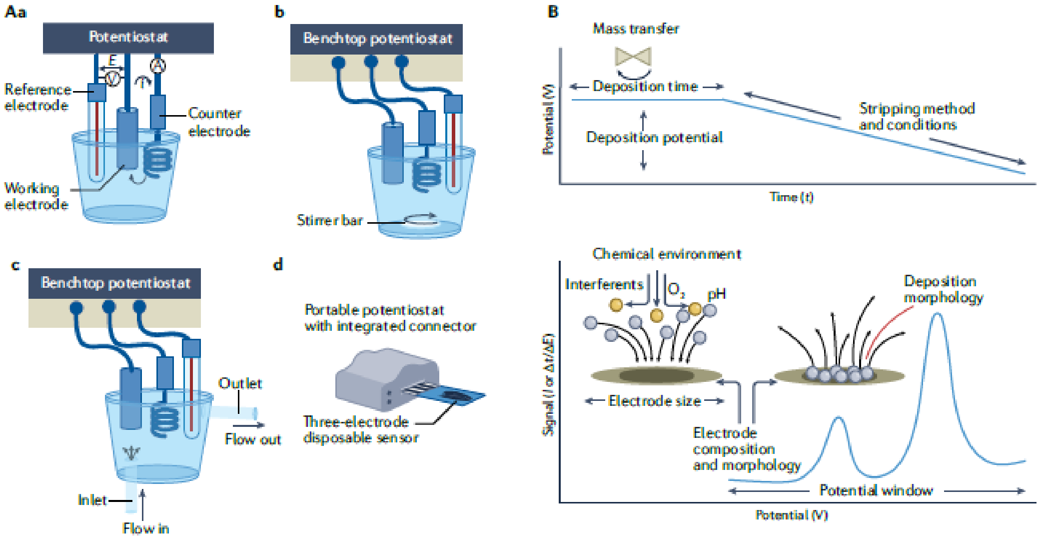

Fig. 4 Signal processing and quantification in ESA. A | Qualitative and quantitative interpretation of the analytical signal in electrochemical stripping analysis (ESA). B | Baseline definition in ESA using two common settings in electrochemical software (linear and polynomial curve) (part Ba) and voltammetric data after baseline subtraction (part Bb). The lower peak heights are obtained with linear curve fitting due to the intrinsic shape of the baseline. C | Effect of smoothing in signal preprocessing. Under- corrected data still display noise whereas overcorrected data lead to wider and lower voltammetric peaks. D | Quantitation approaches using external calibration (part Da) and standard additions (part Db) (dotted trace represents sample response).

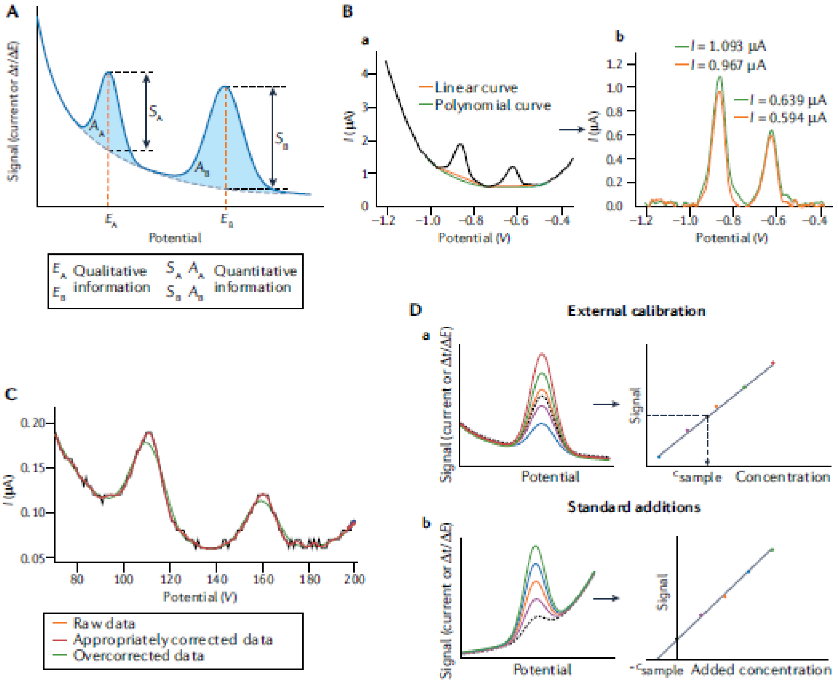

Fig. 5 List of elements that can be determined by ESA. AdSV, adsorptive stripping voltammetry; ASV, anodic stripping voltammetry; CAdSV, catalytic adsorptive stripping voltammetry; CSV, cathodic stripping voltammetry; ESA, electrochemical stripping analysis.

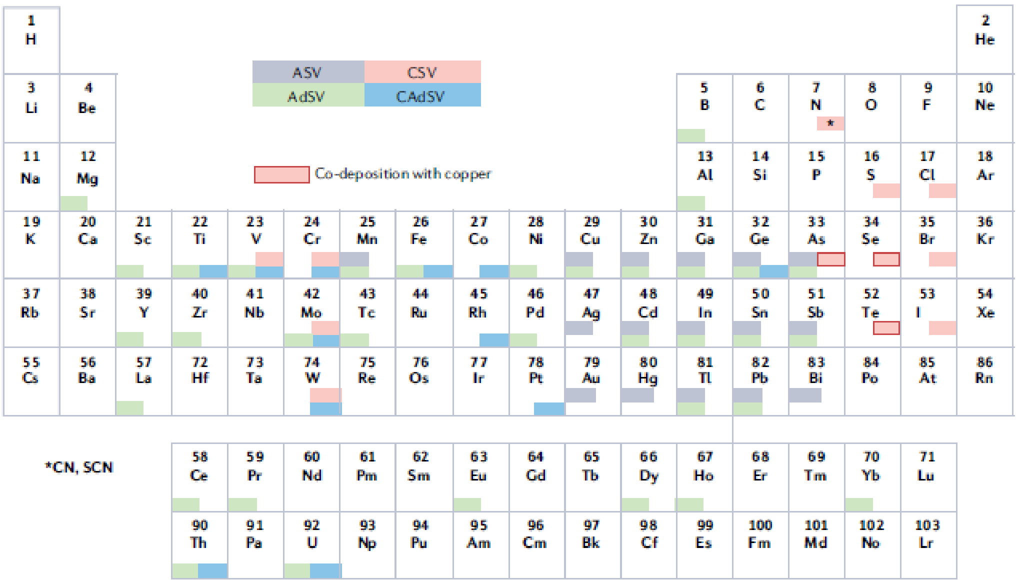

Fig. 6 Application examples of ESA. a | Example of multi- element anodic stripping voltammetry (ASV) analysis in a single run in a sample containing Zn(II), Cd(II), In(III), Pb(II) and Bi(III). b | Adsorptive stripping voltammetry (AdSV) of caffeine at a bare screen- printed electrode (SPE) and SPEs modified with Nafion and Nafion + graphene. c | Principle of affinity biosensing using metal- based nanoparticles as labels and electrochemical stripping analysis (ESA). AuNP, gold nanoparticle; BSA, bovine serum albumin; QD, quantum dot.

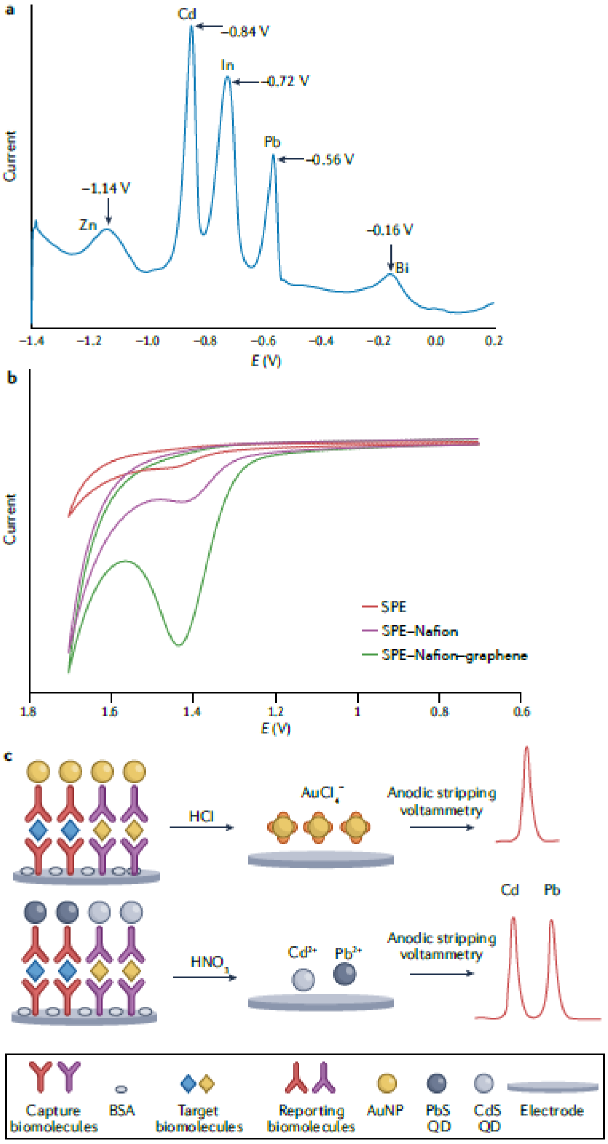

Fig. 7 Examples of limitations in ESA. a | Formation of an intermetallic lead- copper compound in anodic stripping voltammetry (ASV) at a carbon electrode and its effect on the respective voltammogram. b | Separation of the overlapping cadmium and indium peaks in ASV using chemical separation (shift of the cadmium peak upon change of the supporting electrolyte) and chemometric separation (curve fitting using the Peakfit option in OriginLab). ESA, electrochemical stripping analysis.