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Abstract

The electrochemical detection of non-electroactive contaminants can be successfully faced via the use of indirect detection strategies. These strategies provide sensitive and selective responses often within portable and user-friendly analytical tools. Indirect detection strategies are usually based on the change in signal of an electroactive probe, induced by the presence of the target molecule at a modified electrode. This critical review aims at addressing the recent developments in indirect electro-sensing strategies for non-electroactive contaminants in food and environmental analysis. Emphasis is given to the strategy design, the electrode modifiers used and the corresponding attractiveness for technological transfer.

Keywords: Non-electroactive contaminants; Biosensors; Bio(mimetic) sensors; Indirect detection strategies, Electrochemical sensors.

Introduction

Electroanalytical methods are successfully applied to non-electroactive targets using indirect detection strategies. Instead of exploiting the electrochemical behaviour of the target, these methods most commonly record the electrochemical changes of an electroactive probe in the presence/absence of the target at a modified electrode, typically with affinity for the target. These electrode modifications involve bio- and bio(mimetic)receptors such as antibodies, enzymes, peptides, aptamers and molecularly imprinted polymers. For example, indirect detection can exploit the inhibition of an enzymatic receptor and the consequent decrease in the signal of its electroactive products to determine a target able to selectively bind and inactivate the enzymatic receptor [1]. In other cases, the target concentration results to be proportional to the increase of the resistance in the electron transfer at a molecularly imprinted polymer (MIP) after the recognition event [2]. To enhance the sensitivity of the final devices, these receptors are often immobilized on hierarchical nanomaterials and/or nanocomposites giving rise to complex modifications [3]. The indirect monitoring can be also extended to the detection of electroactive targets with a non-characteristic electrochemical fingerprint, especially in complex matrices (such as blood, wastewater, etc.).

In general, the signal amplification and the adaptability of these indirect electroanalytical strategies make them particularly attractive for the detection of non-electroactive contaminants at concentration levels compatible with legal requirements. Furthermore, food and environment contaminants, especially emerging contaminants (EC), including pesticides, personal care and pharmaceutical products, toxins, flame-retardants and hormones require user-friendly, portable and rapid screening tools for *in situ* analysis [4].

Because of the variety of indirect monitoring methods and the large number of environmental and food contaminants, a selection of promising electrochemical (bio)sensors underlying the potentialities of indirect detection strategies is presented and their open challenges are discussed. A critical comparison of their performances (sensitivity, selectivity, and reusability), the design, and the possibility for technological transfer of each detection strategy will be presented within the different sections.

1. Biosensing Strategies

Bio-receptors such as antibodies, enzymes and peptides, are often integrated in indirect electroanalytical strategies. Thanks to their strong affinity for the target molecules, they provide a highly selective and sensitive recognition. Electrochemical immunosensors rely on the antibody-antigen binding event detected with the help of enzyme-labelled antigens [5] or secondary antibodies [6], competitive immunoreactions [7] or simply by recording a change in the electron transfer resistance upon recognition [8] (for a complete overview refer to [9]). Particularly used for mycotoxins detection [10–13], these sensors were successfully combined in competitive or magnetic beads assays by Leonardo *et al.* [14,15], allowing the simultaneous detection of multiple toxins. Labelled-antigens can be substituted by phage displayed mimotopes, peptides that mimic antigen epitopes [16]. Hou et al. [17**] detected ochratoxin A using a competitive immunosensor in which the free primary antibody was bound to the mimotopes and to a secondary antibody labelled with a peroxidase. By adding the peroxidase substrate in solution and recording the peroxidase activity by square wave voltammetry (SWV) a Limit of Detection (LOD) of 2.04 fg/mL was reached (within the 7.17–548.76 fg/mL linear range). Despite the stability and ease of synthesis of mimotope-immunosensors, these sandwich-architectures seem not rapid enough (≈2h 30min per each analysis) and user-friendly to pass the technological transfer step.

Enzyme-less immunosensors appear to be a more promising alternative. Nguyen *et al.* [18] immobilized the anti-diclofenac antibodies by affinity interactions on a diazonium salts modified electrode. Here, one of the diazonium salts worked as probe and the detection strategy was based on the absence/presence of the immunocomplex as showed in Fig.1.

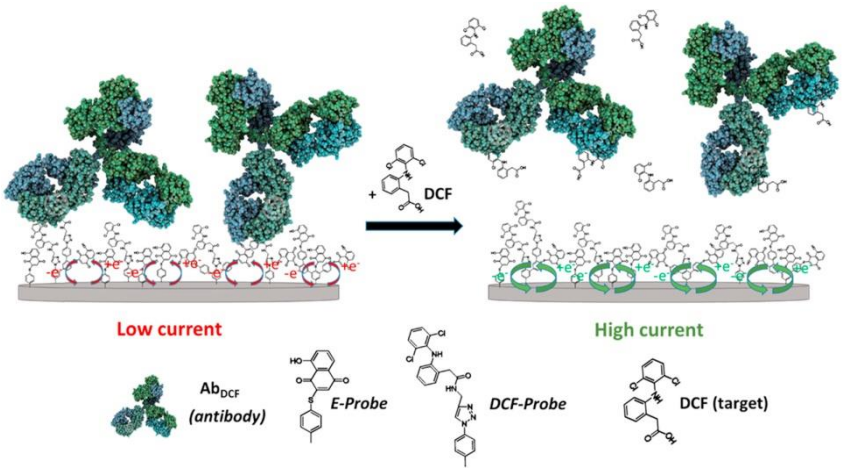

Fig.1 Schematic illustration of the enzyme-less immunosensing strategy proposed by Nguyen *et al*., graphical abstract reprinted from [18].

Regarding enzymatic bio-receptors, acetylcholine esterase (AChE) is often used in electrochemical biosensors where the analytes, mainly organophosphates compounds (OPs), inhibit the activity of AChE enzyme. By limiting AChE interactions with its substrate, acetylthiocholine chloride, there is a considerable decrease in the production of thiocholine. The changes in thiocholine concentration are detected

electrochemically and used to quantify the presence of the OPs. Improved responses can be obtained by associating different modifiers to AChE, for example: Pd-Cu nanowires [19], reduced graphene oxide [20,21], multi-walled carbon nanotubes (MWCNTs) and dicyclohexyl phthalate [22] or bimetallic Pd-Au nanorods [23]. Chen *et al.* [22] reached a LOD of 0.05 µg/L for chlorpyrifos decorating screen-printed electrodes (SPEs) with MWCNTs before the functionalization with AChE. To determine malathion in the linear range of 10^{-14} to 10^{-8} M, a more complex chitosan-transition metal carbides (CS-$Ti_3C_2T_x$) nanocomposite modifier was required [24]. The $Ti_3C_2T_x$ nanosheets enhanced the electrocatalytic properties of the glassy carbon electrode (GCE); in presence of additional nanomaterials, like silver nanoparticles [25], no further improvements in terms of sensitivity were observed. Also He *et al.* [26*] determined ultra-traces of malathion depositing on GCE surface a nanocomposite of hollow carbon spheres wrapped with polyaniline prior to AchE immobilization. The polymeric coating rich in amino groups provides good biocompatibility, stability and a high affinity towards AChE. Similar outcomes were reported by Song *et al.* [1] using a GCE modified with porous bimetallic alloy particles decorated with different nanowires on a MoS_2 monolayer as a substrate for AChE immobilization.

Despite their innovative configurations, AChE-based biosensors are still questionable for the technological transfer because of the controlled-working conditions required by the enzymatic receptors and their relatively short shelf-life. AChE biomimetic sensors are currently driving the attention of the researchers. By substituting the AChE with a functionalized polyacrylamide, the polyhydroxamicalkanoate, it was possible to mimic the enzyme interactions simply through a series of functional groups [27].

Notwithstanding all the advantages of bio(mimetic) materials, bio-receptors still play a fundamental role in electro-sensing application providing outstanding performances. As observed in the examples, biosensors allow further improvements of well-known indirect detection strategies and the design of innovative ones.

2. Aptamer-based Strategies

Aptamers are synthetic oligonucleotides (DNA or RNA) able to selectively bind a target molecule. Their selection against the analytes, from small molecules to microorganisms [28], is performed using SELEX (Systematic Evolution of Ligands by Exponential Enrichment) methods [29–31], eventually coupled with post-SELEX chemical processing [32]. The increased availability of aptamer for ECs [33–36] has led to an exponential growth of aptamer-based sensors (aptasensors) described in literature [37]. However, only a limited amount of aptamers reached the market probably due to the lack of a universally accepted and robust quality control protocol for the characterization of aptamer performances. Aptamers are bio(mimetic)-receptors and their target-induced conformational change can be exploited in indirect detection strategy [38,39], particularly with Electrochemical Impedance Spectroscopy (EIS) [40,41]. To reach pico- or nanomolar detection limits, many different approaches have been exploited: amplification by extension of the aptamer length triggered by terminal deoxynucleotidyl transferase [34]; combination of the aptamers with enzyme functionalized nanoparticles [42]; asymmetric nanomaterials [43] or nanocomposite materials [44]. Madianos *et al*. [45**] reported a dual impedimetric aptasensor (Fig. 3) for the simultaneous detection of the neonicotinoid pesticides acetamiprid and atrazine, using functionalized microwires of platinum nanoparticles (Pt-NPs) to immobilize the aptamers. The bridge-like deposition of the Pt-NPs in between interdigitated electrodes, obtained by sputtering and e-beam lithography techniques, assured a highly sensitive response (LOD of 1 pM, linear range 10 pM - 100 nM) in water samples.

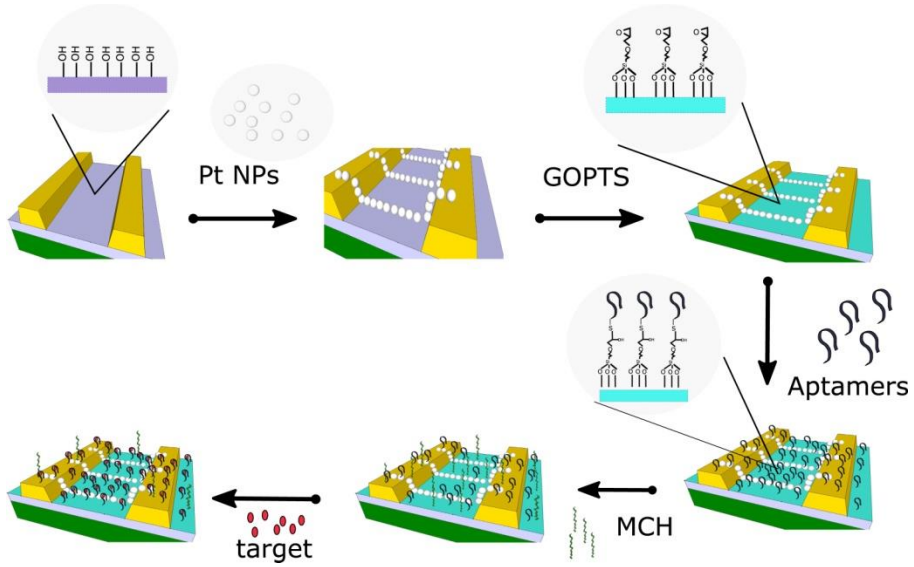

Fig.3 Schematic representation of surface functionalization. Following fabrication of the Pt NP microwires, the surfaces are silanized with GOPTS. Thiol-modified aptamers are covalently immobilized onto the surfaces and non-specifically bound aptamers are removed following incubation with MCH, reprinted from [45].

The acetamiprid aptasensor proposed by Taghdisi *et al.* [46*] based on the target-induced release of the Methylene Blue (MB) showcase an interesting approach, even if with a higher LOD (153 pM). The MB was intercalated in a dsDNA formed by the aptamer and a complementary strand, immobilized on silica nanoparticles coated with streptavidin. Once the aptamer bound the target, the MB is released and measured by CV on bare gold electrodes; the complementary strand degradation enhances its signal. MB-modified aptamers were reported also by Yu et al. [47,48] in displacement-based electrochemical sensors for the detection of ampicillin, a non-electro-active β-lactam. Despite their selectivity, Yu's displacement-based sensors showed limited performances: with alternating current voltammetry the LOD is 1 µM with a 5- 500 µM dynamic range. The limits of these sensors appear evident when they are compared to the second generation of signalling-probe displacement electrochemical aptasensors (SD-EAS), having a LOD of 10 pM and a linear range between 100 pM–1 mM for ampicillin [49].

SD-EAS indirect detection based on the redox probe signal present improved performances thanks to the presence of a $HS\text{-}(CH_2)_2\text{-}[OCH_2CH_2]_6\text{-}OCH_3$ passivation self-assembled monolayer. However, the performances of all type of displacement-based aptasensor can be strongly affected by variation in the aptamer-complementary strand duplex structure [50]. This is true also for the multiplex aptasensor proposed by Li *et al.* [51]. Here, cadmium and lead ions functionalized with kanamycin and streptomycin aptamers were immobilized on the a screen-printed carbon electrode surface through their complementary strands. Once the targets are bound, the labelled ions are free to move and a variation in their DPV currents is recorded reaching a LOD of 74.50 pM and 36.45 pM, respectively. Despite their performances, these approaches are complex and time consuming, and not yet suitable for real world applications.

In between the recently developed aptasensors there are also more user-friendly examples, such as the pesticide Diazinon aptasensor presented by Hassanti *et al.* [52]. In this strategy thiolated aptamers are simply immobilized on Au-NPs, deposited on Au-SPE; the sensor showed a good linear range (0.1–1000 nM), a LOD of 16.9 pM and good applicability in real samples.

As shown by these examples, aptamer-based strategies can show very different designs. However, most of them still require complex architectures, while for the determination of emerging contaminants in complex real samples, a straightforward and robust approach is preferred.

3. Molecularly Imprinted Polymer Based Strategies

In the field of ECs sensing, MIP-sensors have been largely exploited to detect electroactive [11,53,54] and non-electroactive contaminants [55*–57] at nano- or picomolar concentrations in real samples. MIP target-mimetic cavities provide a stable and highly selective recognition, reaching the performances of enzymatic receptors with all the advantages of a synthetic material. MIPs are integrated with the transducer mainly through immobilization after bulk polymerization [58,59], solid-state synthesis [60,61] or direct electropolymerization [2,62,63]. Once the target is entrapped in the cavities, the electron transfer of the redox probe is hindered; thus, the target concentration results to be proportional to the decrease in the current signal. To enhance the sensitivity, MIPs are often realized on hierarchical nanomaterials, as in the MIP-sensor described by Guo *et al.* [64] for the antibiotic patulin. The GCE surface was modified with carbon dots, chitosan and gold nanoparticles prior to the electropolymerization of the MIP. The exponential increase of the surface area leads to excellent performances: the sensor shows a LOD of 0.75 pM and a linear range between 1pM and 1nM. Unfortunately, the large-scale production of complex nanocomposites is still a technological challenge. On the contrary, the synthesis of the magnetic MIP (MMIP) and their combination with portable electrochemical sensors seems more feasible [65]. Zamora *et al.* [66**] exploited the pre-concentration capability of the MIP magnetic nanoparticles [67,68] to detect the pesticide tributyltin in water (linear range of 5 pM to 5 μM and LOD of 5.37 pM), designing a user-friendly and low cost device. Moreover, MMIP electrochemical sensors can detect ECs also in complex matrixes such as fish samples [69].

Another innovative approach is based on the dual molecularly imprinted polymer (DMIP) strategy that involves the imprinting of two template molecules in a single polymer matrix. It enables the detection of both analytes with the same sensor and are largely exploited also in chromatography [70,71]. Ultra-trace of enantiomeric pair targets, such as the cancer biomarkers L- and D-aspartic acid were successfully discriminated [72]. Dai *et al.* [55] designed an electrochemical sensor for electroactive and non-electroactive insecticides based on DMIP. The indirect detection of both targets, the non-electroactive bensulfuron-methyl (BSM) and the electroactive imidacloprid (IMI) was combined with the direct detection of the IMI recording a double DPV signal (LOD of 7.8 nM for BSM and 65 nM for IMI). In the electrode modification procedure, the thionine redox probe is electropolymerized on MWCNT/GCE electrode before the DMIP. This design allows performing the measurements directly in real samples without adding any redox probe. Based on a similar principle, in the electrochemical cross-linked molecularly imprinted polymers (e-MIP) the redox tracer (ferrocene or vinylferrocene) is integrated with the MIP micro- or nanoparticles immobilized on SPE [73–76]. The user-friendly design of e-MIP and MMIP-SPEs together with the possibility of their combination in arrays make these sensors more attractive than DMIP-based ones. These examples underline the key-role of MIPs-based strategies, their adaptability to ultra-trace analysis of ECs even in complex matrices.

4. Nanocomposite and molecular modifiers

Other indirect detection strategies are based on nanocomposites modifiers having a great affinity for small organic contaminants [77,78]. Cao *et al.* [77*] used copper benzene-1,3,5-tricarboxylate (Cu-BTC) metal-organic frameworks at indium tin oxide (ITO) electrodes in a probe signal inhibition sensor for glyphosate herbicide. Despite their simplicity and reproducibility, these devices lack in selectivity and further interference studies are needed to address this issue. Regarding OPs determination, oxime-based electrochemical sensors were commonly used in indirect monitoring. These strategies were largely

innovated by optimizing the working conditions [79] and including nanomaterials modifiers [80] to improve the poor signal sensitivity of oxime probes. Tunesi *et al.* [81] used an ITO electrode coated with CuO nanostructures grown in-situ and functionalized with pimelic acid and pralidoxime chloride (PAM). The sensor exploit the non-covalent PAM-OPs interactions instead of promoting their nucleophilic substitution reaction previously used [82]. The redox-signal inhibition strategy was successfully applied in the determination of chlorpyrifos, fenthion and methyl parathion pesticides reaching lower detectable concentrations of 1.6, 2.5 and 6.7 nM, respectively. However, this recognition mechanism has no inter-class selectivity, a parameter that becomes fundamental when structurally related contaminants are subjected to different restrictions/limitations, as in the case of PFAS. This aspect limits the real sample applicability also for the switch on-off strategy proposed by Fang *et al.* [83**] to detect the perfluorooctanoic acid (PFOA). It exploits the capacity of PFOA to form stable partial micelle structures in the defects of a self-assembled monolayer containing 6-(ferrocenyl)hexanethiol on an Au wafer and to modify the SAM voltammetric response. A better inter-class selectivity was reported by Akyüz *et al.* [84] using a manganese phthalocyanine and a 4-azido polyaniline hybrid modifier on ITO electrodes: in this approach the electrochemical signal of the probe was differently inhibited by the chosen OPs.

Conclusions

Compared to other electroanalytical methods, indirect electro-sensing strategies have shown their advantages in terms of adaptability, improved sensitivity with different amplification strategies and possibility to be integrated in arrays. The reproducibility and the automation of the modification procedures remain an open-challenge in the design of indirect electro-sensing strategies able to maximise the selectivity provided by bio or bio(mimetic)receptors combined with nanocomposite materials. Nonetheless, there is still a lack of applications of electro-sensing in large-scale environmental and food contaminants studies. The development of new technologies and materials, such as the low-cost disposable paper sensors [85] or smart-designed nanomaterials [86], are aimed to further facilitate the automated production of these devices and consequently their daily use. Notwithstanding the proven potential of indirect detection strategies, more efforts are necessary to their implementation and technological transfer to deal with environmental and food related analytical problems.

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Highligths

- Electrochemical sensors for non-electroactive contaminants in past two years are reviewed.
- Innovative bio- and bio(mimetic)sensing strategies are emphasized.
- Even non electroactive contaminants can be determined by electrochemistry.
- Indirect detection strategies can be customized for different contaminants.