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REVIEW

Electrochemical aptasensing for the detection of mycotoxins in food commodities

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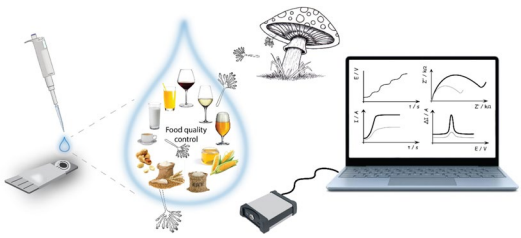
Abstract

The increasing demand for higher quality of wide-ranged food products lead to the overproduction of food commodities in an extremely short time. Such massive product output causes the demands on storage conditions, such as air humidity and regulation, time of storage, and temperature, to rapidly decrease. Therefore, a large variety of pathogenic microbes can be present in food commodities that can trigger a set of serious long-term health issues for human and animal beings. Nowadays, food contamination represents one of the most important worldwide issues that need to be regulated. Among all analytical methods, electrochemical aptasensors have shown to be great candidates for the fast, reliable, and ultrasensitive detection of foodborne pathogens, mainly mycotoxins, in food matrices. This work offers a complex overview of electrochemical aptasensors and their applications in food quality control. It includes modern immobilization strategies in combination with modern electroanalytical methods as detection techniques. This work presents the possibilities to create more practical and effective aptasensing devices with a high level of sensitivity, selectivity, and specificity. These innovations are brought out with a hope to be later involved in the development of miniaturized, portable, and commercially available lab-on-chip devices that would be applicable in a friendly manner for end-users.

Graphical abstract



Keywords Biosensor · Aptamer · Mycotoxin · Food sample · Voltammetry · Impedimetry

Introduction

The rapidly evolving standards of living have led to massive production in every essential industry field. More people have been demanding higher quality of wide-range food products which requires their greater production. However, the current overconsumption of food commodities closely relates to decreasing the demands on storage conditions, such as air humidity and regulation, time of storage, temperature, etc. During the storage, food products are exposed to a large variety of pathogenic microbes that evoke a set of serious long-term health risks for human and animal beings.

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For these reasons, food contamination has been getting more attention and, nowadays, it represents one of the most important worldwide issues [1].

Over the past years, several international meetings have been held to discuss the carcinogenicity of human exposures that include biological toxins, produced by animals, plants, algae, fungi, or bacteria. Among the hundreds of mycotoxins identified so far, several of them include aflatoxins (AFB1 and AFM1), ochratoxin A (OTA), patulin, fumonisins, zearalenone, nivalenol, and deoxynivalenol that are the mostly observed in foodstuffs and present a real concern to human health and livestock. To reduce this potential risk, the WHO [2], as well as the European Commission's Scientific Committee [3], has been setting limits, regulations, and standards on natural toxicant levels in the food industry. The members of WHO met to discuss and review the existing epidemiological approaches, identify, and consider options for eliminating gaps, and provide the strategy development for estimating the global burden of foodborne diseases [4].

The health reliability of food products is the main criteria for avoiding epidemiological situations worldwide, therefore, toxins screening of food matrices in a fast, low cost, and precise way is fully required. Among a wide range of (bio) analytical methods, an appropriate detection mode must be chosen. Frequently used analytical approaches for the detection of mycotoxins are chromatographic methods (HPLC, mostly connected with fluorescence detectors, GC–MS, TLC) as well as immunoassays (capillary electrophoresis, ELISA) [5]. In recent years, electrochemical biosensors have become of interest for food quality control as it comes to meet the requirements of a fast, reliable, and on-field analysis. The detection of mycotoxins in food samples requires ultra-low detection limits that have been achieved by GC and HPLC techniques. However, the limitations like high-cost equipment, the need for well-trained personnel, the application of harmful organic solvents, and complicated sample pretreatment techniques should be considered. Using electrochemical biosensors, these problems could be eliminated while keeping a comparable analytical performance, especially upon using different electrode surface modifiers and signal enhancers [6]. To address this issue, Khataee et al. [7] reviewed the application of (bio)analytical methods for the detection of OTA, discussing the (dis)advantages of individual techniques, including their detection limits as well.

In this field, electrochemical biosensors based on aptamers, as modern biorecognition elements, represent great candidates for tracing mycotoxins in complex food matrices. These "aptasensors" are rapid, simple, and inexpensive biodevices that are able to monitor the mechanisms between an aptamer fixed to the electrode surface and an analyte present in the sample, thus, studying their interactions. The aptamers offer a set of significant advantages. They are often called "artificial antibodies" that successfully compete with antibodies, showing several benefits and providing solutions for many antibodies' limitations [8, 9].

The main advantage of aptamers is their thermal stability. Since the antibodies are considered proteins, they can easily undergo irreversible thermal degradation based on their tertiary structure changes at high temperatures. In contrast, the aptamers are thermally stable and keep their properties constant even after repeated processes of denaturation and renaturation.

A great benefit of aptamers is also their low immunogenicity and practically zero toxicity. This phenomenon is mainly caused by the fact that the living organism does not recognize nucleic acids as pathogenic substances, thus, does not trigger an immunological response. On contrary, antibodies are highly immunogenic which limits a repeat dosing. Unlike antibodies, the use of animals or cell lines can easily be overcome using aptamers. Since they are isolated by in vitro selection, called Systematic Evolution of Ligands by Exponential Enrichment (SELEX), they show high affinity to a wide range of low-to-high molecular targets, including some ligands and molecules that cannot be recognized by antibodies. An example of such substances might be ions or various small molecules. Interestingly, the aptamers can be chemically modified to improve their physical and chemical properties within the SELEX process [10]. To compare, the production and identification of monoclonal antibodies is usually a time- and money-consuming process that includes large antibody-based colony screening [11]. In terms of analytical performance, both immunosensors and aptasensors show approximately the same levels of sensitivity. Karapetis et al. [12] compared the sensitivity of various immuno- and aptasensors for the detection of aflatoxin M1 and found no significant divergence which, regarding many advantages of aptamers, makes the electrochemical aptasensors more effective for mycotoxin detection.

For these reasons, such biosensing tools may represent an adequate alternative to existing analytical approaches according to their low money and time consumption, undemanding sample treatment, low equipment requirements, fast and reliable response, and significant selectivity and sensitivity to matrix effects. Generally, biosensors utilize modern electroanalytical methods, especially voltammetric, amperometric, and impedimetric techniques, that have widely been used in the determination of mycotoxins in food matrices [13]. The combination of these voltammetric and impedimetric approaches allows us to obtain complex information about the redox behavior of (bio)molecules of interest as well as the interaction mechanism happening at the electrode-solution interface. The use of electrochemical aptasensors in food quality control has been noticeable as

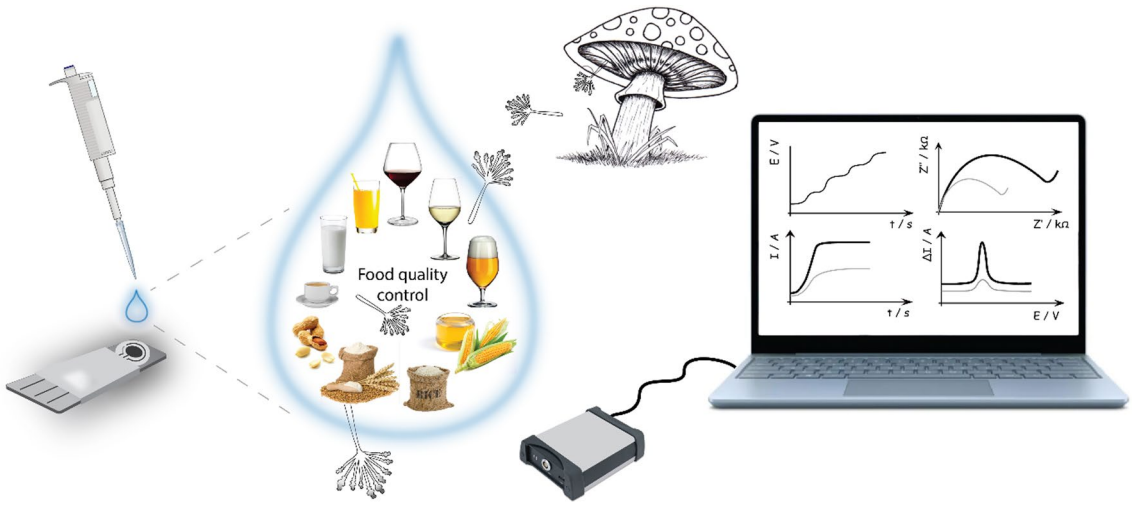

Fig. 1 Schematic illustration for electrochemical detection of mycotoxins in food commodities

well, according to several published experimental works, but there is a lack of published reviews discussing modern strategies for their development.

Therefore, we hereby present a complex overview of modern and advanced strategies for immobilization, detection, and application of electrochemical aptasensors for rapid and reliable monitoring of foodborne toxins in food matrices, illustrated in Fig. 1. This work discusses the possibilities of creating novel, cheaper, more practical (bio)sensors with a high level of sensitivity, selectivity, and specificity. These innovations are bringing out with a hope to be later involved in the development of miniaturized, portable, and commercially available lab-on-chip devices that would be applicable in a friendly manner for end-users.

Electrode materials

For decades, conventional gold and carbon materials have mostly been used within the development of many electrochemical aptasensors for mycotoxin detection. With increasing demands on stability, reusability, and sensitivity of the aptasensors for detecting trace concentrations of mycotoxins in complex food samples, novel materials have been explored to extend the portfolio of actually used electrode substrates, such as graphite, glassy carbon, highly oriented pyrolytic graphite, carbon fibers, or boron-doped diamond (BDD). The surface morphology of carbon-based electrodes as well as their pretreatment techniques represent a key factor for their bioanalytical applications [14].

Pencil graphite electrodes, as an alternative due to their comparable electrical properties at low cost and disposability, were used for the development of label-free impedimetric aptasensor for the determination of OTA in beer samples [15]. Zhang et al. [16] prepared a label-free rolling circle-based aptasensor for detecting OTA in wine using an electrically heated indium tin oxide electrode which showed an excellent signal-to-noise ratio. Over the past years, BDD electrode as an advanced substrate has been implemented in aptasensor fabrication for its good physicochemical properties, especially low background current, noise, and passivation resistance, and wide potential window as well. Therefore, Fojta et al. [17] reviewed the potential application of BBD electrodes in the analyses of biomolecular interactions using proteins, peptides, and nucleic acids.

To enhance the efficiency of analysis, these materials can typically be modified with electrocatalysts and/or redox mediators to increase the sensitivity of the aptasensor (graphene and graphene-like materials, carbon nanotubes, fullerenes, carbon dots, etc.) [18]. Different electrode materials and modifications steps used within the aptasensor fabrication are summarized in Table 1. To perform in situ screening of mycotoxins in food commodities, printable electrodes (SPEs) of a few centimeters are great candidates to determine mycotoxins in many easily pretreated food samples with a high level of sensitivity and specificity. Their relatively simple integration and connection with electrochemical devices could lead to creating disposable and friendly operable electrochemical "aptadevices" for food quality control in real-time. The attractive feature of SPEs is their possibility to be chemically modified in the same way as other conventional electrodes after or even during the screen-printing process.

Table 1 Construction of electrochemical aptasensors for mycotoxin detection in food samples

Pathogen	Electrode modification	Detection	LOD	Sample	Ref
Ochratoxin A	AuE/AQ-hDNA/MCH/Apt_1-Fc + Apt_2-MB	ACV	13.3 pg cm^{-3}	Corn, wheat	[79]
	AuE/cDNA/BSA/Apt_1-AuNRs-Th + Apt_2-AuNRs-Fc	DPV	0.47 pg cm^{-3}	Beer	[80]
	GCE/HG/Chit/$cDNA_1$ + $cDNA_2$/Apt	EIS	0.03 ng cm^{-3}	White wine	[81]
	SPCE/TMSi-Eth-Ar/*p*-NO_2-Ar/Apt	EIS	0.25 ng cm^{-3}	Beer	[47]
	AuE/$cDNA_1$/MCH/Apt + AuNPs-rGO-$cDNA_2$	EIS	0.3 pg cm^{-3}	Red wine	[82]
	AuE/hApt/MCH + $sDNA_1$-AuNPs + $sDNA_2$-AuNPs	DPV	0.5 pg cm^{-3}	Coffee	[83]
	AuE/Apt	EIS	0.12–0.40 nM	Coffee, flour, red wine	[84]
	ITO/f-Gr/CS/SA-BT/Apt	DPV	1.0 fg cm^{-3}	Grape juice	[85]
	AuE/S-R&T/MCH/Apt + H_1 + H_2 + H_3	DPV	0.95 pg cm^{-3}	Red wine	[86]
	AuE/cDNA/MCH/Apt + gCNNS	CV, EIS	0.073 nM	Red wine, juice, corn	[87]
	AuE/$cDNA_1$/MCH + $cDNA_2$-AuNP-Apt + $cDNA_3$-AuNP-sDNA-Fc	DPV	0.001 ppb	Wine	[88]
	SPCE/4-CP/Apt/EA	EIS	0.1 ng cm^{-3}	Beer	[15]
	AuE/AQ-hDNA/MCH/Apt_1-Fc + Apt_2-MB	ACV	13.3 pg cm^{-3}	Corn, wheat	[79]
	SPCE/PEG/Apt	EIS	0.12 ng dm^{-3}	Beer	[89]
	SPCE/PTH/IrO_2 NPs/Apt	EIS	14 pM	White wine	[90]
	AuE/eNR/Botlorn H30-AuNPs/Apt	EIS	0.02 nM	Beer	[91]
Aflatoxin B1	AuE/Apt-MB/MCH	SWV	2.0 nM	White wine	[92]
	AuE/3DOM MoS_2-AuNPs/TDNs/MCH/Apt + TEOS/PDDA/AuNPs/HRP + cDNA	DPV	0.01 fg cm^{-3}	Rice, wheat	[93]
	AuE/CA/GA/PAMAM G4/$NaBH_4$/GA/Apt	EIS	0.4 nM	Peanuts-corn snacks	[94]
	AuE/AQ-hDNA/MCH/Fc-Apt_1 + MB-Apt_2	ACV	4.3 pg cm^{-3}	Corn, wheat	[79]
	AuE/CA/PAMAM G4/Apt	EIS	6.4 nM	Peanuts	[95]
	SPCE/4-CP/Apt/EA	EIS	0.12 ng cm^{-3}	Beer	[96]
	SPCE/4-CP/Apt/EA	EIS	0.25 ng cm^{-3}	Wine	[96]
	BDDE/AuNPs/Apt/MCH	EIS	0.05 pM	Peanut powder	[97]
Aflatoxin M1	SPCE/4-CP/Apt/EA	EIS	1.15 ng dm^{-3}	Milk	[43]
	GCE/TAA/PEI/Apt	EIS	5.0 ng dm^{-3}	Milk	[98]
	AuE/CA/PAMAM G4/Apt	DPV	8.47 ng dm^{-3}	Milk	[12]
	AuE/NA/Fc/Apt	EIS	8.62 ng dm^{-3}	Milk	[12]
Fumonisin B1	GCE/AuNPs/Apt	EIS	2.0 pM	Maize	[99]
	AuE/cDNA/BSA/Apt_1-AuNRs-Th + Apt_2-AuNRs-Fc	DPV	0.26 pg cm^{-3}	Beer	[80]
	GCE/GS-Au-Th/Apt	CV	10.0 pg cm^{-3}	Maize	[100]
	AuE/cDNA/MCH/Apt/Exo I/MB	DPV	0.15 pg cm^{-3}	Beer, corn	[101]
Patulin	SPCE/PEG/Apt	EIS	2.8 ng dm^{-3}	Apple juice	[102]
	GCE/BP NSs/Apt	EIS	0.3 nM	Apple juice	[103]
	GCE/AuNPs-BP NSs/MCH/Apt	EIS	0.03 nM	Apple juice	[103]
	AuE/TDNs-Apts + Fe_3O_4 NPs-rGO	DPV	30.4 fg cm^{-3}	Apple juice	[104]
	AuE/ZnO NF/CS/AuNPs/cDNA/MCH/MB@MOF-Apt	DPV	1.46×10^{-8} µg cm^{-3}	Apple juice	[105]
Zearalenone	PGE/PDDA-MWCNT/dsDNA	DPV	5.0 pg cm^{-3}	Milk, wheat	[106]
	GCE/CS@AB-MWCNTs/Au/cDNA/BSA/CGO-ZBA	DPV	3.64 fg cm^{-3}	Corn oil and flour	[107]
	AuE/CA/PDC/ZEA	SWV	0.017 ng cm^{-3}	Maize	[108]
	AuE/PEI-MoS_2-MWCNTs/Tb/Pt@Au/Apt/MCH	CV	0.17 pg cm^{-3}	Beer	[109]
Deoxynivalenol	GSPE/AuNP/PANI/ Apt/MCH + cDNA/SA-ALP	DPV	3.2 ng cm^{-3}	Maize flour	[110]

3DOM MoS_2-AuNPs three dimensionally ordered microporous MoS_2-AuNPs, *4-CP* 4-carboxyphenyl diazonium salt, *ACV* alternating current voltammetry, *AQ-hDNA* anthraquinone-labeled hairpin DNA, *ALP* alkaline phosphatase, *Apt* aptamer, *AuE* gold electrode, *AuNPs* gold nanoparticles, *AuNRs* gold nanorods, *BDDE* boron-doped diamond electrode, *BP NSs* black phosphorus nanosheets, *BSA* bovine serum albumin, *CA* cystamine, *cDNA* capture DNA probe, *CGO* carboxylated graphene oxide, *CS* chitosan, *CS@AB* chitosan functionalized acetylene black, *DPV* differential pulse voltammetry, *EA* ethanolamine, *EIS* electrochemical impedance spectroscopy, *Fc* ferrocene, *f-Gr* functionalized graphene, *Fe_3O_4 NPs* iron oxide nanoparticles, *GA* glutaraldehyde, *g-CNNS* graphite-like carbon nitride nanosheet, *GCE* glassy carbon electrode, *GS* graphene nanosheet, *GSPE* graphite screen-printed electrodes, *hApt* hairpin aptamer, *HG* hydrogel, *HRP* horseradish peroxidase, *ITO* indium tin oxide, *MB* methylene blue, *MOF* metal organic framework, *MWCNT* multi-walled carbon nanotube, *PAMAM G4* Poly(amido)amine dendrimer generation 4, *PDC* 1,4-phenylene diisocyanate, *PDDA* polydiallyldimethylammonium chloride, *PEG* polyethylene glycol, *PEI* poly(ethylene imine), *PGE* pencil graphite electrode, *Pt@Au* platinum/gold core/shell, *PTH* polythionine, *rGO* reduced graphene oxide, *SA-BT* streptavidin–biotin, *sDNA* signaling DNA probe, *SPCE* screen-printed carbon electrode, *S-R& TAA* thiacalix[4]arene, *SWV* square-wave voltammetry, *Tb* toluidine blue, *TDNs* tetrahedral DNA nanostructures, *TEOS* tetraethyl orthosilicate, *Th* thionine, *ZEA* zearalenone, *ZnO NF* zinc oxide nanoflower

Immobilization techniques

The immobilization of the long-chained aptamers as well as complementary single-stranded oligonucleotides (altogether as nucleic acids, NAs) onto the electrode surface is a crucial step in the construction of aptasensors. Generally, the goal is to use such appropriate optimized method that can ensure the formation of an adequate, highly reproducible, and stable biolayer with the well-oriented aptamer or oligonucleotide sequences. Several immobilization techniques for the construction of NA-based biosensors have been developed [19]. Adsorption is the simplest method to immobilize NA onto the electrode surface which is commonly provided by incubating a working electrode in NA solution for a certain time. By applying a constant potential, it is possible to obtain a stable NA-based layer formed by the electrostatic interactions between the negatively charged NAs and a positively charged pre-treated electrode surface. The physical and electrochemical adsorption method is usually used for carbon-based electrodes. Even though it is a rapid and simple immobilization method that does not require chemical reagents or special modifications in the NA structure, there are also some limitations, such as the desorption of NA from the electrode surface influenced by pH buffer, ionic strength, and temperature. Contrary to the adsorption techniques, NA immobilization through covalent bonding has shown better stability, flexibility, high binding strength, good vertical orientation of NA sequences, and prevents the desorption of the NA monolayer from the electrode surface.

To successfully immobilize NAs onto the electrode surface, structurally related materials (metal nanoparticles, carbon-based nanomaterials, graphene, and its 2D analogues, synthetic polymers, and membranes, etc.) increase a surface-to-volume ratio resulting in a signal enhancement, thus, improving the analytical performance of biosensors [34]. Moreover, an electrochemical signal can be efficiently enhanced, and unspecific adsorption or cross-reaction may be eliminated using advanced immobilization techniques, such as the formation of self-assembled monolayers (SAMs) and the electrografting method. The spontaneous chemisorption of functional group-terminated NA sequences (usually with thiol and amide bonding) [20] and in situ generation of diazonium salts combined with click chemistry [21] represent simple methods for the patterned multiplexing of bioreceptors on a multi-electrode chip ensuring maximum surface coverage, adequate stability of a coated layer, and the same binding affinity as yielded in a solution form [22].

Self-assembled monolayers

SAMs are highly organized molecular assemblies spontaneously formed on metal surfaces mediated by the chemical adsorption of functional groups in a solution that show a strong affinity to the particular surface. There exists a wide spread of different SAMs formed on various materials including alcohols, amines, and carboxylic acids, but the majority of currently utilized SAMs are based on covalent binding of disulfides (R–S–S–R), sulfides (R–S–R), and thiols (R–SH) on gold surfaces, or amine, methyl, hydroxyl, and carboxyl-terminated molecules on the carbon surfaces, and others [11]. An important aspect of SAMs is that the surface attached molecules undergo different mechanisms upon binding targets on the other side of their structure; thus, this knowledge makes them possible to be functionally modified as required. This brings the idea of developing (multi)layered surfaces for sensor applications with desired chemical properties [12]. It should be mentioned that a great variability of electrode types as well as many techniques for surface modifications including SAM constituents have been reported within the development of electrochemical NA-based biosensors, among which the formation of amide (Fig. 2a) and thiol (Fig. 2b) bonds have mostly been used. However, some key factors have a strong influence on the performance of these sensors.

At the development of NA-based biosensors, the formation of SAMs is usually made by the self-immobilization of capture DNA probes (cDNA) or aptamers on metal electrode substrates at an optimized surface density. The optimal surface density of the cDNA/aptamer is important for either monitoring the mechanisms that occur at the DNA phosphate backbone level upon the intrinsic charge or for obtaining the maximized gain of the biosensor. It was shown that the molecular crowding of DNA probes on the electrode surface significantly affects the analytical performance of electrochemical biosensors [13]. Likewise, a signal enhancement is obtained with increasing probe densities upon binding longer and bulkier targets, but in contrast, a sensor equilibration time gradually slows. Regarding the hybridization process between cDNA and target DNA (tDNA) specific for a pathogenic microbe, the optimal compactness of the immobilized probes represents a key factor of the successful hybridization. By overrating the density of cDNA, the incoming target probes would not have enough space to hybridize with their complementary strands. As a result, DNA-modified surfaces with sufficient distances between each cDNA/aptamer can ensure a high hybridization yield [14, 15]. White et al. [16] invented a method for the optimization of the probe packing density of aptamers at the electrode surface to obtain maximum gain values. Similarly, Keighley et al. [17] optimized an electrochemical method to control cDNA probes density on the electrode surface by measuring the electron transfer resistance at the electrode surface using an impedimetric approach. They used the effect of co-immobilization of thiol-modified cDNA and

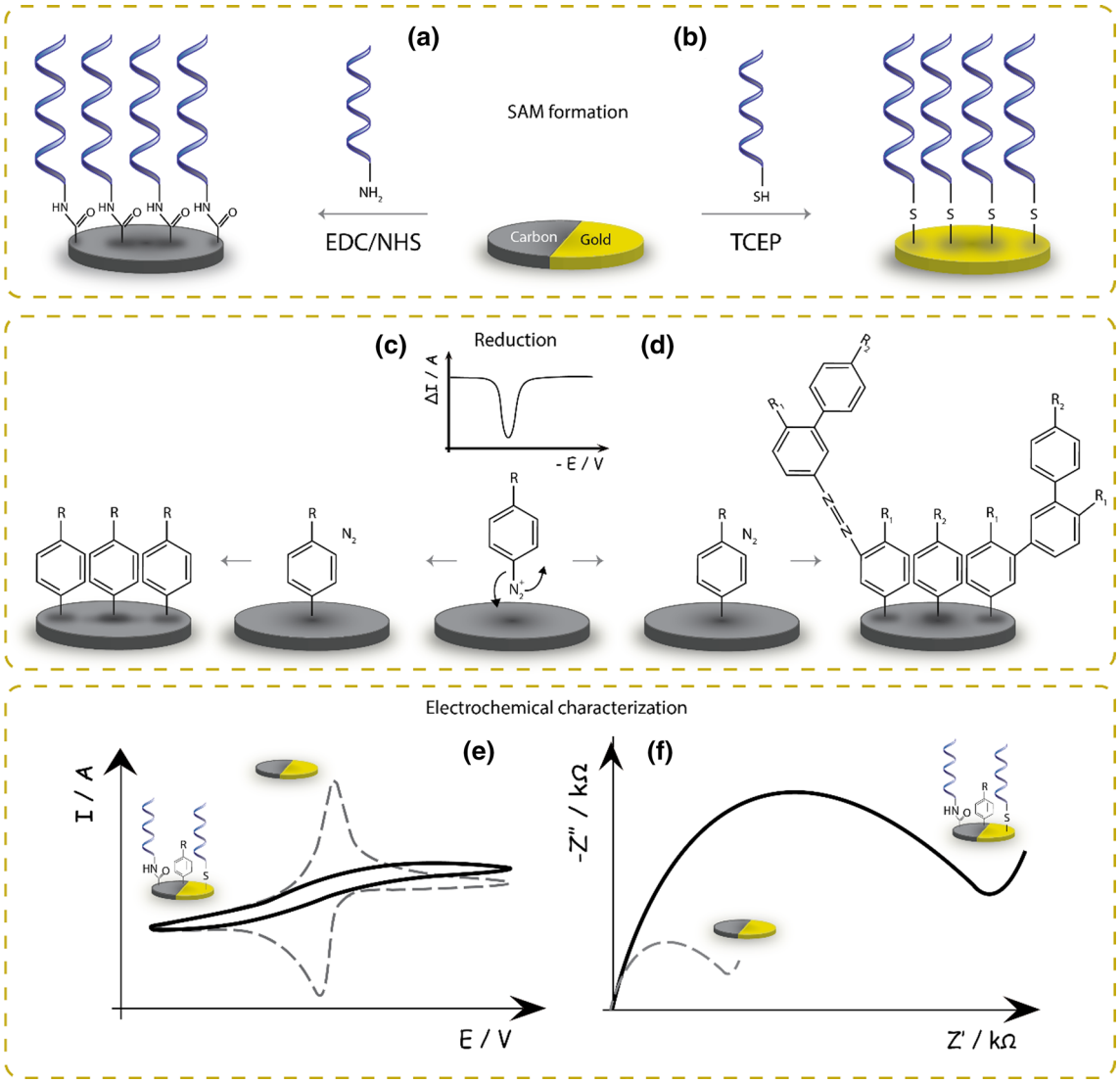

Fig. 2 The SAM reaction mechanisms via the formation of peptide (**a**) and thiol (**b**) bonds as well as the formation of single (**c**) or multiple (**d**) layers of different functional groups on the electrode surface through the reductive electrografting of aryldiazonium salts followed by voltammetric (**e**) and impedimetric (**f**) characterization of prepared layers

mercaptohexanol (MCH) as an effective agent for displacing non-specific interactions of DNA with the gold surface. Zhang et al. [18] investigated the hybridization performance of co-immobilized cDNA probes with MCH on gold nanoparticles-modified and roughened gold surfaces. They found that nanoparticles-based surface provided a more suitable platform for biosensor development because of the increased volume-to-surface ratio. In the case of real food samples, the presence of many other molecules can lead to non-specific interactions with aptamer which affect the sensitivity. To avoid this limitation, ternary SAMs can represent a promising way to detect analytes in complex matrices. Campuzano et al. [19] and Miodek et al. [20] designed ternary SAMs based on cDNA and aptamer, respectively, in combination with various thiolated molecules for detection of molecules in biological fluids, which can be considered as complex as real food samples.

The rather limited surface area of miniaturized metal electrodes used at the biosensor development leads to low faradaic currents and poor signal-to-noise ratios. For these reasons, an electrochemical roughening approach that enhances the analytical performance of small electrochemical biosensors can be utilized [21]. This method is based on applying chronoamperometric pulses during the fabrication process. It allows more functionally modified aptamers to be attached to the electrode with a significantly enlarged microscopic surface area which results in an increased signal-to-noise ratio.

Maximizing the biosensor signals can also be achieved by optimizing the length of DNA probes and linking molecules responsible for either detection or effective DNA hybridization. Corrigan et al. [22] studied the effect of tDNA length on the assay sensitivity using a label-free impedimetric method and found out that the optimal tDNA length was one of 15 nucleotides overhanging in solution upon hybridization with cDNA. This 15-nucleotides-long overhang ensured the highest signal enhancement explained by the formation of electron transfer blockage, contrary to the longer overhangs which caused signal decreasing because of the reduced hybridization efficiency between cDNA and "too-long" tDNA. The important factor is a DNA persistence length defined as the distance over which the DNA backbone undergoes a rigid conformation. It was found that single-stranded DNA probes immobilized onto the gold electrode surface through a short-chained alkane-thiolated SAM change their physical properties upon hybridizing with tDNA from a very flexible state to a rigid one using a DNA label-free [23], methylene blue [24], and ferrocene-labeled [25] detection strategies. However, the signaling mechanism is highly affected by the physical and chemical nature of prepared SAMs at the electrode surface. Several factors as the thickness and self-life of the monolayer, surface charge, steric effects, surface chemistry, etc., influence the analytical performance of the biosensor. For these purposes, Ricci et al. [26] tested different charges of co-adsorbates and lengths (2, 6, and 11 carbons) of hydroxyl-terminated alkanethiols while preparing SAMs on gold electrodes and noticed that a) the surface charge strongly affects the electron transfer rate, hypothetically, because of the attractive/repulsive forces between SAMs and negatively charged DNA backbone or positively charged methylene blue, b) the use of the alkanethiolated SAM with length beyond the optimal one (lower and higher than 6 carbons) leads to the signal suppression, c) the different charge of SAMs can either slow down or favor the hybridization with an unclear origin and d) the length and nature of terminating groups on alkanethiols influence the self-life time and stability of the biosensor showing that thinner SAMs have much poorer stability. In other works, it was stated that the long-chained alkanethiol-mediated distribution of DNA probes at the biosensor surface can lead to the shielding of gold-thiol bonds from the surrounding environment [25] while the shorter alkanethiol chains produce lower background signal, thus, making the detection technique more sensitive [27].

Moreover, the hybridization between cDNA and tDNA might result in increasing negative charge at the biosensor surface which leads to potential shifting. These surface charge alterations, namely to the more negative values, cause the charge transfer hindrance of negatively charged redox-active molecules present in the solution. J. Park and S. Park [28] reviewed electrochemical DNA hybridization-integrated biosensors based on the detection of charge transfer resistance on the electrode surface using electrochemical impedance spectroscopy (EIS), Preuß et al. also reviewed the use of impedimetric aptasensors for food quality control. These aptasensors monitor the presence of mycotoxins and microorganisms in food commodities based on attractive/repulsive forces occurring at the electrode–electrolyte interface upon binding pathogens.

The signal gain of electrochemical NA-based biosensors can also be maximized by optimizing the parameters of pulse voltammetric techniques since the detection principle can also utilize the redox behavior of aptamer-attaching electroactive labels. Upon binding target, the labeled aptamer changes its conformational structure which results in altering the location of redox reporter towards (signal-on) or outwards (signal-off) the electrode surface, thus, the electron transfer rate is altered as well. Therefore, the driving force of the redox reaction as well as the electron transfer kinetics, strongly depend on choosing the optimal amplitude and frequency of potential pulses. P. Dauphin-Ducharme and K. Plaxco [24] prepared an electrochemical aminoglycoside biosensor at which the optimization of several factors like potential pulse parameters, DNA probe density, the nature of redox-active labels, and the thickness of mercaptoalcohol-based SAM coating was performed. They found out that not only the choice of redox-active labels and the SAM thickness are dependent on the biosensor gain, but also the potential pulse parameters as the frequency and amplitude can significantly improve the gain.

Electrografting methods

Various techniques of electrode surface functionalization have been used to increase an electroactive area, aptamer loading, and provide 3D support that facilitates aptamer immobilization and minimizes a steric hindrance. The functionalization of electrodes via the reduction of diazonium salts has widely been investigated during the past decade. The versatility of the method allows the attachment of various substituted functional groups to several surfaces in order to change their surface properties or to immobilize specific chemical functionalities for different applications. In this way, the electrografting of various functional groups permits the subsequent modification of the surface by coupling reactions and provides a useful pathway for the immobilization of more complex structures [41]. Several electrografting methods were developed by Breton and Bélanger using aryl groups having an aliphatic amine, such as 4- and 2-aminobenzylamine, 4-(2-aminoethyl)aniline, *N*-methyl-1,2-phenylenediamine, and *N*,*N*-dimethyl-*p*-phenylenediamine, through diazotation mechanism [42]. The principle

of the electrografting process is generating of aryl radicals produced by the electrochemical reduction of diazonium salts. This process results in the formation of aryl-centered radicals covalently attached to the electrode surface accompanied by the spontaneous elimination of dinitrogen. The electrode surface can be electrografted with either one or multiple types of aryldiazonium salts to create monolayers (Fig. 2c) or multilayers (Fig. 2d), respectively. Indeed, the modification of multilayers is especially relevant in applications where the interface is required to perform multiple functions, and hence different chemical species should be incorporated into the layer or for the analysis of complex food samples. Regarding carbon electrode surfaces, the covalent attachment of an aptamer on a chemically functionalized carbon surface represents an advantageous immobilization technique. Several approaches for amide bonding between the amine-terminated NAs and 4-carboxyphenyl-modified carbon electrodes have been developed [43–45]. Contrary, amide bonding can be performed between carboxyl-terminated biomacromolecules and the amine-functionalized electrode surface. Therefore, an electrochemically controlled process of in situ generation of nitrophenyl groups using *p*-nitrobenzene diazonium and further nitro-to-amine functional groups reduction processes has been presented [46]. For instance, another diazonium salt, 4-[(trimethylsilyl) ethynyl]benzene, was used to fabricate an electrochemical aptasensor for the detection of OTA. The diazonium salts were electrografted onto the electrode surface. After the deprotection of ethynyl groups, in the presence of copper(I) catalyst, they reacted using click chemistry with azide-terminated aptamers [47].

Detection strategies

Regarding molecular detection, an electrochemical steric hindrance hybridization assay allows fast quantitative detection of toxins with ultralow detection limits. Using the steric hindrance, it is possible to detect the whole molecules of toxins or their structural parts, such as proteins [48]. To target the pathogenic DNA/RNA sequences, the monitoring of the hybridization process between cDNA immobilized on the electrode surface and tDNA in the sample solution is required [19]. Understanding the hybridization mechanisms can help researchers develop novel methods for the detection of specific DNA or RNA sequences responsible for many human and animal infections. Importantly as well, DNA molecules can serve as detection tools for determining a wide range of low-to-high molecular targets of interest. For these purposes, the design strategies of electrochemical NA-based biosensors can be divided into four detection modes: (1) target-induced structure switching mode, (2) sandwich or sandwich-like mode, (3) target-induced dissociation or displacement mode, and (4) competitive replacement mode [49].

In target-induced structure switching mode (Fig. 3a), the target directly binds to a specific aptamer accompanied with a corresponding conformational switch of the aptamer to a specific pattern. Upon creating a target–aptamer complex the aptamer changes from a randomly organized conformation to a rigid tertiary structure. Such conformational switches induce the changes of moieties covalently linked to the end of the aptamer sequence leading to the changes of detectable characters, such as (a) the location of a DNA-attached redox reporter that results in the alterations of the electron transfer rate [50, 51], (b) the quantity of the signal moieties adsorbed on the aptamers via electrostatic force, stacking, hydrogen bond, etc. [52, 53], (c) the changes in size or weight of aptamers upon fixing a target that lead to the (de)blockage of the electrode surface [54], or (d) other properties of aptamers, such as the ability to stabilize gold nanoparticles [55].

The target-induced displacement mode (Fig. 3b) is a structure-independent assay where a three-component system takes place that consists of an aptamer, cDNA, and signaling DNA (sDNA). The interaction of a target with the aptamer causes the aptamer displacement and its leaching from the interface. Depending on a detection strategy, the dislocation mechanism can be monitored in different ways. First, the signal decrease is observed because, either a target–aptamer duplex together with a fixed redox-active molecule is leaving the proximity of the electrode surface [56], or the electron transfer resistance at the electrode is decreasing [57]. Otherwise, the signal increase is monitored because the labeled sDNA is hybridizing with cDNA at the electrode surface upon the target–aptamer dislocation [58–60]. Moreover, a three-component-like system can be developed using only two DNA strands where sDNA can hybridize with both, the target-binding region of the aptamer and the DNA sequence as cDNA linking the aptamer to the electrode. Upon binding target, the aptamer region detaches from the signaling probe and forms a G-quadruplex which allows the sDNA-attached redox-active label to reach the electrode surface [61].

In terms of the competitive replacement mode (Fig. 3c), the competition occurs when an aptamer shows a higher affinity towards a target than the complementary cDNA probe attached to the electrode surface. In the absence of the target, the aptamer hybridizes with cDNA, but once the target is present, a target–aptamer duplex is formed. As a result, a measuring signal alters, meaning that if the aptamer is labeled with a redox-active reporter, the current signal is

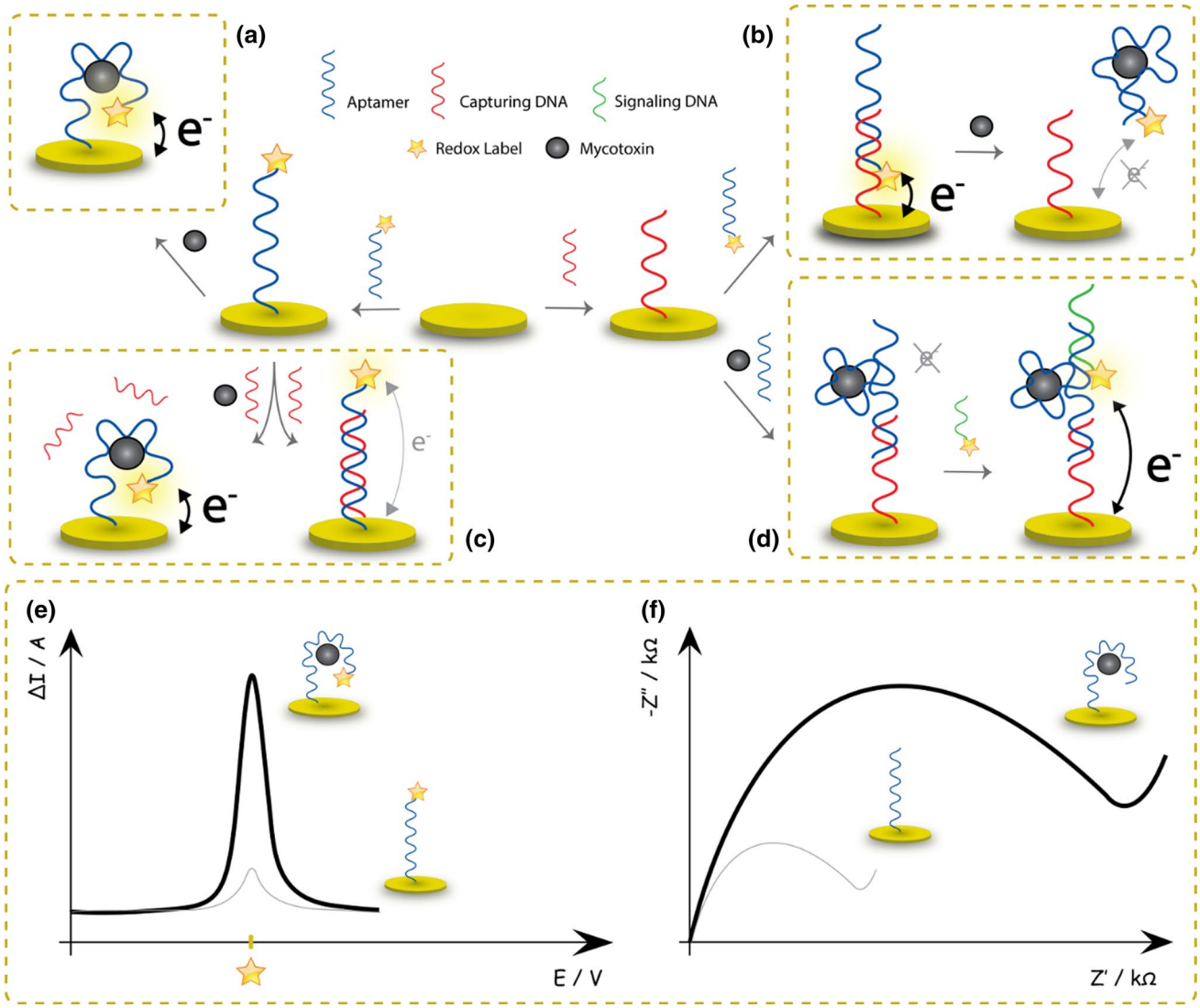

Fig. 3 NA-integrated detection strategies based on (**a**) a target-induced conformation switching, (**b**) a competitive replacement, (**c**) a target-induced displacement, and (**d**) a sandwich-type assay followed by voltammetric (**e**) and impedimetric (**f**) detection methods

reduced since fewer labeled-aptamer molecules reach the electrode [62].

Electrochemical biosensors based on the sandwich-type detection (Fig. 3d) are also known as dual-site binding assays that have commonly been used for the detection of target molecules. In this mode, a selected target is "sandwiched" by two paired DNA sequences, cDNA and sDNA, while the cDNA is often immobilized on a solid surface (electrodes, glass chips, nanoparticles or microparticles) and the signaling probe is connected to a detectable signaling moiety as redox-active molecules, fluorophores, enzymes, nanoparticles, etc. [63–66].

Mycotoxin aptasensing

Because of all potentially severe and acute health problems caused by the overconsumption of mycotoxins, still, novel and more sensitive approaches for the detection of food-borne pathogens and their specific DNA or RNA sequences responsible for various human and animal infections are required [67]. Additionally, as food safety and quality requirements have been rapidly pushed up every year, getting lower limits of detection has become challenging for many analytical approaches. To meet all the criteria, electrochemical aptasensors may represent not only promising tools with

a high level of reliability, specificity, and selectivity, but also a possibility to reach ultralow detection limits. Therefore, these devices have become of great interest in food safety, and environmental monitoring. Several reviews have been published describing the design of electrochemical aptasensors for the detection of mycotoxins for food quality control [6, 68, 69], namely for aflatoxins [70–72], OTA [7, 73–75], or fusarium mycotoxins as fumonisins, zearalenone, nivalenol, and deoxynivalenol [76]. Advances in nanomaterial-based electrochemical biosensors including the construction strategies and modern (bio)materials for detecting microbial toxins and pathogenic bacteria in food have been reviewed [77]. Hong and Sooter published a review about the applications of aptamers as biorecognition elements for the identification and detection of bacterial and viral pathogens as well as selected chemical toxins [78]. Other various examples of aptamer-based electrochemical detection of the most hazardous mycotoxins in non- or partially processed food samples are presented in Table 1. As obvious from the table, the choice of detection mode depends on, whether the oligonucleotide/aptamer is labeled with redox-active labels or not. For unlabeled systems, the impedimetry is usually applied to monitor the charge transfer resistance at the electrode surface, while labeled systems utilize voltammetric techniques to monitor the redox behavior of the redox-active labels (mainly methylene blue, ferrocene, or anthraquinone) upon binding a mycotoxin. Figure 3e and f schematically show the changes in charge transfer rate and resistance before and after the interaction of the aptamer with a target.

Reusability and stability testing

Compared to other detection techniques, electrochemical aptasensors can principally be reusable. Since the character of binding between aptamers and mycotoxins is based on the weak electrostatic or Van der Walls interactions, the regeneration of aptasensors can then be considered as an effective way to overcome some technical and economic issues. The regeneration process includes the incubation of the aptasensor in an acidic [12, 84, 94], basic [85], or salt-enriched medium [80, 111, 112], or the modified electrodes can simply be rinsed with deionized water for a given time [113]. Upon target binding, the regeneration solution is applied to the aptasensor to remove any bound target molecules from the electrode-attached aptamers. Hayat et al. [47] stated that the prepared impedimetric anti-OTA aptasensor showed no significant changes in *R*ct values for up to ten-fold rinsing and the biosensor was stable for 10 days at 4 °C. Wang et al. [113] developed a voltammetric MB-modified aptasensor for the detection of AFB1 which could be regenerated by rapid washing with deionized water. Such biosensor retained reusable and stable for 14 days. Castillo et al. [94] fabricated a dendrimer-based impedimetric aptasensor for the detection of AFB1, regenerable with glycine–HCl. It showed good stability for 2.5 days at 4 °C and the reproducibility was calculated to be 1.73%. In terms of rapid mycotoxins screening, a key factor within the analysis is the reaction time needed. Detection of mycotoxins using electrochemical aptasensing basically takes only tens of minutes, as mentioned in hereby reviewed articles, which is significantly faster than other used analytical methods. For instance, Kaur et al. [85] developed a voltammetric chitosan-modified aptasensor for the detection of OTA that showed 8 min quick response. They used a solution of NaOH for 10 min regeneration and found a good reproducibility (0.45%) and stability for up to 7 days with maintained current values of 85%. Given examples indicate the possibility of preparing electrochemical aptasensors, regenerable and stable for a couple of days without any significant loss of sensitivity. Therefore, the facility of their repetitive usage can reduce the cost and time of the fabrication process.

Conclusions

The current overconsumption of food that leads to the massive short-term production of food commodities has rapidly reduced the demands on storage conditions. An excessive time of storage even in inappropriate air humidity and temperature may lead to the fast reproduction of a large variety of pathogenic microbes in food that can trigger a set of serious health issues for humans and animals.

To ensure the higher quality of food products, monitoring devices, effective in both bioanalytical performance and costs, have started to be essential for food quality control. Nowadays, flexible, hand-held, and readout devices take place in the worldwide market and give a final shape to the concept of out-of-lab analysis. Among them, electrochemical aptasensors might play an unsubstitutable role because they represent great candidates for the fast, reliable, and ultrasensitive detection of foodborne pathogens in food matrices (Fig. 1). In this review, new insights and perspectives of electrochemical aptasensors used for detecting low-to-high molecular toxins for human health monitoring and prevention are reported. The development of modern aptasensors using modern metal electrode materials is presented. Immobilization techniques as physical adsorption, electrostatic deposition, and chemisorption via various functional group coupling are highlighted as the effective methods for attaching short complementary oligonucleotides and aptamers to the electrode surface. To increase the stability

and reproducibility of aptasensors, layer-by-layer modification strategies for the biosensor structure arrangement were present. Therefore, the formation of self-assembled monolayers consisting of either short oligonucleotides/aptamers (Fig. 2a and b) or a variety of different functional groups using "click chemistry" (Fig. 2c and d) are explained. Importantly as well, different detection strategies based on target-depending structural changes of nucleic acids, such as target-induced structure switching and displacement, competitive replacement, and sandwich-type detection are discussed and illustrated in Fig. 3. This work offers an overview of current voltammetric and impedimetric aptasensors for the detection of seven of the most dangerous groups of mycotoxins, such as aflatoxins, ochratoxin A, patulin, fumonisins, zearalenone, nivalenol, and deoxynivalenol which are also summarized in Table 1.

Prospects and challenges

The health reliability of food products is the main criteria for avoiding epidemiological situations worldwide, therefore, toxins screening of food matrices in a fast, low cost, and precise way is fully required. Until now, many analytical approaches have already been used for mycotoxin detection. However, there are still existing challenges that have to be solved as the simultaneous detection of structurally related mycotoxins that might serve as interferences in complex food matrices and significantly affect the sensitivity and selectivity of the method. As presented in this review, electrochemical aptasensors for food quality control are promising tools to address this issue. Taking advantage of flexible, compatible, and durable materials in combination with modern connection strategies, the use of miniaturized aptasensors for toxin screening might be the possibility how to provide continuous readout information about the toxin content in food products within a few seconds or minutes. Moreover, the aptasensors with smart multifunctional and active biolayers consisted of two and more different specific aptamers as biorecognition elements would lead to the multiplex detection of mycotoxins at a time. Some recent works have already presented the simultaneous detection of two different mycotoxins [79, 80]. Another possibility is the use of an extra redox-active molecule-labeled DNA probe, attached to the molecule of interest, that would increase the efficiency and kinetics of DNA hybridization at the electrode surface, thus, increasing the sensitivity [114]. The integration of wireless connection possibilities via smartphones would make these devices even more attractive for end-users and applicable in real-time food analysis. Such a system would significantly improve the abilities of toxin screening in food samples, particularly in countries with low resources. The summarized information on the topic of electrochemical aptasensing could serve as an inspiration for developing future generations of flexible electronics that would be commercially available and applicable in a friendly manner for end-users. However, the successful commercial implementation of electrochemical aptasensors in the food industry has not been achieved yet but regarding their excellent properties, such as good stability over several days, storage in mild conditions, reproducibility without any significant signal loss, great selectivity, and a high level of sensitivity, they show huge potential to be used in real mass practice for mycotoxins screening, especially those that are developed for multidetection [79, 80].

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