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REVIEW

Metallic Nanoparticles and Carbon-Based Materials for the Fabrication of Electrochemical Biosensors aiming the Mycotoxin Analysis in Food

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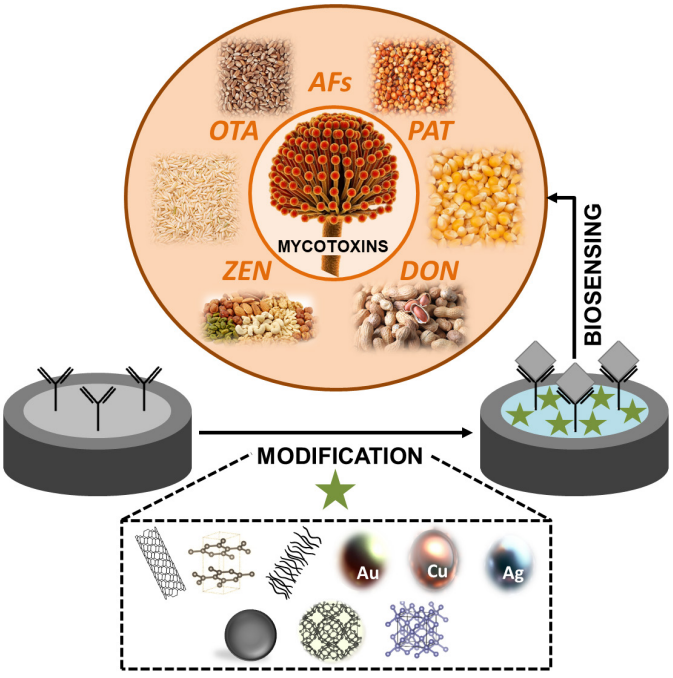

Mycotoxins are low molecular-weight compounds produced by fungi genera as secondary metabolites during pre- and post-harvest storage of crops and foodstuff. Many reports show highly concerning issues ascribed to their carcinogenic, genotoxic, immunosuppressive, and teratogenic properties. Biosensors are compact analytical devices incorporating a biological or biologically-derived recognition element that might be either integrated within or intimately associated with a physicochemical transducer. The most applied bioreceptors are the enzymes (biosensors), DNA and RNA nucleic acids (genosensors), antibodies (immunosensors), aptamers (aptasensors) or living cells (microbial biosensors). The integration of nanotechnology to the biosensors field brought sensitivity and versatility for bioassays, since nanomaterials might play the role as new signal markers, surface subtracts for functionalization and fixation of biomolecules, and generation source

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of analytical signals. For electrochemical biosensors, nanostructures can enhance the sensitivity of electrochemical techniques by filling the gap between the converter and the biorecognition element. Metal nanoparticles are used to improve the analytical sensitivity by refining the electrical connectivity of the interface, increasing both the chemical accessibility of analytes and the sensing surface with higher amounts of bioaffinity recognition sites. Gold nanoparticles are among the most used nanostructures due to their unique electrocatalytic activity and conductivity. In turn, carbon-based nanomaterials are very appealing considering their large specific surface area and high electron transfer rates. Carbon nanotubes (CNTs) and graphene oxide materials are the most employed carbon-based materials. There is no doubt that the whole bioassay has become more versatile, robust, and dynamic with the introduction of the nanoscience, consolidating in an emerging field with current intense research. Hence, this work reviews some selected applications of electrochemical metallic and carbon-based nanobiosensors for the determination of mycotoxins in food, revisiting important fundamentals of the electrochemical bioassay.

Keywords: mycotoxins contamination, foodstuff analysis, immunosensors, aptasensors, genosensors, electrochemistry

INTRODUCTION

The class of the mycotoxins is a group of low molecular-weight compounds produced by filamentous fungi in food. They are secreted as secondary metabolites of several fungi species, like *Aspergillus*, *Fusarium*, *Penicillium*, and Alternaria, during pre- and post-harvest of crops and foodstuff storage. Among commonly studied mycotoxins are the aflatoxins (AF), ochratoxins (OTA), and patulin (PAT).[1] Aflatoxins are the most investigated group, including the aflatoxins B1, B2, G1 and G2, produced by Aspergillus flavus. They have drawn a lot of attention due to their high cytotoxicity and carcinogenicity.[2] *Aspergillus* and *Penicillium* genus produce the ochratoxins mycotoxins, which include ochratoxin A ascribed to toxic pathologies on the human renal system. Penicillium strains can additionally produce some tremorgenic mycotoxins. Other mycotoxins include the trichothecene group generated by the *Fusarium* genus, which can cause oral lesions such as dermatitis, irritation, and bleeding.[3] That is why mycotoxins are contaminants that need to be continuously monitored in critical stages of the food chain to preserve the quality of human life. That includes inspections of raw materials, food supply and processing, final products, and also the storage.[4] Considering the mycotoxins maximum levels allowed in cereals and related cereal products by *e.g.* the European Commission Regulation (1881/2006), there is a substantial challenge for detecting such low concentrations at ppb magnitude order in complex food products. For total aflatoxin (TAF) the maximum concentration allowed is 4 ng/g, while for deoxynivalenol (DON) is from 200 to 500 ng/g, for zearalenone (ZEN) is from 20 to 50 ng/g and, for ochratoxin A (OTA) is 0.5 ng/g. Still, the identification of emerging mycotoxins and their synergistic effects[5] usually requires the use of multi-target procedures, demanding advanced instrumental methods such as the liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI/MS) with long sample processing times, and high instrument costs that impair the screening of a large number of samples.[6]

Many benchtop analytical methods are available to accurately and sensitively detect mycotoxins in foods: thin-layer chromatography,[7] capillary electrophoresis,[8] liquid chromatography coupled with mass spectrometry,[9] and Raman spectroscopy[10] are some examples. However, analytical chemistry is quickly evolving in the last decades, making field measurements feasible (at least for screening analysis) that accelerate the decision-making for the agriculture niche.[11,12] A fast overview of the situation regarding the eventual mycotoxins contamination can not only help in terms of the producers awareness, but with the number of samples to be collected, processed, prepared, and analyzed, saving time and money.[13] This reality can still be highly improved by the full substitution of the lab-bench techniques by *in situ* specific techniques with improved accuracy, precision, and sensitivity. That is the main reason why mycotoxin immunoassay development has approached and nearly surpassed chromatographic methods.[6] Hundreds of immunoassay methods have been developed addressing the fast mycotoxins detection using ELISA, flow

injection immunoassay (FIIA), chemiluminescence (CL) immunoassay, lateral flow immunoassay (LFIA), and flow immunoassay.[6,14–16] Among other immunological methods, ELISA and LFIAS stand out for their simplicity, agility, and long-term stability under different climatic conditions, ascribing them to be suitable for onsite mycotoxin detection.[6]

Another way to perform *in situ* determinations is by the development of miniaturized electrochemical nanoimmunosensors. Immunosensors are a class of highly-specific biosensors that use antibodies as recognizing bioreceptor agents, which specifically interact with the analyte, forming surface immunocomplexes.[17] Among the immunological bioreceptors, aptamers are attracting much attention recently due to their low cost, reasonable stability, and good applicability in wide ranges of pH and temperatures, with the so-called label-free detection.[18] The signal is triggered by the analyte bonding that changes the aptamer conformation or hybridization.[19] Many transducing mechanisms are possible with special regard to electrochemical methods that are considerably simple and sensitive enough for most of the studied applications.[20,21] Meanwhile, the nanotechnology serves several purposes once applied to electrochemical immunosensors.

Nanomaterials are materials with at least one of their dimensions in the range between 1 and 100 nm or are composed of them as the basic unity in a three-dimensional space.[22] Considering their reduced nanosizes, they show large surface area to volume ratios with many special physical and chemical properties when compared to bulk materials, as their catalytic effect due to their higher ratios of reactive surface sites,[23,24] and the quantum effect[25] for very small sizes. By applying different strategies of synthesis as the ball milling, sputtering, electron beam evaporation, laser ablation, and electrospraying (top-down physical processes);[26,27] or the sol-gel synthesis, hydrothermal synthesis, co-precipitation method, microemulsion technique, and chemical vapor deposition (bottom up chemical processes),[27,28] different nanostructures can be obtained as metallic nanoparticles (MNP), nanotubes (NTs), nanowires (NW), nanorods (NR), carbon allotropes, quantum dots (QD), or even their mixing in nanostructured composites. Their composition comprises many materials, including metals, metal oxides, dendrimers, mesoporous silica, micelle, liposome, magnetic materials, polymers, and carbon-based materials[29–31] (Figure 1).

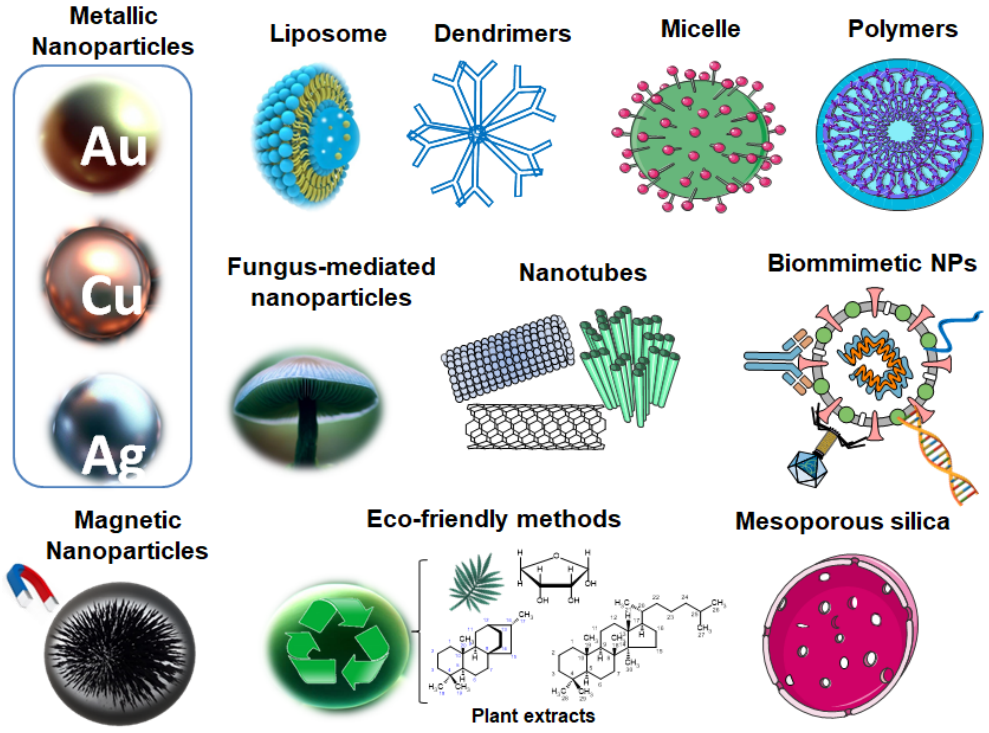

Figure 1. Different nanostructured materials.

Nowadays, the research on nanomaterials field is growing fast as well as its applications in physics, chemistry, materials, biology, and medicine. Additionally, many nanomaterials hold promise to improve the processes of food storage, quality monitoring, food processing, food packaging, and food safety detection and control, consolidating one of the most appealing tools to revolutionize the food production chain.[32] And it is not different for the science of biosensors. Nanomaterials can play different roles: starting from the replacement of traditional markers and signal amplifiers,[4,33] passing through surface functionalization[34] and fixation[35] with biomolecules, until the generation of fluorescence analytical signals.[6] They confer sensitivity and versatility to the analytical methodologies and, regarding specifically to the electrochemical biosensors, nanostructures are used to fill the gap between the converter and the bioreceptor, greatly enhancing the yet high sensitivity of electrochemical techniques.[36] Currently, the modification of electrode surface to access the contamination of mycotoxins in food has applied[37] carbon-based nanomaterials, metal or metal oxide nanoparticles, quantum dots, metal-organic frameworks (MOFs), and covalent organic frameworks (COFs).

Carbon-based nanomaterials are interesting materials considering their large specific surface area and high performance at the electron transfer step.[38] Among them, the carbon nanotubes (CNTs) are the most employed carbon-based nanomaterial used for electrochemical detection. CNTs are classified in two groups according to the number of layers of graphene sheets: the single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs). For instance, Yang *et al.*[39] developed a SWCNTs/chitosan-functionalized glass carbon electrode (GCE) immunosensor for the highly sensitive detection of Fumosin B1 (FB1) in corn. Liu *et al.*[40] applied the MWCNTs to develop a nanobody-based voltammetric immunosensor with horseradish peroxidase concatemer–modified hybridization chain reaction (HRP-HCR) for the detection of aflatoxin B1 (AFB1). Tungsten disulfide (WS_2) and gold nanoparticles (AuNPs) were used to enhance the surface area by the formation of a hierarchical nanocomposite, still improving the material conductivity and the loading capacity of the recognition molecules. Graphene Oxide (GO) is a 2D nanosheet of carbon monolayer with stratified structure and more appealing physical properties than the CNT with, *e.g.*, larger surface area, higher thermal and electrical conductivities. Considering these advantages, GO-based electrochemical sensors have gained great attention of researches.

For instance, Bulbul *et al.*[41] developed a GO-based screen printed carbon electrode (SPCE) to assemble an electrochemical aptasensor for the detection of Ochratoxin A (OTA) with the synergistic contribution of GO and the nanoceria. The GO layer accomplished the role of immobilizing the aptamer and increasing the electron transfer rate, enhancing the sensitivity of the analytical methodology. Li *et al.*[42] created a programmable ratiometric electrochemical aptasensor for the detection of aflatoxin B1 (AFB1) in peanut by using a thionine-functionalized reduced GO (THI-rGO) deposited on a glassy carbon electrode (GCE). Positive charges of THI promoted the dispersibility and prevented the aggregation of the reduced form of graphene (r-GO). AuNPs were electrostatically adsorbed on the THI-rGO surface as the conjugated sites for the s-DNA and the ferrocene-labeled aptamer (fc-apt, signal probe) were fixed to the electrode by the base paring with the s-DNA. The presence of AFB1 in the sample led to the formation of the Fc-apt-AFB1 complex, which stripped the probe from the electrode, fading the current intensity of Fc and increasing the current intensity of THI. Finally, some alternatives to the bottom-up synthesis approach have been recently created and, an example of them is the self-assembly chemical vapor deposition, which allowed the development of microporous 3D graphene.[37] Ong *et al.*[43] prepared 3D-graphene nickel to assemble an electrochemical aptasensor for the selective biosensing of deoxinivalenol (DON). The nanoflorets on the surface of 3D graphene nickel increased the material surface area for the bonding of biomolecules, besides the enhancement of charge transfer properties, consolidating an effective alternative for the DON detection in food and feed samples.

Metals nanoarchitectures have been applied to electrochemical biosensors to improve the analytical sensitivity of methodologies by refining the electrical connectivity of the interface, increasing the chemical accessibility of analytes and the sensing surface by improving the amount of anchored bioaffinity recognition sites.[37] Gold nanostructures as, *e.g.*, spheres, rods, wires, urchins, stars, and cages have been abundantly applied due to their unique electrocatalytic activities and conductivities, providing anchoring sites for thiolate

recognition molecules or redox species through direct bonds with sulfur (S) or nitrogen (N) groups. As a good example, Wu *et al.*[44] developed an electrochemical aptasensor for the detection of AFB1 by the direct deposition of gold nanoparticles (AuNPs) onto a bare glassy carbon electrode (GCE). The role of these AuNPs was to improve the interface electron transfer capacity, allowing the consolidated aptasensor to effectively measure the content of AFB1 in real samples of peanut oil with interesting recovery ratio between 94.5 and 106.7%. One should bear in mind that these gold nanoparticles show physical characteristics of solid spheres, allowing only the outer sphere area to be covered with the anchoring sites of biorecognition elements. Therefore, new nanoarchitectures had to be designed to increase the overall electroactive surface. For instance, the use of porous gold nanocages (AuNCs) with inner and outer walls can improve the effective area for the aptamer immobilization on a screen-printed carbon electrode (SPCE), as reported by An *et al*.[45] As a result, a highly sensitive aptasensor was obtained for AFB1 sensing in a so-called label-free method. By exposing the sensing interface to the AFB1 it was possible to initiate the formation of the aptamer/AFB1 complex, increasing the interfacial electron transfer resistance on the SPCE and leading to a methodology with a very low limit of detection (LOD) of 0.03 pg mL^{-1}.

Electrochemical immunosensors, as all kinds of currently existing immunosensors, can be divided in two main classes: the labelled and label-free types.[46] For the labelled type (Figure 2a), a molecular component as an enzyme is anchored to either the biorecognition element (antibody) or the target molecule (antigen), acting as an electroactive probe that generates and/or amplifies the signal associated with the formation of the immuncomplex, allowing the target detection. The label-free electrochemical immunosensor (Figure 2b) enable the direct detection of the target analyte without labels or redox reporters, which is a tendency in the immunoassay field. These methodologies use *e.g.* the formation of the antibody-antigen (Ab-Ag) immunocomplexes to produce the detectable electrical signal. One of them is immobilized on the electrode surface to stablish the sensing interface. Then, the target analyte binds to form the Ab-Ag complex, changing the interface electrical properties, which include variations in the surface area, electron transfer, and even diffusivity. These events are detectable and allow quantifications to be accomplished by electrochemical techniques such as amperometry, voltammetry, or electrochemical impedance spectroscopy (EIS).[47]

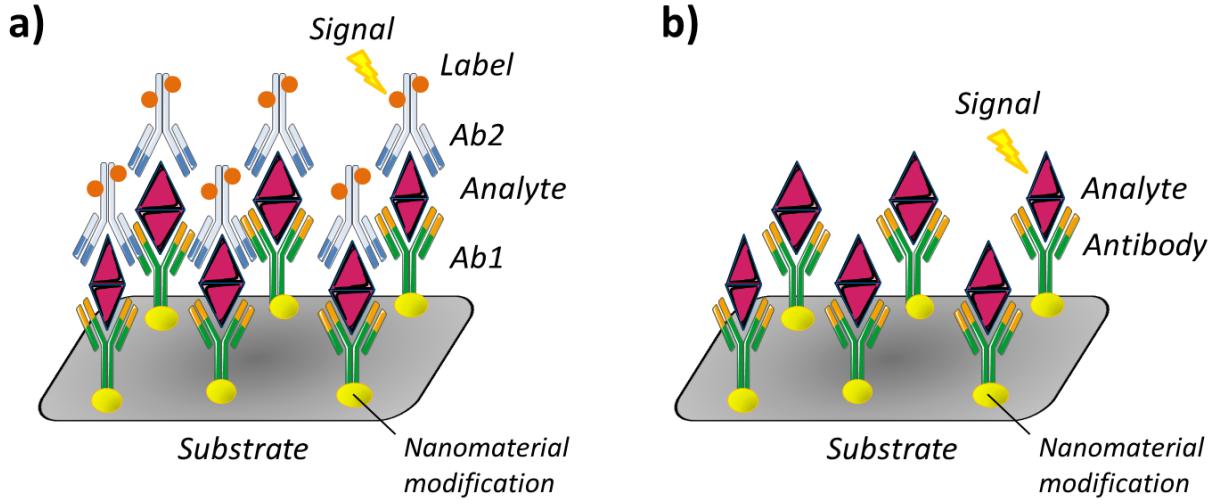

Figure 2. Schematics of: a) a labeled-type immunosensor with the capture antibody (Ab1) and the detection antibody (Ab2); b) a label-free immunosensor with analyte direct detection.

The direct label-free detection shows as its main advantages the elimination of labelling or conjugation steps, simplifying the procedures, reducing the duration and complexity of assays, and minimizing the risks of contamination and interference from the labelling reagents.[48] However, challenges on the label-free immunosensors include the lower sensitivity once compared to labelled assays due to the absence of the

signal amplification step that is typical of labelled reporter molecules,[49] and the potential to eventually allow non-specific binding,[50] since label-free methodologies rely a lot on the surface properties of the transducer and the immobilized biorecognition elements. Layer-by-layer electrochemical characterization is recently advancing as a tool for the development of label-free immunosensors,[51] providing important insights into the relations of structure and functionality of the electrochemical components of the immunosensor, and driving the design of immunological chains. The use of electrochemical complementary techniques as cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), and chronoamperometry allow the real-time systematic monitoring of the properties of each deposited layer, enabling the optimization. Precise control of assembling steps is accessed, optimizing the concentration, incubation time and pH of bioreceptors, blocking agents, and the formation of the Ab-Ag complex. Nice reviews discussing such subjects of label-free electrochemical immunosensors can be found elsewhere.[46,52-54]

This comprehensive review aims to didactically explain the advances of metallic nanoparticles (MNPs) and carbon-based materials to assemble both sensitive and highly specific biosensors for the detection and quantification of mycotoxins that affect crops and the foodstuff production chain. After briefly contextualizing the problem of the mycotoxins in food, the fundamentals of biosensors are presented by introducing the different bioreceptors used as the specific recognition biomolecules, the conventional transducers used for biosensing, and the electrochemical transducers. Finally, distinctive selected applications from the last decades of metallic nanoparticles and carbon-based immunosensors for the mycotoxin detection are discussed, pointing out challenges, opportunities, and perspectives for future research.

THE RISK OF MYCOTOXINS IN FOOD

Mycotoxins represent a category of food contaminant whose presence in edible material is considered unacceptable. It is defined as the fungal secondary metabolites produced by filamentous fungi, meaning the diverse group of microorganisms with a single unit structure of slender filaments, providing morphological complexity and capacity to secrete large amounts of different enzymes.[55,56] Secondary metabolites (also known as natural products) are chemical compounds playing fungal interactions with other organisms or plants, while primary metabolites comprise essential compounds for fungi growth that cannot be obtained from the medium. Accordingly, secondary metabolites are the result of a truncated process of polymerization of the primary metabolites by an enzymatic cocktail that vastly alters their bioactivities.[57,58] Concerning the food safety, although the Fungi kingdom encompasses a variety of organisms from unicellular yeasts, multicellular molds, until the macroscopic mushrooms, solely mycotoxins are significant inasmuch as yeasts and molds may cause food spoilage without safety implications. It is worth highlighting that the toxins produced by mushrooms or even those affecting only plants or lower animals (insects) are not included in the definition of mycotoxin.[30] Furthermore, the toxic response of animals and humans to the ingestion of mycotoxins can happen at different stages of the agrifood chain – before and after the harvest, during the processing or storage.[59-61]

Mycotoxins are thermally stable under conventional food-processing temperatures (80 – 121 °C), displaying high bioaccumulation ability and carrying-over into animal fluids, organs, and tissues even in very low concentrations.[62,63] Typical environmental agents as humidity, temperature, insect damage, and weather status are suitable scenarios for the growth of mycotoxin-producing fungi in agricultural products. Meanwhile, the occurrence of mycotoxin in food and beverages is caused by direct contamination of plant materials, animal tissues, milk, and eggs after the intake of contaminated feed.[64-66] Mycotoxins represent a very diverse group differing from each other structurally, which results in different toxic levels: over 500 different mycotoxins have been recognized and, indeed, one fungal species may produce more than one type of mycotoxin, and several fungal species may simultaneously grow in food and feed products. Favorably, there are around 20 mycotoxins found in food and feed produced by *Fusarium*, *Penicillium*, *Claviceps*, *Alternaria* and *Aspergillus* that can impact the human and animal health.[67] *Fusarium* (Figure 3) produces the specific mycotoxins Deoxynivalenol, Nivalenol, Zearalenone, and Fumonisin, while *Alternaria* synthesizes Alternariol, *Penicillium* the Ochratoxin and Patulin, and *Aspergillus* the Aflatoxins and Ochratoxin.[68] Furthermore, plant

metabolism has the potential to engender toxic byproducts from mycotoxins, which is an emerging concept called “hidden mycotoxins”.[69] A compilation of the most prominent mycotoxigenic fungi in the food industry can be found in Table I.

Table I. Important mycotoxins related to agriculture, economics, public health and their effects on humans

Mycotoxin	Types of mycotoxins	Main Production Fungi	Food Source	Human Risks	Authors
Aflatoxins (AFs)	AFB_1, AFB_2, AFG_1, AFG_2, AFM_1, AFM_2	*Aspergillus* spp., *A. flavus,* *A. parasiticus,* *A. niger,* *A. nomius,* *A. tubingensis,* *Fusarium* spp., *Mucor* spp.	Grains (maize and rice), peanuts, seeds, spices, dried fruits; animal products (milk and meat)	Carcinogenic, genotoxic, liver damage, hepatocellular carcinoma	56, 70–75
Ochratoxin A (OTA)	--	*Fusarium* spp., *Aspergillus* spp., *A. carbonarius,* *A. ochraceus*, *Penicillium* spp., *P. nordicum,* *P. verrucosum*	Cereals, particularly maize, wheat, oat, barley, coffee, grapes, raisins, red wines, meat (pork and poultry), milk, infant formula and infant cereals	Carcinogenic, genotoxicity, cytotoxicity, mutagenic, teratogenic, hepatotoxic, immunosuppressive	76–79
Fumonisin (FUM)	FA_1, FA_2, FA_3, $PHFA_{3a}$, $PHFA_{3b}$, HFA_3, FAK_1, FBK_1, FB_1, Iso-FB_1, $PHFB_{1a}$, $PHFB_{1b}$, HFB_1, FB_2, FB_3, FB_4, FB_5, FC_1, N-acetyl-FC_1, Iso-FC_1, N-acetyl-iso-FC_1, OH-FC_1, N-acetyl OH-FC_1, FC_3, FC_4, FP_1, FP_2, FP_3	*Fusarium* spp., *F. sacchari,* *F. proliferatum,* *F. verticillioides*	Maize and maize products, coffee, banana	Carcinogenic, esophageal cancer, neural tube defect disease, cells apoptosis, neurotoxicity, immunotoxicity, reproductive toxicity, tissue and organ toxicity	80–84
Zearalenone (ZEA)	--	*Fusarium* spp., *F. graminearum*, *F. culmorum*, *F. cerealis*, *F. equiseti*, *F. crookwellense*, *F. semitectum*	Maize, sorghum, wheat, rice, barley, nuts, soybeans, sesame	Hepatotoxic, immunotoxic, carcinogenic, nephrotoxic effects, severe reproductive and sexual dysfunctions	75, 78

(continues on next page)

Table I. Important mycotoxins related to agriculture, economics, public health and their effects on humans (continuation)

Mycotoxin	Types of mycotoxins	Main Production Fungi	Food Source	Human Risks	Authors
Patulin (PAT)	--	*Fusarium* spp., *F. sacchari,* *F. proliferatum,* *Penicillium spp.,* *P. expansum*	Fruits and processed products	Cytotoxicity, genotoxicity	76, 85–87
Deoxynivalenol (DON)	--	*Fusarium* spp., *F. andiyazi*, *F. fujikuroi*, *F. temperatum*, *F. subglutinans*	Cereal crops, maize, oat	Nausea, vomiting, diarrhea	75,88
Citrinin (CIT)	--	*Penicillium* spp., *P. citrinum*, *P. verrucosum*, *P. expansum*; *Aspergillus* spp., *A. carneus*, *A. niveus*, *A. terreus,* *Monascus* spp., *M. ruber*	Cereal and fruits, grains, spices and condiments, citrus fruits, herbs, processed fruit juices, beers	Carcinogenicity, nephrotoxic, genotoxic	86, 87, 89, 90
Alternaria (AT)	AOH, AME, ALT, ATX-I, ATX-II, ATXII, TeA	*Alternaria* spp., *A. alternata*	Cereal crops, vegetables, citrus fruits	Genotoxic, mutagenicity	87, 91
Trichothecenes (TH)	--	*Fusarium* spp., *F. langsethiae*, *F. sporotrichioides*	Cereal crops, oat	Problems in the hematologic and immune systems	92, 93

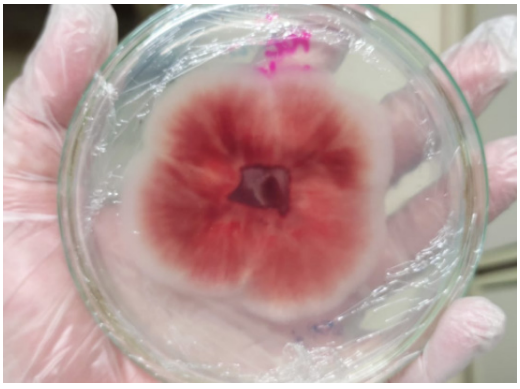

Figure 3. Reddish pigment bikaverin produced by mycotoxigenic fungi *Fusarium oxysporum*.

Under favorable conditions as elevated temperatures, torrential rain, high moisture, and poor hygienic practices, field and storage fungi[94] can be produced. The agriculture products, food, and other commodities might be contaminated in the field or during any step of the harvest, handling, transportation, or storage. Therefore, mycotoxin contamination poses a worldwide threat to the international trade, social development, and the human health itself. Plant-derived foods as vegetables, cereals, and fruits are liable to the growth of

mycotoxin-production fungi due to their nutritional components that are essential for these microorganisms.[95–97] As an example of the aforementioned posed risk, Azaiez *et al.*[98] reported that 160 samples from a total of 228 fruits purchased from the Tunisia and Spain markets were contaminated with mycotoxins, with incidence ratios of 83% for red dates, 80% for raisings, 64% for figs, 59% for apricots, and 26% for plums. And still of these, 51% of the samples were contaminated with more than one mycotoxin at the same time, achieving until six types for the same product.

Furthermore, Kosicki *et al.*[99] analyzed the content of deoxynivalenol (DON), nivalenol, T-2 and HT-2 toxins, zearalenone (ZEN), fumonisins (FMs), ochratoxin A (OTA), and aflatoxins (AFs) in 143 maize silage samples, 295 maize samples, 480 complete feed samples, and 466 small grain cereal samples. DON and ZEN showed the highest incidence ratios of 89% and 92% in corn, 86% and 88% in corn silage, and 97% and 98% in small grains samples. Their contents exceed the EU recommendation in 24 samples. Regarding to the completed feed samples, more than 90% of them were contaminated with ZEN, HT-2 and T-2 toxins. In other study,[100] 17 *Alternaria* free and modified mycotoxins were investigated in 56 tomato sauce, 39 sunflower seed oil, and 100 wheat flour samples. The most frequently-found mycotoxins were: alternariol monomethyl ether (AME: 1.2–6.6 ng g^{-1}), alternariol (AOH: 0.5–1.3 ng g^{-1}), tentoxin (66–161 ng g^{-1}), and tenuazonic acid (0.1–0.5 ng g^{-1}).

Concerning the mycotoxins in animal-origin foodstuff[101] as flesh, dairy products, milk and milk products, poultry, and eggs, the occurrence is also increasing due to the improper storage and the limited ability of animals to degrade mycotoxins after consuming feed and other contaminated food, which usually takes from 10 to 19 days to be completely eliminated from their organism.[102] Thus, the intake of animal tissues with mycotoxin residues for a long period exposes the consumer to potential chronic poisoning. Zadravec *et al.*[103] studied the incidence of mycotoxins in Croatian products of traditional dry-cured meat, finding out that the OTA contamination up to 6.86 mg kg^{-1} was more frequently than the AFB1 up to 1.92 mg kg^{-1}, achieving 14% against 8% of samples, respectively. Xu *et al.*[104] quantified the content of mycotoxins, pesticides, and veterinary drugs in eggs using a QuEChERS and magnetic multi-walled carbon nanotubes-based UPLC-MS/MS method. They found the incidence over 23% of the samples with three kinds of analytes. Aflatoxin B1 (AFB1) was detected in more than 10 egg samples with high contents of 83.1, 83.6, 142.0, and 144.9 mg kg^{-1} in 4 samples. In another work,[105] residual amounts up to 0.039 mg kg^{-1} of aflatoxin M1 (AFM1) were found in milk and skimmed milk samples. Finally, Cao *et al.*[106] analyzed multiple mycotoxins in human blood, urine, and edible animal tissues (as liver and muscle) from swine and chickens. They found out that 5 samples were contaminated with AFB1, and one swine liver sample was simultaneously contaminated with AFM1, AFB1, and AFB2. These findings by themselves indicate the serious danger of the humans' exposure to mycotoxins by the ingestion of animal-based foods.

Traditional oriental medicines are another class of products vulnerable to fungal contamination and consequent residues of aflatoxins (AFs), ochratoxins (OTs), zearalenone (ZEN), and fumonisins (FMs) mycotoxins.[107–111] Root herbs,[112] ginseng,[112,113] red yeast rice,[114] *Radix Paeoniae Alba*,[115] and edible medicinal foods as lotus seed, ginger, malt, and yam, show rich nutrient contents that provide ideal substrates for the growth and reproduction of various fungi from the planting to the storage processes, exhibiting increased chances of mycotoxin contamination which reduce the product quality and efficacy. For instance, lotus seed is frequently used as an edible medicinal food in pharmacy compounding and is even highly ingested in the table diet, showing high market value. But with the high rate of mycotoxin pollution, its ingestion is becoming a threat to human health.[111] For example, 30% of batches of lotus seed samples purchased from the China market showed AFB1, FB2, T-2, and ZEN contamination and, as a worse scenario, some samples were contaminated with more than 3 mycotoxins simultaneously.[116] Wei *et al.*[109] revealed a very concerning conjuncture too: one or more mycotoxins were detected in 26 commercially available lotus seed samples, with AFB1, AFB2, OTA, and CIT as the predominant toxins.

Chinese yam and malt are other kinds of food or traditional oriental medicine susceptible to mycotoxins contamination. An investigation[117] of 27 batches of yam, yam powder, and related products collected from several markets and pharmacies showed that one normal sample and four mold samples were contaminated

with different mycotoxins, achieving AFB1 concentrations that exceeded the maximum residue level in 2 mold samples. Bolechova *et al.*[118] analyzed 52 batches of barley and malt samples collected from the Czech Republic, and they found out that all of them were contaminated with one mycotoxin at least. Finally, Xiao *et al.*[119] reported that 2 out of 16 malt samples obtained were contaminated with OTA. Other edible and medicinal foods exposed to the mycotoxin contamination are the Hibiscus sabdariffa,[108] Areca catechu[120] and locusts.[121] It is important to mention that some mycotoxins as the aflatoxins (AFs) can transfer from the raw types of *Hordei Fructus Germinatus*, *Lilii Bulbus*, *Bombyx Batryticatus*, and *Nelumbinis Semen* to their decoctions,[122] posing serous risk over the customers that ingest the decoctions prepared from these edible medicinal foods contaminated with AFs. So, one should be aware of the heavy exposition to mycotoxins from the consumption of traditional oriental medicines, generally considered as "more natural" or even "healthier" by the consumers.

Lastly, even infants and young children might be exposed to mycotoxins contamination, especially those who consume domestic and industrially processed complementary foods. Ojuri *et al.*[123] studied the exposure of children to AFs at Nigeria and concluded that those under 12 months of age were less exposed than kids from 12 to 24 months. Furthermore, about 69% and 75% of infants and young children which consumed household grains and "Tom Bran" (a cereal-legume weaning food) were co-exposed to mycotoxins with commensurate risks and, 47% of them were co-exposed to until four types of mycotoxins: aflatoxins (AFs), citrinin (CIT), fumonisins (FMs), and ochratoxins (OTA).

Considering the above, it is predictable the urgency to develop quick and sensitive analytical methodologies for the simultaneous high-throughput detection and quantification of multiple mycotoxins in food, agricultural products, and pharmaceuticals to guarantee the quality and safety of such products. Several immunosensors have been reported exploiting the broad application in mycotoxin determinations, since worldwide scenario with global warming and climate changes seems to harden the food safety control regarding to mycotoxin contamination, mainly, due to the acclimatization of mycotoxigenic fungi to the new environmental conditions, potentially becoming even more aggressive pathogens.[124,125]

TYPES OF BIOSENSORS AND THEIR BIORECEPTORS

According to the gold book of the International Union of Pure and Applied Chemistry (IUPAC)[126] and its recommendations in the glossary for chemists of terms used in biotechnology[127] from 1992, a biosensor is *"a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals."*. According to more recent IUPAC[128] recommendations from 1999, a biosensor is an independently integrated receptor transducer device that is capable of providing selective quantitative or semiquantitative analytical information using a biological recognition element. Considering that two-to-three decades have passed since these IUPAC definitions, the concept of biosensor have expanded and some new alternative approaches have been proposed, incorporating novel sensing principles and different recognition elements, such as *e.g.* the aptamers,[129] and the molecularly imprinted polymers.[130] Therefore, ultimately, a "biosensor" is short for "biological sensor" and is defined as a compact analytical device incorporating a biological or biologically-derived sensing element that might be either integrated within or intimately associated with a physicochemical transducer.[131]

There are two fundamental operating principles of a biosensor: the "biological recognition" and the "real sensing". So, generally, biosensors can be divided in three basic components connected in series: (*i*) a biological recognition system, usually called "bioreceptor"; (*ii*) a transducer and; (*iii*) the microelectronics. The basic functioning principle of a biosensor is to detect the molecular recognition step and to convert it into another type of signal using a transducer. The recognition system provides a degree of selectivity to the sensor for the target analyte, meanwhile the interaction between the analyte with the bioreceptor should produce a measurable response effect on the transducer, transforming the biological information into a measurable electrical or optical signal.[131] Its purpose is to provide fast, real-time, accurate, precise, and reliable information about the target analyte. Ideally (but rarely fully achieved), it should be a device

capable of responding continuously, reversibly, and shall barely perturb the sample, finding applications in several fields like medicine, agriculture, and food safety.[132]

As stated, biosensors[133,134] show a biological component that act as the real sensor, and the electronic component to detect and transmit the generated signal. So, the biological material is immobilized in direct contact with the transducer. The analyte shall interact with this biological material to form a bounded analyte that is responsible for the electronic response that is measured. In some cases, the analyte is converted into a product that might be associated with the release of heat, gases, electrons or hydrogen ions. The role of the transducer is to transform the product-linked changes into electrical signal, which can be amplified and measured. This relations lead to some proper classification of biosensors as: an affinity sensor (binding of analyte and the recognition bioelement), a metabolic sensor (analyte leads to chemical changes used to the analytical measurements), and a catalytic sensor (biological element combines with the analyte forming an auxiliary substrate).[135] Further biosensor classifications are regarded to the type of bioreceptor and transducer used. Figure 4 shows examples of typical bioreceptors currently used for the assembling of biosensors.

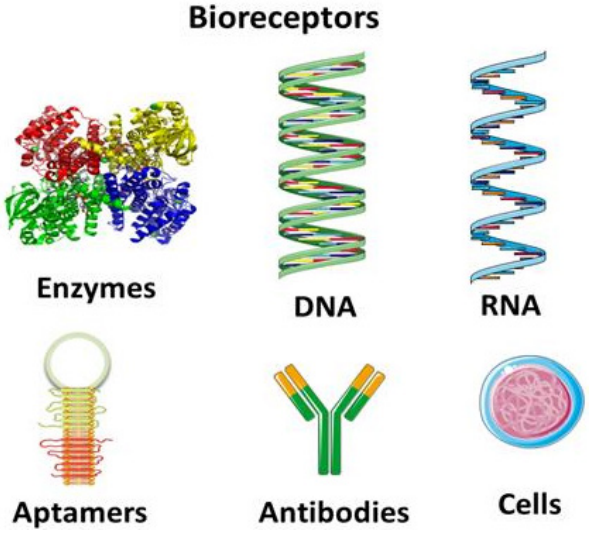

Figure 4. Bioreceptors currently used for the assembling of biosensors.

As above mentioned, bioreceptors[136] are the recognition key elements that confer some specificity to the bioeletronic device, featuring as a significant distinguishing characteristic of a biosensor. In terms of constitution, a bioreceptor is a molecular species that uses a biochemical mechanism for recognition, being responsible for the binding of the analyte on the surface of the sensor for the measurement. The types of molecular recognition can be classified as static or dynamic molecular recognitions.[137] The static molecular recognition is usually compared in analogy to a “lock and key” mechanism with a 1:1 complexation between a host molecule and a guest molecule to form the host-guest complex. To achieve advanced status of recognition by the static model, the recognition sites should be highly specific for the guest molecules. In the dynamic molecular recognition, there are two guests and two binding sites and the biding of the first guest to the first site affects the association constant of the second guest with the second binding site, consolidating an allosteric control system. For positive allosteric systems, the binding of the first guest increases the association constant of the second guest, while for the negative allosteric system, the binding of the first guest decreases the association constant of the second guest. Dynamic molecular recognition is particularly important since it provides a clear mechanism to regulate the binding in complex biological systems, and is currently being studied for applications in high functional chemical sensors using bioreceptors and further

molecular devices. Regarding to the classification of bioreceptors, they can be generally subdivided in five major categories: enzyme, antibody/antigen, nucleic acid/DNA, cellular structure/cell, and biomimetic. The sampling component contains a so-called biosensitive layer, comprising bioreceptors or is even made by the covalent attaching of bioreceptors to the transducer. The most common bioreceptors used in the literature are the enzymes and antibodies.[131]

Enzymes are commonly used as bioreceptors[138,139] due to their specific binding capabilities and catalytic activity, coining the term "biosensor" for such sensors. When the detection in a biosensor is amplified by a catalytic reaction, the recognition is classified as a biocatalytic mechanism.[140] Despite of a small group of catalytic ribonucleic acids, all the enzymes are proteins (Figure 4) and some of them even do not require further chemical groups than their own amino acid residues to exert their catalytic activity. Some others require a cofactor as Fe(II), Mn(II) or Zn(II) inorganic ions or even more complex organic or organometallic coenzymes. The catalytic activity of enzymes leads to high sensitivities and lower limits of detection (LODs) than reference binding techniques, depending only on the integrity of their native protein conformation.[131] When enzymes are denatured or dissociated into their subunities, their catalytic activity is inhibited. So, enzyme-coupled receptors[141] can be used to modify the recognition mechanism by the modulation of the enzyme activity by the binding of a ligand, enhancing the enzymatic activity by an enzyme cascade with complex reactions. Enzymes are usually the primary choice for biosensors by most authors since they are natural proteins with high specificity to the substrate, which is catalytically converted into a product, *i.e.*, without the enzyme consumption during the reaction. Their mechanism of operation might involve (*i*) the conversion of the analyte into a detectable product, (*ii*) the detection of an analyte that acts as an enzyme inhibitor or activator, or even (*iii*) the monitoring of the enzyme properties upon interaction with the analyte.[131]

Antibodies[142] can be used as bioreceptors to detect specific antigens, consolidating the so-called immunosensors. Immunoassay embraces the most specific analytical methodologies with extremely low LODs and is applicable to a wide range of analytes, especially for the identification and quantification of proteins.[131] The term immunoassay is used for tests based on immunoreactions, while the term "immunosensor" is specifically applied to describe the whole instrument as short of "immunoreactions-based biosensors". Antibodies are heavy plasma proteins with about 150 kDa. Also called glycoproteins, they show two heavy chains and two light chains forming the traditional Y shape (Figure 4). They are produced by animals as an immunological response to antigens foreign agents. The antibody binds the antigen with high affinity, allowing analytical methods to detect the target analyte even in the presence of interfering substances of the sample matrix. There are two types of antibodies applied in immunosensors: the polyclonal, highly sensitive but less specific due to the possibility of recognition of different epitotes (antigen binding sites) on their target antigen and; the monoclonal that are produced from one type of immune cells and are bounded to the same epitote of their specific antigen without cross-reactions, making their immunoassays highly specific.[143] Monoclonal antibodies are excellent to be used as the primary antibody in immunoassays or for the detection of specific antigens in the presence of interfering molecules, being considerably less susceptible to background staining than polyclonal antibodies.[131]

The hybridization of DNA or RNA (Figure 4) can be used as another biorecognition mechanism with highly specific affinity from the binding reaction between two single-stranded DNA (ssDNA) chains to form a double-stranded DNA (dsDNA), the so-called nucleic acids-based biosensors.[144,145] DNA biosensors or genosensors[146] detect the individual nucleotides that comprise the specific DNA genome molecule with rapid and non-destructive sequencing of DNA molecules. The biological recognition agent is the ssDNA with specific oligonucleotides that is commonly called the DNA probe and is combined with a transducer. Among the different types of genosensors figures the optical, the piezoelectric, and the electrochemical, the last one with great advantages of simplicity, rapidness, low cost, high sensitivity, and prone to the development of inexpensive portable devices.[131] Electrochemical genosensors usually monitors the sequence-specific hybridization events measuring the oxidation signal of DNA electroactive nucleotide bases, detecting the DNA electroactive indicators forming complexes with DNA nitrogenous bases or enzyme-labeling oligonucleotides. The electrochemical impedance spectroscopy (EIS) is a very important electrochemical technique for the

study of DNA hybridization, being an effective method for probing interfacial properties as the capacitance or the electron-transfer resistance of DNA-modified electrodes, sparing the use of oligonucleotide labeling for the DNA detection.[147–149]

A typical genosensor configuration uses the ssDNA probe sequence immobilized within the biosensor recognition layer, place where base-pairing interactions recruit the target DNA to the surface.[131] The repetitive and uniform structure of DNA makes a well-defined assembly on the recognition surface, where the critical dynamics of target capture happens to generate the recognition signal. So, it is crucial for the device performance to immobilize the nucleic acid probe sequences in a predictable manner while keeping their inherent affinity for the target DNA. The recognition event depends mainly on the method used for the signal transduction. In the electrochemical DNA biosensor,[150,151] the three main events of detection mechanism are (*i*) the formation of the DNA recognition layer, (*ii*) the actual hybridization event, and (*iii*) the conversion of the hybridization event into an electrical signal, which happens basically by label-free or labeled immunoassays. For the label-free detection,[152] the decrease or increase of the oxidation or reduction peak current of electroactive DNA bases (*e.g.* guanine or adenine) is directly monitored. This detection pathway relies on the intrinsic DNA signal with guanine and adenine being the most electroactive bases of DNA due to their easy adsorption and oxidation on carbon-based electrodes. The electrochemical signal from free adenine and guanine usually decreases with their binding with thymine and cytosine after hybridization. In the labeled detection,[153] the alteration of the oxidation or reduction peak current is monitored for the electrochemical label that selectively binds with the dsDNA/SSDNA. There are two types of label-based electrochemical detection of DNA hybridization: the intercalative redox active probe, which basically the hybrid modified electrode is immersed in a solution with the redox-active molecule and the DNA binding molecule and; the redox-active probe, which is constituted of a capture probe, the target, and a signaling probe. The signaling probe is tagged with *e.g.* ferrocene, enzyme or metal nanoparticle and serves to label the target upon hybridization. The flow of electrons to the electrode only happens when the target is present and the specific hybridization of both signaling and capture probes is achieved.[131] This principle has been used in a DNA chip technology[154] called *eSensor™* developed by the Motorola Life Science Inc.

Aptamers[156] can be used as the recognition element in the so-called aptasensors.[157,158] Aptamers are single-stranded RNA or DNA molecules that bind to their target molecules (usually proteins) with high affinity and specificity (Figure 4). They are more stable and adapted to the real sample conditions, rivaling the antibodies in an interesting number of applications. Aptamers are very small in size (from 30 to 100 nucleotides) once compared to other biorecognition molecules as antibodies or enzymes. This characteristic allows an efficient immobilization process with high aptamers density and easier production, miniaturization, integration, and biosensor automation than with antibodies. After the selection, aptamers can be synthesized with high purity and reproducibility.[131] They are classified as DNA, RNA, or peptide aptamers. DNA aptamers[159] are chemically stable and allow the reusability of biosensors,[160] while the RNA aptamers[161] are susceptible to degradation by endogenous ribonucleases found in cell lysates and serum, being able to be used for only single-shot measurements in biological matrices.[162] Furthermore, DNA and RNA can be chemically modified to undergo analyte-dependent conformational changes. Possible aptamers detection modes include the label-free methods as *e.g.* the surface plasmon resonance (SPR) and the quartz crystal microbalance (QCM), and labeled methods as the electrochemical, fluorescence, chemiluminescence, and field effect transistor ones.[131] Aptamers are typically isolated from combinatorial libraries by an *in vitro* process of evolution called systematic evolution of ligands by exponential enrichment, or simply SELEX. SELEX process[163,164] is used for the election of aptamers with high specificity in binding and function due to their nucleotide sequence and shape. SELEX stages involve: (*i*) the library generation containing 1 x 10 single-stranded oligonucleotides with random sequence region flanked by the binding site; (*ii*) the binding and separation by the incubation of the library with the immobilized target molecule, the consequent filtering of unbound nucleic acids from the solution, and the elution of the bound nucleic acids from the target and; (*iii*) the amplification, which the bound nucleic acids are copied using the polymerase chain reaction (PCR) to create a new library and, this new library will be further used in a new round of SELEX to optimize the

quality of aptamers, proceeding until the identification of the highest binding species through competitive binding methodologies.[165]

Aptasensors can be classified according to the transduction mechanism. Electrochemical aptasensors[166] use an electrode surface as a platform to immobilize the sensing aptamer and the analyte-binding event is monitored based on current (or potential) variations using the faradaic impedance spectroscopy (FIS), differential pulse voltammetry, alternating current voltammetry, square-wave voltammetry, potentiometry, or amperometry.[166] The receptor-target interaction can lead to an increase or decrease of the detector response, consolidating a positive or a negative readout signal, respectively. Optical aptasensors[167,168] use label-based aptamers with fluorophores, luminophores, enzymes or nanoparticles, or label-free detection systems as the surface plasmon resonance (SPR). Considering the possible analytical formats, fluorescence and colorimetry are the most relevant techniques, while the SPR rely on changes generated in the optical parameters of the layer closest to the sensitive surface.[169] Finally, mass sensitive aptasensors are devices that measure any property that scales proportionally with the mass associated with the sensitive surface that is assembled with capture probes. They are considered label-free bioassays using SPR, QCM or surface acoustic wave for analytical measurements.[157]

Microbial biosensors[170,171] are analytical devices that immobilize living microorganisms (Figure 4) onto a transducer for the detection of target analytes. Bacteria and fungi are usually used to detect specific molecules or simply to sense the overall state of the surrounding environment. Analytical response comes from the specific interaction between enzymes or proteins (the “real” bioreceptors) contained in the immobilized living cells, avoiding the expensive and time-consuming process of purification.[172] The microorganisms of microbial biosensors can be integrated to several transducers as amperometric, potentiometric, calorimetric, conductometric, luminometric, and fluorimetric ones. The measurement principle is based on the metabolism of the microorganism that is usually accompanied by the oxygen or carbon dioxide consumption.[173] The integration of the microorganism to the transducer is pivotal to achieve a reliable and reusable microbial biosensor. During its functioning, the analyte enters the cell and is converted using the intracellular enzymes, consuming cosubstrates and generating products that can be readily detected using *e.g.* electrochemical sensors. The monitoring of dissolved oxygen concentrations, medium ionic composition, and other parameters in the layer of immobilized cells can be used as metabolic indicators of the cell state, and act as the background for the electrochemical determination of the biologically electroactive compounds of interest.[131]

CONVENTIONAL TRANSDUCERS FOR BIOSENSORS

The transducer is the component of the biosensor with the noble role of converting the biorecognition event into a detectable analytical signal, which can be of electrochemical (potentiometry, conductometry, impedimetry, amperometry or voltammetry), optical (colorimetric, fluorescence, luminescence, interferometry), calorimetric (thermistor), mass change (piezoelectric or acoustic wave) or magnetic nature.[131]

Optical biosensors[174,175] are powerfull analysis tools that induce a change in the phase, amplitude, polarization or frequency of an input light in response to the physical or chemical change produced by the birecognition process. As the main advatanges are the specificity, remote sensing, isolation from electromagnetic interferences, quick processing, real-time measurements, multiple channels and multi parameters detection, compact design, minimally invasive for *in vivo* measurements, possibility of choice of optical components for biocompatibility, and the detailed information obtained from the analytes. The instrumentation components are the light source, the optical transmission medium (as fibers and waveguides), the immobilized biological recognition elements, and the optical detection system. Optical biosensors can be generally classified on diverse parameters with two possible detection protocols: the fluorescence-based detection and the label-free detection.[131]

In the fluorescence-based detection,[176,177] either the target molecules or the biorecognition molecules are labeled with fluorescence tags as dyes, and the intensity of fluorescence indicates both the presence of the target molecules and the strength of interaction between the target and the biorecognition molecules. For instance, nucleic acids or antibodies can be used to tag with a fluorochrome and convert the hybridization

interaction between two complementary DNA strands into an optical signal.[178] Label-free modes use non-labelled target molecules that are detected in their natural form without molecular modifications, which is a more rare option considering that most of the biological-sensing elements and target analytes do not possess intrinsic spectral properties. Whole cells can be used in fluorescent biosensors too by immobilizing them on the surface of a bioactive sensor layer that is usually placed in front of the tip of an optical fiber bundle to generate the fluorescent signal. Optical fibers are required to directionate the excitation radiation on the fluorescent bioelement and convey the fluorescence radiation up to the fluorimeter. Optical translucent supports are important to improve the simplicity and reliability of fluorescent-based biosensors, enabling the fluorescent detection emitted by algal cells.[131]

A common fluorescence protocol used for the biosensing is the sandwich-type assay,[179,180] which the analyte is selectively bound to a surface by a targeting molecule (as antibodies) that are covalently immobilized on the surface of a well or other cell. The analyte molecule is labelled with a fluorescent tag and its surface concentration may be measured by highly sensitive fluorescence spectroscopy. Several green fluorescent proteins have been extensively used for the assembling of fluorescent protein-based biosensors, or simply FP-based biosensors.[181] In such biosensors, the sensing element consists of one or more polypetide chains that act as the molecular recognition element by suffering conformational changes upon the binding with the analyte that changes the fluorescence pattern. FP-based biosensors can be further classified into three types of assay considering their structure: the Forster or fluorescent resonance energy transfer (FRET)-based biosensors,[182] the bimolecular fluorescence complementation (BiFC)-based biosensors and, the single FP-based biosensors.[131]

FRET[183] is the phenomenon of nonradiative energy transfer between an excited blue-shifted fluorescent chromophore (the donor, in a higher energy state) and a chromophore with a red-shifted absorption spectrum (the acceptor) through a dipole-dipole coupling. More importantly, the efficiency of the energy transfer is determined by the distance and orientation between the donor and the acceptor proteins, and the recording of fluorescence emission spectrum can be used to determine the proximity of the two chromophores. In the FRET-based biosensors,[182] two fluorescent proteins are genetically linked either to each end of a polypeptide chain (the molecular recognition element: MRE) or two separate polypeptides, MRE and the analyte protein. Upon interaction with the analyte, conformation of the protein changes and so the distance between the two chromophores, changing the fluorescence intensities of both donor and acceptor that is measured by the FRET efficiency. Increased FRET efficiency indicates that the two FPs are aligned together, while the decreased FRET efficiency indicates that both are separated. These FRET-based biosensors are widely applied to detect a range of molecular events as proteins binding interactions, protein conformational changes, enzyme activities, and the concentration of biomolecules. The (BiFC)-based biosensors[184] are used to visualize the protein-protein interaction in live cells. Here, the FP and MRE are splitted up and the MRE is linked to one portion and the analyte protein is linked to the other portion. When both proteins interact, the two fragments are fused together, refolding properly into the 3D-strucutre that produces a typical fluorescence signal. In the FP-based biosensors, the MRE can be either exogenous or endogenous and the analyte binding to the MRE causes conformational changes of the fluorescent protein and, consequently, alters its fluorescent properties.[131] Fluorescence is an extremely sensitive technique with LODs down to a single-molecule detection,[185] besides the fact that it is relatively easy and cheap to perform and allows quantitative and kinetic measurements of molecular interactions. On the other hand, major drawbacks reside in the additional complexity of time-resolved instrumentation in time, frequency domains or in both, and is not suitable for the real-time monitoring.

The optical label-free protocols[186] for biosensing usually uses the surface plasmon resonance (SPR)[187] to observe the binding interactions between an injected analyte and an immobilized biomolecule in real time. For the conventional SPR measurements, a thin metallic film is coated on one side of a prism to separate the sensing medium from the optical disperser element. The SPR effect is sensitive to the binding of the analyte due to the mass increase that causes a proportional increase in the interface refractive index, which is experimentally observed by the shift in the resonance angle. SPR biosensors use the surface plasmon

electromagnetic waves to detect the changes from the target analyte interaction with the biorecognition element on the sensor. Therefore, when a target analyte interacts with the immobilized biomolecule on the sensor surface, it produces changes in the refractive index and these changes produces a variation in the propagation constant of the surface plasmon wave, and so this variation is measured to produce the analytical reading. A spectrometer is usually used to measure the absorption spectrum of the sample in real-time monitoring without radioactivity and fluorescence. Several biorecongintion elements have been incorporated with SPR biosensors such as proteins, antibodies-antigens, nucleic acids, and enzymes.[188,189] Advantages of SPR biosensors are the high detection sensitivity, the real-time detection, the anti-interference capability, the absence of samples pretreatment, rapidness, and the high throughput of analysis with less reagents and samples. Biological applications include the measurement of adsorption and desorption kinetics, antigen-antibody binding, and the epitote mapping for the determination of biomolecular structures and interactions of proteins, DNA, and viruses.[131]

Luminescence[190,191] is the emission of light from an electronically excited state returning to the ground state in a compound. Chemiluminescence[192] occurs during the course of some chemical reactions when an electronically-excited state is generated. As the rate of photons production can be monitored, the produced light intensity depends on the rate of the luminescent reaction and is directly proportional to the concentration of the limiting reactant involved. Considering the modern detection instrumentation,[193] the light intensity can be measured at very low levels, allowing the development of sensitive analytical methods with the aid of optical fibers and photomultiplier tubes (PMTs). In the chemiluminescent biosensor,[194,195] the reaction between the analyte and the immobilized biomolecule that has been marked with a chemiluminescence species will generate light as a result of a biochemical reaction. It is an emerging tool for the diagnosis with extremely high sensitivity along with the simple instrumentation of devices, fast dynamic response, and wide calibration range. Chemiluminescent-based transducers have been widely applied for biosensing of nucleic acid hybridization,[196] with LODs as lower as 10^{-13} mol L^{-1} magnitude order, and is gradually substituting the fluorescence for the development of biochips and microarrays. Nevertheless, chemiluminescence transduction shows as the main drawbacks the lower accuracy according to the short lifetime, the non-suitability for real-time monitoring, and is still considered an expensive method.[131]

The piezoelectric biosensor[197] is a class of microelectrochemical system based on the changes in the resonance frequency of an oscliating crystal due to the interaction between the bioreceptor and the analyte. The trasnducer is made of a piezoelectric material as quartz with the surface coated with the biosensing material, which vibrates on a certain frequency that can be modulated by the circumstaces in the surrounding enviroment.[198] Once coated with the biosensing material, the actual frequency depends on the mass of the crystal and the coating. The resonant frequency can be easily measured with accuracy, making it possible to calculate the mass of analyte adsorbed on the crystal surface. Piezoelectric methods are sensitive and can use antibodies, enzymes, and antigens as biological elements to achieve LODs down to the picogram levels. There are two main types of piezoelectric sensors: the bulk acoustic wave piezoelectric sensors (BAW) and the surface acoustic wave piezoelectric sensors (SAW).[131]

As explained, piezoelectric acoustic wave sensors apply an oscilating electric field to create a mechanical wave that propagates through the substrate and is then transformed back into an electric field for the measurement. The bulk wave happens when the wave propagates through the susbtrate, and devices operate in thickness shear mode resonator (TSM)[199] or the shear-horizontal acoustic plate mode (SH-APM).[200] TSM is commonly widely referred to as the quartz crystal microbalance (QCM), and is considered as the best-known and simplest acoustic wave device.[201] The BAW simplest configuration[202] uses a quartz material sandwiched between two metallic electrodes. The natural oscillating frequency of the material and the coating deposit thickness are used as design parameters to obtain the desired operating frequencies. However, if the wave propagates on the surface of the substrate, it is known as a surface acoustic wave (SAW). SAW sensors[202] are made of a thick plate of a piezoelectric material, that is usually quartz, to sense the so-called Rayleigh waves that propagate along the upper surface of crystals. The most common SAW devices are the SAW sensor[203] and the shear-horizontal surface acoustic wave (SH-SAW) sensor,[204]

also known as the surface transverse wave (STW) sensor. SAW-based sensors are built on single crystal piezoelectric materials and, according to the different cut angles, it can produce largely different results. That is why the design of the sensor needs to be adapted for each application by selecting the appropriate design alternative.[131]

The piezoelectric transducer has been used for the DNA and protein detection with LODs as low as 1 ng cm^{-2}.[205] Its applications embrace the diagnostic detection of cholera toxin,[206] hepatitis B,[206] hepatitis C,[207] and foodborne pathogen detection,[208] achieving a LOD of 8.6 pg L^{-1} for the DNA of hepatitis B virus, and 25 ng mL^{-1} for cholera toxin detection.[206] As its main advantages we can point it out the low production cost, high sensitivity, small size and portability, fast response, robustness, high accuracy, and compatibility with integrated circuit technologies.[131]

Magnetoelastic biosensors[209,210] work similarly to the quartz crystal microbalance (QCM) except for the magnetoelasticity principle instead of piezoelectricity. A magnetoelastic material changes its dimensions once exposed to a magnetic field, so a thin strip of such kind of material forms the resonator with the shape of a tuning fork. When the strip with the coated biomolecules film is exposed to a short magnetic pulse, it starts to oscillate emitting a magnetic field in return. The frequency, amplitude, and damping of this emitted magnetic field supply the information about the sensor status and the coating surrounding it. As an application, magnetoelastic biosensors have been used for the monitoring of blood coagulation.[211] The ribbon magnetoelastic sensor oscillates at a fundamental frequency and shifts it linearly in response to an applied mass load of changing elasticity. The sensor emit the magnetic flux that is detected by a remotely located pickup coil without any physical direct connection. During the blood coagulation, its viscosity changes due to the formation of a soft fibrin clot, shifting the characteristic resonance frequency of the magnetoelastic sensor, and enabling the real-time continous monitoring of this biological event. The signal output might be monitored as a function of time and distinct blood clotting profiles can be found and compared. Advantages of magnetoelastic biosensor are the wireless detection with antenna-to-sensor range of a few decimeters in air and a few centimeters in liquids, the non-invasive and passive sensor without the need of batteries or other power supply sources, and the low sensor cost since it is made from cheap materials and is well suited for disposable sensors applications.[131]

Field effect transistor-based biosensors (or FET-based biosensors),[212,213] as the name suggests, are based on one of the most commonly used semiconductor devices of eletronics. All FETs show three terminals called the source (S), the drain (D), and the gate (G). There is no physical contact between the source and the drain, but it does exist a current path that is called the conduction channel S-D. The gate-to-source voltage (V_{gs}) will turn on or off the device considering that FET-type devices can work as switches. The strength of the generated electric field serves as a control mechanism that is associated with the voltage applied to the gate. For a *n*-type FET, the applied gate voltage will cause electrons to pass through the S-D channel . If a positive voltage is applied to the gate of an *n*-type FET, a channel is created and the charge effect on the conductance across the channel increases accordingly. However, if a negative gate voltage is applied, the *n*-type channel will pinch off. For a *p*-type FET, quite the opposite is observed as the positive (negative) gate voltage will turn off (on) the transistor device. Therefore, a FET uses an electric field to control the conduction channel and its charge-carriers. The flow of charge-carriers between the source and the drain can be tuned by modifying the size and the shape of the conducting channel by the application of an electric field to the gate. In analogy, the FET-based biosensor have been developed to study biomolecular interactions that are the key drivers of biological responses for *in vitro* or *in vivo* systems. FET-type biosensor is one of the most appealing electrical biosensors considering its sensitive measurements, portable instrumentation, easy operation with small sample consumption, low-cost under mass production, and high analytical speed.[131]

The biosensor configuration[212,213] consists of a nanowire channel between the source and the drain terminals. The surface of this nanowire is biofunctionalized so that the biorecognition binding can create an electric field, similar to the electric field control of conventional FETs by the gate. Then, the FET sensor is connected to an eletronic circuit so as the specific conductance of the sensor surface can be monitored. The configuration of FET-type biosensors includes all the three usual terminals of FET (gate, source and

drain), with the gate being generally replaced by a biofilm layer material with a receptor enzyme, antibody, DNA or other type of biorecognition molecule. The analyte interaction with this biorecognition molecules in the biomodified gate modulates the channel conductivity, leading to changes in the drain current that brings the desired quantitative analytical information. As an example of application, ion-selective field effect transistors (ISFET)[214] have been applied to selectively measure the ion activity in electrolytes, since they act as conventional ion-selective electrodes with low output impedance. The association of the ISFET with a membrane modified with biorecognition materials (as enzymes or microbes) allows the measurement of organic compounds activity with very high specificity.[215]

Calorimetric biosensors[216] measure the changes in temperature during the reaction between the biorecognition element and the suitable analyte. These changes in the temperature can be correlated to the amount of reactants consumed or the products formed. The heat change is measured by the device using either a thermistor of metal oxides or a thermopile of ceramic semiconductors. The major advantages[131] of thermal detection are the stability, increased sensitivity, and miniaturization possibility. These methodologies are classified as label-free assays and are used for the screening of biomolecules interactions. Calorimetry can rapidly detect *e.g.* the DNA hybridization, and is currently being used in food industry.[217]

ELECTROCHEMICAL BIOSENSORS

Electrochemical detection is the main transducing method used in biosensors due to the low cost, ease of use, portability, and simplicity of device construction.[218,219] The electrochemical reaction that is being monitored usually generates a measurable current (amperometry), charge accumulation or potential (potentiometry), or even alters the conductive properties of an electrolyte between two measuring electrodes in a conductivity cell (conductometry).[220] Electrochemical impedance spectroscopy (EIS) is another transducing alternative for biosensors, measuring both resistance and reactance of bioelectrodes.[220] As a surface technique, electrochemical detection offers advantages for the biosensing as the independence from reaction volume, the use of very small sample volumes,[221] and the high sensitivity that allows achieving very low LODs with little or none sample preparation.[222,223] Besides, electrochemical measurements are not affected by sample components as chromophores, fluorophores, and can be accomplished in turbid samples as, *e.g.,* whole blood, without interference from fat globules, red blood cells, hemoglobin, and bilirubin.[224,225]

Voltammetric techniques are characterized by the application of a potential to a working electrode (WE) by an auxiliary electrode (AE) and the measurement of the generated current.[226] The potential applied on the WE is referenced against the reference electrode (RE). The current is a result of the electrolysis observed in the whole electrochemical cell by means of a reduction (cathodic current) or oxidation (anodic current) of the analyte on the surface of the WE. The current is controlled by the kinetics of the electrochemical reaction that might be ruled, *e.g.*, by the mass transport rate of the analyte from the bulk of the solution to the electrode surface, once the system might be considered electrochemically reversible and a high enough potential is applied.[226] The term voltammetry is usually regarded to those techniques which the potential is scanned over a set potential range, forming a peak or plateau as the expected analytical response. Voltammetric methods include the linear sweep voltammetry, cyclic voltammetry, hydrodynamic voltammetry, differential pulse voltammetry, square-wave voltammetry, AC voltammetry, polarography, and stripping voltammetry.[226]

In amperometry the generated current is monitored in function of time while a constant potential is sustained at the WE against the RE.[227] The absence of a scanning potential is what distinguishes the amperometry from the voltammetry. The technique is applied by stepping the potential directly to the desired value and then measuring the consequent current or, in flow injection analysis (FIA), by passing samples across the biased WE. The measured current is usually directly proportional to the concentration of the electroactive species present in the sample. Some authors sustain that amperometric biosensors have additional selectivity since the potential used for the detection is characteristic of the oxidation or reduction of the analyte species.[218] The amperometric detection is usually used with biocatalytic or affinity assays due to its simplicity and low LODs achieved.[228] Advantageously, the fixed potential during the whole experiment allows the stabilization of the background current, decreasing the capacitive component on it. Furthermore, amperometry permits

the use of the hydrodynamic condition that enhances significantly the mass transport of the analyte to the electrode surface[226,229] by the WE rotating or vibrating in relation to the solution,[230,231] or during the flow analysis when the sample solution is pumped and passes over the stationary electrode.[229,232,233]

Electrochemical sensors are part of electrochemical cells that consist of three electrodes: the working electrode (WE) of a chemically stable solid conductive materials as platinum, gold, or carbon materials; the reference electrode (RE), with a stable and known potential usually consisting of silver metal coated with a layer of silver chloride (Ag/AgCl) immersed in a separated compartment with a porous junction containing saturated KCl (3.5 mol L^{-1}); and a platinum auxiliary electrode (AE) to apply the potential. This three-electrode system is mainly interesting due to the fact that the potential is applied by the AE instead of the RE, protecting the RE from changing its potential. The two-electrode systems with the WE and the RE are only used if the current-density is low enough (< μA cm^{-2}) for the RE to carry the charge without no adverse biasing effect.[227] It is usually preferred for disposable sensors considering that the long-term stability of RE is not necessary, and the project shows lower costs. These three electrodes are easily miniaturized with new dimensions on the order of μm or smaller,[234-236] exhibiting higher sensitivities[220] and requiring lower sample volumes of μL or less.[237,238] Also, electrochemical detectors and their controlling instrumentation are easily miniaturized with relatively low cost by micromachining, manufacturing field-portable instruments for biosensing purposes. Considering that working currents are temperature-dependent in voltammetry, the detection cell shall be maintained in a constant temperature for running the calibration with standards and the sample, so as accurate and precise results can be obtained.[239]

Screen-printed (SPEs) minielectrode systems with WE, RE, and AE have become popular in electrochemical biosensors for their low cost, ease fabrication, and fast mass production using thick films technology.[221] SPEs are produced by printing different inks on various types of plastic or ceramic substrates. As an example, polyester screens are generally used for printing with patterns designed by the analyst according to the analytical purpose. The composition of several inks used for printing the electrodes determines the selectivity and the sensitivity required for each analysis.[131] SPE can even be miniaturized for microfluidic systems and portable meters. The typical patterned WE is made of conductive carbon ink with rough surface and uncertain surface area.[240] As an application example, disposable SPEs have been widely used in biosensors to measure the blood glucose content.[241]

Interdigitated array (IDA) electrodes are good amperometric transducers for biosensors. They are made of two pairs of WEs made of parallel strips of metal fingers that are interdigitated and separated by an insulating material.[242,243] One electrode array is used as the anode and the other as the cathode. The main advantage of IDA is the redox cycling of the electroactive product or mediator, which happens once different potentials are applied to the pair of electrodes, causing the oxidation-reduction cycling for reversible electrochemical reactions. Lower LODs are achieved due to the multiple contribution of each redox active species to the measured current,[242,243] improving consistently the signal-to-noise ratio. The signal enhancement increases as the spacing and width of the metal fingers decrease altogether with the diffusion distances for the redox species. Typical IDA signal enhancements are about 3 to 10 times and can achieve 1000 times depending on the cell dimensions.[243] In terms of applications, IDA has been consistently used as detector in electrochemical immunoassay.[244]

Handling small volumes of liquids with high precision is one of the challenges in the development of the next generation of electrochemical biosensors. Devices are becoming smaller and more sophisticated, so the difficulty in handling the analytical reagents for the electrodes production is increasing. Liquid-handling biosensor devices allow the detection of biomolecular interactions in a liquid. The use of labels is spared and the methods are performed with high-throughput. Some interesting advances in transducers designs make possible the production of one million measurements points on a 1 cm^2 chip. This kind of approach still suffers from a poor incorporation of the biological reagent onto the surface of such arrays. Ink-jet techniques are suitable for depositing droplets of less than 1 nL in volume with very high speeds and still poor droplet resolution. Other liquid-handling techniques include the syringe-type processes as the “Cravo deposition”, usually involving “touching off” a droplet onto a surface. Another method picks up reagents on

a “pin” with a concave head and deposits it onto the surface of the device, a technique adapted from certain pharmaceutical applications. Additional developments on the fabrication techniques of electrochemical biosensors involve lithography and photolithography processes.[131]

Conductometry detection monitors changes in the electrical conductivity of the sample solution or a medium, as their composition changes during the course of a chemical reaction. Conductometric biosensors often use enzymes as the biorecognition element as their conversion products with electric charge increase the medium conductivity. Such systems have been applied for the detection mode in biosensors of environmental and clinical analysis. For instance, a tyrosinase biosensor was developed to measure ppb amounts of diuron and atrazine pollutants.[245] They also have been applied for the detection of foodborne pathogens as enterohemorrhagic *Escherichia coli* O157:H7 and *Salmonella* spp. using a low volume immunosensor with a sandwich-type immunoassay.[246] Drug detection of methamphetamine in human urine is another subject that has been accomplished using a conductometric biosensor.[247]

Potentiometric sensors are based on the measurement of the potential of electrochemical cells while draining negligible current. Conventional examples include the glass pH electrode and ion-selective electrodes for K(I), Ca(II), Na(I), and Cl(I). An electrochemical cell with two electrodes is used to measure the potential across a membrane that selectively reacts with the charged ions of interest. Potentiometric biosensors can be produced by coating electrodes with a biological element as an enzyme to catalyze the formation of the ion that is specifically detected by the electrode. As an application example, a penicillin sensor has been developed by coating a pH electrode with penicillinase that catalyzes a reaction of penicillin that also generates protons (H^+).[248] As the electrode senses the pH reduction on its surface, an indirect correlation with the penicillin content might be drawn.

Electrochemical impedance spectroscopy (EIS) is a technique that measures the resistive and capacitive properties of a material using small amplitude sinusoidal AC excitation signals, typically between 2 and 10 mV,[227,249] and over a wide range of frequencies to obtain spectra. Both in-phase and out-of-phase current responses are determined to access the resistive and capacitive components of the impedance, usually using fitting models of analogic circuits. The electron-transfer resistance is accessed at high frequencies while mass transfer rate at low frequencies. Regarding to biosensing, impedimetric detectors were used for affinity biosensors at first,[241] being used for the monitoring of the Ab-Ag complex binding on the electrode surface. Small changes in the impedance are proportional to the concentration of the measured species, as the antigen (Ag). During next stages of development, the surface of the WE could be modified with a highly specific biological recognition element and, during the detection step, a known tension signal was applied to this electrode and the resulting current was measured. The electron transfer resistance at the electrode/solution interface changes slightly by the binding of the analyte, allowing the recording of positive or negative signal readouts.

As shown at Figure 5, the formation of antibody-antigen conjugated layers might provide a label-free immunoassay, which the formation of a blocking layer (Ab-Ag) gradually suppresses current amperometric signals using a redox probe. By EIS, the increase on the charge-transfer resistance can be observed for such immunological system, allowing the characterization of the bioelectrode surface in addition to evaluating the kinetics of Ab-Ag binding.[250]

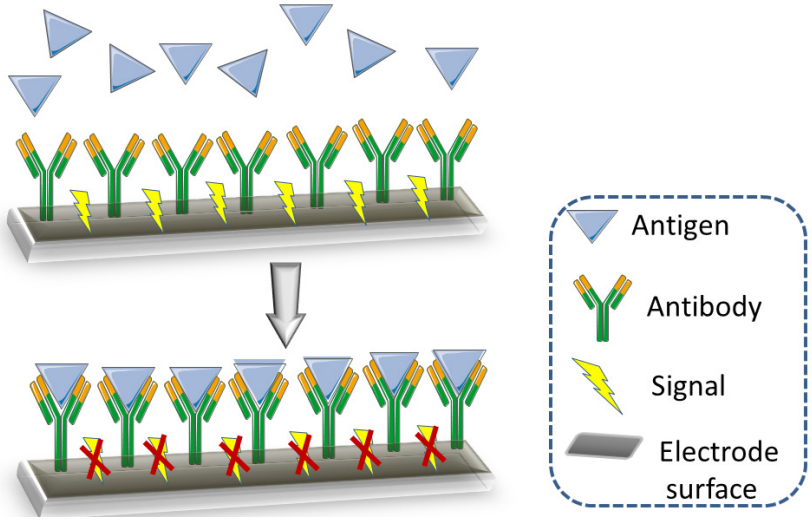

Figure 5. Formation of the blocking layer by the Antibody-Antigen complex in a hypothetical non-labeled assay with redox probe.

The direct monitoring of the formation of Ab-Ag conjugated layers provides a label-free detection mode with many advantages as higher signal-to-noise ratios, easy detection, lower costs of assay, faster experiments, and shorter detector response times. Nevertheless, the surface regeneration after the first measurement of an impedimetric biosensor is typically time-consuming, and measurements are not enough reproducible, which constitutes one of the biggest limitations of immunosensors involving the Ab-Ag complexes with high affinity constants. Sometimes, own regeneration conditions can be aggressive enough to damage and release the immunoreagent that is bounded to the bioelectrode.[241]

Now, once compared to the EIS, amperometric detection shows some drawbacks as the necessity of an easy accessibility of the participating species of the biologically-mediated redox reaction to the analyte solution and to the electrode surface. Still, redox mediators have been used to help overcome this accessibility and proximity limitations, but it causes the detection to be limited by the mass transfer rate of the mediator itself. Furthermore, additional redox active species of the sample matrix (*e.g.* urate and ascorbate) can contribute indistinctly to the amperometric signal depending on the detection potential of choice. Impedimetric immunosensors monitoring the Ab-Ag complex can bypass all these aforementioned limitations, since they are insensitive to most possible matrix disturbances once the impedimetric detection have been carefully designed to minimize nonspecific binding of the analyte.[251] Nanomaterials as gold nanoparticles and carbon nanotubes are very beneficial to chemical impedance sensors due to the increased electrode surface area, improved electrical conductivity of the sensing interface, higher chemical accessibility of the analyte, and some possible electrocatalytic effects.[249]

Miniaturization is a trend in the analytical chemistry and in order to design and fabricate small electrocemical biosensors, bioelectrodes need to be greatly reduced in size. Manufacturing capabilities of depositing microelectrodes on surfaces are growing and microelectrodes can easily be assembled on microfluidic chips using the vapor deposition technologies.[221] Microelectrodes are defined as electrodes with a diameter in the micrometer scale and can be made as disks or cylinders of carbon fibers or metal microwires.[234,235] Their applications include the measure of electroactive species in small critical places as inside mammalian brains[234] and live biological cells.[252] This is possible considering that electrochemical reactions occur on the electrode surface instead of the bulk solution, and very small sensing microelectrodes can be easily inserted in very small drops or spaces without disturbance or damage. For instance, carbon fiber microelectrodes have been used to detect 190 zmol of catecholamine released from a single stimulated rat nerve cell to monitor this species in cultures of adrenal cells.[253] The release of serotonin from neuronal vesicles have been monitored achieving 4.8 zmol LOD,[254] and a detector in microvolume electrochemical immunoassay

have been developed, both using carbon fiber microelectrodes too.[238] The measured currents are usually in the nA to pA magnitude order, so as the method can be classified as nondestructive,[234] besides the fact that the signal amplification is almost mandatory.[221]

Despite of the continous development of several types of transducers for biosensors, the electrochemical type is very interesting for portable point-of-care devices since they are small, simple, easy to use, cost-effective, and disposable for most of the cases. Electrochemical sensores are the smallest among all types of sensors (including the optical and piezoelectric sensors), providing the bioassays with the great advantage of portability that allowed the miniaturization of instruments to small pocket-size devices that are applicable even for the consumer home use. Furthermore, the sensitivity and response of the electrochemical sensors are considerably higher than most of optical or piezoelectric sensors. That is why there is an immense motivation in the literature to explore the field of electrochemical biosensors, especially for the detection and quantification of analytes with very low concentrations in sample matrices with challenging interferences, such as those found for mycotoxins in food.

METALLIC NANOPARTICLES BIOSENSORS FOR MYCOTOXINS DETECTION

Metal-based nanoparticles (MNPs) are commonly applied for electrochemical sensing due to the enhancement of both sensitivity and selectivity of proposed methodologies. Gold, platinum, palladium, silver, copper and cobalt are some examples of pure metals used in nanoparticulate form for the assembling of sensors.[255] Besides, MNPs show interesting biocompatibility and good conductivity. They might act as immobilizing platforms,[256] electron transfer enhancers,[257] catalysts of chemiluminescent reactions,[258] amplifiers of mass[259] and refractive index.[260] They can even work as electron conductors transporting the charge to the receiving transducer.[257] Furthermore, MNPs can directly act as suitable mediators for modified electrodes due to their high electrical conductivity without great cost increase on the sensing project. That is true since there is a considerable cost difference between noble metal macroelectrodes and synthesized NPs. In general, their synthesis is accomplished by the reduction of the precursor metal salt in the presence of capping agents such as phosphines, thiols, polymers, and amines.[261–263]

An example of a nanobiosensor assembling with MNPs involves: (*i*) the deposition of a mediator on the substrate electrode to catalyze the biochemical redox reaction; (*ii*) the immobilization of MNPs on the mediator-modified electrode to work as the immobilizing platform and; (*iii*) the immobilization of the biomolecule recognition agent. The detection mechanism indicates that the analyte is converted to the specific product, which involves an oxidation or reduction reaction. The biomolecule changes its form to the reduced or oxidized form, while the mediator regenerates it to the original active species. Finally, the analytical signal is generated by the donation (acceptance) of electrons by the underlying substrate electrode to (from) the mediator.[264]

Among the aflatoxin, AFB1 might be considered as one of the most hazardous due to its toxic, carcinogenic, mutagenic, and genotoxic character.[265] It is found in contaminated and moldy crops and beverages. Many electrochemical biosensors have been developed for AFB1 detection.[266–269] Most of them are cheap and easy to operate, despite of their lack of sensitivity in comparison to the maximum permissible limits of AFB1 established by rulers worldwide. For US and China, the tolerable limit for foodstuff is 20 ng/g, while for Korea and Japan is 10 ppb. For rice in the EU, the tolerable limit is 5 ng/g.[270]

Zhang *et al.*[271] developed an electrochemical immunosensor for the detection of AFB1 using Pd–Au nanoparticles supported on functionalized PDDA–MWCNT nanocomposites (CNTs / PDDA / Pd-Au immunosensor). The PDDA (positively-charged polyelectrolyte) was used to avoid the aggregation of MWCNTs, facilitating their dispersion in aqueous medium and allowing the formation of homogenous films on the electrode. PDDA still enriched the surface of CNTs with positive charges that promoted the adsorption of the negatively-charged Pd–AuNPs. These MNPs were used as the supporting substrate for the antibody immobilization. The analytical performance of CNTs/PDDA/Pd-Au immunosensor was studied using the differential pulse voltammetry under optimal conditions found. A satisfactory linear relation with AFB1 concentration in the range between 0.05 and 25 ng/mL was obtained with a LOD of 0.03 ng/mL. Comparing

with other reported AFB1 biosensors, the linear range showed 4 orders of magnitude in concentration that is higher than the one found for CNT-ionic liquid,[266] Silica gel-ionic liquid,[272] Prussian blue,[273] and AFB1-BSA[274] biosensors; it is comparable to the one of chitosan/Au nanoparticles,[269] and barely worse than the one for the Polypyrrole/pyrrolepropylic acid.[275] It showed one of the best LOD values, only worse than the Silica gel-ionic liquid.[267] The analysis of real samples showed recovery tests in the range between 98.2% (50 µg/kg) and 103.2% (100 µg/kg) for samples of non-contaminated spiked rice with simple sample treatments. Ultimately, the CNTs/PDDA/Pd-Au immunosensor showed interesting low LOD with satisfactory reproducibility, selectivity, and storage stability. The strategy is still valid for the immobilization of other antigens using their corresponding antibodies for the quantification of other toxins.

Wang *et al.*[35] proposed the use of metal ions as signal tags for the design and fabrication of sensitive immunosensors. Signal tags are used for the amplification of the transduction signal to improve the methodologies sensitivity. The most common tags are the enzymes, dyes, and quantum dots. Metal ions are compelling tags since they are cheap, readily available, and can be sensitively detected using stripping analysis voltammetry. Most difficulties of using metals as tags reside in the fact that it is hard to establish a direct contact of targets and the metal ions information. Therefore, the authors addressed this challenge by replacing Ca(II) ions by Cu(II) in the hydroxyapatite composition to consolidate an ion-exchange approach, forming the Cu-apatite. AuNPs were used to modify the screen-printed carbon electrode (SPCE) and complete the competitive-type immunosensor, where Cu(II) ions were released from apatite through acidolysis and its concentration was determined by stripping voltammetry, successfully establishing correlation with the analyte quantities. A satisfactory linear relation was observed between the peak current and the logarithm of AFB1 concentration in the range of 1 pg/mL to 100 ng/mL with LOD of 0.2 pg/mL. Comparing to other immunoassays of the until-date literature,[270,273,276–283] the Cu(II)-tag immunosensor showed superior performance with detection range meeting the limits for the AFB1 in human foodstuff in the European Union (2 ng/mL), and in the United States (20 ng/mL). Milk and peanut butter were used as real samples spiked with 1 ng/mL and 20 ng/mL of AFB1 for recovery tests, respectively. Recoveries in the range of 95.5-110% and 90-102% were observed, with small issues concerning the accuracy and the matrix effect. Nevertheless, the prototype concept has been proved, reducing the production cost of the immunosensor and making possible the use of leaked metal ions as signal tags.

Bhardwaj *et al.*[284] fabricated an electrochemical label-free immunosensor via antigen-antibody interactions using chemically prepared graphene quantum dots modified with gold nanoparticles (GQDs-AuNPs) that were deposited on hydrolyzed ITO by electrophoretic deposition (EPD). AFB1 antibodies were immobilized by cross-coupling chemistry using N-ethylN-(3-dimethylamino propyl) carbodiimide (EDC) and N-Hydroxy succinimide (NHS). GQDs were preferred over conventional graphene nanosheets due to the limited number of edge planes and the zero graphene band-gap, which improves the surface reactivity, dispersibility, biocompatibility, and the ratio of edge-to-basal planes that favors the bio-nano conjugation[285]. That remarkably increases the rate of heterogeneous charge-transfer, improving the immunosensor sensitivity and stability. AuNPs were combined with GQDs for the immunosensor assembling due to its high electrical conductivity and catalytic properties,[286] offering a multifold signal enhancement that provides precision, accuracy, and sensitivity for the involved methodologies. The electrochemical response of the BSA/anti-AFB1/GQD-AuNPs/ITO immunosensor was evaluated by cyclic voltammetry in the presence of ferricyanide/ferrocyanide redox probe, showing an anodic peak signal that is directly proportional to the AFB1 concentration until 1.0 ng/mL. The signal positive readout has been explained by the formation of an electro-transfer layer by the Ag–Ab immuncomplex, some possible changes in the conformational structure, and improvements of the conductive pathway between the redox couples and the transducer. Sensitivity and LOD were of 382 µA/ng mL^{-1} cm^{-2} and 0.008 ng/mL, respectively. Results were compared to other until-date published immunosensors, and GQDs-AuNPs/ITO showed comparable LOD results to PEDOT/AuNPs/ITO[287] and SWCNTs/Chitosan,[288] while much better value than PTH/Au/GCE,[289] CNTs/c PDDA/Pd-Au,[271] CS-AuNPs/gold microelectrode,[290] and rGO/ITO.[291] Non-contaminated maize with several spiked concentrations of AFB1 was used as real sample, achieving linear range between 0.1 ng/mL–2.5 ng/mL and LOD of 0.11 ng/mL, demonstrating the

applicability of BSA/anti-AFB1/GQD-AuNPs/ITO to the real analysis of AFB1 in maize even in concentrations under the maximum tolerance level of EU regulations.

Table II summarizes the electrochemical biosensors discussed according to the type of biomaterial, the target mycotoxin, the type of sample, LOD, and linear range of response.

Table II. Information of electrochemical biosensors discussed, including the type of material, the target mycotoxin, the type of sample, the limit of detection (LOD), and the linear range

Electrochemical biosensors	Mycotoxin / sample	LOD	Linear Range	Refs.
SPCE/Au NPs	AFB1/ corn	0.2 pg mL^{-1}	0.001 - 100 ng mL^{-1}	35
GCE/AuNPs	AFB1/ olive oil	0.05 ng mL^{-1}	0.1 - 10 ng mL^{-1}	266
Graphene/Polymer/AuNPs	AFB1/ rice	3.3 pg ml^{-1}	0.01 - 10 ng mL^{-1}	268
Au/nanomagnetic material	AFB1/ rice	0.01 ng mL^{-1}	0.03 - 10 ng mL^{-1}	269
GCE/Pd-Au/PDDA (MWCNTs)	AFB1/ corn	0.05 ng mL^{-1}	0.1 - 10 ng mL^{-1}	271
GCE/cysteine/MAb	AFB1/ rice	0.1 ng mL^{-1}	0.1 - 10 ng mL^{-1}	274
CGE/Pd-Au/ MWCNTs	AFB1/ corn	0.05 ng mL^{-1}	0.1 - 10 ng mL^{-1}	271
QCM electrode/AuNP	AFB1/ rice	0.05 ng mL^{-1}	0.05 - 10 ng mL^{-1}	276
Au electrode	AFB1/ peanut	0.05 ng mL^{-1}	0.05 - 10 ng mL^{-1}	281
ITO electrode	AFB1/ maize	0.1 ng mL^{-1}	0.1 - 3.0 ng mL^{-1}	284
GCE/ Au-Ag/graphene/GQD	AFB1/ aqueous solutions	0.05 ng mL^{-1}	0.05 - 10 ng mL^{-1}	286
GCE/ZnS QDs	SEB/ aqueous solutions	0.1 ng mL^{-1}	0.1 - 10 ng mL^{-1}	287
GCE/ SWCNTs	AFB1/ corn	0.02 ng mL^{-1}	0.05 - 10 ng mL^{-1}	288
GCE/PTH/AuNPs	AFB1 /food sample	0.07 ng mL^{-1}	0.6 - 2.4 ng mL^{-1}	289
SPCE/MWCNTs	AFB1/ wheat	0.05 ng mL^{-1}	0.1 - 10 ng mL^{-1}	290
AuNPs/MWCNTs/CS	AFB1/ wheat	0.002 ng mL^{-1}	0.001 - 100 ng mL^{-1}	292
Au/Bi2S3/ERGO/CF	AFB1/ cornflour	8 pg mL^{-1}	10 pg - 20 ng mL^{-1}	293
AuNPs/Zn/Ni-ZIF-8-800@ graphene	AFB1/ peanut oil	0.18 ng mL^{-1}	0.18 - 100 ng mL^{-1}	294
Au electrode	OTA/ coffee	0.15 ng mL^{-1}	0.5 - 100 ng mL^{-1}	295
CF/PdNPs	OTA/ coffee	0,096 ng mL^{-1}	0.5 - 20 ng mL^{-1}	296
Au/SPGE/CMD	AFB1/pistachio	1 ng mL^{-1}	0.5 - 1 ng mL^{-1}	297

CARBON-BASED ELECTROCHEMICAL BIOSENSORS FOR MYCOTOXINS DETECTION

Carbon chains might organize themselves in several forms to assemble different structures, resulting in diverse materials as graphene, diamond, graphite, carbon nanotubes, fullerenes, carbon fibers, and carbon black (Figure 6).[298] These materials can display different properties despite their same chemical composition depending on their electronic structure. They are classified according to their geometric structure: particles admit the shape of tubes, horns, spheres or ellipsoids. Tube-shaped or corner-shaped particles are called carbon nanotubes (CNTs) or carbon nanorods (CNHs), respectively. 0D nanodiamonds, 1D nanotubes,

and 2D graphene nano-sheets can act as nanocomposites[299] (Figure 6). Advances in carbon nanomaterial synthesis have resulted in sensing systems that show improved analytical performance, providing new detection routes.[298]

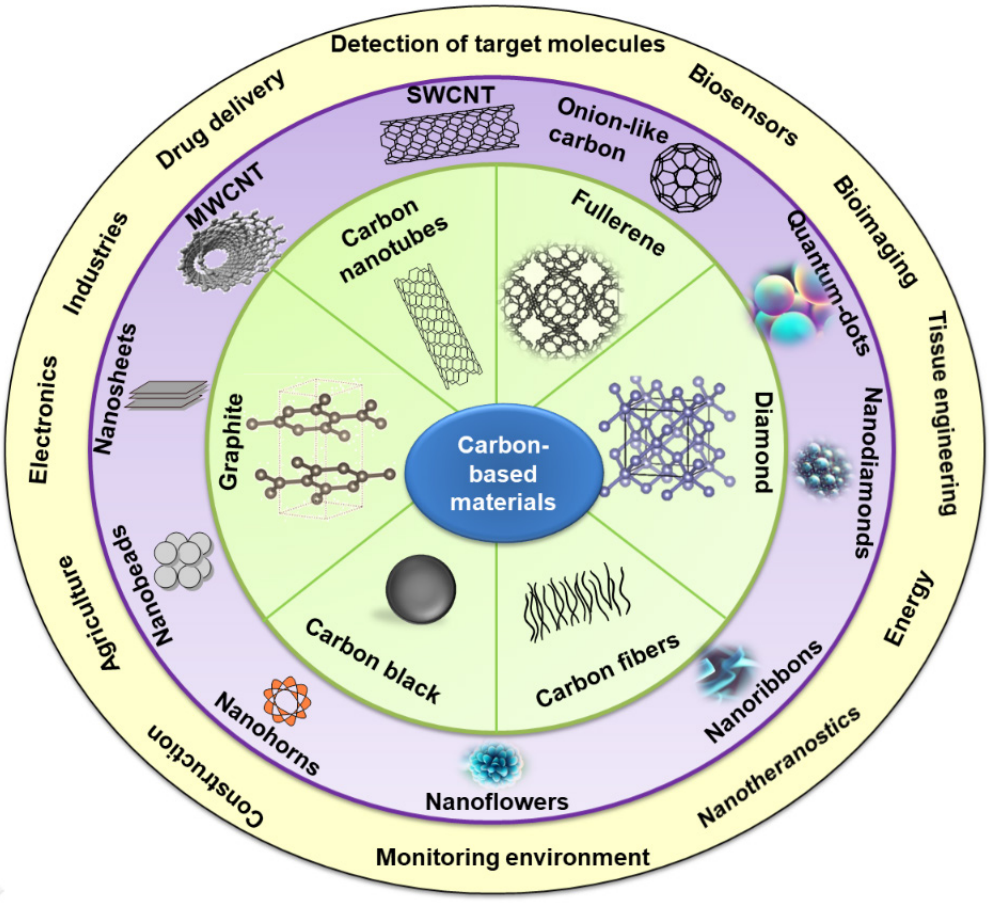

Figure 6. Carbon-based materials and their applications.

Furthermore, carbon-based sensors have demonstrated biocompatibility, good sensitivity, selectivity, and low LODs for a wide range of molecules. Due to their unique characteristics, carbon nanomaterials are among the most investigated materials.[298] They show high specific surface areas, high electrical conductivity, and flexibility that ascribe them to a wide range of applications including electronics, construction, agriculture, energy, nanotheranostics, and the detection of toxins in foodstuff.[300–303] Herein, we will focus our discussion on the two main carbon-based materials used for mycotoxin nanobiosensing: graphene-type and carbon nanotubes materials, although some important applications can be found elsewhere for carbon nanofibers,[304] nanodiamonds,[305] fullerene,[306] and Carbon-Black.[307]

Honeycomb two-dimensional graphene gained considerable attention since its discovery in 2004.[308] Curiously, graphene shows very alike physical and chemical intrinsic properties than graphite as the high surface area and the numerous surface active sites. The difference comes from the higher electron transfer kinetics of such active sites, and the increased thermal conductivity, mechanical flexibility, and biocompatibility[309] that make graphene very compelling for the application in electrochemical sensing platforms. There are many reported methods for the graphene preparation,[309,310–316] but the most scalable, cost-effective, and productive is the graphite exfoliation on graphene-type materials as graphite oxides (GO).[317] GO is obtained as a highly oxidized form of graphene that is produced by its surface reaction with strong oxidizing agents, resulting in a material with excellent surface functionality and amphiphilicity.[318] The Hummer's method

(Figure 7) is frequently used to synthesize the graphene oxide and includes the oxidation of graphite by potassium permanganate and sulfuric acid,[319] followed by the sonication to generate the graphite functionalized salts, the GO precursor. This material should be reduced to form the reduced-graphene oxide (rGO) analogue with interesting properties for desirable electrochemical applications. Many reduction pathways can be followed as the thermal annealing or the chemical reduction with hydrazine or sodium borohydride.[320]

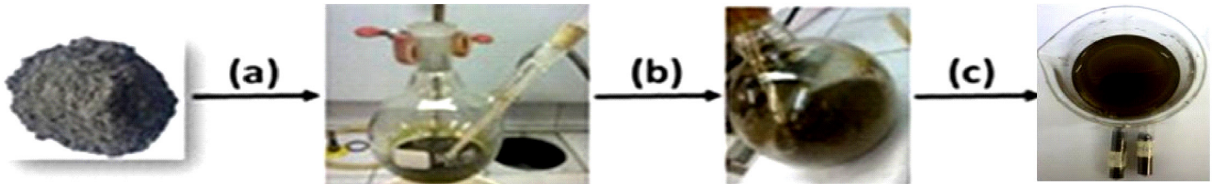

Figure 7. Schematic representation of graphite oxidation to obtain GO using Hummer's method: system containing graphite powder, sodium nitrate, sulfuric acid, and potassium permanganate (a), addition of hydrogen peroxide and deionized water (b), and resulting material after centrifugation and drying (c).

In general, pristine graphene is considered chemically inert and interacts with other molecules by weak physical adsorption, being necessary the introduction of surface defects of functional groups to improve its reactivity by the adjustment of surface and electronic properties. Surface functionalization can turn pristine graphene or GO into chemically sensitive and dispersible materials, making them suitable for sensing applications. Covalent functionalization is one of the most common surface modification methods for graphene. The structural change may take place both on the basal surface and at the margins/corners. Graphene can be covalently functionalized through reactions with its unsaturated bonds so as amino, hydroxyl, sulfonate, or alkyl groups are introduced through covalent bonding.[321,322] These groups can also act as anchoring sites to embed proteins, amino acids, and polymers.[322,323] The covalent carbon-carbon bonding involving the basal plane of carbon atoms offers key advantages such as the greater stability of the hybrid material, the controllability over the functionalization degree, and the reproducibility. As a disadvantage, although covalent strategies can effectively install functionalities, they unavoidably cause a loss of the free π-electron charge-carriers.[320] The non-covalent functionalization basically requires the adsorption of appropriate atoms on the graphene surface, which does not influence the material conductivity.[324] The polymer wrapping, the adsorption of surfactants or small aromatic molecules and their interactions with porphyrins or biomolecules as DNA are all examples of non-covalent functionalization.[298] This method allows the reversible functionalization while preserving the original structure of graphene. However, physical adsorption is nonspecific and there is little control over the degree of functionalization, being less stable, reproducible, and susceptible to environmental conditions during applications.[325]

Carbon nanotubes (CNTs) are cylindrical structures made of carbon atoms arranged in a hexagonal lattice. CNTs can be divided into two types: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs).[326-328] SWCNTs consist of a single graphene sheet rolled into a seamless cylinder with diameters on the nanometer size, ranging from 0.4 to 3 nm.[329] MWCNTs consist of multiple concentric layers of graphene sheets with larger outer diameter compared to SWCNTs, typically ranging from 2 to 100 nm.[330] The presence of multiple layers contributes to the MWCNTs enhanced mechanical performance compared to SWCNTs, still exhibiting higher thermal conductivity and efficient heat transfer along graphene layers. CNTs exhibit remarkable electrical, mechanical, and chemical properties[327,331] and their good charge-transfer characteristic is appealing for their application in the assembling of electrochemical biosensors and sensing platforms. Common methods of CNT synthesis include electric arc discharge,[327] chemical vapor deposition (CVD),[331] laser ablation,[329] chemical vapor infiltration (CVI),[332] and template-assisted synthesis.[333] Considering the differences between the synthesis methodologies, materials should be purified prior to the chromatographic separation.[334,335] CNTs purification consists on the dissolution of contaminating catalysts and fullerenes by-products, and the removal of the remaining graphite large particles and further

aggregates by simple filtration. The main strategies are the acid treatment,[336] ultrasonication,[337] filtration (or chromatographic method),[335] thermal or oxidative treatment,[338] and density gradient ultracentrifugation (DGU).[339]

Although CNTs exhibit remarkable physical and chemical properties, their low dispersibility in aqueous and organic solvents has hindered their early application.[340] To circumvent this hindrance the functionalization has been used to modify CNTs surface, attaching functional groups or molecules to increase their ease of dispersion, manipulation, and processability. Main functionalization strategies are based on substitution reactions, such as the replacement of carbon atoms in the tube wall by boron or nitrogen. The choice of functionalization method depends on the desired properties, stability, and intended applications. CNTs are functionalized by irreversibly binding polymers to their walls or at defect points located at edges: the so-called grafts.[340] Functionalization can be achieved through covalent or non-covalent methods (Figure 8) as seen above for graphene. For the electrochemical biosensing applications, the non-covalent biomolecular functionalization[341] is the most relevant strategy, since it allows biomolecules as DNA, proteins, and antibodies to be attached to CNTs as the biorecognition element for specific analyte targeting.

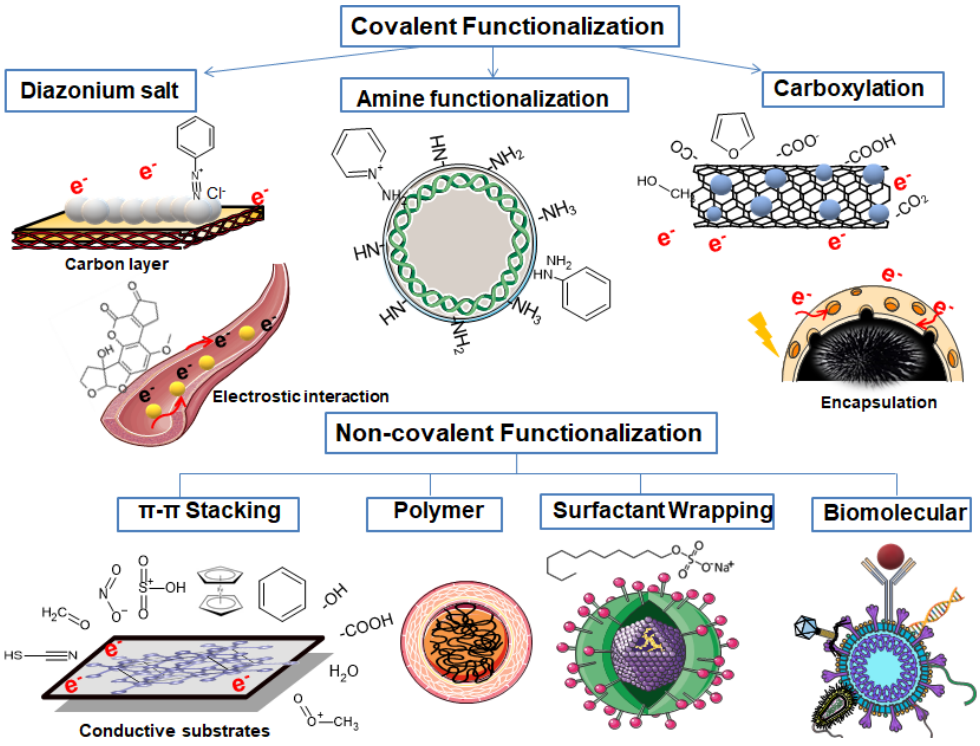

Figure 8. Different kinds of functionalization strategies used for carbon nanotubes (CNTs).

Gaozhi Ou *et al.*[304] developed a label-free electrochemical immunosensor for the determination of aflatoxin B1 (AFB1) based on Au nanoparticles decorated with urchin-like Bi_2S_3 (Au/Bi_2S_3) anchored on electrochemically reduced graphene oxide (ERGO) modified carbon fiber (CNFs) microelectrode (Au/Bi_2S_3/ERGO/CF). Under the optimum conditions, the label-free electrochemical immunosensor detected AFB1 within the linear range of 10 pg mL^{-1} to 20 ng mL^{-1} with a LOD of 8 pg mL^{-1} and sensitivity of 0.48 μA/ng mL^{-1}. The immunosensor was applied to detect AFB1 in corn flour samples, offering excellent reliability and accuracy compared with typical detection methods. Glassy carbon electrode modified with nickel/nickel hydroxide NPs-decorated reduced graphene oxide (Ni/$Ni(OH)_2$-rGO) was used for non-enzymatic detection of xanthomegnin.[342] Ni/$Ni(OH)_2$-rGO composites were synthesized through a simple microwave-assisted technique with a less harmful reducing agent. The sensor exhibited a limit of detection

of 0.12 µmol L^{-1}. The selectivity, stability, and analytical recovery proved the potential use of the sensor for the detection of xanthomegnin in real samples.

Molecularly imprinted electrochemical sensors were exploited to detect zearalenone (ZEA) by the synergistic effect of reduced graphene nanoribbons (rGNRs) and gold nanoparticles (AuNPs).[343] The oxidized GNRs were firstly produced by an improved Hummers' oxidation method, and then reduced and modified with AuNPs onto a glassy carbon electrode by electrodeposition. It was found that the constructed sensor showed a wide linear range of 1–500 ng mL^{-1} for ZEA, with a LOD as low as 0.34 ng mL^{-1}. Singh *et al.*[344] prepared composite c-MWCNTs/ITO electrodes by one-step electrophoretic deposition of c-MWCNTs on ITO glass. BSA/anti-AFB1/MWCNTs/ITO immune electrode was prepared by covalently coupling aflatoxin monoclonal antibodies. The results showed that the method had high sensitivity in the linear range of 0.25–1.375 ng mL^{-1} and LOD of 0.08 ng/mL.

Wang *et al.*[345] developed a molecularly imprinted electrochemical method using a stepwise approach for the detection of AFB1 in gutter oil. Au/Pt bimetallic nanoparticles were electrodeposited on glassy carbon electrode modified with MWCNTs. The performance of the imprinted sensor showed a linear range of 1.0×10^{-10} to 1.0×10^{-5} mol L^{-1} with a LOD of 0.03 nmol L^{-1}. Zhang *et al.*[346] developed an electrochemical immunosensor for detection of aflatoxin B1 in agricultural products by modifying multi-walled carbon nanotubes (MWCNTs) with ferrocene (FC) fixed on the surface of a screen-printed carbon electrode (SPCE) via MWCNTs and chitosan (CS). The increase in the specific surface area of SPCE modified by Fc/MWCNT/CS facilitated the binding of AFB1-Bovine serum albumin, while the excellent electrical conductivity of FC/MWCNT/CS promoted a good electron transfer rate. These advantages not only amplified the immunosensor signal, but also improved the immunosensor sensitivity and stability.

Solis *et al.*[347] developed an electrochemical microfluidic immunosensor for T-2 quantification in wheat germ samples. The detection was carried out using a competitive immunoassay method with monoclonal anti-T-2 antibodies that were immobilized on poly(methyl methacrylate) (PMMA) in a central channel. A platinum wire modified with reduced graphene oxide (rGO)-nanoporous gold (NPG) was used as the working electrode and positioned at the end of this channel. The detection mechanism comprised the T-2 competition with T-2-horseradish peroxidase (HRP) for the specific recognizing sites of immobilized anti-T-2 monoclonal antibodies, so as HRP in the presence of hydrogen peroxide catalyzes de oxidation of 4-tert-butylcatechol (4-TBC) which reduction was monitored at the nanostructured electrode at −0.15 V (*vs.* Ag/AgCl). According to authors, the new microfluidic assay contributed to the *in situ* analysis of mycotoxins in agricultural samples, making it faster and even more secure.

Jubeen *et al.*[348] prepared an overview of the scenario of recent studies using electrochemical sensors and biosensors for mycotoxin detection for food safety. Authors provide a critical inspiration for future applications of electrochemical analysis and point-of-care testing for mycotoxins, pointing out the electrochemical sensors as a viable method for addressing specificity and sensitivity in detection, considering their ease of use, sensitivity, low cost, and miniaturization capability. Many graphene-based devices are herein discussed as well. Kalambate *et al.*[349] reported a review which outlines a variety of electrochemical sensing platforms. Authors claim that the electrochemical sensing platforms emerged as feasible devices to address specificity and sensitivity issues, even privileging the effectiveness, efficiency, and user-friendly nature. The review offers valuable perspectives on the existing challenges, discussing great advancements using graphene-based nanocomposites. Jiang *et al.*[350] reviewed the significant work on electrochemical sensors for mycotoxins detection in food samples aiming the mechanisms and portable use for the toxin detection, including carbon nanostructured materials. They summarized recent advances providing a new perspective on future trends of portability.

Yang *et al.*[351] developed a immunosensor for the mycotoxin FB1 detection in food, based on chitosan functionalized nitrogen-doped graphene and polyaniline (N-G@PANI@CS) with electrodeposited gold nanoparticles (AuNPs) on its surface. The immunosensor showed a broad linear range of 0.50 ng mL^{-1} to 800.00 ng mL^{-1} and LOD of 0.07 ng mL^{-1}. Authors discuss that their study provides a novel, reliable, and convenient mean to detect FB1 in contaminated food. Deng *et al.*[352] reported a study with an ultrasensitive

Nafion-immobilized functionalized multiwalled carbon nanotube (MWCNT)-based electrochemical (EC) immunosensor for the trace detection of AFB1. Nafion is herein used to stabilize the MWCNTs suspension to provide uniform distribution of the material all over the surface of gold electrodes. MWCNTs were used as signal amplifiers with large surface area, several active sites for anti-AFB1 monoclonal antibodies (mAbs) coupling, and high conductivity to improve the charge-transport. The immunosensor selectivity was herein tested in the presence of three other types of mycotoxins, while the methodology accuracy was studied by measuring the AFB1 concentrations in fortified malt, lotus seed, and hirudo samples, achieving 92.08 to 104.62% of recovery.

Zhang *et al.*[353] reported a chitosan–graphene nanosheets (CS-GNs) electrochemical immunosensor. The CS-GN nanocomposite was used as a modifier layer to increase the specific surface area and biocompatibility of the immunosensor, enhancing the electron-transfer rate and the efficiency of the antibody immobilization. Results showed good correlation between the current transients and the AFB1 immunoreaction with interesting specificity and stability. Linear range was from 0.05 to 25 ng/mL with LOD of 0.021 ng/mL and recovery rates ranging from 97.3% to 101.4% in real corn samples. Authors claim that their methodology show promising performance, indicating a remarkable prospect for the mycotoxins detection in grains.

Carbon-based materials such as graphene and CNTs highlighted here have gained significant attention in the development of biosensors due to their exceptional electrical, mechanical, and chemical properties. All applications of carbon-based immunosensors discussed in this review are summarized in Table III.

Table III. Main carbon-based immunosensors discussed, including the material, the target mycotoxin, the type of sample, limit of detecton (LOD), and linear range

Nanoimmunosensor	Mycotoxin / sample	LOD	Linear Range	Refs.
Au/Bi_2S_3/ERGO/CF	AFB1 / cornflour	8 pg mL^{-1}	10 pg mL^{-1} – 20 ng mL^{-1}	304
AuNP-rGNR	ZEA / –	0.34 ng mL^{-1}	1 – 500 ng mL^{-1}	343
c-MWCNTs/ITO	AFB1 / –	0.08 ng mL^{-1}	0.25 – 1.375 ng mL^{-1}	344
(POPD)-grafted Au/Pt MWCNT	AFB1 / hogwash oil	0.03 nmol L^{-1}	10^{-10} – 10^{-5} mol L^{-1}	345
Fc/MWNT/CS SPCE	AFB1 / agricultural products	0.159 pg mL^{-1}	10^{-3} – 2 10^{-4} ng mL^{-1}	346
PMMA rGO-NPG T-2 HRP	T-2 / wheat germ	0.10 µg kg^{-1}	0.0 – 1000 µg kg^{-1}	347
AuNPs/N-G@PANI@CS	FB1 / –	0.07 ng mL^{-1}	0.50 – 800.00 ng mL^{-1}	351
Nafion–MWCNT	AFB_1 / fortified malt, lotus seed, and hirudo	0.021 ng mL^{-1}	0.05 – 100 ng mL^{-1}	352
CS-GNs	AFB1 / corn	0.021 ng mL^{-1}	0.05 – 25 ng mL^{-1}	353

CHALLENGES AND FUTURE RESEARCH DIRECTIONS

Despite of significant advancements in the development of electrochemical nanoimmunosensors for mycotoxin detection in food, several challenges remain that must be addressed to fully achieve their potential in commercial applications and real-world use. These challenges span issues related to sensor sensitivity, selectivity, matrix effects, and practical deployment in diverse food matrices. Addressing these challenges will require multidisciplinary approaches, collaboration, and continued innovation.

Matrix Effects and Sample Preparation: one of the most pressing challenges in the detection of mycotoxins in food using electrochemical sensors is the interference from complex sample matrices. Sometimes, the detection of mycotoxins based on a single analytical signal has proven to be false negative or false positive due to matrix effects.[354] Agricultural products and foodstuffs often contain various components as proteins,

lipids, sugars that can affect the accuracy and reproducibility of sensor measurements. The presence of these matrix components can lead to signal interference, reducing the effectiveness of electrochemical sensors. While ultrafiltration techniques and fouling-resistant coatings have been explored as solutions, these methods often require further refinement to ensure their practical feasibility. Future research should focus on developing robust sample preparation protocols that effectively mitigate matrix effects while maintaining the integrity and sensitivity of the sensors. An example is the use of multimodal biosensors[355] that can generate different analytical signals resulting in linearity increase and accuracy.

Improving Sensitivity, Selectivity, and Reproducibility: although electrochemical nanobiosensors offer enhanced sensitivity and selectivity compared to traditional methods, further optimization is needed. The current generation of sensors often faces limitations in detecting mycotoxins at low concentrations, particularly when multiple toxins are present in a sample.[356] Enhancing the sensitivity and selectivity of these sensors will require advances in nanomaterial design, sensor surface functionalization, and the development of more efficient biorecognition elements. Furthermore, reproducibility remains a key challenge, especially when sensors are exposed to variable environmental conditions. Future research should focus on improving the consistency and reliability of electrochemical nanobiosensors to ensure their suitability for commercial applications.[357,358]

Labeled *vs.* Label-Free Sensors: a significant challenge resides in the choice between labeled and label-free bioassay protocols. While labeled biosensors often provide higher sensitivities, they require additional steps for label conjugation and detection, potentially complicating the sensing process. Label-free biosensors, on the other hand, offer advantages in terms of simplicity and cost, but they may struggle to match the sensitivity of labeled systems. Future research could explore hybrid approaches that combine the benefits of both labeled and label-free technologies, improving the overall performance and versatility of electrochemical nanobiosensors.[46]

Integration with Portable and Wearable Devices: one of the most promising aspects of electrochemical nanobiosensors is their potential integration with portable and wearable devices for real-time mycotoxin monitoring.[350] The growing demand for point-of-care testing[358] and continuous monitoring of food safety in various settings as agricultural fields and food processing plants has led to increasing interest in wearable electrochemical biosensors.[359] However, the development of flexible, durable, and user-friendly sensors that can operate in real-world conditions remains a significant challenge. Research into the integration of electrochemical sensors with flexible substrates,[360] microfluidics,[361] and wireless communication systems is essential to overcome these hurdles. Wearable devices that can offer real-time and continuous monitoring of mycotoxins would provide a valuable tool for food safety professionals and consumers.[359]

Multiplexed Detection for Simultaneous Monitoring: another critical challenge in mycotoxin analysis is the need for simultaneous detection of multiple mycotoxins in a single sample.[356] Many electrochemical nanoimmunosensors have been designed for the detection of a single target, and the ability to perform multiplexed detection remains limited. Developing sensors capable of simultaneously detecting a wide range of mycotoxins in complex food matrices will be a significant breakthrough.[362] Advances in microfluidics,[361] sensor arrays,[363] and signal processing algorithms[364] could enable the development of these multiplexed systems, expanding the applications of electrochemical sensors in food safety monitoring.

Commercialization and Regulatory Approvals: finally, one of the biggest challenges for the widespread adoption of electrochemical nanobiosensors is the commercialization process, including obtaining regulatory approvals. For these sensors to be accepted by regulatory bodies, they must meet stringent requirements for accuracy, reliability, and reproducibility. Additionally, manufacturers must address issues related to production scalability, cost-efficiency, and users training. Ongoing collaboration between researchers, industry

stakeholders, and regulatory agencies will be crucial to ensure that electrochemical nanobiosensors can be effectively deployed in the real world.

CONCLUSIONS AND PERSPECTIVE

Herein we have revised the types and mechanisms of biosensors based on the biorecognition elements (enzymes, antibodies, cells, aptamers, and nucleic acids), the transducers (electrochemical, optical, piezoelectric, magnetoelastic, FET, calorimetric, and acoustic), and the applied metallic and carbon-based (graphene and CNTs) nanomaterials. The application of such nanomaterials in biosensors led the field to a rapid growth in the recent decade due to the employment of new biorecognition elements and transducers, progress in miniaturization, design and manufacture of nanostructured devices at micro–level, besides the new techniques of nanomaterials synthesis, bringing together life and physical scientists with engineers and further technology professionals. The sensing technology in general has become more versatile, robust, and dynamic with the introduction of the nanoscience, improving significantly the transduction mechanisms with greater sensitivity, quicker detection, shorter response time, and better reproducibility by the application of different nanomaterials, each one with its own characteristics within biosensors. Electrochemical biosensors are not different from that: they have much to gain in terms of sensitivity by coupling with nanomaterial science.

Besides the clear advantages of using nanostructured materials in biosensors applications, some major drawbacks unfortunately still hinder the evolution of applications for the next level. Examples of some important issues are the insufficient investigation on the sustainability of nanostructures in sensor applications and in the fabrication of such nanostructures, and the few studies about nanomaterials toxicity that may change according to their physical properties. These limitations certainly should be better investigated and addressed during the expansion of new nanostructured materials for their use in biosensors. Still, most biosensor devices for biomedical applications require large sample volumes for detection, otherwise leading to some false-positive or false-negative results. Electrochemical nanobiosensors devices can help that since they require very low sample volumes with fast, versatile, and reliable results using simple instrumentation that even favors the point-of-care testing approach with portable devices.[133]

With that said, it is important to remind that very few biosensors have attained the commercial success at global level, besides the electrochemical glucose sensors and lateral flow pregnancy tests. Production costs of the nanostructure-based biosensors should be better revised and optimized so as affordable device costs altogether with rapid and reliable results in a user-friendly interface can lead to commercial success. For instance, nanomaterials should be incorporated in tiny “lab-on-a-biochip” devices integrating the sample handling and the multiplexed analysis. Also, electrochemical biosensors still should improve in terms of the simultaneous quantification of multiple biomarkers. New prototypes should embrace the artificial intelligence with nanotechnology for designs and fabrication. Therefore, more research should be done in this regard to turn the ongoing biosensor academic research into commercially viable prototypes by industries in the near future.[133]

Regarding to the deleterious effects of fungi and their mycotoxins, a number of detrimental health effects in humans have been reported. As the mycotoxins are secondary metabolites of fungal pathogens, they represent a diverse range of chemical structures. Most researches have focused on major incidence toxins as aflatoxins, fumonisins, trichothecenes, zearalenone, ochratoxin A, and patulin. Some mycotoxin groups even contain structurally related analogs. Afterwards, a suitable combination of biorecognition element, bio-fabrication, and compatible transducers will be the solution for the successful development of efficient and robust mycotoxin biosensors. Many up-to-date developed biosensors can detect profusely only a few or particular mycotoxins, while the future trend is most certainly the development of the multiplexed biosensing-based detection. Upcoming methods for biosensor developments seem to integrate multiple detection technologies with application of genetically engineered microbes. Evaluation of biological contaminants related to emerging diseases to avoid chronic illness with high mortality is one feasible possibility of future direction of toxins investigations.[365]

In recent years, the mycotoxin biosensors development emerged as a field of intense research due to their capacity of specifically detecting such toxic molecules in very low concentrations even in complex sample matrices. The combination of nanomaterials with biomolecules to fabricate single molecule multifunctional nanocomposites, nanoelectrodes, and nanofilms seem to be a trend to be explored. However, the single-molecule biosensors with high throughput assay shall be also focused on. Metabolite biosensors with multiple targets, mechanisms of action, and applications in metabolic engineering are an upcoming subject of research too. Ultimately, considering the further advance of nanomaterials science, the imminent research theme in biosensors is expected to be mostly focused on the transducer technology, the sample matrix treatment, and the development of new biorecognition sensing elements.[365]

Conflicts of interest

The authors declare no conflicts of any possible nature.

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