



# Recent progress and future perspectives of polydopamine nanofilms toward functional electrochemical sensors

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## Abstract

Since its discovery in 2007, polydopamine nanofilms have been widely used in many areas for surface functionalization. The simple and low-cost preparation method of the nanofilms with tunable thickness can incorporate amine and oxygen-rich chemical groups in virtually any interface. The remarkable advantages of this route have been successfully used in the field of electrochemical sensors. The self-adhesive properties of polydopamine are used to attach nanomaterials onto the electrode's surface and add chemical groups that can be explored to immobilize recognizing species for the development of biosensors. Thus, the combination of 2D materials, nanoparticles, and other materials with polydopamine has been successfully demonstrated to improve the selectivity and sensitivity of electrochemical sensors. In this review, we highlight some interesting properties of polydopamine and some applications where polydopamine plays an important role in the field of electrochemical sensors.

**Keywords** Polydopamine · Surface functionalization · Electrochemical sensors · Nanomaterials · Electrochemical devices

## Polydopamine—brief introduction

Surface functionalization plays a key role in developing electrochemical devices with improved sensitivity, selectivity, and stability. To attach nanomaterials and/or macromolecules to the interface, a proper chemical linker (polymer, molecule, and/or macromolecule) is often added to anchor the desired substance. Depending on the material that will be functionalized, i.e., carbon and gold, which are the most used in electrochemical biosensors, there are plenty of routes available. For instance, gold interfaces have been explored using the well-known thiol chemistry where it is possible to tune the thickness of the self-assembled monolayer. The plethora of commercial thiol-based molecules enables

surface modification with many different chemical groups. In the case of carbon surfaces, oxidation by chemical and electrochemical routes generates oxygen-rich functionalities that can be explored along with  $\pi$ - $\pi$  stacking. The type of material and its surface chemistry are always considered when selecting the functionalization protocol, making it difficult and challenging to establish a universal route for electrode modification.

In 2007, Lee et al. [1] reported the preparation of a simple, fast, and versatile multifunctional coating on many different types of surfaces, independent of their surface chemistry. The authors took as inspiration the facility of mussels to adhere to all kinds of surfaces in water, including adhesion-resistant materials such as poly(tetrafluoroethylene) (PTFE). By considering that the interface of the plaque structure of the mussel and the substrate is rich in 3,4-dihydroxy-L-phenylalanine (DOPA) and lysine amino acids, the authors hypothesized that the molecule dopamine could be used for the formation of a thin and adherent film since it contains both catechol (DOPA) and amine (lysine) residues. The polymerization occurs in a buffered solution at pH 8.5 in the presence of dopamine and all objects immersed in this solution are functionalized by a thin film of polydopamine (PDA). The thickness of the nanofilm can be tuned roughly from 5 to 50 nm by controlling polymerization time. Importantly, the variation in the atomic composition of the coating

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was minimal for different substrates, thus suggesting the universal character of the nanofilm. In addition, catechol/quinone and amino groups can be used to attach redox mediators and many other substances on the interface.

After the work reported by Lee et al. [1], we noticed a rapidly increasing number of publications in many areas using self-polymerization of dopamine [2–5]. It is important to highlight that polymerization of molecules containing catechol moieties for electrocatalytic detection of biomolecules has been reported since the 1990s [6]. However, in electrochemical routes, the polymer is only formed at the interface electrode-solution, thus requiring a conductive material and a more complicated experimental setup to conduct the polymerization. On the contrary, the self-polymerization method occurs in the bulk solution and can provide nanometer-thick coatings on semiconductive, insulating, and conductive materials with no additional electric power needed. We attributed this route to a paradigm shift in surface science. Since PDA adheres onto all kinds of surfaces, the only point to be addressed is how to take advantage of its functional groups to explore this unique and versatile functionalization route.

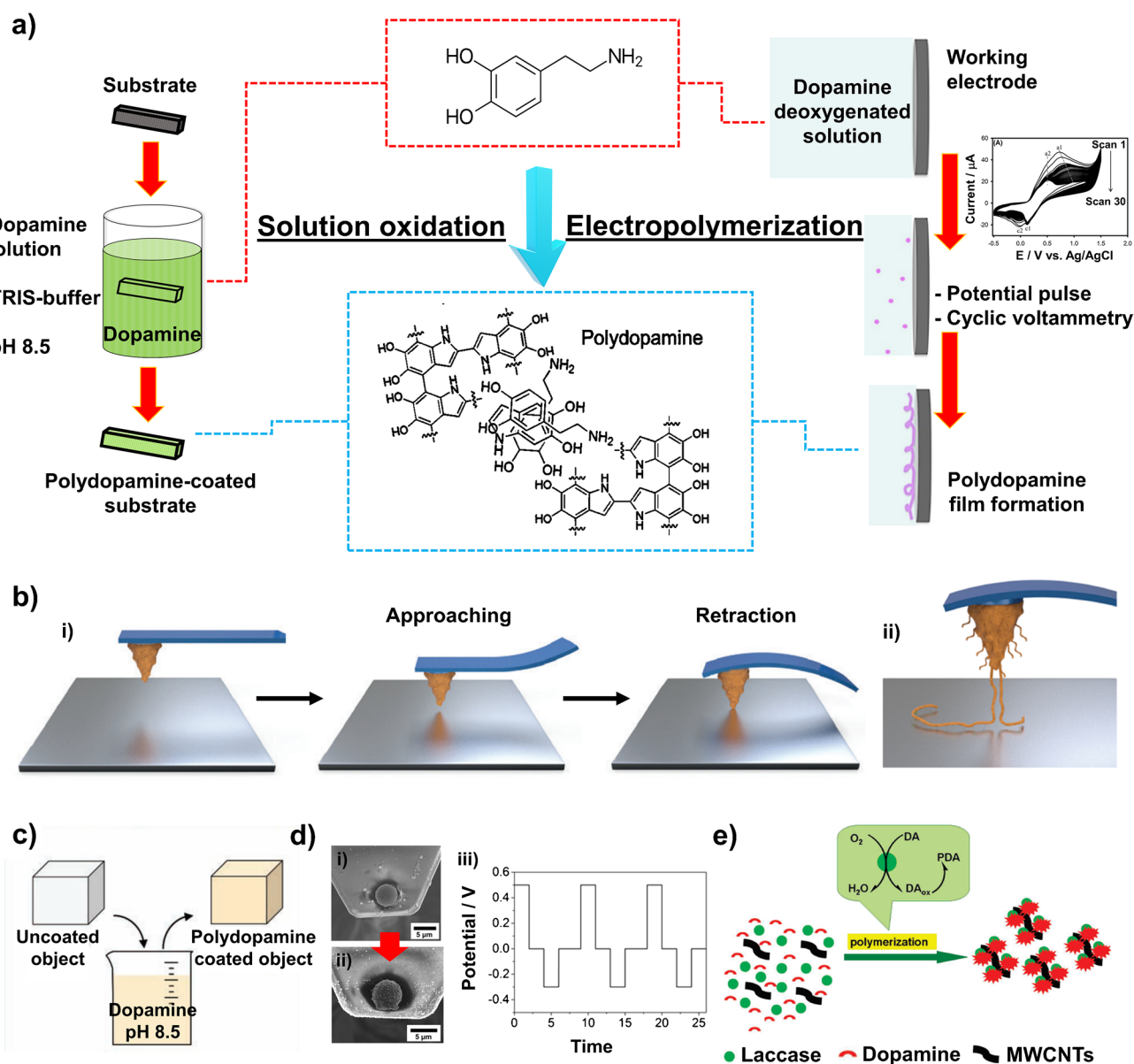
In this review, we will highlight the most recent works where PDA plays a pivotal role in the preparation of electrochemical sensors and biosensors. The synergic effect of PDA and different nanomaterials (2D materials, nanotubes, and nanoparticles) toward electrochemical sensing will be discussed. In addition, the combination of PDA along with other polymers will be highlighted. Finally, we will discuss some future applications and conclude the impact of PDA in the field of electrochemical sensors.

## Mechanism—methods of synthesis

Although PDA covers a wide range of applications and has an increasing number of publications involving its use, there is still no consensus regarding its formation mechanism and final structure [2, 5, 7, 8], mainly due to its chemical heterogeneity [9] and insoluble nature [10]. In general, it is well accepted that in the early stages of its formation, there is a process of autoxidation of dopamine leading to the formation of dopamine quinone that later undergoes a cyclization process to form 5,6-dihydroxyindole (DHI) considered to be the main precursor of PDA [1, 11, 12]. However, different studies have already observed the presence of other intermediates such as non-cyclized dopamine derivatives, indicating that conversion to DHI does not occur completely [13]. In addition, the presence of derivatives from the degradation of catecholic rings generating pyrrole with carboxylic acid in the final structure has already been observed [14, 15]. In fact, considering the self-polymerization method (solution oxidation) of PDA film formation, the change in conditions

such as type of buffer solution and oxidizing agent used results in different final structures obtained. However, regardless of the conditions, the formed film is commonly called as PDA. Regarding its final structure, although the material has been called “poly” dopamine since its discovery, there was not any evidence definitely indicating this characteristic, and different works proposed different structures such as eumelanin-like structure [2], noncovalent aggregates [16], linear-chain [10, 13], and a combination of covalent and noncovalent dopamine<sub>2</sub>/DHI assembly [17]. Figure 1a displays a scheme representing the formation of polydopamine from dopamine solution through two different approaches. However, more recently, this long-lasting debate seemed to get closer to an end. In a recently published work, Delparastan et al. [10] employed single-molecule force spectroscopy (SMFS), a very effective technique to study interactions at a molecular level, to demonstrate that PDA is composed of high-molecular-weight polymer chains with covalently bonded subunits. In an interesting approach, the authors modified a cantilever tip with PDA, approached the tip to an oxide surface, and observed that its retraction exhibited remarkable features of a polymeric material (Fig. 1bi), giving the first direct evidence of the polymeric nature of PDA (Fig. 1bii). Considering the above-mentioned questions, in spite of the still existing uncertainties with relation to its final structure and formation mechanism, methods of synthesis of PDA films are, in general, well established, and they can be formed from solution oxidation, electropolymerization, or enzymatic oxidation.

In the most widely used method, i.e., solution oxidation (Fig. 1c), a dopamine hydrochloride solution is prepared under alkaline conditions. In most works, a concentration of 2 g L<sup>-1</sup> of dopamine hydrochloride in a TRIS buffer solution at pH 8.5 with oxygen acting as an oxidizing agent is used [18]. Under these conditions, it is described that dopamine undergoes a process of spontaneous autoxidation [1, 9, 19]. Then, a surface can be modified by dipping into or depositing the solution, and the thickness can be controlled according to polymerization time [19, 20]. For such described conditions, thicknesses between 50 and 70 nm can be obtained after 20 h of deposition [21, 22]. In fact, with regard to the solution oxidation method, the change of conditions such as the initial dopamine concentration, the oxidizing agent, the pH, and the buffer solution used play a crucial role in the formation kinetics and in the final thickness of the PDA film [20, 21]. As indicated in previous works, the increase in dopamine concentration leads to a higher final thickness for the PDA film. Similarly, it was observed that the final thickness follows an increasing trend with increasing pH between 5 and 8.5, reaching a plateau from this last value [20]. Another important factor to be mentioned is that the oxidizing agent also influences the formation of the PDA film. From the use of dissolved oxygen, for example, the



**Fig. 1** a Scheme representing the formation of polydopamine through solution oxidation and electropolymerization. Reprinted with permission from Hong et al. [17]. Copyright (2012) Adv. Funct. Mater, permission from Xie et al. [37]. Copyright (2016) ACS Biomater. Sci. Eng., permission from Kanyong et al. [30]. Copyright (2016) Sensors and Actuators B. b (i) Scheme of the SMFS experiment representing a PDA-coated cantilever approaching an uncoated substrate and deflecting when in contact with it, (ii) representation of the polymeric nature of PDA when retracting the cantilever. Reprinted with permission from Delparastan et al. [10]. Copyright (2019) Angew Chem Int.

c Schematic representation of the solution oxidation method to produce PDA films. Reprinted with permission from Lee et al. [1]. Copyright (2007) Science. d Electropolymerization of PDA on Au colloidal AFM-SECM probe. (i) Bare Au probe, (ii) PDA-coated probe, (iii) potential pulses applied to produce PDA electrochemically. Reprinted with permission from Daboss et al. [32]. Copyright (2020) Anal Chem. e Enzymatic formation of PDA to cover MWCNTs. Reprinted with permission from Tan et al. [34]. Copyright (2010) The Journal of Physical Chemistry B

formation of PDA is practically not observed at pH lower than 5, whereas, when  $\text{Cu}^{2+}$  is used, PDA can be formed at pH 4.5 and, although the kinetics of formation is slower, higher thicknesses can be obtained [21]. Moreover,  $\text{Cu}^{2+}$  ions can be trapped in the PDA structure and have useful

applications such as in the electrochemical detection of uric acid without interference of ascorbic acid [23]. In addition, other oxidants have already been used such as potassium permanganate ( $\text{KMnO}_4$ ) [24], Ce (IV) or Fe(III) [25], and sodium periodate ( $\text{NaIO}_4$ ) [26].

Alternatively, the electropolymerization route can be adopted when the surface is electrically conductive [27, 28]. It is well known that electrochemical oxidation products of catecholamines (such as dopamine) can be polymerized, leading to the formation of insulating films on the electrodes [29]. Different works aiming the formation of PDA through this method employed different electrochemical techniques to promote it, for instance, consecutive cyclic voltammeteries in a given range of potential (e.g.,  $-0.5$  V to  $+1.5$  V vs. Ag/AgCl in Britton-Robinson buffer solution at pH 7 [30],  $-0.7$  V to  $+0.7$  V vs. SCE in PBS buffer at pH 7.2 [31], and  $+0.65$  V to  $-0.6$  V vs. Ag/AgCl in phosphate buffer at pH 6.5) [27] or potential pulse sequences in deoxygenated dopamine solution (e.g.,  $+0.5$  V for 2 s,  $0.0$  V for 2 s,  $-0.3$  V for 2 s, and  $0.0$  V vs. Ag/AgCl for 3 s in PBS buffer at pH 7.4) [32]. Figure 1di–ii depict an Au-coated atomic-force microscopy–scanning electrochemical microscopy (AFM-SECM) probe with PDA before and after electropolymerization. Figure 1diii shows pulse sequences applied to produce the PDA film. Through the electropolymerization route, the thickness of the film can be controlled according to the number of potential pulse cycles or voltammetric scans applied. A major drawback of the electropolymerization route, unlike solution oxidation, is that it can be applied only on electrically conductive materials. However, it allows the film to be formed in a more controlled manner and is spatially selective [27].

Complementarily, PDA can also be prepared through an enzymatic method based on the biosynthesis of eumelanin and pheomelanin, featuring an environment-friendly procedure as described [2, 29, 33]. However, due to the utilization of enzymes, this method typically presents a higher cost. In a previous work, the authors used the enzyme laccase to promote the oxidation of the diphenolic structure of dopamine (Fig. 1e). The oxidated species can be polymerized to form PDA on multi-walled carbon nanotubes (MWCNTs) in acetate buffer at pH 6 [34]. Using this method, after the polymerization, the enzyme was entrapped in the PDA structure allowing further application on the development of a biosensor for the detection of hydroquinone and glucose. Laccase was also incorporated during electropolymerization of PDA for the development of phenolic electrochemical sensors [35]. In addition, urease has also been demonstrated to promote PDA polymerization [36].

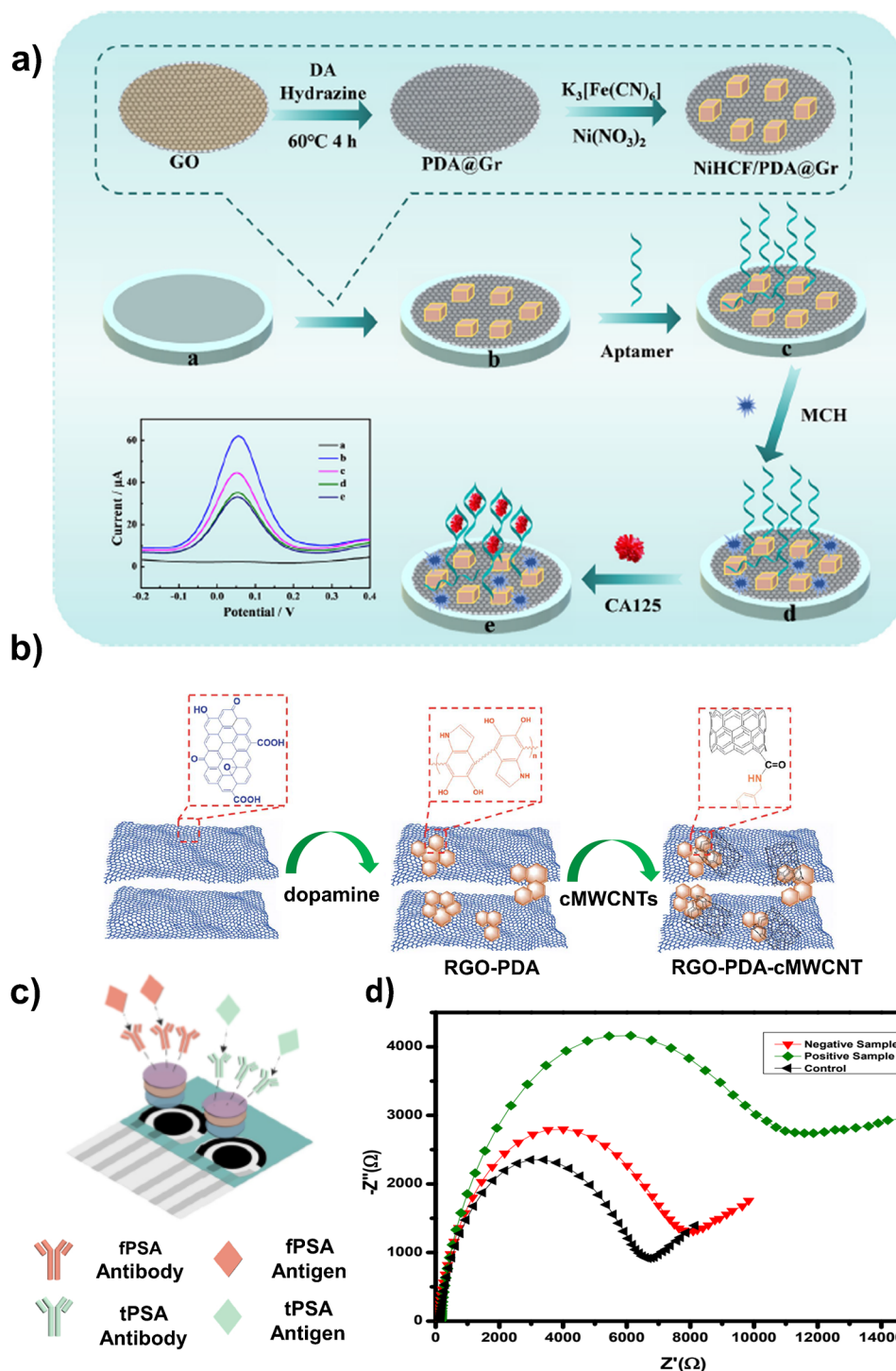
## 2D materials and PDA

Two-dimensional materials have been contributing significantly to improving the sensitivity of electrochemical biosensors due to their tunable conductivity and high surface area, where the latter is attributed to the basal plane rather than the edges. Thus, the basal plane offers a platform for

functionalization aiming at the improvement of the sensitivity of electrochemical sensors. In this scenario, graphene oxide is one of the most used materials for electrochemical application in the field of sensors due to the presence of oxygen-rich functionalities. The many different types of functional groups open a plethora of functionalization routes toward the development of electrochemical devices [38]. For instance, biological recognizing elements, redox mediators, nanoparticles, and electrocatalysts have been successfully attached to the surface of the 2D materials. However, one aspect that should be considered when using graphene oxide for electrochemical applications is the poor conductivity of the material [39]. This issue can be particularly circumvented by using chemical and electrochemical routes to reduce the material and restore the  $sp^2$  bonds that are responsible for electrical conductivity. Thus, some of the functional groups that are important to develop the sensors or biosensors are removed to minimize charge transfer resistance, which ultimately decrease the sensitivity of the sensors. Since PDA can be formed on any type of surface, the combination of 2D materials, especially graphene, and PDA has been recently explored to prepare a variety of electrochemical sensors and biosensors.

The preparation of electrochemical biosensors using graphene oxide and PDA was demonstrated recently to accurately detect biomarkers. The development of electrochemical biosensors that allows early-stage diagnosis is important to provide the best chance for a successful treatment to patients. For example, Zhang et al. [40] reported the fabrication of an electrochemical aptasensor to detect carbohydrate antigen 125 (CA125), which is a serum marker for endometriosis. The electrochemical biosensor is a potential alternative to minimize the limitations observed in conventional tests, for instance, complicated testing process, expensive instrumentation, and time-consuming analysis. Figure 2a shows a scheme of the main fabrication steps of the electrochemical aptasensor. PDA plays a pivotal role in the fabrication of the proposed electrochemical biosensors; it covers the surface of rGO and provides functional groups to immobilize the aptamer that will ultimately recognize the targeted analyte. In addition, the high surface area of rGO was used to deposit nickel hexacyanoferrate nanocubes (NiHCF), which work as a stable redox mediator. The presence of the target analyte promotes a decrease in the analytical signal observed in cyclic voltammetric experiments. By using electrochemical impedance spectroscopy (EIS), the authors achieved a linear range of  $1.0 \times 10^{-13}$  to  $1.0 \times 10^{-6}$  g mL<sup>-1</sup> and a limit of detection of  $0.076$  pg mL<sup>-1</sup>. The feasibility and applicability of the electrochemical biosensor were investigated using human serum samples and the results presented were very promising. The recovery studies were obtained from 98.1 to 103.5%, indicating that the proposed biosensor is accurate and reliable. However, among the main issues in the field is

**Fig. 2** **a** Schematic figure illustrating the main fabrication steps of the electrochemical aptasensor to detect CA125. Reprinted with permission from Zhang et al. [40]. Copyright (2022) Journal of Electroanalytical Chemistry. **b** Functionalization of graphene oxide with PDA and carbon nanotubes for electrochemical detection of catechol and hydroquinone. Reprinted with permission from Chang et al. [53]. Copyright (2021) RSC Adv. **c** Schematic illustration of the recognition layer deposited on screen-printed electrodes. Reprinted with permission from Li et al. [57]. Copyright (2022) Sensors and Actuators B: Chemical. **d** Nyquist plot for negative and positive nasopharyngeal swab samples. Reprinted with permission from Yadav et al. [59]. Copyright (2022) J Mater Chem



still the lack of data regarding long-term stability, which can limit the translation from laboratory to market.

PDA-functionalized graphene-based materials have also been recently employed to prepare electrochemical biosensors to detect carcinoembryonic antigens (CEA) [41, 42]. CEA is an acidic glycoprotein with human embryonic

antigenic properties that is often used as a biomarker to detect gastrointestinal malignancies, breast cancer, lung cancer, and other malignant tumors [43, 44]. Yang et al. [41] reported the use of two different nanoparticles, i.e., Ag and Au, to decorate the PDA-rGO. The Au nanoparticles were used to adsorb CEA antibody while Ag nanoparticles

were employed to deliver a faradaic current at the interface that can be monitored for analytical applications. Thus, the authors monitored the decrease of the anodic peak current as a function of the CEA concentrations and achieved a limit of detection of  $0.286 \text{ pg mL}^{-1}$ .

A combination of nanoparticles on PDA-functionalized graphene was reported to detect CEA in diluted human serum samples using an electrochemical aptasensor. The nanosheets offer a large surface area for the modification of Pd and Pt nanoparticles that are used to monitor the reactive species. One of the disadvantages of the proposed method is the need for hydroquinone and hydrogen peroxide in the supporting electrolyte. The presence of these reagents may limit some of the applications of the biosensor. In addition, the limit of detection obtained is around 1–2 orders higher when compared with the above example, indicating that the modifications done on the surface were not so effective. However, the use of aptamers represents an interesting choice for the configuration of electrochemical biosensors. In general, aptamers are more stable when compared to enzymes and other biological recognizing elements and have the potential to increase the shelf-life of the biosensor.

Despite the significant advances in developing biosensors, the use of 2D materials and PDA is majority applied to electrochemically detect organic [45–53] and inorganic compounds [31, 54] without using biological recognizing elements. For example, Chang et al. [53] reported the preparation of an electrochemical sensor to simultaneously detect hydroquinone and catechol using a nanocomposite made of reduced graphene oxide, carbon nanotubes, and PDA. Figure 2b shows the main fabrication steps of the electrochemical sensor. By using a bare glassy carbon electrode, a single peak for both compounds was obtained, making it impossible to quantify both compounds. When the nanocomposite was employed, the difference between oxidation peaks was more than 100 mV, highlighting the importance of using the nanocomposite. rGO and carbon nanotubes provide different adsorption sites that can improve the selectivity and sensitivity of the sensor. For instance, the linear range was found to be in the range of 0.5–5000  $\mu\text{M}$  and the detection limit in the order of 0.06  $\mu\text{M}$  for both compounds. The simultaneous quantification of three compounds is even more challenging but still possible. Shi et al. [49] reported the use of rGO and PDA to detect ascorbic acid, dopamine, and uric acid in aqueous solutions. The use of Au nanoparticles decorated on rGO/PDA showed high electrocatalytic activity toward the three analytes [49].

Graphene and carbon nanotubes still dominate most of the electrochemical platforms [55, 56]; however, transition metal dichalcogenides are emerging as functional electrode materials in the field of electrochemical sensors. The most recent applications are focused on detecting prostate-specific

antigens [57], cardio-selective  $\beta$ -blocker drugs [58], and SARS-CoV-2 nucleocapsid protein (N protein) [59]. Li et al. [57] reported the fabrication of electrochemical sensors using  $\text{MoS}_2$ /metallic nanoprism functionalized with PDA. The latter was added to increase the number of binding sites. The biosensors were fabricated on portable screen-printed electrodes, which represent a step toward large-scale fabrication (Fig. 2c). The analytical curve was obtained using differential pulse voltammetry (DPV), showing a wide detection range of 0.0001 to  $100 \text{ ng mL}^{-1}$  and a limit of detection of  $0.1 \text{ pg mL}^{-1}$ . However, the fabrication reported by the authors involves many steps, which may compromise scalability. On the other hand, Lee et al. [58] demonstrated  $\text{MoS}_2$  exfoliation and self-polymerization of PDA to detect cardio-selective  $\beta$ -blocker drugs using DPV. The functionalized electrode was applied to detect the analyte in pharmaceutical formulation and presented a limit of detection of  $5 \text{ nmol L}^{-1}$ .

A nanocomposite consisting of  $\text{MoS}_2$  and PDA was applied in the construction of rapid, low-cost, and sensitive electrochemical analysis to identify the SARS-CoV-2 virus efficiently [59].  $\text{MoS}_2$  surfaces possess fewer chemical alternatives for functionalization when compared to graphene oxide, where the latter has different types of oxygen-rich functionalities. Thus, the authors explored the use of PDA to add R-OH and amine groups on the surface of  $\text{MoS}_2$ . PDA is interesting because it helps with the adhesion on the electrode and offers functional groups to attach biorecognizing elements that will ultimately dictate the number of attached molecules. After immobilization of the anti-SARS-CoV-2 nucleocapsid IgG antibody (Ab), the EIS technique was employed to detect the SARS-CoV-2 nucleocapsid protein (N protein) with high sensitivity, as shown in Fig. 2d. The electrochemical biosensors showed a linear range from 10  $\text{ag mL}^{-1}$  to  $100 \text{ ng mL}^{-1}$  and limit of detection of  $2.80 \text{ ag mL}^{-1}$ . The biosensor was applied to nasopharyngeal swab specimens and the results were consistent when compared to gold standard tests. The remarkable results still need to be scrutinized by analyzing a statistically relevant number of samples.

The large surface area of 2D materials was expanded in the field of electrochemical sensors by using polydopamine to fabricate many different electrochemical sensors and biosensors. In many cases, the preparation of the sensor involves many steps that may compromise scalability. Another important aspect is related to the choice of the 2D material in terms of conductivity. It is recommended to use 2D materials with high conductivity since PDA is an organic semiconductor with limited conductivity. In fact, the thickness of PDA nanofilms must be controlled in order to guarantee the incorporation of active elements (enzymes and bioreceptors) and minimize the charge transfer resistance.

## Nanotubes

Carbon-based materials, such as carbon nanotubes (CNTs), have received increasing attention in the field of electrochemistry for the modification of bare electrodes, due to their large surface areas and remarkable electrocatalytic properties. CNTs are sheets of graphene rolled together, found as single-layer CNTs (SWCNTs) or multi-layer CNTs (MWCNTs). It is composed mainly of carbon atoms with sp<sup>2</sup> hybridization, hence the high conductivity and surface area [60]. However, the lack of functional groups on pristine nanotubes limits some of the applications in the development of electrochemical sensors. Thus, PDA is a strong candidate to contribute to the functionalization of nanotubes and generate biocompatible interfaces [61]. In the literature, electrodes modified with CNTs and PDA refer to CNTs coated with PDA in which dopamine polymerization occurs by chemical or electrochemical methods. In addition, nanoparticles can be attached onto PDA to expand the properties of the electrochemical sensors in terms of biocompatibility, selectivity, and sensitivity [62].

Sabeti et al. [63] developed a simple and sensitive electrochemical sensor for morphine detection in biological fluids. The sensor is a glassy carbon electrode that has been modified with MWCNTs and electropolymerized PDA. According to the authors, the modification of MWCNTs and PDA promoted a decrease in the charge transfer resistance. Thus, the modification successfully improved the electrochemical activity for morphine oxidation when compared to other electrochemical sensors, showing a low detection limit (0.06  $\mu\text{M}$ ) and remarkable selectivity. In another similar study, a glassy carbon electrode was modified with MWCNTs and electropolymerized PDA on CNTs for the detection of ciprofloxacin in human urine and plasma samples [64]. The nanostructured interface used for the electrooxidation of ciprofloxacin presented a low detection limit (0.04  $\mu\text{M}$ ) and selectivity. In addition, stability tests were evaluated and the anodic currents kept 94.3% of its initial value after 1 month of storage, thus indicating acceptable stability.

PDA also plays an important role in the development of electrochemical biosensors. For example, a commercial glucose sensor typically uses the enzyme glucose oxidase (GOx) and electron transfer mediators based on iron and ruthenium. However, since GOx is sensitive to oxygen, some studies focused on the use of the O<sub>2</sub>-insensitive glucose dehydrogenase (GDH) enzyme, which should be employed in the presence of Ru(dmo-bpy)<sub>2</sub> Cl<sub>2</sub> as a redox mediator. The latter does not adhere well to the electrode surfaces, so efforts have been made to improve such fixation. Thus, Jeon's group [65] developed a screen-printed carbon electrode modified with a PDA-MWCNT suspension to effectively attach the GDH enzyme and promote glucose detection, with dopamine being

polymerized by the solution oxidation method. The modification promoted better fixation of the enzyme and mediator due to the presence of amine and catechol groups present in the PDA structure. The excellent attachment of both mediator and enzyme on the interface was confirmed by the increase of current as the concentration of glucose was also increased. Thus, the authors addressed some issues in the development of glucose biosensors by using PDA to attach the functional chemical compounds and minimize alterations in the response due to the presence of dissolved O<sub>2</sub>.

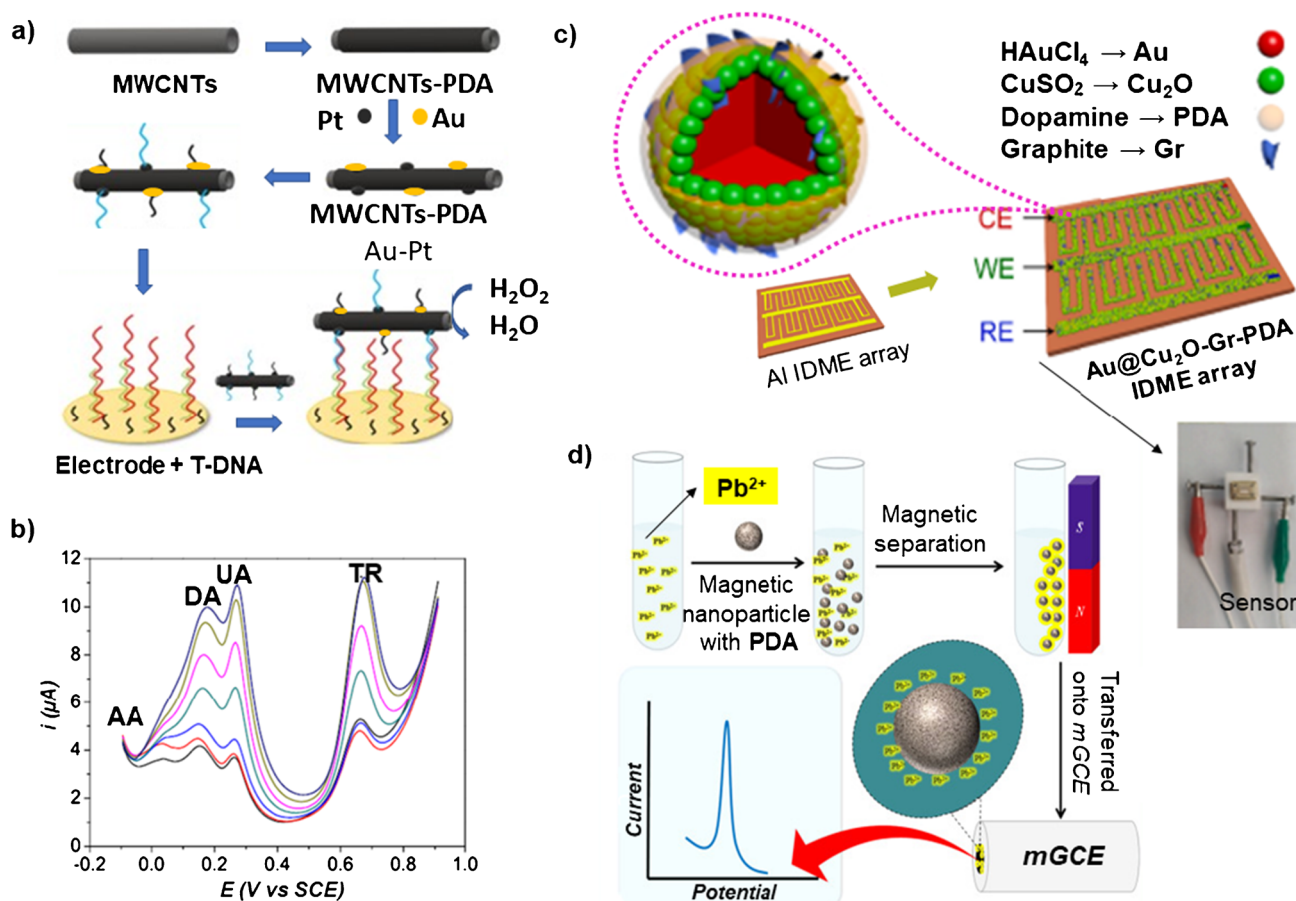
One of the goals in the direct electrochemical detection of organic compounds, e.g., catechol, is to improve the sensitivity of conventional carbon electrodes. Thus, one of the alternatives to improve the sensitivity consists of modifying the electrodes with high loadings of CNTs. However, CNTs may leach from the surface when higher loadings are used for surface modification. To circumvent this issue, Wang and colleagues [66] used the adhesive properties of PDA to fix two layers of CNTs on the working electrode, thus obtaining a sandwich-type of sensor. The glassy carbon electrode was first modified with a layer of MWCNTs, followed by a layer of PDA and  $\beta$ -cyclodextrin ( $\beta$ -CD) and a second layer of MWCNTs. In this case, PDA was obtained by polymerization using ultraviolet irradiation. PDA was important to promote the adhesion of MWCNT bilayer. The successful role of PDA was directly observed in the peak currents obtained in the presence of a single- and double-layer MWCNT film; the latter was twice higher than the former. The presence of  $\beta$ -CD was also important to interact with catechol groups. The authors achieved one of the lowest detection limits in the literature 0.04  $\mu\text{M}$  in comparison with other works that employed carbon nanotubes.

To further improve the sensitivity and detection level of modified electrochemical sensors with CNTs and PDA, the incorporation of nanoparticles and ions has been used as a strategy for signal amplification of the modified sensors. For example, nanocomposites containing nanoparticles can improve electron transfer and increase the number of active sites [67, 68]. Gold nanoparticles (AuNPs) are the most used due to their advantages, such as simple surface modification, electrocatalytic properties, and biocompatibility [69].

DNA detection is extremely important for monitoring genetic cultures, diagnosing, tracking diseases, and detecting pathogens. Many methods are used for DNA analysis, the most common being DNA sequencing, Raman scattering, fluorescence, and electrochemical analysis [70, 71]. The latter has gained attention for its quick response and portability. Thus, modified electrodes containing CNTs and PDA were described to improve the performance of electrochemical devices. Han and colleagues [62] developed a modified electrochemical biosensor with SWCNTs, and PDA nanocomposites designed with AuNPs for DNA detection. First,

dopamine was electropolymerized on the gold electrode and the DNA probe was bonded to amine groups of PDA by the Schiff base reaction. After hybridization of the probe DNA with the target, the AuNPs functionalized with a duad-DNA (reporter and linker) were introduced in the sensing interface via DNA hybridization. Next, end-modified SWCNTs with DNA were attached to the interface of the AuNPs via linker-DNA hybridization. The resulting interface is a three-dimensional (3D) urchinlike nanocluster that shows remarkable electrochemical sensing features. For instance, the high electron transfer between AuNPs-SWCNTs and the gold electrode enabled high sensitivity and low detection limit of 5.2 fM. Furthermore, the good performance of the biosensor is also attributed to PDA that ensured biocompatibility along with AuNPs.

In this same line of DNA detection with electrochemical electrodes, Zhao et al. [61] made a sandwich sensor for circulating tumor DNA analysis (ctDNA) related to triple-negative breast cancer. They employed MWCNTs coated with chemically polymerized PDA and decorated with Au and Pt nanoparticles for the anchoring and hybridization of the DNA strands (Fig. 3a). The sensor showed a low detection limit of  $5.0 \times 10^{-16}$  M and unprecedented selectivity for incompatible DNA sequences. The remarkable electrochemical performance was attributed mainly due to the PDA-coated MWCNTs, offering a large functionalized surface area for the attachment of the nanoparticles. Furthermore, the excellent catalytic activity for  $H_2O_2$  reduction enabled the obtention of current levels to detect the target DNA and discriminate DNAs of mismatched bases.



**Fig. 3** **a** Schematic illustration of the fabrication of the multilayered MWCNTs coated with chemically polymerized PDA and decorated with Au and Pt nanoparticles for the anchoring and hybridization of the DNA strands. Reprinted with permission from Zhao et al. [61]. Copyright (2021) Microchemical Journal. **b** Differential pulse voltammetry measured (DPV) at pH 6.0 in PBS containing 40  $\mu$ M of each analyte (first DPV), subsequent additions of 80, 120  $\mu$ M AA (subsequent two DPVs), and subsequent simultaneous additions of 160, 200, 240, and 280  $\mu$ M AA and 80, 120, 160, and 200 of each

DA, UA, and TR (subsequent four DPVs). Reprinted with permission from Arroquia et al. [79]. Copyright (2020) Materials Science & Engineering C. **c** Schematic illustration of the core-shell Au@Cu<sub>2</sub>O-graphene-polydopamine interdigitated microelectrode array sensor. Reprinted with permission from Liu et al. [83]. Copyright (2021) Sensors and Actuators: B: Chemical. **d** Schematic illustration of Pb<sup>2+</sup> target capture, isolation, and detection with magnetic core-shell nanoparticle com PDA. Reprinted with permission from Wang et al. [84]. Copyright (2020) Journal of Electroanalytical Chemistry



In addition to sensory analysis, electrodes modified with nanotubes and PDA can also serve as catalysts to improve the electrochemical oxidation of monosaccharides in implantable fuel cells. Li and colleagues [72] developed a PDA-coated SWCNT-modified graphite electrode for ascorbate monosaccharide oxidation and oxygen reduction for enzyme-free implantable fuel cells. By exploring the combination of SWCNTs and PDA, the short-circuit current density ( $i_{sc}$ ) and maximum power density ( $P_{max}$ ) showed a 5.2-fold and 12.7-fold increase, respectively, when compared to electrodes modified with SWCNTs only. The hybrid SWCNTs-PDA can act simultaneously as an anodic and cathodic catalyst for ascorbate monosaccharides–glucose (AA-Glu) oxidation and  $O_2$  reduction.

We believe that the functionalization of carbon nanotubes with PDA has enormous potential to be used in direct electron transfer studies. Enzymes can be immobilized on functionalized nanotubes for many bioelectrocatalytic studies. Another interesting feature is functionalization to improve the dispersion of carbon nanotubes in water. Functional inks made of carbon nanomaterials and PDA were not explored yet and can contribute to the field of flexible electronics.

## Nanoparticles

Metallic nanoparticles have a 35 to 45% higher surface area-to-volume ratio compared to larger particles, and this guarantees their excellent intrinsic properties such as high surface reactivity with other species and biocompatibility, making them very attractive for diagnostics, drug delivery, cosmetics, sensors, and other areas [73, 74]. In electrochemical sensors, nanoparticles are used for the immobilization of biological components and for signal amplification due to the large surface area. However, for better results, it is necessary that they are homogeneously dispersed over the electrodes, so PDA nanofilms have been recently used to incorporate nanoparticles on the interface of electrochemical sensors. The catechol and amine groups of PDA are capable of reducing the metallic ions forming metallic nanoparticles that can homogeneously distribute on the surface of the nanofilm. Thus, the resulting nanostructured surface contributes to improving the electrochemical and biocompatibility properties of the electrode [75].

Biosensors have been widely used for the determination of triglycerides; however, many methods have their limitations in relation to the electrode assembly. Thus, in order to expand the use of electrochemical biosensors, less sophisticated and cost-effective synthesis procedures are required [76]. Zhang and collaborators [77] developed a simple route to prepare an electrochemical biosensor coated with PDA and AuNPs for triglyceride detection. In brief, they

polymerized dopamine with AuNPs on the ITO electrode and then immobilized the enzyme lipase on the interface. The electrode proved to be efficient for detecting tributyrin with a detection limit of up to  $0.84 \text{ mg dL}^{-1}$ . The low limit of detection was attributed to the excellent association of materials that facilitate charge transfer. The specificity of the electrode was also evaluated, and the results indicated the minimal influence of other compounds. Thus, the electrode modified with PDA was demonstrated to be efficient for bio-sensing of triglycerides based on other biosensors found in the literature that use the lipase enzyme.

The simultaneous determination of ascorbic acid (AA), uric acid (UA), and dopamine (DA) is extremely important for disease control. Due to the redox properties of these molecules, the use of electrochemical sensors has been explored because of their relatively low cost and fast response when compared to chromatographic methods. However, the simultaneous detection using conventional electrodes can suffer from fouling issues that negatively impact reproducibility. Thus, conventional electrodes can be modified with nanofilms to avoid problems associated with fouling and also increase the surface area. Li and colleagues [78] modified a gold electrode with PDA nanospheres, made by chemical routes decorated with silver nanocubes to improve DA and AU detection in the presence of AA. After surface modification, the DA and UA oxidation peaks increased and it was possible to measure such peaks even in the presence of AA. Arroquia et al. [79] pushed the limits a little bit further and simultaneously detected AA, DA, UA, and tryptophan (TR) using a carbon electrode modified with PDA nanospheres decorated with gold. At pH 6.0, the electrodes simultaneously detected the 4 molecules with high stability and reproducibility (Fig. 3b). Thus, functional groups incorporated on the surface of the electrochemical sensors by PDA not only contribute to signal amplification but also minimize surface fouling.

Another interesting aspect of PDA is its ability to promote a tunable coating on nanoparticles. Thus, core–shell structures using PDA as the coating materials can improve biocompatibility and stability to the dispersions of nanoparticles, and increase the catalytic activity of electrochemical sensors. Khan and collaborators [47] synthesized core–shell nanoparticles made of PDA@SiO<sub>2</sub> and incorporated Au nanoparticles into them. The PDA@SiO<sub>2</sub> nanoparticles decorated with Au were added to an rGO-modified glassy carbon electrode for the detection of cefotaxime (antibiotic) in pharmaceutical samples. The presence of PDA nanocoatings resulted in a homogeneous distribution of Au nanoparticles on PDA@SiO<sub>2</sub>, which was important to facilitate electron transfer and increase electrocatalytic activity. The electrode showed a detection limit of  $1.0 \times 10^{-10} \text{ M}$  for cefotaxime, which is an interesting value when compared to other electrochemical sensors and other analytical methods.

Another remarkable example of the use of nanoparticles and PDA is in the fabrication of non-enzymatic electrochemical sensors for glucose, once enzyme-based electrodes have some disadvantages such as complicated enzyme application methods, long-term instability, and high cost [80]. Thus, Zhai and collaborators [81] developed a non-enzymatic electrochemical sensor for glucose by modifying a glassy carbon electrode with core-shell structures of nanosheets of metal-organic frameworks (MOF) (based on N, N-dimethylformamide (DMF) and cobalt), coated with PDA and decorated with Ag nanoparticles. The PDA-coated interface prepared using solution oxidation promoted the reduction of  $\text{Ag}^+$  ions and improved uniformity, dispersibility, and conductivity of the Ag nanoparticles without the presence of reducing agents. The non-enzymatic sensor showed good performance for the electrocatalytic oxidation of glucose, due to the synergistic effect between MOF and Ag nanoparticles. The sensor presented a wide linear range from 1  $\mu\text{M}$  to 2 mM for glucose, in addition to good selectivity and long-term stability.

The development of electrochemical devices for the agricultural field has recently shown its importance for monitoring the health of plants and leaves [82]. Salicylic acid (SA), for example, plays an important role in plants, and changes in its concentration may indicate levels of environmental adaptability and the pathological state of the plant. However, the *in situ* and real-time analysis of this component is very little explored to evaluate the conditions of the plant. Liu et al. [83] developed an aluminum (Al) interdigitated electrochemical sensor, modified with Au and Cu core-shell structures, coated with PDA and graphene sheets for the detection of SA. The core-shell, graphene, and PDA nanostructures were densely packed on the Al electrodes using the electrodeposition method with different potentials (Fig. 3c). The authors explored the well-known biocompatibility properties of PDA and noticed a better distribution of nanoparticles and graphene sheets on the interface. For example, catechol moieties of PDA can promote  $\pi$ - $\pi$  interaction with graphene in the adsorption process. The sensor proved to be efficient for SA detection and quantification due to the synergistic electrocatalytic effect of the electrode modification and the compact array of nanoparticles. The sensors presented a linear concentration range of 0.01 to 100  $\mu\text{M}$  for SA and a limit of detection of 1.16 nM. Finally, the geometry of the electrode was found to be suitable for attachment onto plant tissues, especially for the *in situ* detection of SA in leaves.

Another environmental analysis was done using a glassy carbon electrode modified with metallic core-shell structures of iron oxide ( $\text{Fe}_3\text{O}_4$ ) coated with PDA and manganese dioxide ( $\text{MnO}_2$ ) for detection of lead (Pb) in water [84]. The authors employed a magnetic composite

to increase the adsorption capacity; however, bare  $\text{MnO}_2$  particles can aggregate during the analysis. Thus, by coating the iron nanoparticles with PDA, one can improve the colloidal stability of the material for the analysis. In their study, the high adsorption capacity of  $\text{MnO}_2$  shell was simply introduced to the surface of PDA due to the redox activity between PDA and  $\text{KMnO}_4$ . The innovative aspect of this work is that the authors first used metallic structures to capture Pb and then modified the electrode for the detection using DPV at a potential of  $-0.6$  V (versus saturated calomel electrode) (Fig. 3d). The proposed sensor presented an excellent performance in sensitivity due to the high adsorption capacity of  $\text{MnO}_2$ ; the amount of charge of the prepared electrode is significantly increased for the capture of Pb, besides being a very attractive way to detect heavy metals due to the magnetic property of the composite.

PDA offers a biocompatible layer to functionalize metallic and inorganic nanoparticles, as demonstrated above. However, biofouling issues that may compromise the performance of the biosensors are not studied in detail. Additional functionalization may be required to avoid such issues that negatively impact the sensitivity and selectivity of the sensors. For example, proteins can adsorb on PDA and hinder pre-designed interactions. The redox activity of the PDA on nanoparticles must be studied in future works in the field. The catechol moiety of PDA is electroactive and can contribute to increasing the current observed on the sensor. A more detailed characterization of the nanoparticle interface is encouraged to obtain a better explanation of the events occurring on the sensing layer.

## Polydopamine and polymers

Conductive polymers can improve the sensitivity of electrodes for the detection of molecules in biological systems. For example, polypyrrole (PPY) when combined with PDA becomes a strong conductive layer due to the delocalization of electrons  $\pi$  throughout the carbon chain, in addition to PDA favoring the adhesion of PPY and increasing biocompatibility. Adeosun et al. [85] modified a glassy carbon electrode with PPY and PDA to electrochemically detect uric acid. The film was prepared by first mixing dopamine and pyrrole and then polymerizing the material at the interface. The thickness of the conductive nanofilms can be controlled by adjusting the number of cycles in the electrochemical experiment. Thickness control is important to maintain the electrocatalytic properties of the material and avoid the passivation of catalytic sites. The interaction between PPY and PDA films increased the charge transfer capacity of the glassy carbon electrode surface, leading to sensitive and selective electrochemical

analysis for uric acid oxidation. Another study involving the use of PPY and PDA electrochemically deposited on electrodes was done to record or stimulate electrophysiological signals in cells and living tissues by electrical signals [86]. The use of PPY in bioelectrodes is recognized for allowing efficient mediation of electrical signaling in biological systems, but together with PDA biocompatibility is improved and impedance is minimized due to the agile electronic exchange between layers. Thus, by the PPY/PDA modification on the gold electrode, the electrical signals from the biosensor efficiently stimulated the growth and differentiation of myoblasts and neuronal cells, and these increased further neurite outgrowth.

In certain biological environments such as blood, plasma, and urine, nonspecific biofouling in electrochemical sensors is a common issue due to the presence of numerous other species, for example, cells and proteins, that can hinder electrical signals [87, 88]. For this reason, efforts have been made to develop biosensors with anti-biofouling properties. The group of Xu et al. [89] modified a glassy carbon electrode with PDA and poly(sulfobetaine methacrylate) (PSBMA) for the detection of carcinoembryonic antigen (CEA) in complex biological media. The modification with PSBMA promoted anti-biofouling capacity to the biosensors while PDA facilitated both deposition of PSMMA and immobilization of the aptamer to recognize the probe. Thus, the biosensor quantitatively detected its target analyte in real samples due to the recognition of the specific aptamer and the superior antifouling capacity of PSBMA. The device showed high sensitivity and excellent results when compared to the standard clinical method (electrochemiluminescence). In another work, the authors used biopolymer hyaluronic acid (HA) as an anti-biofouling layer on electrodes with the aid of PDA to attach HA to the surface [90]. The modified ITO electrode showed significant resistance to the adsorption of non-specific proteins and to cell fixation, as the hydrated portions of HA prevented this adsorption. In addition, they showed excellent biocompatibility promoting scar tissue attenuation, demonstrating their potential as implantable bioelectrodes.

The functionalization of the inner channels of microfluidic devices (e.g., PMMA or PDMS) using PDA can bring remarkable features by minimizing biofouling and increasing sensitivity by immobilizing enzymes or other catalysts on the channel. At the end of the channel, the miniaturized cell can be placed without any modification on the surface of the electrodes. For conductive polymers, it is necessary to characterize the electrical properties of the materials prepared in the presence of PDA. Atomic force microscopy coupled to other techniques (kelvin probe or conductive-AFM) can help the researchers to identify the electrical properties of the conductive films containing PDA. In addition, it is

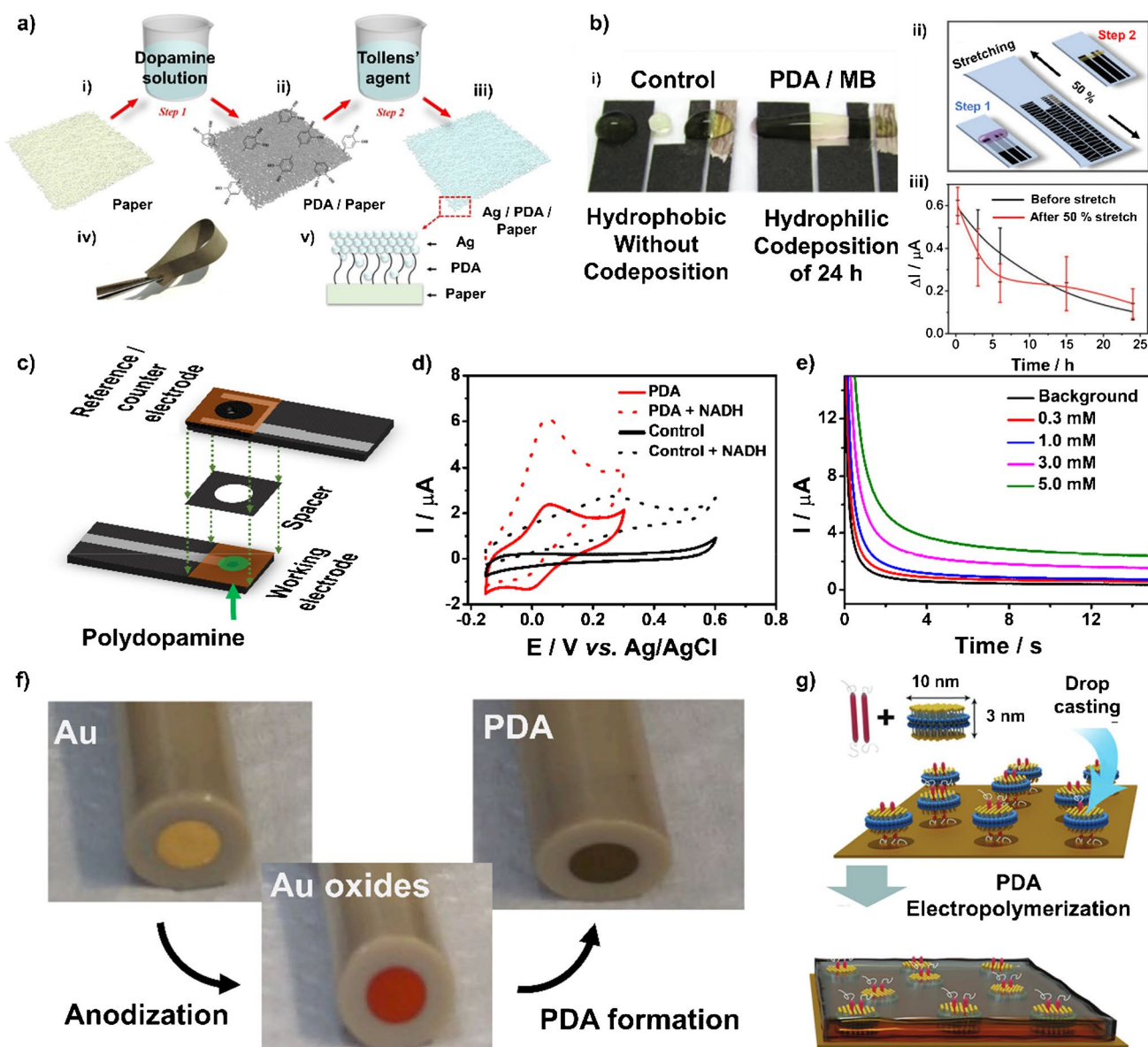
important to identify the chemical groups available in the interface for further functionalization. In this way, x-ray photoelectron spectroscopy can be used to identify elements and study the chemical environment.

## Polydopamine—paper-based and gold electrodes

During the last decades, paper-based substrates have drawn attention for electrochemical applications due to their notorious advantages such as low cost, flexibility, biodegradability, hydrophilicity, high porosity, lightweight, and high availability all over the world [91–93]. PDA in association with paper can further enhance its performance and applicability by introducing new surface functionalities and redox groups and, in some cases, improving hydrophilicity [5, 7, 94]. In this section, we will present a few works related to the association of paper and PDA. Moreover, PDA on gold electrodes will be briefly discussed.

Although paper possesses all the above-mentioned advantages, one major issue related to this material for electrochemical applications is its insulating characteristic. In order to solve this problem, Niu et al. [10] initially dipped cellulose paper into a dopamine hydrochloride solution for 24 h to form a PDA film layer over the paper [75]. The authors further took advantage of the richness of catechol groups offered by the presence of PDA to explore its reducibility and metal binding ability and promote the electroless deposition of a conductive Ag nanoparticles layer (Fig. 4ai–iii). In order to perform this, after the formation of PDA, the cellulose-based substrate was immersed in Tollens' reagent and glucose solution. The catechol groups of PDA were responsible for the reduction of  $[\text{Ag}(\text{NH}_3)_2]^+$  and anchored the generated Ag nanoparticles. Figure 4aiv and 4av show the flexibility and the structure of the developed electrode, respectively. Moreover, because of the high porosity of paper, the authors also verified the  $[\text{Ag}(\text{NH}_3)_2]^+$  could penetrate in those porous and, through its reduction, form a 3D conductive network. In this work, a high electrical conductivity of  $4058.1 \text{ S m}^{-1}$  and low sheet resistance of  $6.5 \text{ } \Omega \text{ sq}^{-1}$  were observed [75]. In fact, the electroless deposition with PDA represents an interesting approach to depositing metal onto paper and has already been applied with other materials such as copper [1].

Paper can also be directly converted into a highly conductive porous material during a temperature-induced process at a low oxygen concentration environment—pyrolysis [95–97]. The carbonaceous product of pyrolysis, commonly called pyrolyzed paper, although it is entirely converted into a conductive material, presents some drawbacks such as mechanical fragility [22, 95]. To circumvent this issue, our research group has previously reported [22] the integration



**Fig. 4** **a** (i–iii) Scheme representing paper coating with PDA and formation of Ag nanoparticles layer, (iv) picture of the developed sample, (v) scheme of the structure of the electrode. Reprinted with permission from Niu et al. [75]. Copyright (2020) ACS Sustainable Chem. **b** (i) Pictures of the device with and without PDA/MB, (ii) schematic representation of “before” and “after” stretching (step 1 and step 2, respectively) the device at 50%, (iii)  $\Delta I$  variation versus PDA/MB co-deposition time. Reprinted with permission from Damasceno et al. [22]. Copyright (2020) Adv Electron Mater. **c** Assembly of the paper-based electrochemical device in sandwich-like configuration. Working electrode (2 mm diameter) is attached to the reference/counter electrode (4 mm diameter) side of reference/counter electrode using a paper

spacer. **d** Cyclic voltammograms obtained for functionalized (PDA) and non-functionalized (control) samples in the presence and absence of 3 mM NADH. **e** Chronoamperograms obtained for a PDA-functionalized device in NADH concentrations between 0.3 and 5 mM. **c–e** Reprinted with permission from Hasimoto et al. [98]. Copyright (2021) Biopolymers. **f** Anodization of gold electrode and modification with PDA. Reprinted with permission from Sukeri et al. [99]. Copyright (2020) Electrochemistry Communications. **g** Deposition of lipid nanodiscs by drop casting on a gold surface and further formation of a PDA film through electropolymerization. Reprinted with permission from D’Alvise et al. [100]. Copyright (2020) Advanced Functional Materials

of pyrolyzed paper into an elastomeric matrix of polydimethylsiloxane (PDMS), generating a flexible and stretchable electrochemical device that can be folded, bent, twisted, and stretched at 75% without compromising significantly its electrochemical performance. However, although the

problem related to the fragile nature of pyrolyzed paper has been solved, both the carbonaceous material and the elastomer are hydrophobic preventing proper confinement of aqueous droplets. To solve this issue, the well-known hydrophilic nature of PDA was explored. The functionalization process

occurred through the solution oxidation method and was applied simultaneously to the deposition of Meldola's blue (MB) to bring electrocatalytic properties to the surface. As can be seen in Fig. 4bi, due to the hydrophilicity of the PDA film, water droplets homogeneously spread along the surface in the regions of the presence of this mussel-inspired material. This feature could further be explored to self-capture aqueous solutions in proper regions of the electrode. The so-called multifunctional cooperative nanofilms of MB + PDA on the pyrolyzed paper surface were then applied to the electrocatalysis of nicotinamide adenine dinucleotide (NADH). The oxidation peak was found at lower potentials and a linear correlation between current variation and NADH concentration. However, it is worth noting that because of the quinone/catechol redox couple, PDA could also be directly applied as a redox mediator. Moreover, the PDA film showed good adhesion properties on the surface once the device was stretched at 50% and kept a similar behavior obtained before stretching (Fig. 4bii–iii).

Besides an adhesion layer and a hydrophilic film, because of the presence of quinone/catechol redox couple, PDA on paper-based electrodes can also be directly applied as a redox mediator. The electrodes can be functionalized with PDA by using the solution oxidation method [98] in a short period of time (30 min). An advantage of the solution oxidation is that this method allows the formation of PDA not only on the conducting surface, but also on the insulating patterned adhesive tape used to delimitate the working electrode area. Considering the geometric diameter of 2 mm and 4 mm for the working and reference electrodes, respectively, and given PDA hydrophilicity, after the assembly of the electrochemical device in a sandwich-like configuration, it was easier to wet the region between the two electrodes for electrochemical measurements (Fig. 4c). Moreover, it was allowed to demonstrate the electrocatalytic properties of PDA toward NADH. In fact, by forming a PDA film on the surface of the electrode, a cathodic shift of approximately 200 mV and electrocatalytic currents more than 30 times higher when compared to samples without PDA were obtained (Fig. 4d). Moreover, it was observed higher current values at a fixed potential when increasing NADH concentration (Fig. 4e). Although PDA can be directly applied as a redox mediator, it is worth noting that this is not an electrically conducting material; in fact, after the PDA film formation, it was observed a decrease in the measured currents. However, due to the thin thickness and porous nature of the formed film, the surface is still able to promote electrochemical reactions. To summarize, it was demonstrated that PDA has a good ability to improve both hydrophilicity and adhesion aiming for proper electrolyte confinement and secondary functionalization on the surface of paper-based electrochemical devices. Furthermore, due to the presence of a catechol/quinone redox couple, PDA can be directly

applied as a redox mediator aiming for further applications in the development of promising biosensors.

Beyond paper-based electrodes mainly developed with a carbon conducting surface, gold electrodes present remarkable advantages such as a wide electrochemical window and the possibility of further functionalization mainly through self-assembled monolayers. The association of gold surfaces with PDA can bring even more advantages that will be briefly discussed. Sukeri et al. [99] developed a self-supported gold film electrode functionalized with PDA for  $H_2O_2$  and dopamine detection. To begin with, the gold electrode was submitted to anodization at 2.0 V for 15 min in order to form an oxide layer. Following the anodization, the electrode was dipped into a dopamine solution in order to chemically form PDA (Fig. 4f). Interestingly, the authors explored the redox capabilities of PDA to convert the Au oxide layer into AuNPs and at the same time oxidize dopamine to PDA. The electrode was then applied to electroreduction of  $H_2O_2$  and electrooxidation of dopamine presenting outstanding results regarding the increase in peak current and remarkable decrease in overpotential. In fact, these results could be achieved due to the high surface area of the Au nanoparticle-based electrode and the redox couple catechol/quinone offered by PDA functionalization film.

In another work, D'Alvise et al. [100] explored the fact that electropolymerization only promotes the formation of PDA onto electrically conductive surfaces to obtain a semi-permeable film by embedding phospholipids nanodiscs on PDA film. First, the authors adsorbed lipid nanodiscs onto a gold electrode surface by drop casting, and next, they promoted the electropolymerization of PDA (Fig. 4g). Basically, besides the possibility of polymerization only in conductive regions (excluding regions of previous deposition of lipidic nanodiscs), the electropolymerization was useful to obtain a better thickness control, through the number of voltammetric cycles applied. This is important to form a film with high mechanical properties and at the same time prevent the formation of the film over the lipidic nanodiscs. Finally, the authors explored the ion permeability to electrochemically detect two redox probes, a positively charged ruthenium hexamine chloride and the negatively charged  $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ . As observed, due to the presence of the negatively charged bilayer phospholipids, the membrane showed good permeation for the positively charged ruthenium hexamine while the repulsive forces prevented the electrochemical detection of negatively charged species. The work showed interesting possibilities for developing semi-permeable ultrathin films that could even be associated with anchored enzymes aiming for application for flexible biosensors with improved selectivity. However, although gold is an excellent electrically conducting material, it must be considered that the formation of PDA causes a reduction in the electron transfer rate.

Once considered that polydopamine films are typically formed through solution oxidation and electropolymerization on paper-based and gold electrodes; the difference between the two methods should be taken into account when choosing which one will be adopted. Electropolymerization, for example, enables better control over the thickness and produces a less rough film. However, it can only be formed on electrically conducting surfaces. Solution oxidation on the other hand can be employed to modify insulating regions. It is also worth mentioning that polydopamine is not electrically conducting and surfaces modified with this material typically present a lower electron transfer rate. With this consideration, the thickness of the PDA film is a very important parameter, but many works do not usually study its influence in terms of the performance of the developed device. The precise control of PDA patterns using microfabrication routes may expand the use of PDA for sensing applications. By fabricating arrays of PDA layers on specific regions of the electrode (e.g., PDA micropillars), it will open the possibility to use thicker PDA nanofilms to incorporate enzymes while minimizing charge transfer resistance.

## Perspectives

We foresee the use of PDA in many applications in the field of electrochemical sensors and biosensors. The versatility of PDA in attaching to virtually any surface combined with the introduction of amine and oxygen-rich functionalities is one of the main attractive characteristics of this functionalization route. There are still many unexplored possibilities in the field of electrochemical sensors and biosensors. For instance, the combination of emerging 2D materials and PDA is in the early stage and there is a lot of room to be explored by combining tunable electronic properties of 2D materials with the adhesive properties of PDA. In addition, there are many recent 2D materials reported that were not applied in the field of electrochemical sensors that can offer a wide functionalization area to improve sensitivity and selectivity.

The preparation of miniaturized devices functionalized with PDA has the potential to bring additional advantages in decentralized analysis. PDA nanofilms increase hydrophilicity of the interfaces and it has the potential to be used in microfluidic devices, facilitating the manipulation of aqueous samples. For example, microfluidic devices can be combined with electrochemical devices where PDA can play a central role in delivering capillary flow and electrode functionalization. In addition, microfabrication routes can be used to pattern hydrophilic regions on the electrode by using PDA.

Recently, the use of free-standing PDA nanofilms opened a new door for electrochemical sensing [101]. PDA nanofilms

can work as very thin hydrophilic filters to minimize the influence of possible interferences in electrochemical analysis. Moreover, PDA can bring active materials from the solution to the interface in a very simple way. Thus, the codeposition of enzymes and inorganic catalysts can be explored to fabricate new electrochemical sensors. Codeposition has the advantage of minimizing the number of fabrication steps which can be an excellent alternative for the scalability of devices.

## Conclusions

We witnessed remarkable applications of PDA to improve the selectivity, sensitivity, and hydrophilicity of devices in the field of electrochemical sensors and biosensors. The combinations of materials that can be formed on the interface are limitless due to the remarkable advantages of PDA demonstrated in this review. For instance, the use of PDA and nanomaterials have opened many avenues for electrode modification. Nanomaterials can improve the analytical signal and increase the surface area while PDA works as a biocompatible binder and offers chemical groups for further immobilization of catalysts or recognition elements. Among the nanomaterials employed, it is possible to highlight the synergistic effect of 2D materials, nanotubes, and metallic nanoparticles in several examples. Moreover, in many works several examples, it was noticed the combination of a 2D material and a second nanomaterial, i.e., nanotube or nanoparticle, for instance. Thus, a lot of effort has been dedicated to bringing new advantages to the electrochemical sensing interface.

Polydopamine nanofilms and nanocomposites are mainly used on conventional electrodes such as gold and glassy carbon. However, we observed that after fundamental studies were applied onto conventional electrodes, the applications are being slowly directed to portable and miniaturized electrochemical cells. Thus, we can expect some interesting point-of-need applications of electrochemical sensors in the next years. The examples highlighted in this work are very promising, but the next applications of electrodes should be accompanied along with long-term stability tests. In addition, most electrochemical sensors using PDA are not fully validated by analyzing with a proper number of samples. We understand that at this moment some proof-of-concept applications are valid but in order to expand the practical use of PDA such issues should be addressed.

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## Declarations

**Conflict of interest** The authors declare no competing interests.

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