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Dear Dr Maria Teresa Menes Vazquez,

we are sending the manuscript entitled: "Polydopamine: successful applications and future perspectives in (bio)analysis and (bio)sensing" by P. Palladino, F. Bettazzi, and S. Scarano*, which we would like you consider for publication as *Trend Article* as ABC young investigators special issue (invited contribution).

We believe that our manuscript is of interest for the *ABC* readership because it proposes a short survey on polydopamine applications for surface coating, molecular imprinting, and electrochemistry. Nonetheless, the peculiar physicochemical properties of dopamine and its polymer, due to the reduction potential of catechol moiety, are not fully exploited. We have confidence in possibility to spread its applications through a large variety of research approaches, including the use of naturally occurring or synthetic dopamine analogues and co-polymers. Accordingly, our efforts in this direction are focused in proposing the role of this polymer for quantitative applications, evaluating analytical performances, costs, reproducibility and versatility of the developed methods also revisiting standard (bio)analytical platforms.

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Polydopamine: successful applications and future perspectives in (bio)analysis and (bio)sensing

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Abstract

Dopamine oxidation and self-polymerization has recently gained a large interest arising from the versatile chemistry of this endogenous catecholamine. Particularly stimulating appear the applications of this biopolymer for surface coating, molecular imprinting, and electrochemistry, here reviewed, covering the broad fields of medicine, material science, and (bio)analytical chemistry. Nonetheless, the peculiar physicochemical properties of dopamine and its polymer, due to the reduction potential of catechol moiety, are not fully exploited. We have confidence in possibility to spread its applications through a large variety of research approaches, including the use of naturally occurring or synthetic dopamine analogues and co-polymers. Accordingly, our efforts in this direction are focused in proposing the role of this polymer for quantitative applications, evaluating analytical performances, costs, reproducibility and versatility of the developed methods also revisiting standard (bio)analytical platforms.

Keywords Polydopamine, Molecularly Imprinted Polymers, Surface coating, Electrochemistry, Biosensing, Bioanalysis

1. Introduction

The huge significance of endogenous Dopamine (DA) for human renal, hormonal and central nervous systems, and the consequent severe clinical conditions associated with DA concentration anomalies, including Schizophrenia, and Parkinson's disease, has generated more than 200 thousand scientific papers over the past 80 years. A more recent and intriguing outcome from this plethora of information is represented by DA oxidation and self-polymerization [1-3]. The electrochemical and chemical

reaction pathway for polydopamine (PDA) formation in aqueous solutions requires the synthesis of 5,6-indolequinone (IQ) monomer from dopamine molecule [1,4,5]. Notably, the polymer growth is inhibited by low pH (below 4) and high-concentration of various electrolytes that impair the preliminary intramolecular cyclization of oxidized dopamine by decreasing the nitrogen nucleophilicity [1]. Since the pioneering investigations and application on dopamine polymerization by electrodeposition [1,2], and then by O_2/pH-induced oxidation [3], thousands of papers involving the PDA synthesis, study and application have been published. Notably, the last four years represent almost 80% of all the scientific production, underlining the enhanced interest arising from the versatile chemistry of this endogenous catecholamine and its complex polymerization mechanism [6-9]. The reactivity of dopamine and its polymer is associated to the reduction potential of catechol moiety that has been exploited to produce optically and catalytically active metal nanoparticles *in situ* [10-12]. This feature responsible for the cross-linking of dopamine can be enhanced by chemical oxidants [13-15], UV [16], or microwave irradiation [17], influencing the coating of PDA at nanometric scale employed for a variety of physical, chemical and biological studies [7, 8]. However, this field of research is still young and challenging in application of PDA-coated surface to medicine, energy and industrial manufacturing, for example [7,8]. In particular, a promising field of PDA research is the surface coating for molecular sensing and affinity separation for pharmaceutical studies and clinical applications [18,19], following the peculiar physicochemical properties of PDA, including the photo/thermo/electro/chemical reactivity [10-12], and the molecular immobilization and imprinting capability of this biopolymer [2, 20-23]. Here we report a survey of this demanding area of bioanalytical research, focusing on the state-of-art of PDA applications for coating, imprinting, and electrochemistry, and offering a long-term vision for the capability of this polymer to be exploited to its full potential.

2. Polydopamine imprinting

The preparation of molecularly imprinted polymers (MIPs) requires non-covalent interactions or formation of reversible covalent adducts between a molecular template of interest and functional monomer(s) prior to the polymerization of the latter. Subsequent template removal generates synthetic binding sites within the polymer with high selectivity and sensitivity toward the template molecule [24-27]. In this framework, dopamine appears particularly suitable for molecular imprinting thanks to its hydrophilicity, biocompatibility, self-assembling, and universal coating capability [3,7]. In particular, the simple dopamine-analyte co-polymerization and the subsequent analyte removal has been used to generate a robust and biocompatible nanometric film for quantitative analysis of

molecule without an additional self-assembled sublayer. Here we review selected publications useful to categorize the research lines for PDA application in MIP based on substrate geometry and composition, or following the template size (Fig. 1).

2.1 MIP substrates: geometry and composition

Among the variety of PDA layer applications [18,19,21], PDA adhesion for molecular imprinting is essentially associated to solid phase extraction and microextraction [18]. The majority of these functional nanocomposites are nanoparticles (NPs), and materials with similar geometry like carbon dots (CDs) and quantum dots (QDs). Less abundant are the studies involving the PDA coating and imprinting on nanotubes (NTs), graphite oxide (GO), macroscopic surfaces (gold and quartz), and hydrogels [18]. Commonly, the deposition and imprinting has been studied via scanning electron microscopy (SEM), transmission electron microscopy (TEM), dynamic light scattering (DLS), and atomic force microscopy (AFM) before and after the polymer adhesion to determine the morphological features, *i.e.* shape, size distribution and dispersibility of nanocomposites and topography of extended surfaces.

2.1.1 MIP on Nanoparticles. The size of the imprinted particles is dependent on the synthetic protocol and may differ of some orders of magnitudes, determining huge differences between the preparations in terms of amount of PDA per nanoparticle, and, more in general, the surface-to-volume ratio and the properties of the nanocomposites. In detail, magnetic molecularly imprinted polymers (MMIP) are built using a core of Fe_3O_4, which can contain additional shells, mainly SiO_2, contributing to the global structural and physical features of MMIPs [18]. However, the outer shell of PDA constituting the MIP is independent from substrate size and composition, appearing tunable in a thickness range of 5-100 nm for a single growth step [28-31]. For example, very small fluorescent carbon dots with magnetic Fe_3O_4 core (mean diameter around 12 nm) have been coated with a shell of PDA of about 25 nm [32]. Nevertheless, much larger particles (up to micrometer) still preserve an outer shell of PDA with similar size [33,34,35].

2.1.2 *MIP on Nanotubes*. Porous tubular structure at nanometric scale has been reported in form of carbon nanotubes (CNTs), multi-walled carbon nanotubes (MWNTs), halloysite nanotubes (HNTs), [36-40] and their magnetic counterparts are obtained by Fe_3O_4 nanoparticles grafted onto nanotubes [36,39]. The outer diameter of nanotubes is variable, but in the range of a few tens of nanometers [36-40]. The PDA-coating shell before and after the template imprinting procedures ranges between very few nanometers [36-38, 40] to a thickness of 40 nm [39]. Although morphology changes for imprinted nanotubes upon analyte rebinding have not been reported, notably, a smaller thickness of MIP in comparison with NIP has been ascribed to dopamine polymerization inhibition by template [38]. Very

peculiar appear the HNTs owning a chemically reactive hollow tubular structure, which can assume negatively charged silica layer on the outer surface and positively charged alumina layer on the inner surface. Although successfully imprinted, the coating layer appears not uniform likely because of redox properties of HNTs surface [40].

2.1.3 *MIP on Flat surfaces*. Bidimensional imprinting (2D-MIP) has been achieved by PDA adhesion on molecular (GO) or extended (Au/SiO_2) flat surfaces. In detail, sheets of GO have been commonly synthesized from graphite and then coated with PDA, thus obtaining a larger surface-to-volume ratio, and a higher number of binding sites per volume, in comparison to nanoparticles [41]. Nevertheless, Fe_3O_4 NPs can be also deposited on GO sheets prior of imprinting to confer magnetic properties to these substrates [41]. Electron microscopy images show curved surface for these nanocomposites before and after the imprinting [41,42]. Furthermore, the 2D-MIP morphology analysis (AFM, SEM) allows to observe both the thickness of GOs (ca. 1 nm) and the PDA adhesion layer (few nanometers) [42]. There are not observable differences between MIP and NIP because the size of template and, consequently, the dimensions of its binding site are below the limit of resolution of the microscopy techniques. On the other hand, this morphology conservancy of nanocomposites upon imprinting, template removal, and its rebinding, confirms the stability of the PDA layer and gives an indirect proof that the larger binding capacity of MIP in comparison to NIP has to be ascribed to the effective molecular imprinting and not to PDA not-specific assembly modification. Regarding the extended deposition and imprinting of PDA, gold chips or SiO_2 bare crystals has been employed as substrates for molecular detection and analysis via surface plasmon resonance (SPR), quartz crystal microbalance (QCM), and electrochemical (EC) techniques [20,43-45]. Based on theoretical design, the PDA thickness has been tuned between few and few tens of nanometers to obtain the best template orientation during the molecular imprinting. This to achieve the most analyte-accessible functional cavities into polymer layer [43]. Surface morphology of bare substrate, NIP and MIP have been usually investigated by AFM [44,45] measuring film thickness, roughness, and homogeneity after coating, imprinting and washing stages, leading to a topographic characterization of PDA deposition and imprinting [45].

2.2 MIP templates size: Mesoscopically Imprinted Polymers

The first example reported in the literature involved a PDA-based molecularly imprinted polymer (MIP) for the capacitive sensing of nicotine [2]. Later on, PDA has been employed as recognition element of much larger targets, like proteins, or viruses. Therefore, it appears reasonable that several new applications of PDA-based MIP will be related to the imprinting and sensing of living cells and viruses in biological and environmental samples. This expansion of MIP applicability as specific

recognition element of larger and much more complex analytes has been possible thanks to self-assembling of dopamine in aqueous media that generates a biocompatible polymer. In fact, PDA-unique features have easily overwhelmed the problem associated to poor stability of biological molecules in organic solvents previously necessary for solubilization and reaction of other kind of functional monomers and cross-linking agents. Consequently, mesoscopically imprinted polymers appears a more suitable and comprehensive name for the current and future developments of biopolymers imprinting strategy in biosensing.

2.2.1 Small molecules imprinting

To the best of our knowledge, nicotine has been the first molecule imprinted in PDA for molecular detection [2], anticipating plentiful applications in MIPs sensors development, mostly by using nanoparticles as substrate. In particular, the imprinting of small molecules (0.1 kDa < MW < 1 kDa) has regarded amino acids [33], estrogens [34], flavorings [37], colorants [38], phenolic acids [39], toxins [44], antibiotics [45], sugars [46], and chemotherapeutic agents in cancer [47]. Notably, it has been reported that the release of an anticancer molecule imprinted on PDA-coated Fe_3O_4 nanoparticles increases in presence of a magnetic field, resulting in an effective control of tumor growth in animal models [47], thus paving the way for future studies and applications of MIPs on magnetic substrates.

2.2.2 Oligonucleotides, enzymes, and immunoglobulins imprinting

After an early report on human hemoglobin-imprinted PDA showing high rebinding capacity and specific recognition in aqueous media [48], several PDA-imprinted substrates have been developed for rapid and specific recognition of proteins and oligonucleotides with potential application to separation of analytes from real and complex matrices [21]. The adsorption selectivity and binding specificity has been evaluated comparing MIPs and NIPs towards the template calculating the imprinting factor (IF), and towards competitive analytes with similar shape, size and isoelectric points, i.e. the selectivity coefficient (SC). For example, studies on BSA imprinting and separation from blood samples have given values of IF between 1.7 and 6.2 and SC between 1.3 and 4.5 [40,41,49]. Similar studies have been reported for different oligonucleotides, enzymes, immunoglobulins with a molecular weight ranging from 7 to 150 kDa, up to a few tens of nanometers in length [21].

2.2.3 Viruses imprinting

Very recently, trace amounts of several viruses have been directly and specifically detected by using virus-imprinted PDA. Namely, Hepatitis A Virus (HAV) and bacteriophages (f2, T4, P1, and M13)

[23, 50,51]. In case of HAV, sensing has been achieved also in in human serum by using virus-imprinted SiO2@PDA, or magnetic Fe_3O_4@PDA, NPs with a low limit of detection down to ca. 10^{-11} M and an imprinting factor (IF), i.e. the binding capacity ratio between MIP and NIP, around 2 [50,51]. Remarkably, electron microscopy images of modified nanoparticles present surface protuberances between the PDA-imprinting and washing stages, and hollows after template removal, with a size and shape compatible with the HAV units (30 nm in diameter), giving a direct evidence of the virus imprinting. In case of bacteriophages reported above, it has been shown that the virus morphology severely affects the PDA imprinting on silica particles, and consequently its binding selectivity and kinetics, that get worse with size increase from the smallest and spherical phage f2 (ca. 26 nm in diameter) to the largest and elongated phage M13 (900 nm) [23]. However, the authors recognize that the apparent negative correlation between dimensions and imprinting requires further investigations to exclude other factors, e.g. the influence of specific capsid proteins of the investigated viruses [23].

3. Electrochemical and photoelectrochemical characterization and exploitation of PDA films in sensing and biosensing

Due to their intrinsic characteristics of being potentially fast, easy and low cost, electrochemical and photoelectrochemical techniques are widely used for the development of bioassays for the detection of analytes of clinical interest such as clinical biomarkers [52,53]. Therefore, sensor surface modification strategies are often challenging because biosensing applications require highly biocompatible and properly functionalized surfaces to bind the biorecognition material and retaining its biological activity. Moreover, the binding should be sufficiently strong to avoid the leaching of the biomaterial from the sensors surface [54]. The increasing need of easy, efficient and versatile immobilization methods in bioanalytical assays development lead to the investigation of the PDA potential applications.

3.1 Deposition of a polydopamine layer on an electrode: chemical oxidation vs electrodeposition

The fundamental mechanism of the formation of PDA is still not fully understood [55,56]. In most of the applications, the polymerization of dopamine is achieved via the chemical process reported by Lee et al. [3]. Briefly, a combination of bulk and surface polymerization is induced at a basic pH. Simple immersion of substrates in a dilute aqueous solution of dopamine, buffered at typical marine environments pH (10 mM tris, pH 8.5), resulted in spontaneous deposition of a thin adherent polymeric film. Polymerization occurs involving the oxidation of catechol to quinone that further

reacts with amine and the other catechols and quinones, leading to the formation of the polymeric film. Despite the film is not chemically homogeneous, the coating obtained with this straightforward procedure shows a great reactivity toward amine and thiol groups [54,57-58]. Such kind of coatings, often called pseudo-melanin, can be also easily modified as single step reaction leading to several kinds of modified surfaces including metal nanoparticle decorated surface [59-61], such as silver NPs [62] or gold NPs [63,64], via the reduction from solution of the corresponding cations. This reduction step is possible through the presence of the catechol groups that undergo an oxidation at the quinone functional groups during the reduction of the metallic cations. This reactivity of residual quinone groups in PDA films could be advantageously exploited for the covalent immobilization of biomolecules [65,66] for biosensor development [54,67].

A possible drawback of this method is the difficulty in controlling the localization and the surface morphology of the deposited PDA film. Despite this polymerization strategy is easily reproducible and universally established for a wide range of materials [65], an alternative method for the preparation of PDA can be achieved by an electrochemical polymerization process. Since the electro-polymerization occurs just at the interface of the electrode, PDA films can be generated in a highly controlled and spatially selective manner. The mechanism of PDA electro-polymerization has been thus deeply investigated since the late seventies [68, 69], in which Adams et al. proposed essentially two electrochemical mechanisms related to DA oxidation namely the so-called ECC and ECE mechanisms (where E and C denotes the electrochemical and the chemical step, respectively). The oxidation of DA is considered to finally leading to melanin-like polymers and thus the result of the whole process is complex. In the ECE mechanism the polymerization goes through three steps: in the first step the formation of o-dopaminoquinone occurs after exchange of two electrons and two protons. It is commonly known that the quinones are quite reactive and can undergo nucleophilic coupling. Depending on the experimental conditions used, mechanisms with more complicated sequences electrochemical and chemical steps were also proposed [65, 69]. Dopaminoquinone contains both an electron-deficient ring and an electron-donor amine group. As the results of a 1,4 Michael addition and upon deprotonation of the amine group, a cyclization reaction can occour. Therefore, in the second step the o-dopaminoquinone undergoes intramolecular cyclization which leads to leucodopaminochrome, which is easily oxidized in the third step to dopaminochrome that may be transformed into melanin polymers.

Voltammetric studies of DA have further elucidated the oxidation steps leading to PDA formation [70, 71], In detail, during the consecutive scans, has been reported a continuous decrease of the peak current intensities, due to the formation of PDA layers (Fig. 2a-b). This effect demonstrates that the electrode surface is affected by the fouling of the electrode caused by the PDA layers as it grows with

successive scans up to a complete electrode fouling. Nevertheless, two redox peaks are still present and can be attributed to the oxidation and reduction of the catechols and quinones units present in PDA [55,72]. Furthermore, the linearity of the anodic and cathodic peak currents versus scan rate indicates a surface confined voltammetry corresponding to a "thin layer" type [71], and the electrode transfer reaction appears controlled by both adsorption and diffusion [70]. The effect of the pH showed that the oxidation peak potential moves to lower values with increasing the solution pH, indicating the involvement of protons in the electrochemical reaction [71]. These features have been also exploited in the fabrication of a pH sensor based on glassy carbon electrodes and PDA films [55].

It clearly appears that the accurate assignment of all the redox processes occurring on PDA films is a challenging task [54]. The easy and universal application of PDA and the wide variety of exploitation in sensing and biosensing assays development is in contrast with the complex electrochemical behavior. Moreover, this is also in contrast to the well-established redox processes of common conducting polymers, such as polypyrrole, polythiophene, or polyaniline [73,74].

3.2 Photo-electrochemical properties of PDA and photoelectrochemical bioassays

Photoelectrochemical (PEC) biosensors are powerful and reliable tools for bioanalysis, due to the inherent operational simplicity, low back-ground current and high detection sensitivity [75-77]. Recently, photoelectrochemistry has been applied to the detection of several analytes, such as H_2O_2 [78], microRNA [77], nucleic acids [79], proteins [80] and glucose [81].

The effectiveness of the PEC assay mainly relies on the performance of the photo-active material. Recent studies demonstrated that quinones can be successfully exploited in energy applications through the hybridization of these of molecules with several kind of materials [82, 83]. In this framework, some recent reports demonstrated that the synthesized PDA exhibited semiconducting properties and special charge transfer capability inferred by the presence of the □□□□system. The presence of a highest occupied molecular orbital (HOMO) and a lowest unoccupied molecular orbital (LUMO) makes PDA a useful photosensitizer, to promote the absorption of visible light, improving light harvesting efficiency and charge collection efficiency in PEC bioassays (Fig. 2c) and offering interesting opportunities for high-performance optoelectronic devices development [83,84].

4. Future outlooks on the role of polydopamine in bioanalytical chemistry

The intriguing versatility of PDA has drawn its relevant role in a number of research fields, first of all in the science of biocompatible materials for drug delivery and cancer therapy. Undoubtedly, the auto-assembling and coating abilities of this polymer are the most exploited features in such applications. Functional surface moieties (quinones/cathecols and amines) add further facilities in the subsequent (bio)chemical modification of PDA coatings, expanding their role beyond expectations. However, at present it is surprising the lack of innovative uses of PDA in the field of (bio)analytical chemistry, excluding those aforementioned for the synthesis of MIPs and, in general, for electrochemical-based applications. In this framework, original and unexplored ways of looking for the possible use of dopamine/polydopamine with direct impact in quantitative (bio)analytics are under study. One of the poorly investigated aspects of DA polymerization to give PDA films is the kinetics of formation of these layers at the surface of the considered material. For example, during the formation of the PDA adhesive layer at polystyrene surface (*i.e.* disposable laboratory equipment such as microtiter plates, UV-Vis cuvettes, tips etc.), the polymerization step may be perturbed in significant ways to obtain analytical information useful for macromolecules, *i.e*. protein detection in complex matrices [9].

In particular, the co-presence in solution of proteins directly impairs the thickness of the final PDA layer adhered on the substrate [9]. This approach, considered until now a drawback in MIP production for protein detection, deserves on the contrary further investigations. The broad absorption band of PDA in the visible range permits to investigate the optical response at almost any wavelength, and on low-cost and widely used plate readers commonly used in immune-based assays (*i.e.* ELISA). The perspective application of such a bioanalytical method would open new and crucial scenarios in favor of the serious fails of current methods for quantification of total protein in biological fluids (Fig. 3a). Behind this, application to nanoplasmonic-based detection of low molecular weight analytes has been very recently reported. In particular, our group has explored the possibility of developing 'Plasmonic cuvettes' by *in-situ* growth of controlled AuNPs by PDA, for Localized Surface Plasmon Resonance (LSPR)-based quantitative assays at fixed wavelength, using a conventional spectrophotometer [11]. This research starts from the consideration of the role of PDA films decorated with metal nanoparticles. Despite the presence of numerous papers dealing with the *in-situ* reduction of metal ions at PDA surface to obtain nanoparticles, no indication on the rationale behind the process is provided; we recently obtained some results in that direction, both by modulating the PDA formation protocol [11] before its exposure to Au(III), and by varying the metal ion concentration leaving fixed the PDA film features [12]. In the first case, we clarify the crucial role played by PDA morphology in obtaining different populations of gold NPs, providing different plasmonics behaviors. The surprising evidence is that not only the reducing power of PDA towards Au(III) increases linearly

with thickness, but also that the plasmonic behavior of AuNPs changes accordingly. Considering the increasing demand of low-cost protocols to modulate different LSPR regimes for biosensing applications [85, 86], this result stimulated further investigation. In fact, deposited nanostructures with different features (size, geometry, density, etc.) generally express a hybrid behavior between pure wavelength sensitivity (S_λ, nm RIU^{-1}) at constant extinction, and pure absorbance sensitivity (S_{Abs}, Abs RIU^{-1}) at constant wavelength. The significant result is that PDA thickness is able to modulate the plasmonic response from the classical wavelength shift to the absorbance intensity one (Fig. 2b). This approach was applied to the quantitative determination of fermentable sugars in beer wort, with excellent analytical performances compared to routine refractometers used in cellars. Moreover, the easy reading of the 'photonic' UV-Vis cuvettes at fixed wavelength on portable spectrometers allows to figure out further applications in clinical, food, and environmental controls. PDA-based nanocomposites for quantitative assays based on catalytic activity of metal NPs may represent a further easy and low-cost approach for colorimetric determination of (bio)analytical targets in human specimens [12]. In other words, by going deeper in understanding of PDA behavior, novel analytical applications can be developed by combining PDA redox characteristics and kinetic of film formation.

By the reverse approach, once fixed the PDA film typology, the role of different metal ion concentrations in producing different AuNPs populations deserves also further investigation. In this context, PDA films decorated with *in-situ* grown AuNPs (AuNPs@PDA) substrates were tested for their catalytic activity towards nitrophenol (NPh) isomers. As widely reported in literature, AuNPs (in solution or supported) act as efficient catalysts in a large variety of organic reduction and oxidation reactions. But, to now, the reduction of NPhs and in particular of p-NPh has been reported prevalently as case study to characterize and compare different catalytic substrates, whereas for its quantitative determination HPLC and HPLC-MS with the use of radiolabels generally remain the techniques of choice. In a recent study, the *in-plate*, fast, low-cost, and high throughput determination of p-NPh on AuNPs@PDA substrates in aqueous solution and in urine was achieved, providing very new information on the behavior of these nanocomposites during the catalytic process. Different AuNPs populations may show different catalytic ability and chemical resistance on the base of the preparation protocol (in terms of Au(III) concentration) used. Only a specific concentration range of Au(III) guarantees AuNPs@PDA resistant to the reduction process, whereas out of this range the complete dissolution of the nanocomposite occurs. The result is easily obtained by a routine ELISA reader at 415 nm, where the absorbance decreases of the p-nitrophenolate ion (the optically active species generated by p-NPh with an excess of $NaBH_4$) gives quantitative and linearly correlated information on the p-NPh present in the sample (Fig. 3c). Concluding, recent advancements on PDA decorated

with metallic nanoparticles widen the possibilities in this emerging field. Several metallic precursors are reducible at PDA surface, giving NPs with different and exciting optical, catalytic, and functional properties. Therefore, we envisage that the development of innovative PDA-based nanocomposites applicable to bioanalytical chemistry will mark the near future also in the (bio)analytic chemistry.

As a whole, PDA consists in a very promising tool not only in the already explored fields of applied medicine and in material science, but also in the near future of (bio)analytical chemistry. Our efforts in this direction are focused in proposing the role of this polymer for quantitative applications, evaluating analytical performances, costs, reproducibility and versatility of the developed methods also revisiting standard platforms, as ELISA readers, portable spectrophotometers and electrochemical devices. The reactivity of DA to give PDA in different environmental conditions remains only partially explored, and we have concrete indications in several directions to push up its use through a large variety of strategies, also involving dopamine homologues and other suitable co-polymers playing different roles in this extremely fast raising research field.

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Conflict of interest

The authors declare that they have no conflict of interest.

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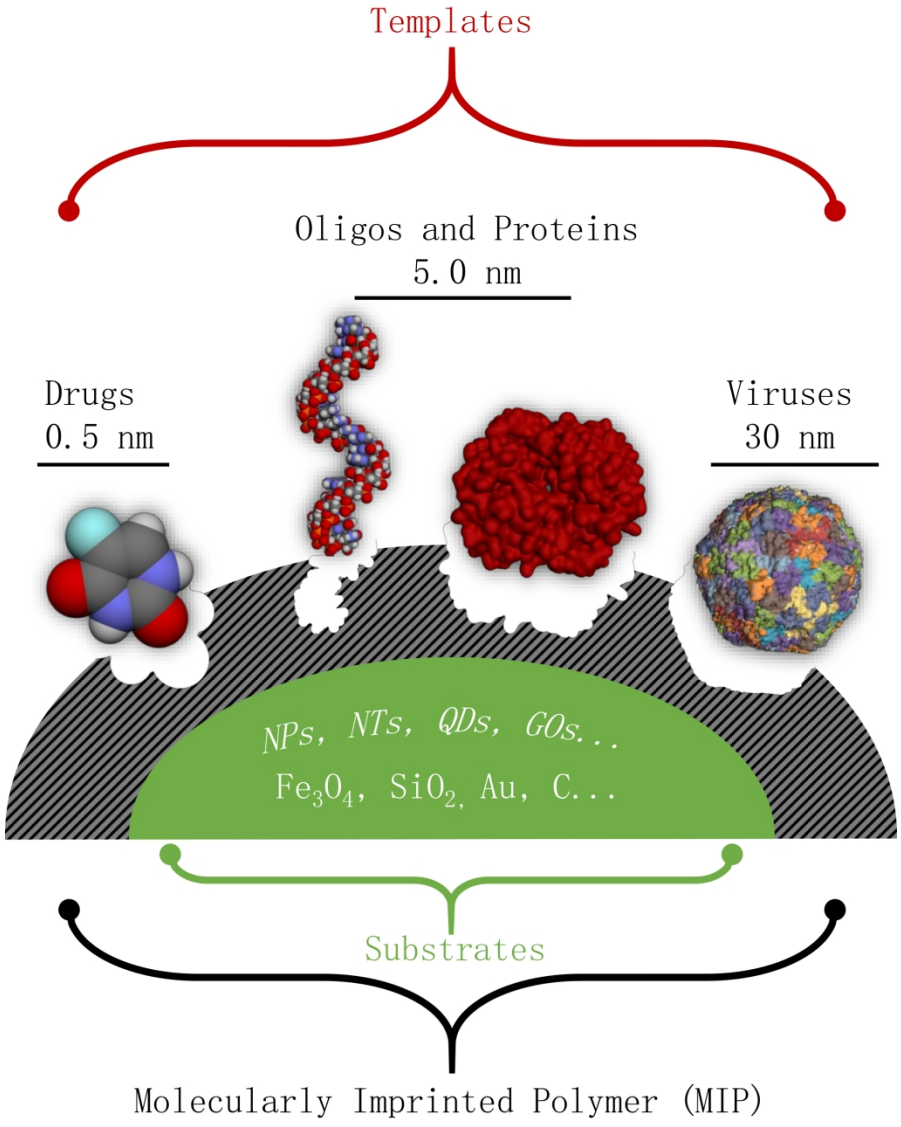
Figure legends

Fig. 1 Schematic representation of PDA imprinting on substrates with several kinds of geometries and composition. Dopamine-template co-polymerization and the subsequent template removal generates synthetic binding sites within the polymer with a broad range of dimension.

Fig. 2 (a-b) PDA electropolymerization by CV at screen-printed carbon electrode (5.0 mM DA, pH 7.0, 100 mV s^{-1}), reprinted with permission from [71]. (c) Mechanism of photo-induced charges separation caused by the PDA. Polydopamine-assisted decoration of TiO_2 nanotube arrays with HRP and subsequent photocurrent decrease in the presence of H_2O_2 due to insoluble enzymatic product formation. Redrawn with permission from [78].

Fig. 3 Innovative uses of PDA in the field of (bio)analytical chemistry. (a) Competition-based assay for quantification of total protein in biological fluids. (b) (LSPR)-based quantitative assay at fixed wavelength for applications in clinical, food, and environmental controls. (c) Catalytic-based assay for redox reactions.



Schematic representation of PDA imprinting on substrates with several kinds of geometries and composition. Dopamine-template co-polymerization and the subsequent template removal generates synthetic binding sites within the polymer with a broad range of dimension.

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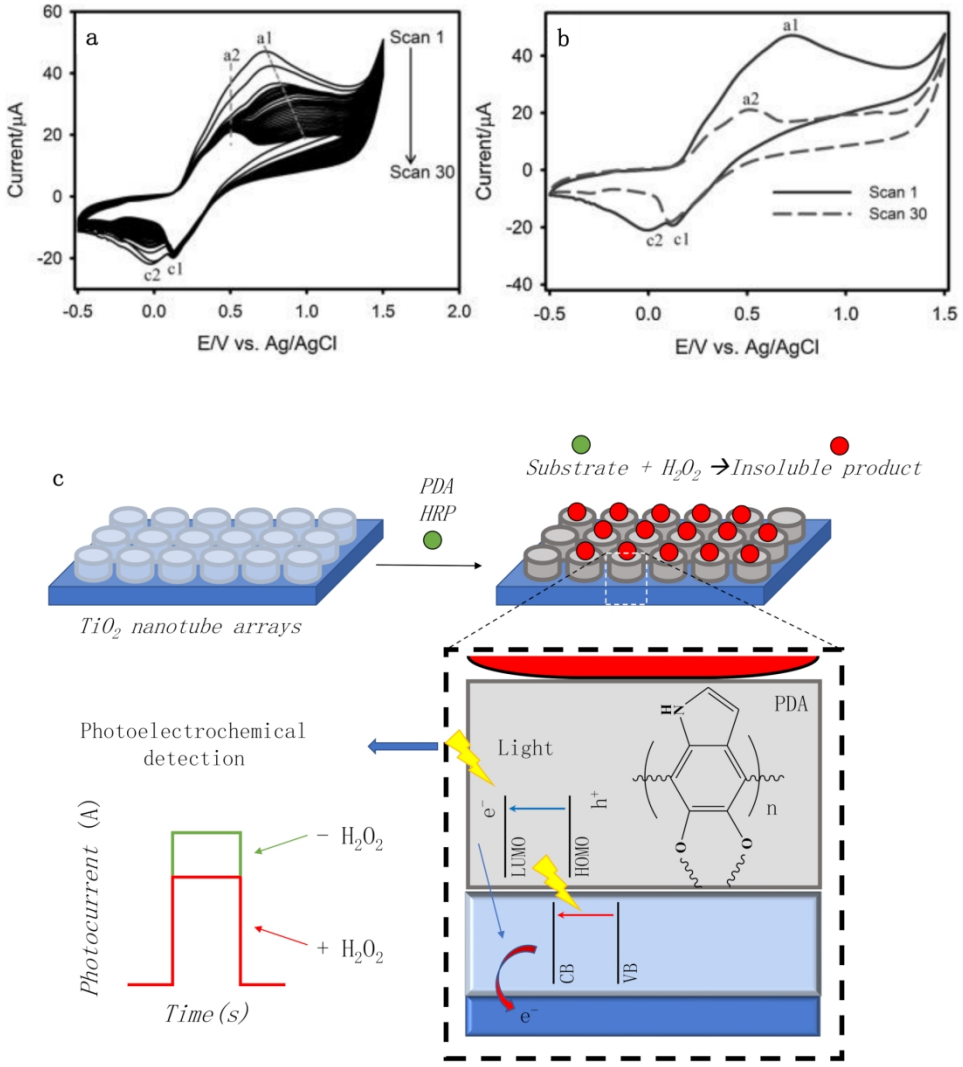

(a-b) PDA electropolymerization by CV at screen-printed carbon electrode (5.0 mM DA, pH 7.0, 100 mV s−1), reprinted with permission from [71]. (c) Mechanism of photo-induced charges separation caused by the PDA. Polydopamine-assisted decoration of TiO2 nanotube arrays with HRP and subsequent photocurrent decrease in the presence of H2O2 due to insoluble enzymatic product formation. Redrawn with permission from [78].

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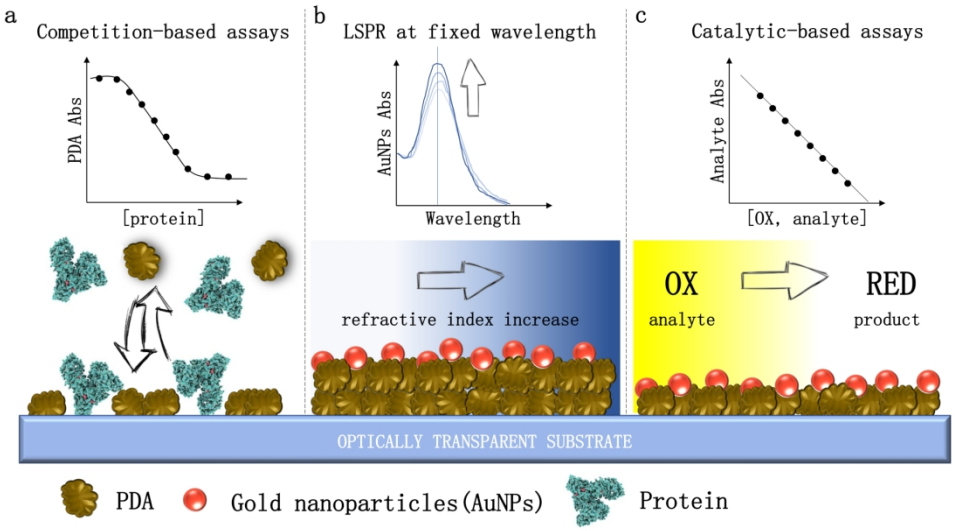

Innovative uses of PDA in the field of (bio)analytical chemistry. (a) Competition-based assay for quantification of total protein in biological fluids. (b) (LSPR)-based quantitative assay at fixed wavelength for applications in clinical, food, and environmental controls. (c) Catalytic-based assay for redox reactions.

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