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CRITICAL REVIEW

Optimisation of electrochemical sensors based on molecularly imprinted polymers: from OFAT to machine learning

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Abstract

Molecularly imprinted polymers (MIPs) rely on synthetic engineered materials able to selectively bind and intimately recognise a target molecule through its size and functionalities. The way in which MIPs interact with their targets, and the magnitude of this interaction, is closely linked to the chemical properties derived during the polymerisation stages, which tailor them to their specific target. Hence, MIPs are in-deep studied in terms of their sensitivity and cross-reactivity, further being used for monitoring purposes of analytes in complex analytical samples. As MIPs are involved in sensor development within different approaches, a systematic optimisation and rational data-driven sensing is fundamental to obtaining a best-performant MIP sensor. In addition, the closer integration of MIPs in sensor development requires that the inner properties of the materials in terms of sensitivity and selectivity are maintained in the presence of competitive molecules, which focus is currently opened. Identifying computational models capable of predicting and reporting the best-performant configuration of electrochemical sensors based on MIPs is of immense importance. The application of chemometrics using design of experiments (DoE) is nowadays increasingly adopted during optimisation problems, which largely reduce the number of experimental trials. These approaches, together with the emergent machine learning (ML) tool in sensor data processing, represent the future trend in design and management of point-of-care configurations based on MIP sensing. This review provides an overview on the recent application of chemometrics tools in optimisation problems during development and analytical assessment of electrochemical sensors based on MIP receptors. A comprehensive discussion is first presented to cover the recent advancements on response surface methodologies (RSM) in optimisation studies of MIPs design. Therefore, the recent advent of machine learning in sensor data processing will be focused on MIPs development and analytical detection in sensors.

Keywords Electrochemical sensor · Molecularly imprinted polymer · Optimisation · Chemometrics · Experimental design · Machine learning

Introduction

Over the past decades, progression in the field of electrochemical sensors has faced the development of point-of-care (POC) devices for the rapid determination of a plenty of molecules of interest. Hence, superior recognition capabilities, with addressed improved selectivity properties have been recognised in the field of molecularly imprinted polymers (MIPs) [1–3]. These are synthetic engineered materials recognised as upper sensitive and selective receptors of a wide range of analytes. The polymerisation process is the core of MIP formation: at the first stage, the selection of functional monomers is fundamental in obtaining the sensitive polymeric material. As a rule, precursors of polymeric structure must be able to arrange the specific analyte

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(template) through their accessible functional groups. Thus, the analyte is being surrounded in the presence of cross-linker agents in a definite orientation. At the end, elution procedures can extract the target leading to the formation of mould-memory cavities—binding sites—with promising selectivity properties imparted for shapes, size, and charge of the imprinted template. MIPs can be easily prepared by chemical procedures of polymerisation [4–6] and by the application of electrochemical methods (EM) obtaining the electropolymerised MIPs (e-MIPs) [7–9]. Within these polymerisation procedures, different quantitative and qualitative variables are intimately involved, so reflecting the effective recognition capability of the MIPs during rebinding processes and its sensitivity towards target. The importance of optimisation in MIP production and use has been pointed out in very few reviews already published [10–12], which were mainly focused on chemometrics methods coupled electrochemical sensors and sensor signal processing [13–15]. However, when talking about optimisation, it is important to remember that the use of artificial intelligent methods to design MIPs requires an accurate planning of the activities before they are carried out. It is necessary to clearly demonstrate the benefits of applying the most advanced chemometrics and artificial intelligence methods, so that MIPs research makes use of these tools right from the design stage. To this aim, starting from very recent applications of the simplest (but inefficient) optimisation method (OFAT), an excursus to the most advanced application of artificial intelligence to the production and application of MIPs and e-MIPs is reviewed.

Optimisation through OFAT

A number of strategies in MIPs synthesis optimisation have been explored in the past, including one factor at a time (OFAT) [16] and chemometrics [17, 18]. Classically, OFAT approach is the one preferred, in which experiments of optimisation are driven intuitively by fixing all process variables except for one. After the best value for that variable has been optimised, another set of experiments is executed to further optimise another variable. Recent reports on various developed sensors based on MIPs explored OFAT approach in optimisation studies of variables. As example, George *et al.* reported the development of an electrochemical sensor based on e-MIPs for tartrazine determination in food matrices [19]. Here, different variables have been chosen to be optimised in stages, such as the template-monomer concentration ratio, the type and pH of the supporting electrolyte in template sensing, the effect of scan rate, and the number of scans during sensor design. Another prepared e-MIP amperometric sensor for bacteria detection has been optimised via OFAT [20] iteratively changing the main parameters affecting the synthesis and performances of the sensors, such as the number of cycles during electropolymerisation, concentration of target, concentration of the employed electroactive functional monomer, and applied potential range during sensing. In another work, nanoparticles of MIPs prepared by suspension polymerisation have been integrated at the carbon paste electrode for sensing of a pesticide in environment and food [21]. Investigated factors were both those affecting preparation/immobilisation of nanoparticles onto electrode surface and those involved in the sensor signals after rebinding. Of course, OFAT gives a partial picture of the variable domain, disregarding any existing synergic effect between variables, leading to a possible suboptimal result. However, studying the experimental conditions of chemical synthesis requires a comprehensive knowledge of the relevant multidimensional variable space, where several possible interactions between these variables are considered with significance. Hence, structured experimental design (DoE) takes place as robust and chemometric efficient technique [22] into the multidimensional space evaluation of synthetic chemical variables. The term "experimental design" means planning experiments based on a series of algorithms in order (i) to evaluate the influence of variables on a certain response with high statistical significance, (ii) to consider interaction existing between the studied variables, and (iii) to optimise the experimental conditions using a limited number of experiments. OFAT ignores interactions between variables and fails in prediction in the cases of those large contributions. Alternatively, DoE as a formal structured method is designed to address complex problems where numerous variables interact each other to reach a response solution.

Experimental design in MIP synthesis

During MIPs preparation, a large number of variables regarding the composition of polymerisation mixture, such as concentration of template, functional monomers, cross-linker, initiator, pH, temperature reaction, and reaction time, are being studied, all involved in preparing best-performant recognition units. All those factors are strictly correlated (i) to the preparation of rebinding sites for their respective templates and (ii) to their availability during rebinding processes, exploiting varying sensitivity features at the obtained MIP sensor (e.g. imprinted factor (IF), limit of detection (LOD)). Briefly, composition of polymerisation mixture naming in the amount of functional monomers and cross-linker agents, pH, temperature, and reaction times are the main responsible to obtain stable organised structures of polymeric backbones. The percentage of total functional monomers in relation to target concentration modulates the fruitful interaction between chemical moieties of monomers-target. This remains essential to ensure practical goodness of imprinting technology. Concentration and reaction time

of porogen acts to remove the imprinted target from the polymeric structure play an important role to obtain a number of available reactive binding sites on MIPs structures. Moreover, design of e-MIPs includes additional variables, such as the number of scans in cyclic voltammetry during polymeric layer formation, or the time to completely elute the target from polymeric network. Since the influence of a large number of variables during MIP synthesis whose interaction cannot often *a priori* excluded, a comprehensive multivariate optimisation is necessary to obtain the best MIP preparation. Experimental designs (DoEs) are increasingly adopted to improve design of sensor based on MIPs, which allow the rational selection of such affected variable enabling minimisation of trial-and-error procedures. In the following subparagraphs, different screening experimental designs adopted during MIP preparation are elucidated. Then, more comprehensive experimental design based on quadratic models moved towards optimisation of synthetic parameters in MIP design and those affected analytical performances will be presented and discussed.

Screening designs

Response surface methodology (RSM) relies on mathematical models based on the fitting of polynomial equations to experimental data including any synergic effects existing between the simultaneously acting variables. Here, the dataset is fitted with the objective of making statistical predictions about one or more responses (independent variables). However, before RSM application, other mathematical models able to discriminate the significant influence on a certain response are the first-order experimental design, named in techniques such as the *full* (or *fractional*) *factorial* design, *Placket-Burman* design, and *definitive screening* design (Fig. 1). These models, very useful during the setup of a new process, do not present curvature along the multidimensional variable space, so they provide a sort of linear fit to experimental datasets, but they can help in excluding not significant parameters and, more important, generally require few experiments [23].

Full factorial design

A simple full screen factorial design $2^{n(=3)}$ was recently applied in the development of electrochemical sensors based on MIP receptor to detect irbesartan [24]. Hence, the experimental design was able to determine the significant contribution of pre-polymerisation monomers to achieve the maximum sensitivity of the developed acrylate polymeric structure. To this respect, three variables were intuitively selected as the most involved in obtaining a best-sensitive MIP, such as the volume of porogen, concentration of functional monomer, and concentration of added cross-linker agents. However, MIPs selectivity is also governed by the ratio between concentration of total functional monomers and concentration of the employed target, which is important to obtain the maximum amount of recognition cavities onto MIP structures, and thus, improved sensitivities towards the analyte of interest.

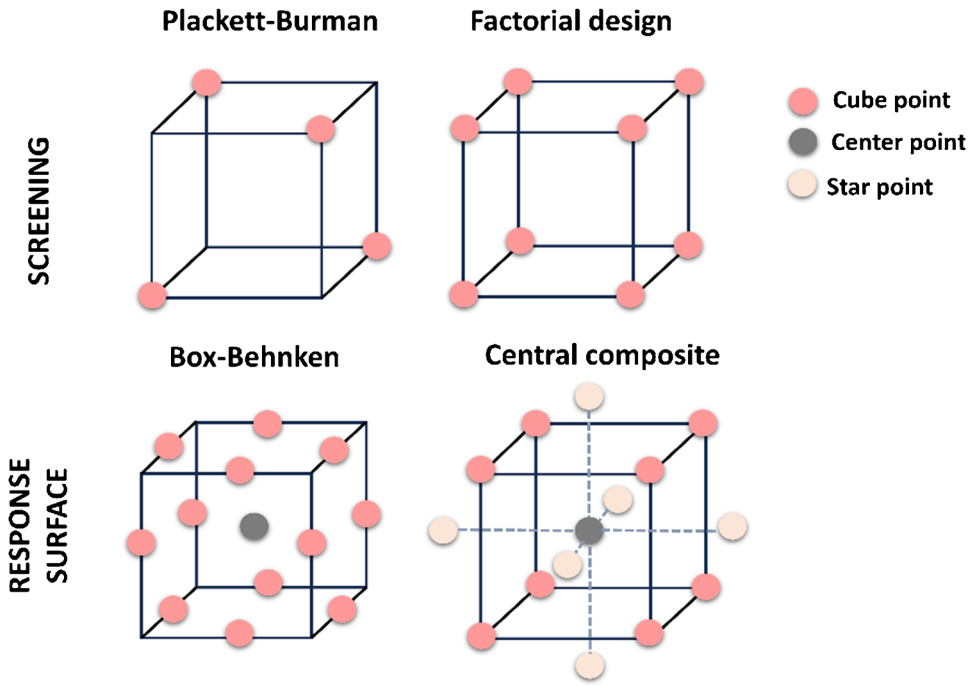

Fig. 1 Experimental region of screening and response surface experimental design: Plackett-Burman, Factorial design, Box-Behnken design, Central Composite design

In comparison, a 2^5 full factorial design in MIP sensor development involved 32 total experiments (performed twice) comprising optimisation of components of polymerisation mixture together with the voltammetric parameters of square wave voltammetry (SWV) [25].

Our work [26] reported the preparation of ion imprinted electropolymerised polymeric films (IIPs) for sensor development to selectively recognise Cu(II) ions in aqueous samples. A 2^4 full factorial design with 19 experimental runs was performed to establish the main factors affecting sensor sensitivity towards increased nM concentrations of Cu(II) ions. It was notable as the concentration of employed monomer and time of elution to extract Cu(II) were the main significant in observing different sensitivities features at the developed imprinted films.

Compared to the OFAT approach, the employed screening designs show the significant factors and factor interactions, which is essential in understanding the electrochemical response variations. However, the full factorial designs are limited in the development of best-performant sensors, since it only provides estimation of negative or positive effect of factors on a certain response [27].

Plackett-Burmann design

Of utmost importance in electrochemical sensors design is the integration of MIPs onto element transducer, which should be focused on the maximisation of sensor performance retaining the inner features of MIPs. Electropolymerised MIPs (e-MIPs), directly obtained on transducer, are favourable in both the control of the design of receptors and the feasibility in analytical detection of targets. To this respect, the influence of several factors related to MIP-based sensor development—based on the electropolymerisation of pyrrole monomer—on the DPV ratio of MIP to NIP responses was investigated through the screening Plackett-Burman design (Table 1). The adopted screening design consisted of 12 experimental runs in 2-level factors evaluation. According to the effect magnitude shown from Pareto chart, 3 out of 10 of the selected factors were the most significant in the sensitivity variation of MIPs compared to NIP, greatly simplifying the subsequent RSM application for sensor optimisation. Those reports confirmed the importance of the screening designs to efficiently reduce number of variables, to carry on a more-focused optimisation process but also to reduce time and reagent consumption.

Response surface methodology

We have seen that the use of screening designs is mandatory, in order to (a) ascertain the significant variables for a certain response and (b) delimitate the multidimensional variable space. However, optimal (and robust) responses can be only obtained through the RSM. The term "RSM" relies on a series of mathematical and statistical methods able to model experimental data in a n (often 2^{nd})-order space until reaching optimal statement fit obtained from trained experimental designs. There are a series of stages during the application of RSM in optimisation problems. First, the experiments in the variable space are properly selected to evaluate the factors and their interactions with minimum confounding and variance of the model coefficient; then, the experiments are executed; finally, a polynomial function describing the significance of coefficient per studied variable is fitted and evaluated. The validation of the RSM requires a not significant difference between the predicted optimal values and the experimental results in the selected conditions.

Central composite design

Thanks to its orthogonality, uniformity and rotatability properties, central composite design (CCD) has been used in optimising MIP synthesis. A plenty of developed sensors based on polypyrrole MIPs films have been proposed in the literature for the determination of drugs [28–33], resins [34], and sugars [35] using multivariate optimisation coupling PBD and CCD experimental design for screening and critical optimisation, respectively.

Nanomaterials, e.g. multi-walled carbon nanotubes (MWCNTs), metal nanoparticles (AuNPs, AgNPs), and core-shell nanoparticles [36], enhanced sensor responses, so their use spreads [37–46]. Therefore, it is not surprising that MWCNTs concentration and deposition time were the most significant variables and positively contributed to sensor responses variation, as resulted from [28, 30, 33]. On the other hand, integration of metal nanoparticles at the electrode surface before MIP preparation, as reported in [29, 31], appeared to be much more directly correlated with the variation of MIP responses during analytical assessment of molecules, opening the scenario in distinctive optimisation of MIPs composites at the different stage of preparation and their analytical performances during target rebind.

If the system under study is well known, the variable reduction by PCB, such as in the preparation of e-MIP film based on poly-oPD by CV method [47] or in the co-polymerisation of p-aminobenzoic acid and 4,4-diaminodiphenyl sulfone [48], can be avoided. Our work reported a CCD method in optimising sensitivities properties of the Cd(II)-IIP film [49] voltammetric sensors based on p-aminophenylcarboxylic acid (p-APA) monomer. Variable concentrations of employed monomers, ions concentration at the polymerisation mixture, CV scans during electrosynthesis, and time of elution with NaOH solvent were included into two-level CCD model and optimal responses could be more rapidly gathered.

Table 1 Plackett-Burmann design (PBD) coupled with central composite design (CCD) in optimising electrosynthesised MIP (e-MIP) films sensors based on pyrrole monomers.

Name of sensor	Analyte	Method	Parameter in screening design	Parameter in RSM	Number of trials	Reference
MWCNT/MIP-PPY film[a]	Triamterene	DPV	[MWCNTs], MWCNTs deposition time, [monomer], [target], CV scans, CV scan rate, pH, loading stirring rate, loading time	[MWCNTs], MWCNTs deposition time, CV scans	32	[28]
AgNPs/MIP-PPY film[a]	Mebeverine	DPV	[monomer], [target], CV scans, CV scan rate, AgNPs deposition time, pH, loading stirring rate, loading time	CV scan rate, pH, loading stirring rate, loading time	42	[29]
MWCNT/MIP-PPYy film[a]	1,4-Dihydroxyanthraquinone	DPV	[MWCNTs], MWCNTs deposition time, CV scans, CV scan rate, pH of polymerisation mixture, [monomer], [target], loading time, stirring rate, pH of carrier	pH of carrier, CV scan rate, MWCNTs deposition time	32	[30]
AgNPs/MIP-PPy[a]	Metformin hydrochloride	DPV	[monomer], [target], CV scans, CV scan rate, loading time, loading stirring rate, pH, AgNPs deposition	pH, loading time	25	[31]
PPy[a]	Lansoprazole	DPV	[monomer]/[target] ratio, pH, CV scan rate, CV scans, loading time, stirring rate, % porogen	[monomer]/[target] ratio, stirring rate	25	[32]
MWCNT/PPy[a]	Metoprolol	DPV	[MWCNTs], MWCNTs deposition time, pH of polymerisation mixture, [monomer], [target], CV scan rate, CV scans, pH of porogen, loading time, stirring loading time	[MWCNTs], pH of polymerisation mixture, pH of porogen	32	[33]
MIP/GO-Fe_3O_4@SiO_2[b]	Melamine	CV	[GO-Fe_3O_4@SiO_2], [MIP-GO-Fe_3O_4@SiO_2], [monomer]/[target] ratio, extraction solvent, [$FeCl_3$], loading stirring rate, polymerisation time, loading time, loading stirring time	Extraction solvent, loading stirring rate, [MIP-GO-Fe_3O_4@SiO_2]	32	[34]
PPy[c]	Lactose	DPV	[monomer], [target], CV scans, target removal, pH of polymerisation mixture, loading time, pH of carrier	[monomer], loading time, pH of carrier	38	[35]

Transducer elements: [a]*PGE*, pencil graphite electrode; [b]platinum electrode; [c]graphite paper electrode

Box-Behnken design

Among response surface methodologies, Box-Behnken designs (BBD) are considered efficient because all the points are in the cube region (Fig. 1), often representing the safe operating zone [50]. Moreover, it is also less expensive: it only needs 15 runs for three variables, while CCD takes 20 runs, and this advantage increases with the variable number. However, unlike CCD, BBD cannot extend an existing factorial design, and this fact may have limited its use.

Box-Behnken methodology should be more used because of the effectiveness with respect to other designs. A three-level five-factor design (pH, monomer-target concentration ratio, number of CV scan cycles, supporting electrolyte concentration, and target elution time) permitted the optimisation of the DPV analytical responses in probe solution after interaction with the target analyte [51], and, under the optimised conditions, the imprinting factor of MIP with respect to NIP film was 15.08. Similarly, an impedimetric sensor based on mutual recognition between metal organic framework (MOF) and MIP receptor for the fM determination of an anticonvulsant (pregabalin) optimised by using BBD design [52] exhibited high recognition abilities compared to NIP films (IF of 24.5), joined to superior selectivity features against 100-fold concentrated structurally similar drugs.

Machine learning: brief introduction

Artificial intelligence (AI) is an area of computer science that emphasises the creation of intelligent machines and devices that work and react by mimicking human behaviour. In the field of AI, the classification is divided into the machine learning (ML), which uses statistical methods to enable machines to improve with experience without relying on rules-based programming, and the deep learning (DL), which is a kind of machine learning that trains a model using multilayer neural networks (NN) and requires almost no human intervention but a larger dataset.

By definition, *training* in ML is the process that teaches an ML framework to achieve a specific goal, by discovering relationships between the input and output data [53, 54]. The *training* process in ML is continuously improved by adding a large number of experimental trials, which is also directly correlated to maximise the performance of the developed frameworks. Among the different learning approaches, supervised learning remains the most landed in MIP fields. Supervised learning algorithms are trained using independent variables (features) as input and labeled data as output response, in which new entry data is grouped into the predicted label based on its features. It can be noted as this approach is more compatible when dataset history is well known. From the point of view of MIP-based sensors, ML methods are increasingly adopted to optimise sensor synthesis and analytical performances of developed device [55]. Here, algorithms can be trained to solve regression and classification problems related to MIPs. Regression refers to quantify the unknown concentration of new input data, whereas classification provide qualitative information (identification) of chemical species. A validation experiment is then conducted for each algorithm, comparing experimental values to predicted values, so facilitating the assessment by a direct comparison of the data metrics. So, it is possible to obtain species and concentration information by model training and data fitting-based machine learning, simultaneously achieving both qualitative and quantitative analysis (Fig. 2). Compared to the RSM methodology, ML shows superiority as modelling technique for datasets with non-linear relationships, both for prediction and data fitting.

From the analysis of literature in the field of MIP sensors, we found as RSM and ML methods are jointly during the optimisation process. Along with the following sections, we concern on the advantage in utilisation of DoE as the methods for choosing the best combination of parameters to optimise the training process of ML models.

From electrochemical sensing data to ML implementation

Electrochemical methods (EM) are very advantageous in sensors design, thanks to their rapid signal acquisition, easy portability, and low-cost equipment. Of course, the different EMs, grouped into potentiometric, voltammetric/amperometric, and impedimetric, can provide a spectrum of output sensing data with a certain order and dimensionality, and the presence of noise due to capacitive currents and instrumental artifacts as well. A potentiometric sensor can measure a potential difference between the working and reference electrodes, where no current flows. Here, the electrochemical measurement led to a single value per measurement, defining a zero-order (or zero-dimensional) output data. Alternatively, voltammetric and amperometric sensors give first-order data, as these methods generate a value of a dependent variable from the variation of an independent variable, e.g. the current as a function of potential difference—in CV or DPV measurements—and the measurements of changes in current at a fixed potential as a function of time—in chronoamperometric measurements. These one-dimensional data are generally treated to be reduced at zero-order data, for example selecting a single data point at a particular potential or using principal component analysis (PCA) to dimensionally reduce multidimensional datasets to 2D plots (Fig. 3).

When arranging voltammetric data responses, the starting point is to create a matrix of rows of currents at the recorded samples (or voltammogram) versus columns as

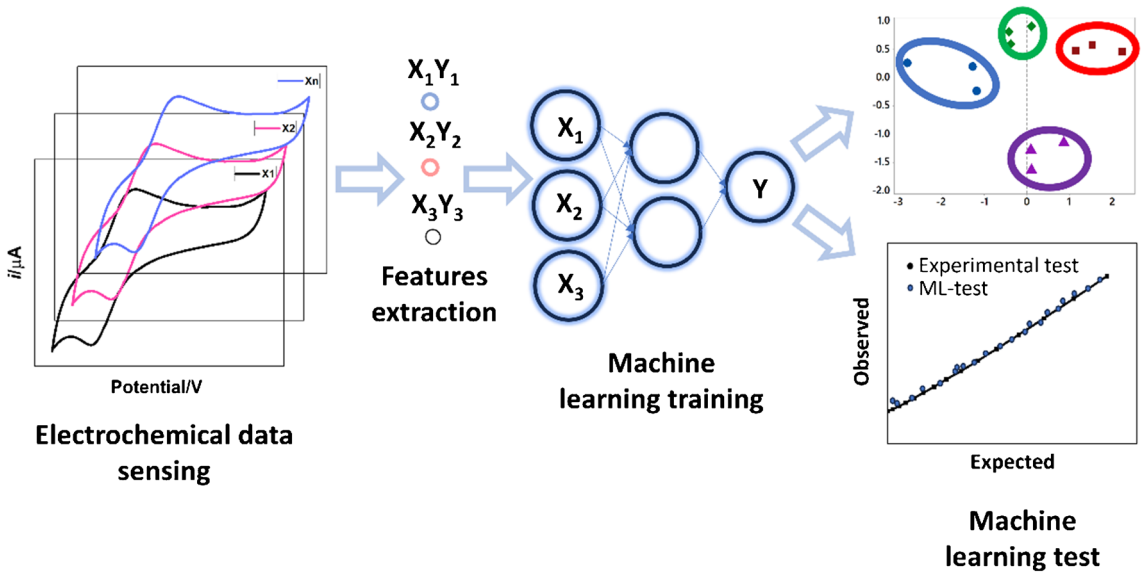

Fig. 2 Schematic representation of machine learning integration with electrochemical data sensing. As first, electrochemical sensor responses are subjected to features extractions by mean of specific algorithms based on the nature of the response. Therefore, a neural network workflow can be trained based on those inputs, by manipulating the number of neurons in each layer. Therefore, ML can be used for predictive results or pattern recognition purposes

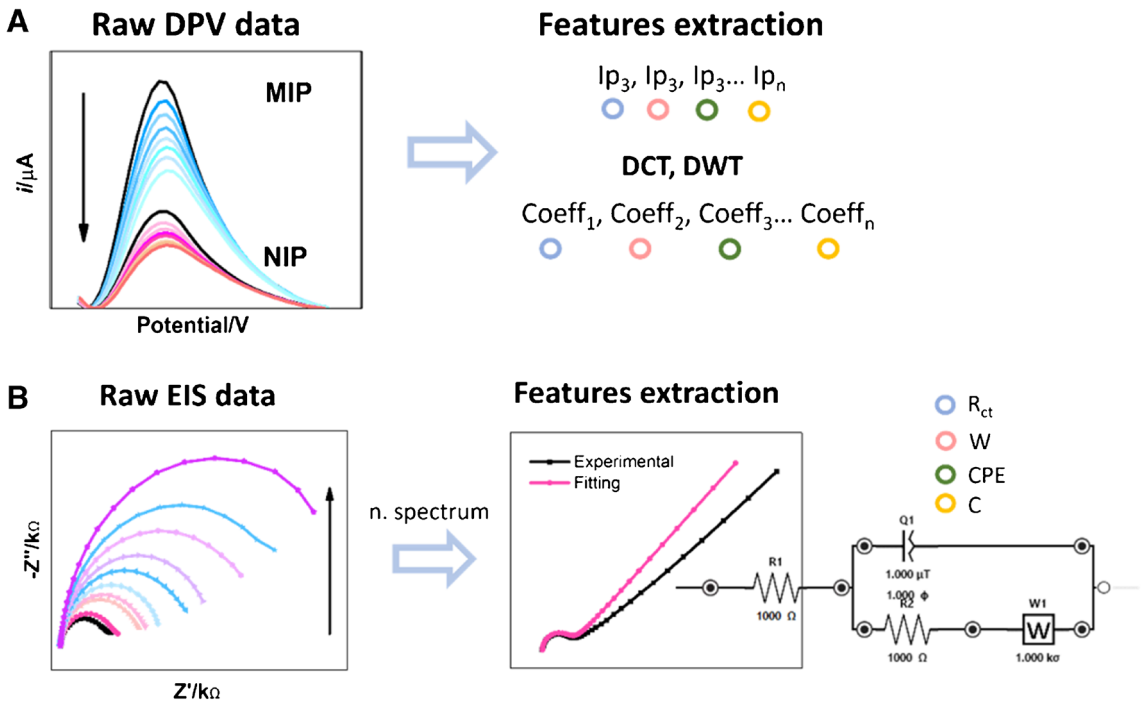

Fig. 3 Illustration of raw MIP data sensing acquired from the different electrochemical methods (**A** differential pulse voltammetric measurements, DPV; **B** electrochemical impedance spectroscopy measurements, EIS)

the potentials scanned during the measurements. The goal of the chemometric approach is to decompose this matrix to obtain information related to concentration and the individual voltammograms related to the specific analyte. PCA uses all experimental points but there is high collinearity among data which can be problematic. Recently, a common data transformation of DPV signals has attracted great attention among other applications, namely the discrete cosine

transformation (DCT) algorithm [56]. It removes the baseline effectively, also reducing noise and compressing data [57]. This transformation of DPV data is critical during ML implementation to reduce the acting variables that explain most of the dataset's variation and possibly to resolve overlapped signals related to multiple analytes. Another possible transformation of voltammetric data can be achieved by the discrete wavelet transform (DWT) [58] (Fig. 3A).

Impedimetric signals (Nyquist plot) give kinetic and mechanistic data of the electrochemical system employed in chemical sensing. EIS methods can only provide one kind of signal (e.g. the charge transfer resistance R_{ct}) after sensor exposure to the target, and resolving two affecting variables together, i.e. target nature and concentration, is particularly difficult. Nyquist plots depend on R_{ct} but also on solution resistance (Rs), Warburg impedance, constant phase angle element, and capacitance (C) (Fig. 3B). All these parameters can be extracted by fitting the experimental data but the identification of a mathematical model able to discriminate signal contributions would be a profound progress to overcome the difficulties in sensor signals interpretation, especially in the presence of several competitors of MIPs binding sites. Specific ML algorithms, such as the eXtreme Gradient Boosting (XGBoost) [59], demonstrated useful in modelling prediction responses.

Introduction to neurons and neural networks

Neural networks (NNs) represent a good choice for processing of big datasets. NNs are inspired from the biological model of neuron. It consists of nucleus, dendrites, and axons interconnected between each other. Very briefly, a neuron takes a signal input through the dendrites, processes it in the soma, and outputs the processed signal through the axon to one or more connected neurons, these nodes being the synapses. The signals activate neurons only when some criteria are met. As there are a lot of connected neurons in our brain, there are many layers of neurons, organised hierarchically, and processed information is passed from the first or lowest layers of neurons to the next until the response is finally obtained.

As definition, classification methods are chemometric tools that assign an object to a group (class) according to shared qualitive characteristics. The classification problem of assigning several observations into different groups plays an important role in ML working principle.

Basically, algorithms of ML can be descriptive (classification of what happened in the past), prescriptive (so that can help to automate recognition and identification), and predictive (when tailored to forecast and prediction). The simplest scenario of a dataset in 2D and binary linear classification is shown in Fig. 4. The non-linear binary classification problems (also called as two-group discriminant analysis problems) are conveniently solved by artificial neural networks (ANN), possibly the most common supervised learning approach. In general, ANN is composed of multilayers of neurons, divided as follows: (3) input layer, which consists of a number of neurons representing the input signal (features); (2) hidden layers, a number of neurons connected to each other to mimic connection of the synapses of the human brain; (3) output layer, which consists of neurons used to represent the output signal (Fig. 5).

Machine learning model for design optimisation of MIP-based sensors

Multi-objective optimisation by means of ML has been focused on the different stage of sensor preparation based on MIPs. Some are strictly related to optimise parameters involved in the synthetic procedure of cavities formation, to improve as much as possible the affinity properties of MIPs towards their templates, such as quality properties of imprinting factors [60]. To this respect, one of the first approaches in implementing ANN model to study MIPs receptors was in 2005 [61]. Here, an ANN model was built to calculate the imprinting factor between MIPs and NIPs as a function of different inputs variables, such as the molecular

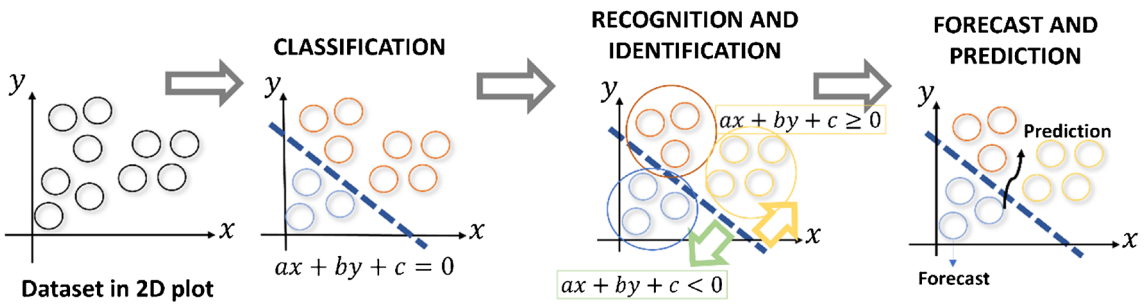

Fig. 4 Binary linear classification as the basic concept for application of algorithms-based machine learning

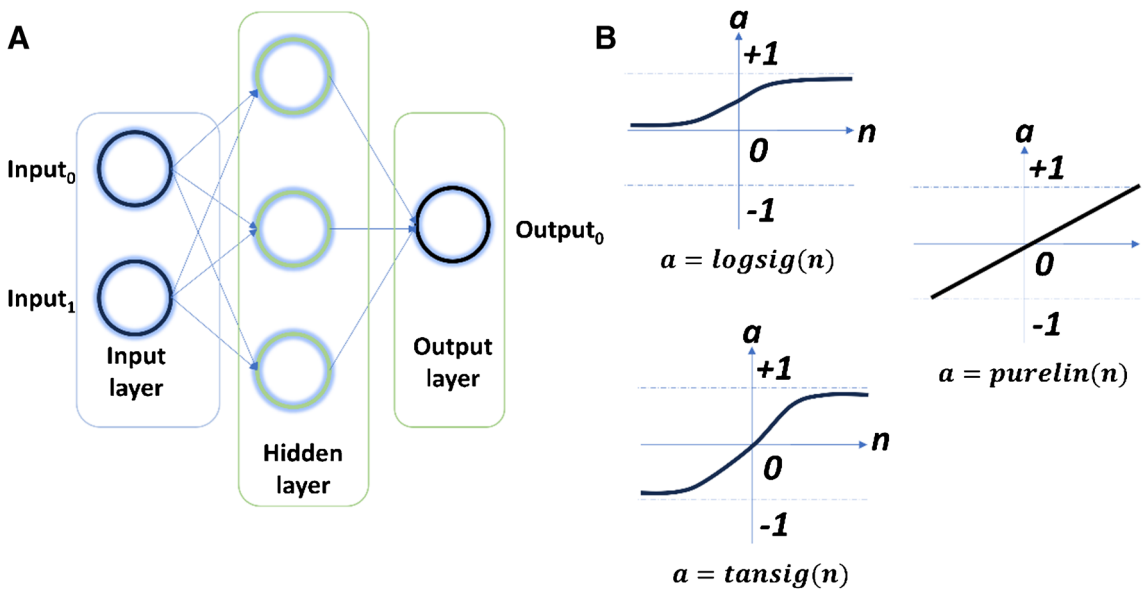

Fig. 5 **A** Schematic architecture of a typical of multilayer perceptron adopted for ANN workflow. **B** Typical transfer functions (activation functions) adopted during training of artificial networks: log-sigmoid transfer function, tang-sigmoid transfer function, linear transfer function. Adapted from MatLab website help

descriptor of template, functional monomers, and mobile phase descriptor. Two datasets were employed to build an ANN model, based on different MIPs size obtained from suspension aqueous polymerisation and bulk polymerisation, respectively. In fact, the preparation of MIPs by the different ways can provide heterogeneity in the number and association constants of the cavities, making a machine learning approach, such as the developed ANN model, useful to predict the imprinting factors. Despite this paper is of about two decades ago, ML approaches have not been extensively exploited until recently.

The effectiveness of ML and in particular ANN methods in design optimisation of MIP-based sensors was shown by Nezhadali *et al.* for celecoxib [62] and pantroprazole [63] sensors. After factor screening by PBD, CCD was used to generate models for MIP and NIP responses and to obtain the optimal conditions for maximising the IF. At the optimal conditions, the IF was about 8 so ANN-GA method was performed to find, if any, higher MIP to NIP response ratio. Three neurons (the factors of CCD models) constituted the input layer; the optimal number of neurons in the hidden layer [6] was found by trial-and-error considering its effect on mean square error method. In order to increase the dimensions of the training matrix to fit the model, the triple CCD experimental data was used to train the ANN. MSE= 0.717 was obtained after 61 iterations. Optimisation was carried out by a genetic algorithm (GA) using the trained ANN model as fitness function. Among the solutions, when the optimal Pareto front was achieved, the best IF was about 17.4, more than double the CCD optimum. The accuracy was also good as triplicate analysis in the optimal ANN-GA conditions gave an IF of 18.

A recent paper on ML-based predictions of IF showed that ensemble algorithms, like gradient boosting (GB) or random forest, had better performance in predicting the IF, compared to non-linear regression algorithms, including classification and regression tree, support vector regression, and *k*-nearest neighbours [60].

Machine learning for predictive quantification of MIPs sensor response

In a recent work [64], the implementation of ANN for predictive quantification at the MIP-based sensor is presented. Input layers were neurons representing the different tested concentrations of catechol (1–50 µM) investigated at the MIP-based voltammetric sensor, whereas analytical sensor responses (DPV signals) were chosen as output. The trained ANN model could predict catechol concentration with minimum error. In addition, the use of ANN in the data processing allowed the measurement of the catechol oxidation current at concentrations close to the LOD, which is not applicable at the laboratory.

Similarly, in the case of an e-MIP based on co-polymerisation of o-aminophenol and o-phenylenediamine sensor for propachlor determination in food matrix, machine learning algorithms for data analysis enabled the performance of the sensor to be improved [59]. XGBoost algorithm was used for its computational speed. However, despite the accuracy in determining higher concentration of the analyte,

drop-casting methods operated by users strictly influence the sensor's sensitivity at lower concentrations.

A very recent report shows the application of developed ML based on random forest algorithm (RFA) in both qualitative and semi-quantitative determination of three pathogenic bacteria in different matrices (milk, seawater) by evaluating EIS data of e-MIPs [65] based on 3-aminopheylboronic acid as the monomer. Simultaneous imprinting of the bacteria resulted in a sensor that provides reliable quantitative detection in the concentration range of 10–10^6 CFU/mL, but the response cannot distinguish which bacterium is present in unknown samples. Given the claimed selectivity of the device, the simultaneous detection of the three bacteria is a promising line of research, with an array of e-MIPs potentially overcoming the known drawback.

Multi-way calibration using second-order sensing data from MIP sensors

A continuous progress in biosensing systems covering different voltammetric transductions is ongoing nowadays for further ML implementation. In this area, there is a need to efficiently analyse such higher-order dataset to extract essential information. PARASIAS and PARAFAC2 rely on decomposition algorithms proved to be efficient tools in analysing multi-way data [66]. In addition, multi-way calibration methods enable to determine the analyte of interest even in the presence of uncalibrated interference [67], with the advantageous selectivity features at the stage of applied method of transduction. In this section, we have reviewed some representative works that reported the use of such second-order voltammetric measurements obtained on electrochemical sensors based on MIP receptors.

As an example, the processing of hydrodynamic DNPV data (HDNPV) collected from a newly triple-imprinted polymers in the simultaneous determination of antibiotics (amoxicillin, tetracycline, penicillin) in dairy product has been reported [68]. Resulting second-order voltammetric dataset was processed by both multivariate curve resolution alternating least squares (MCR-ALS) and PARASIAS (parallel factor analysis applied to shift invariant amplitude spectra) to obtain the three-way calibration of the developed system. MCR-ALS performed better and the relevant results were comparable to those obtained by HPLC-MS.

Similarly, the same authors compared PARASIAS and PARAFAC2 to build three-way calibration models for processing of hydrodynamic linear sweep voltammetric (HLSV) responses from MIPs sensor used to monitor insulin, proinsulin, and c-peptide simultaneously [69]. Again, PARASIAS performed excellently in the analysis of both artificial and real human serum samples (Table 2).

Sensor arrays based on MIPs

The superior stability and the punctual recognition mechanism between MIPs and its template open the feasibility of synthetic procedure in developing a series of MIP-based sensors to be coupled in an array platform. In this context, electronic tongues (ETs) coupling sensitive recognition elements are gaining popularity [70, 71], exploiting the advantage in the simultaneous discrimination and quantification of a mixture of analytes. The conventional application of ETs refers to the analysis of liquid phases, where an array of sensors is coupling together leading to an exhaustive and complete analyte response especially in mixtures. Here, the configuration of each combined sensor should be comparable, at least

Table 2 MIP-based sensors optimised by applying ANN model for maximisation and prediction of imprinting factors

Name	MIP-celecoxib	MIP-pantoprazole	MIP-catechol
Input	Polymerisation stirring rate, template concentration, CV scan rate	Pre-polymerisation mixture, pH, uptake step stirring rate	Catechol concentration
Output	MIP/NIP DPV response ratio	MIP/NIP DPV response ratio	DPV response
Layers	3	3	3
Hidden layer	1	1	2
Hidden neurons	6	6	5
Transfer function	Tanh/pureline	Tanh/pureline	Logsig/Logsig/pureline
Train function	Trainbr[b]	Trainbr	Traingdm
Minimum error achieved	3.36×10^{-2}	0.717	2.66×10^{-12}
Best performance (epoch)	168	61	778
Reference	[62]	[63]	[64]

Trainbr, Bayesian regulation backpropagation training function

Traingdm, Gradient Descent with Momentum Backpropagation training function

Tanh, hyperbolic tangent transfer function; *logsig*, log-sigmoid transfer function; *pureline*, linear transfer function

sharing the same transduction principle. Data processing and analysis of electrochemical signals are commonly provided by the application of chemometric methods, ranging from unsupervised statistical analysis towards the machine learning implementation. Compared to the conventional single sensor approach, an array of sensors assisted with chemometrics can potentially overcome problems related to sensors, such as mutual communication, overlapping of electrochemical signals, drift, interference, and matrix effects. In addition, when the analysis interests a mixture of analyte, it is very common seeing overlapping signals at different potential peaks, which are correlated to the different electrochemistry of analytes presented in solution. The main adopted solution is to deconvolute each electrochemical signal to reach single contribution of the analyte and assess the related peak heights or area [56]. In this direction, the incorporation of MIP-based sensor in ET device can really provide a prompt advancement in development of monitoring systems, while chemometric data modelling can overpass the detection of interferences improving the selectivity of immobilised receptors. However, despite the advantages of the MIP former, a very few number of publications have been found exploiting arrays of MIP-based and e-MIP-based electrochemical sensors (Fig. 6, Table 3).

Bueno *et al.* reported the synthesis of four-hydrogel MIP-based voltammetric sensors for protein profiling [72]. Here, using PCA for pattern recognition problems in conjunction with voltammetric responses of CV obtained at the different prepared hydrogel-MIPs was demonstrated. The imprinted cavities played a significant role in discriminating the affinity capability of each prepared MIP, which was clearly elucidated by the 4 obtained clusters classification by HPCA (Fig. 6A). The use of PCA to interrogate the detection capabilities of different prepared MIPs opens the possibility of rational, reliable selection of high-sensitive MIPs during sensor design.

A simultaneous determination of pharmaceutical compounds by means of selective e-MIPs based on pyrrole monomer demonstrated the potential uses of chemometrics based on machine learning techniques [75] (Fig. 6B). DPV

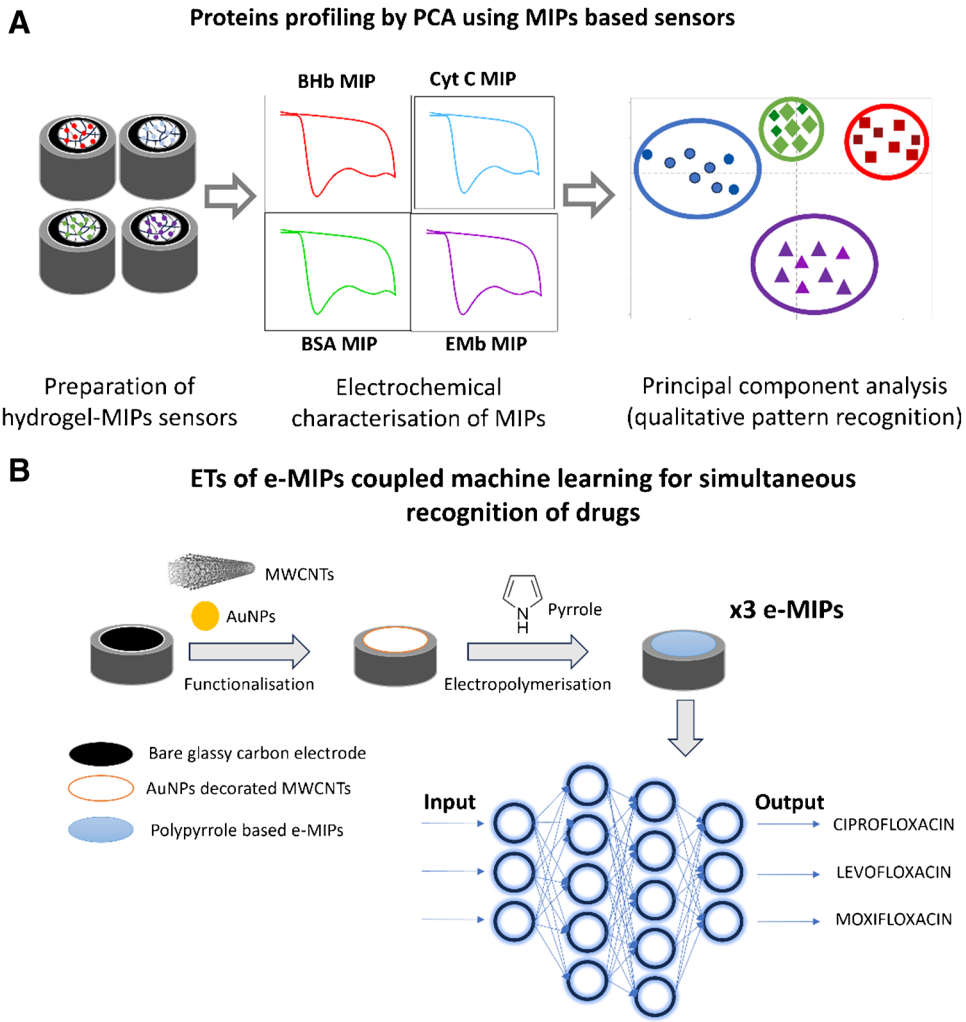

Fig. 6 Example of **A** MIPs and **B** e-MIPs sensor array for pattern recognition and quantitative determination of templates. Adapted from ref. [72, 75]

Table 3 MIP-based sensor arrays coupled machine learning for qualitative and quantitative determination of analytes

Name	Hydrogel MIP[c]	e-MIPs	Microbeads MIPs[b]	e-MIPs
Analyte	BHb EMb CytC BSA	CFX LFX MFX	4-EP 4-EG	PA AAc UA
No. of incorporated MIPs	4	3	2	3
Polymerisation method	Water phase polymerisation	Electropolymerisation	Sol-gel immobilisation	Electropolymerisation
Monomers	AA, bis-AA	Pyrrole	DVB, EGDMA, AIVN	Pyrrole
Amplifier	None	MWCNTs, AuNPs	Graphite powder	None
Method of transduction	CV	DPV	DPV	DPV
Data processing	Selection of Ip	DCT compression	DWT compression	DCT compression
Method for classification	PCA, HPCA	PCA	PCA	PCA
Method for quantification	None	ANN	ANN	ANN
Reference	[72]	[73]	[74]	[75]

Transducer elements: [b]graphite epoxy electrodes; [c]*GCE*, glassy carbon electrode

Acronyms: *4-EP*, 4-ethylphenol; *4-EG*, 4-ethylguaiacol; *AA*, acrylamide; *AAc*, ascorbic acid *AIVN*, 2,2′-azobis(2,4-dimethyvaleronitrile); *AuNPs*, gold nanoparticles; *BSA*, bovine serum albumin; *BHb*, bovine haemoglobin; *bis-AA*, *N,N′*-methylenebisacrylamide; *CFX*, ciproflaxin; *CytC*, cytochrome C; *DVB*, divinylbenzene; *EGDMA*, ethylene dimethacrylate; *EMb*, equine myoglobin; *LFX*, levofloxacin; *MFX*, moxifloxacin; *MWCNTs*, multi-walled carbon nanotubes; *PA*, paracetamol; *UA*, uric acid

signals of sensors were first compressed and therefore used to build an ANN model that regularly predicted the quantitative amount of a mixture of drugs. PCA was also used to establish the discrimination of these analytes towards their respective selective MIP-based sensor, confirming the potentiality of chemometric-assisted methods for ETs device.

A recent ET was developed by incorporating three different sensitive e-MIPs based on pyrrole monomer for the simultaneous determination of pharmaceuticals [73]. Sensors were developed by electropolymerisation in the presence of pyrrole and the three pharmaceutical targets separately dissolved in the polymerisation mixtures, to obtain the three sensitive e-MIPs onto hand-made screen-printed electrode surfaces. Raw DPV signals were collected towards increased concentration of the respective analytes and compared, indicating a clear overlapping of signals appearing at the same potential. Therefore, DPV signals were processed by DCT algorithms to reduce dataset into 12 significant coefficients which further employed the PC scores at the PCA plot. The screening analysis helped in the successful discrimination of the analytes based on different structural interactions of the developed polymeric film. For predictive quantification, the transformed data were interpolated to build an ANN model, and real samples of spiked human urine were tested. Residual plot *vs* expected values fitted in good agreement by minimising the root mean square error at value of 0.03. Another example, Herreira *et al.* synthesised a bio-ET based on sol-gel immobilised MIP-based voltammetric sensor for the classification and quantification of volatile phenolic compounds [74]. For classification purposes, samples were prepared by opportune mixing the interested analytes with others that did not reveal an analytical response towards the binding with the prepared polymers. Therefore, dataset was subjected to PCA to establish the differentiation abilities of the prepared towards mixture of analytes. A full factorial experimental design employing 4 levels per factor based on different concentrations of the analytes was used for quantification studies to train and validate an ANN model, showing a linear correlation with the experimental trials which constituted the test set.

Conclusions and outlooks

This review outlines the prospective of optimisation methods for practical application to maximise sensitivity and selectivity features at MIP-based electrochemical sensors, by discussing the intrinsic properties of such superior recognition units to analyse a plenty of molecules of interest. MIP-based sensors optimised via OFAT approach have been introduced, by stressing the need for further evaluation of unresolved interactions. Application of chemometric tools spacing into the different RSM methods has proven to be efficient to optimise sensor preparation as well as to amplify electrochemical analytical signals acquired at the MIP-electrodes interfaces. Combination of chemometric tools and electrochemical sensors based on MIPs enables to (i) reduce the number of experiments, (ii) improve working capabilities of developed devices, and (iii) reduce waste generation. Although some MIPs electrochemical sensors show great

promise for practical applications, the challenges associated with punctual recognition of analytes when simultaneously present in mixture remain enormous. In fact, cross-reactivity of MIPs has a chance to occur, especially in the presence of electroactive analytes exhibiting analogous redox behaviour.

Artificial intelligence coupled to MIPs sensor is still in its infancy but offers unique opportunities to manage such electrochemical signals, which are usually complicated to be efficiently and comprehensively interpreted. Developing advanced algorithms (ML or DL) will be the key helpers in analysing multiple electroactive species, as well as reducing manual operation and pre-treatments of complicated electrochemical sensing data.

Next generation of MIP-based sensors to be used in point-of-need scenario should be designed with a robust method that considers training sets of additional sensor parameters from the environment, such as temperature, pressure, and working pH of carrier, thus improving sensor drifts from cross-talking interferences. Over the medium- and long-term recording, the power of predictive maintenance of machine learning is expected to be exhaustive in including those inputs without affecting overall sensor capabilities.

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Declarations

Conflict of interest The authors declare no competing interests.

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