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Bioelectronic tongues: New trends and applications in water and food analysis

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ABSTRACT

Over the last years, there has been an increasing demand for fast, highly sensitive and selective methods of analysis to meet new challenges in environmental monitoring, food safety and public health. In response to this demand, biosensors have arisen as a promising tool, which offers accurate chemical data in a timely and cost-effective manner. However, the difficulty to obtain sensors with appropriate selectivity and sensitivity for a given analyte, and to solve analytical problems which do not require the quantification of a certain analyte, but an overall effect on a biological system (e.g. toxicity, quality indices, provenance, freshness, etc.), led to the concept of electronic tongues as a new strategy to tackle these problems.

In this direction, to improve the performance of electronic tongues, and thus to spawn new application fields, biosensors have recently been incorporated to electronic tongue arrays, leading to what is known as bioelectronic tongues. Bioelectronic tongues provide superior performance by combining the capabilities of electronic tongues to derive meaning from complex or imprecise data, and the high selectivity and specificity of biosensors. The result is postulated as a tool that exploits chemometrics to solve biosensors' interference problems, and biosensors to solve electronic tongues' selectivity problems.

The review presented herein aims to illustrate the capabilities of bioelectronic tongues as analytical tools, especially suited for screening analysis, with particular emphasis in water analysis and the characterization of food and beverages. After briefly reviewing the key concepts related to the design and principles of electronic tongues, we provide an overview of significant contributions to the field of bioelectronic tongues and their future perspectives.

Contents

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1. Introduction

The last decade has seen an increasing demand for fast, highly sensitive and selective methods of analysis to meet new challenges in environmental monitoring, food safety and public health. In response to this demand, industry is focusing research on fast-response and low-cost devices, such as chemical sensors, to screen or quantitatively detect contaminants, that may have been purposely added or may result from spoilage or natural contamination, and to guarantee quality control standards.

Traditional research in the field of chemical sensors has been mainly focused on improving sensitivity and selectivity towards specific analytes. Unfortunately, there are only few chemical sensors which do not suffer from interferences and matrix effects when dealing with real sample analysis. The difficulty to obtain sensors with appropriate selectivity and sensitivity for a given analyte led to the concept of electronic tongues (ETs) as a new strategy to tackle these problems (Vlasov et al., 2005).

These analytical systems are inspired by the sensory ability of taste in mammals, where a few receptors can respond in a distinct way to a large variety of substances (Toko, 2001). This principle is then coupled with a complex data treatment stage analogous to the brain functioning, which allows to quantify or classify a large amount of analytes (Fig. 1). These biomimetic systems, unlike conventional approaches, are directed towards the combination of low selectivity sensor arrays, which may show cross-response features, to obtain added value in the generation of the analytical information.

To improve the performance of ETs, and thus to spawn new application fields, biosensors have recently been incorporated to ETs, leading to what is known as bioelectronic tongues (BioETs) (Tønning et al., 2005). BioETs provide superior performance by combining the capabilities of ETs to derive meaning from complex or imprecise data, and the high selectivity and specificity of biosensors. The concept is to exploit chemometrics to solve interference issues in biosensors, and biosensors to address the lack of selectivity in electronic tongues.

In this context, the review presented herein aims to illustrate the capabilities of such systems over different scenarios, with special emphasis in water analysis and the characterization of food and beverages. After briefly reviewing the key concepts related to the design and principles of ETs, this manuscript provides with an overview of significant contributions to the field of BioETs and their future perspectives.

2. (Bio)electronic tongues

According to the agreed IUPAC definition (Vlasov et al., 2005), “the electronic tongue is an analytical instrument comprising an

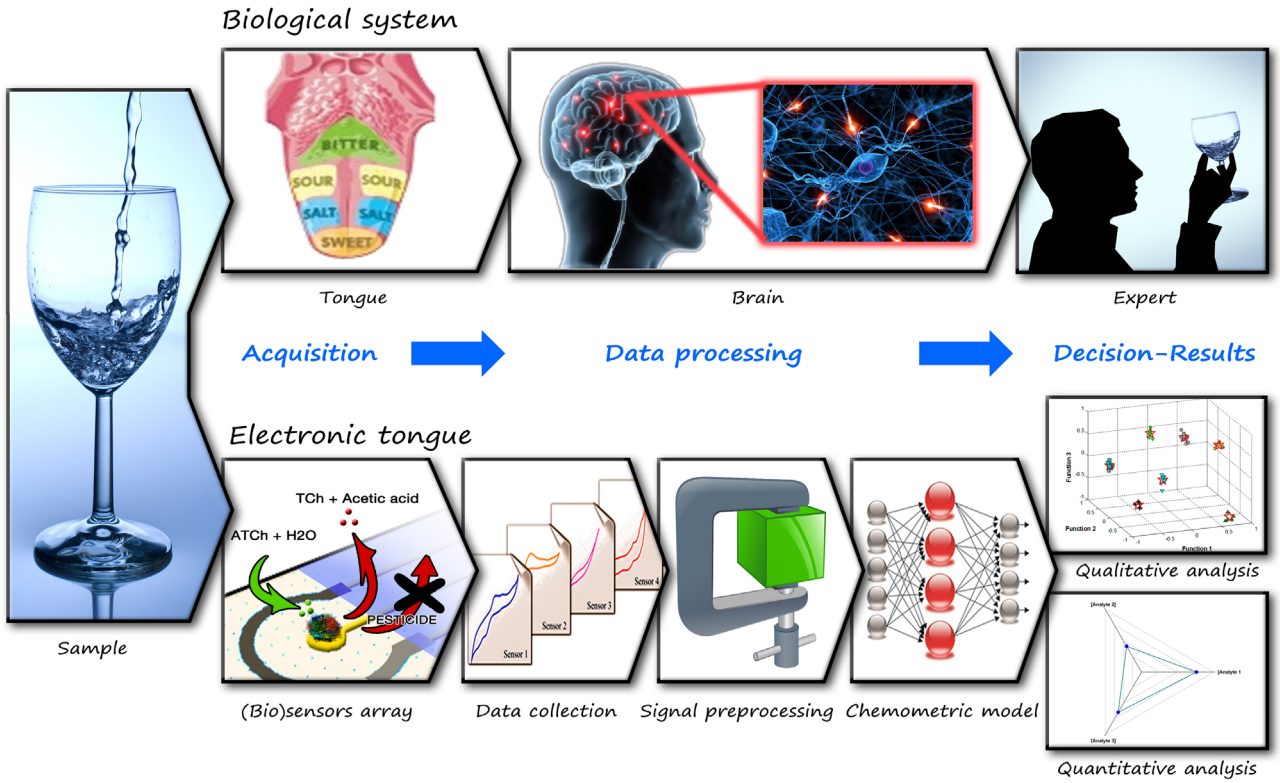

Fig. 1. Comparison of the biological recognition process of a sample with the biomimetic ET approach.

array of nonspecific, low-selective, chemical sensors with high stability and cross-sensitivity to different species in solution, and an appropriate method of PARC and/or multivariate calibration for data processing".

The term BioET was coined by Tønning et al. (2005), but the approach had already been used in the past (Bachmann and Schmid, 1999). Despite there is not yet a strict definition, it is widely accepted that BioETs are only distinguished from "ETs" by the combination of one or several biosensors into the sensor array, commonly sharing the same transduction principle to facilitate their compatibility.

Although biosensors are usually thought to be highly selective and specific towards the target of interest, and accordingly their usage might seem to differ from the ETs principles, the truth is that bioreceptors often cross-react with different species and thus biosensors also show certain cross-sensitivity and suffer undesired matrix effects. Therefore, not only fitting perfectly in this approach, but even adding some advantages over the "conventional" ETs.

As the definition states, (Bio)ETs combine an array of (bio) sensors able to provide a wide and complete response of the analysed species, plus a modelling tool able to interpret and extract meaningful data from complex readings. Therefore, the main advantages of ETs lie in their ability to provide comprehensive information of the sample within a few seconds, while tackling the simultaneous detection of a large spectrum of compounds in one step. Besides, the data processing stage may offset any matrix or interference effect from the sample itself, or allow the resolution of the interferences, drifts or nonlinearity obtained with the sensors (Gómez and Callao, 2008). Thus, this methodology can allow the parallel determination of a large number of analytes in a complex sample, without performing any pretreatment, by counterbalancing any interference effect (Escandar et al., 2007).

Over the next subsections, we will focus on those two components: (bio)sensor arrays and chemometric tools.

2.1. (Bio)sensor arrays

From an analytical point of view, a sensor is a device designed to perform selective measurements of physical, chemical or biological parameters, generating a quantifiable physical signal (Hulanicki et al., 1991; Janata and Bezegh, 1988). The higher specificity of biosensors is afforded by the incorporation of a biological recognition element, which is retained either in direct spatial contact or integrated within a transduction element (Thévenot et al., 1999).

ETs and BioETs have mainly been developed using chemosensors and biosensors with electrochemical transduction (namely, potentiometric, voltammetric or impedimetric) (del Valle, 2008; Riul et al., 2010), although optical or piezoelectric (bio)sensors have also been used. Furthermore, it is even possible to combine the responses obtained from different sensors employing different transduction principles, a strategy known as data fusion (Klein, 2004). This review will mainly focus on electrochemical BioETs.

As stated, when developing a (bio)sensor, the aim is to ideally obtain a sensor that presents specific response towards the analyte of interest. Unfortunately, there are only few interference-free chemical sensors featuring non-significant matrix effects when dealing with real sample analysis.

To overcome those limitations, (bio)sensors are designed to work under well-defined conditions, towards specific analytes in certain types of samples. Occasionally, a sample pre-treatment step might be considered in order to mask or remove the interfering species (Workman et al., 2001). However, this increases the number of analysis steps, an antagonistic situation to the principles of (bio)sensors, which aim to combine in one all the steps of the analytical process (Hulanicki et al., 1991). Besides, those processes are laborious and time-consuming (increasing analysis cost), and tend to be specific for each of the interfering compounds; a problem that exponentially increases when analysing multiple analytes at a time.

Alternatively, a new trend based on the usage of sensor arrays emerged over two decades ago. With this approach, reproducible non-specific sensors are combined in an array and used for the multicomponent analysis based on the usage of signal processing methods and a multivariate calibration model; thus, shifting the complexity from the analytical field to the processing side (Fig. 1). In this way, it is possible to extract additional information from the system to overcome issues unsolved using traditional methods (Esteban et al., 2006; Ni and Kokot, 2008). A very good example of the latter is what is known as "soft sensor" (James et al., 2002), that is, when an unmeasured variable is estimated from other measured variables by means of a mathematical model.

Sensor arrays can be categorized in three classes: arrays of redundant sensors, arrays of selective sensors and arrays of cross-sensitive sensors (del Valle, 2010). The latter are the ones that led to the appearance of ETs around the 1990s (Otto and Thomas, 1985; Vlasov and Legin, 1998); whereas first approaches employing biosensors did not appear till the end of that decade (Bachmann and Schmid, 1999).

As stated, these biomimetic systems are inspired by the sensory ability of taste in mammals, where a few receptors can respond to a large variety of substances; and oppositely to conventional approaches, directed towards the combination of highly stable and cross-sensitive sensors to add value to the generated analytical information. Moreover, they can also be used to correct drift and nonlinearity issues of the sensors during the modelling stage (Artursson et al., 2000; Gómez and Callao, 2008).

2.2. Chemometrics and multivariate data analysis

Data analysis, in conjunction with an appropriate sensor array, is a fundamental part of any ET system. In this regards, chemometrics is the discipline devoted to extract information from chemical systems by data-driven means (Brown et al., 1996). That is, the discipline that uses mathematical and statistical methods to obtain knowledge about chemical systems, usually through the design and optimization of experimental procedures, or to extract knowledge from the chemical analyses.

As could be expected, the mathematical background behind these methods can be quite complex and bewildering for the non-expert (Bro, 1998; Richards et al., 2002). However, nowadays it is possible to find many software packages (e.g. *EasyNN*, Neural Network Software; *The Unscrambler*, CAMO Software; *Matlab*, MathWorks; *R*, R Development Core Team) that allow their easy usage, only requiring knowledge of the conceptual and theoretical basis (i.e. the advantages and limitations of each method), without the need of knowing all their internal operating mechanisms (i.e. incorporating all the scripts to run the mathematics). Hence we only need to know the analytical problem we are tackling, and based on its nature, choose the most appropriate tool to solve it. To assist in this process, developers of chemometrics software have released complete training packages, which include easy-to-read introductory texts and exercises (e.g. Beale et al., 2012; Esbensen, 2002).

The chemometric tools that might be used, can be classified according to the extracted information and to the learning rule (Richards et al., 2002). Namely, in the former case, we will distinguish between qualitative and quantitative methods, depending on the type of extracted information; i.e. the ones that address the classification or discrimination of a set of samples, and the ones

Table 1
Overview of the most common preprocessing methods: (+) main advantages and (−) disadvantages.

Feature selection methods (e.g. causal index, genetic algorithms)	+ Allows identifying the most important features in the raw data − Time required − Dependence on the parameters of the selection algorithm used, selected sets are not unique
Windowed slicing integral, "kernels"	+ Conceptual and mathematical simplicity − Arbitrariness in the selection of the number of sections
PCA	+ Provides a measure of signal representativeness + Simplicity − It focuses on the maximum variance between samples, hence giving less importance to small differences which in some cases could be significant (cannot see the forest for the trees)
FFT, DWT	+ Can be undone, what allows to measure signal reconstruction + Coefficients are a representation of the whole signal + 'Denoises' signal during the feature extraction process − Higher complexity compared to previous ones

DWT: discrete wavelet transform, FFT: fast Fourier transform, PCA: principal component analysis.

that focus on the quantitative determination of a certain index. While in the latter, methods are categorized according to the information provided to the learning tool during the processing of the data; depending on whether they seek a hidden structure in unlabelled data (unsupervised methods) or infer a response model from labelled training data (supervised methods).

Among the different methods that can be implemented, principal component analysis (PCA), partial least squares (PLS) and artificial neural networks (ANNs) are the most widely employed in ET applications (Ciosek and Wroblewski, 2007). Concretely, PCA is the most common one, being used either as a preprocessing step or as a qualitative visualization tool; whereas most advanced qualitative modelling may be achieved with the use of PLS-discriminant analysis (PLS-DA), linear discriminant analysis (LDA) or support vector machines (SVMs). In the case of quantitative applications, simpler models can be built either using multiple linear regression (MLR) or principal component regression (PCR) (Scott et al., 2006), although more powerful methods, such as PLS or ANNs, can provide better results. The latest trends in data analysis are mainly related to the use of trilinear approaches such as PARAFAC or Tucker models for qualitative analysis, and multiway PLS (nPLS) for quantitative models (Bro, 2006; Olivieri et al., 2011). For an in-depth revision of the most significant developments and trends in the field, readers may consult the series of 19 reviews published by Lavine and Workman (17 under the title of "Chemometrics") (Lavine and Workman, 2013).

The data processing stage can be divided into three different steps: weighting, signal compression and modelling. Despite only the last one is mandatory, the usage of the other two improves the (Bio)ET performance, and is therefore recommended.

2.2.1. Weighting

To ensure a proper modelling, the quality of the recorded data is a key factor: if the initial information is erroneous or inadequate, this will cause a lack of accuracy in the analytical information extracted by the model. So certain precautions need to be taken prior to the modelling stage to ensure the reliability of the measurements.

Moreover, another key factor to be considered when building a model that encompasses the responses of each sensor from the array is the relative importance of the changes of each variable, to equate their *a priori* contribution into the final model (Scott et al., 2006). For this reason, regardless of the methods used either at the modelling or at the signal compression stages, a data-centering and/or normalization step should be carried out before constructing the model. To this aim, some of the strategies that can be used are: centering, standardization, normalization or auto-scaling of the data (Bro and Smilde, 2003; Palit et al., 2010; Scott et al., 2006).

2.2.2. Signal compression

Despite the progress made in the fields of chemometrics and computing, the high dimensionality of the generated data by an array of sensors still represents a limitation from both the modelling and computational perspective; and hence, a data pre-processing stage is required to achieve data compression and/or reduction of the high dimensionality of the generated data (generally by its unfolding into a 2D matrix (Cartas et al., 2011)), while preserving the relevant information in a format compatible with the modelling tool. This is especially critical when data come from e.g. arrays of voltammetric sensors (samples × sensors × polarization potential) or kinetic systems that include dynamic profiles of arrays of sensors (samples × time × potential/current); even more when additional variables, such as pH, are considered as well (Maggio et al., 2011; Serrano et al., 2014).

The use of a pre-processing stage also avoids redundancies in input data and provides a model with better generalization ability (Cetó et al., 2013a). And despite not being a requirement for some of the standard chemometric modelling tools (e.g. PCR or PLS), it has been demonstrated that, even in such cases, the usage of a compression stage can improve the performance of the generated model (Cetó et al., 2012c; Palacios-Santander et al., 2008).

For this purpose, some of the methods reported in the literature are: feature selection algorithms (Balabin and Smirnov, 2011), PCA (de Carvalho et al., 2000), Legendre polynomials (Simons et al., 1995), "*kernel*" functions (Gutiérrez-Osuna and Nagle, 1999), windowed slicing integral method (Cetó et al., 2013b), fast Fourier transform (FFT) (Cetó et al., 2012a) or discrete wavelet transform (DWT) (Moreno-Barón et al., 2006). A description of these methods can be found in (Cetó et al., 2013a), and their main advantages and drawbacks are summarized in Table 1.

Alternatively, there is also a straight-forward solution focused on using trilinear approaches, such as PARAFAC or Tucker models for qualitative analysis (Bro 1997), and nPLS for quantitative models (Bro, 2006); or even quatrilinear methods for much more complex data sets (Maggio et al., 2011). Those represent new trends in chemometric analysis, and are the response to the growing needs of most powerful analysis tools able to cope with the advances in instrumental data generation and collection. However, the complexity of these techniques is still hindering their implementation (Bro, 1998).

2.2.3. Modelling: qualitative analysis

This is the most common and widely used type of analysis, allowing the discrimination or classification of the samples based on maps generated using various chemometric tools (Lavine and Rayens, 2009); namely, PCA (Jolliffe, 2002), LDA (Mitteroecker and Bookstein, 2011), PLS or PLS-DA (Vinzi et al., 2010; Wold et al., 2001), ANNs (Beale et al., 2012; Despagne and Massart, 1998) and SVMs (Cortes and Vapnik, 1995), among others. It is worth noting

that even though PCA provides a better representation of samples (dis)similarities, it cannot be properly considered as a pattern recognition method as it does not perform samples classification, albeit being used in conjunction with a modelling tool such as PLS or ANNs (Richards et al., 2002). However, it is still a useful visualization tool to check whether the samples group together in clusters or remain unrelated. Further description of these methods can be found in Kumar et al. (2014).

2.2.4. Modelling: quantitative analysis

Quantitative analysis methods can be further categorized based on the regression analysis form; distinguishing between linear and nonlinear ones. Namely, in the case of nonlinear methods, the data set is modelled by a function, which is a nonlinear combination of the model parameters, and depends on one or more independent variables adjusted using an iterative method. While in the case of linear methods, data are modelled using linear predictor functions, normally adjusted through the least-squares method.

This modelling stage can be achieved using either linear methods such as MLR (Martens and Naes, 1991; Richards et al., 2002), PCR (Martens and Naes, 1991; Richards et al., 2002), PLS (Vinzi et al., 2010; Wold et al., 2001) or nPLS (Bro, 1998), or nonlinear ones such as ANNs (Beale et al., 2012; Despagne and Massart, 1998), as more common ones. Further description of these methods can be found in Cetó et al. (2013a), Ni and Kokot (2008), Richards et al. (2002) and Kumar et al. (2014), and their main advantages and drawbacks are summarized in Table 2.

2.3. Evaluation of model performance

Upon completion of the modelling stage, the next step is the evaluation of its performance. To this aim, predicted and actual values are compared, followed by calculation of proper metrics as required.

An important step in the assessment of the chosen model's error rate and generalization ability is the selection of the validation or testing subset, to avoid an overly optimistic assessment of the model's performance (Despagne and Massart, 1998).

2.3.1. Validation methods: data division

The first step is the division of the set of samples into two subsets: training (tr) and testing (ts, also known as validation). The former is used to build the model, providing the system with responses (X_{tr}) and target (Y_{tr}) matrices to adjust the model parameters; whereas the latter is required to assess and validate its performance, providing the system only with responses matrix (X_{ts}) as input data to be interpolated in the built model and calculate the predicted targets matrix (Y_{ts}). Next, real and predicted data are compared to evaluate the quality of fit and detect overfitted systems.

At this stage, the importance of the testing subset has to be emphasized. That subset must not be used during the modelling

Table 2
Overview of the most common modelling techniques: main (+) advantages and (−) disadvantages.

Qualitative methods	PCA	+ Provides a visual output of samples (dis)similarities + Simplicity + Although as many principal components (PCs) as variables in the original data are generated, almost all the variance carried by the original variables can be summarized in a few PCs − Cannot be used as a classifier by itself, requiring its coupling with a modelling tool − It focuses on the maximum variance between samples, hence giving less importance to small differences which in some cases could be significant (cannot see the forest for the trees)
	LDA, CVA[a]	+ Supervised method, suitable for samples classification + Discriminant functions (DFs) are built based on a linear combination of the original variables that maximizes the separation between groups + Only (*#groups*-1) DFs are generated − Linear model
	SVMs[b]	+ Can handle nonlinearities by means of the *kernel trick* + Unique solution in comparison to ANNs − Higher complexity
Quantitative methods	MLR	+ Simplicity − Only one target variable (y, column vector) can be modelled at a time from the responses matrix (X). Individual models have to be built for each Y variable − Fails when there are more variables than samples
	PCR	+ Simplicity; two step method based on PCA+MLR + Performs particularly well when the various response variables express common information, i.e. when there is a high level of correlation, or even collinearity (Esbensen, 2002) − Captures only the characteristics of the X variables − PLS has overtaken PCR as the preferred choice among chemists
	PLS	+ Several Y-variables are modelled at a time with PLS-2, although not with PLS-1 + Both X and Y matrices are simultaneously decomposed to find the latent variables (LVs) in *x* that will best predict the latent variables in *y*; bilinear factor models + Convergence of the system to a minimum residual error is often achieved in fewer factors than using PCR − Poorly modelling of nonlinear systems
	nPLS	+ Extension of PLS to the multiway case + Takes advantage of any multiway structure in the data, opposite to bilinear methods where unfolding of the data is performed prior to their modelling − Higher complexity compared to PLS
	ANNs[b]	+ More flexible modelling methodologies, since both linear and nonlinear functions can be used (or combined) in the processing units − Complexity of its architecture − Requires a preprocessing step for data reduction − Obtained model is not unique, might vary slightly upon rebuilding

ANNs: artificial neural networks, CVA: canonical variate analysis, LDA: linear discriminant analysis, MLR: multiple linear regression, nPLS: multiway partial least-squares regression, PCA: principal component analysis, PCR: principal component regression, PLS: partial least-squares regression, SVM: support vector machines.

[a] LDA is limited to the discrimination between two groups of samples, whereas its extension to multiple groups should be referred as canonical variate analysis (CVA). However, this distinction is unusual, being both referred as LDA (e.g. even in *R* code).

[b] Both SVMs and ANNs can be used either in qualitative or quantitative modelling. Similarly, PLS discriminant analysis (PLS-DA) is also used in qualitative modelling.

stage so as to be used as blind set of samples. How the division between the two subsets is performed is also important (Molinaro et al., 2005). To address this important issue, the more common strategies used in ET applications are:

- *Split sample*: this method consists on performing only one division between the training and testing subsets, generally in the ratio of 60:40 to 80:20, respectively. This strategy is particularly useful when using an experimental design that defines the samples of the training set; otherwise, the division can be randomly done.
- *Leave-X-out* or *k-fold*: the set of samples is randomly divided in k subsets. Then k-1 subsets are used as the training subset to build the model, the performance of which is afterwards evaluated towards the subset that has been left out. This process is repeated k times (the folds), employing each of the k subsets as validation. Afterwards, data are averaged (or otherwise combined) to produce a single estimation. The main advantage over the previous method is that all observations are used for both training and testing. However, similar to other cross-validation methods, it can lead to over-optimistic results, especially when X is close to 1 (Despagne and Massart, 1998; Kirsanov et al., 2012).
- *Leave-one-out*: this is a particular case of the previous method ($X=1$ or $k=n$), where only one sample is left out of the modelling process each time. Thus, each sample is quantified or classified using the model generated with the remaining samples, repeating the process as many times as samples are in the study (n). This particular strategy is commonly used with reduced sets of samples.
- *Repeated random sub-sampling*: this method is halfway between the *split sample* and *k-fold* methods. That is, samples are randomly split between training and testing subsets, and for each split, a model is generated and its performance is evaluated. This random subdivision of data between training and testing subsets is repeated k times, and as for the *k-fold* method, results are averaged over the splits. The differentiating advantage of this method is that the dependence of the prediction on the specific division of samples between training/testing subsets is eliminated and the number of samples in each subset is independent of the number of folds; besides, this method allows the calculation of model uncertainties and provides unbiased data (Shao and Tu, 1995).

2.3.2. Performance indicators of qualitative models

In qualitative approaches, usually the confusion matrix is firstly built (Table 3). This allows to easily and quickly assess the performance of the classifier model by checking if there is any value different from 0 out of the diagonal, and if it is the case, to also identify which classes are the ones being confused.

To numerically quantify the performance of the qualitative models, several metrics calculated from the confusion matrix can be used (Broadhurst and Kell, 2006). However, we should mainly focus on the following three (Appendix A):

- Classification rate: total proportion of objects that are correctly assigned to their corresponding class. This rate simply indicates the proportion of cases correctly identified regardless cases poorly rated or the size of each group; hence, it can yield misleading results.
- Sensitivity: the percentage of objects of each class correctly identified by the model; i.e. the proportion of true positive (TP).
- Specificity: the percentage of objects from different classes correctly rejected by the model; i.e. the proportion of true negative (TN).

Table 3
Example of a confusion matrix for a binary classification problem, cross-tabulating the observed and predicted outcomes. TP: true positive, TN: true negative, FP: false positive, FN: false negative.

	$A_{predicted}$	$B_{predicted}$
A_{actual}	TP	FN
B_{actual}	FP	TN

As already stated, although PCA cannot be considered as a proper recognition method, it is widely used to evaluate samples (dis)similarities. However, it is an unsupervised method that lacks of a learning rule to classify or distinguish groups of samples. Therefore, a statistical approach should be sought when not used in conjunction with a modelling tool, rather than "subjectively drawing a circle" around the samples of interest.

If we consider each of the groups individually, being those formed by sample replicates, the scores can be assumed to follow a normal distribution (Wagner and Castner, 2001), and consequently, the t distribution can be used to calculate the confidence limits for the scores of each of the groups on a given PC. The confidence limits for a subgroup on a cross-plot of two PCs are then determined by performing PCA on the mean-centered set of the subgroup scores and using the eigenvalues to determine the confidence limits for the scores on the secondary PCs. These confidence limits are the major and minor axes of a confidence ellipse drawn around the scores. The loadings can then be used to rotate the ellipse and the scores from the secondary PCs back into the original PC plot.

2.3.3. Performance indicators of quantitative models

Similarly, in quantitative approaches, a comparison graph of predicted *vs.* expected values is initially built, and the regression parameters estimated from the linear regression of the data are used as indicators of the modelling goodness (Fig. 2A). This allows to easily identify how well the model is performing by just looking at the plot. Moreover, to numerically assess the performance of the quantitative model, some parameters are usually calculated (Appendix B):

- Regression parameters: the slope, intercept and correlation coefficient of the linear regression are compared to the ideal values (1, 0 and 1, respectively). Additionally, the confidence intervals for both the slope and intercept, estimated from the regression statistics, determine if there are significant differences between the actual and predicted values at a certain significance level by checking whether the theoretical values are contained in those.
- The root mean squared error (RMSE) provides a measure of the difference between the predicted and actual values. Its value represents the average vertical distance of the actual data points from the fitted line, in the same units; providing in this way, a direct measure of the goodness of fit directly interpretable in terms of units, unlike the correlation coefficient.

Besides, to remove its dimensionality dependence, RMSE can be normalized to the range of the observed data (NRMSE).

- Ratio of standard error of performance to standard deviation (RPD) and range error ratio (RER) are two statistics widely used in NIR spectroscopy (Fearn, 2002), but rarely considered in ETs applications. RPD and RER relate the error of prediction to the variance and range in the sample set, respectively, providing similar information to the coefficient of determination (R^2) (Fearn, 2002). Both are dimensionless statistics that increase as model performance does. This attribute allows them to be used

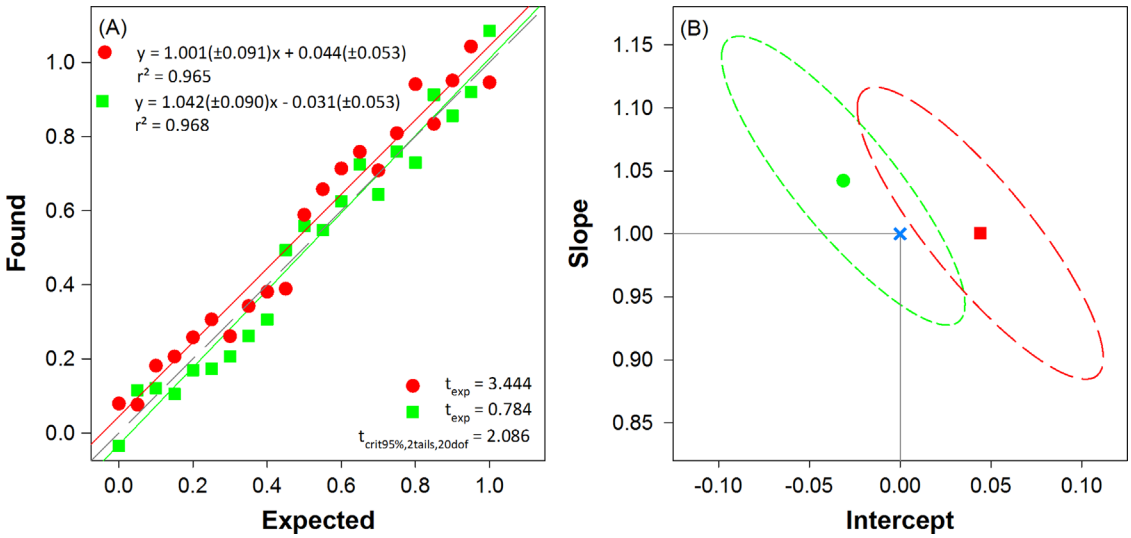

Fig. 2. (A) Comparison graph of predicted vs. obtained values: (grey dashed line) theoretical, (solid red line, •) data set 1 and (solid green line, ■) data set 2. (B) Joint confidence intervals plot for the previous data; the ideal point (1,0) is also plotted (blue, **x**) and the intervals calculated at the 95% confidence level. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

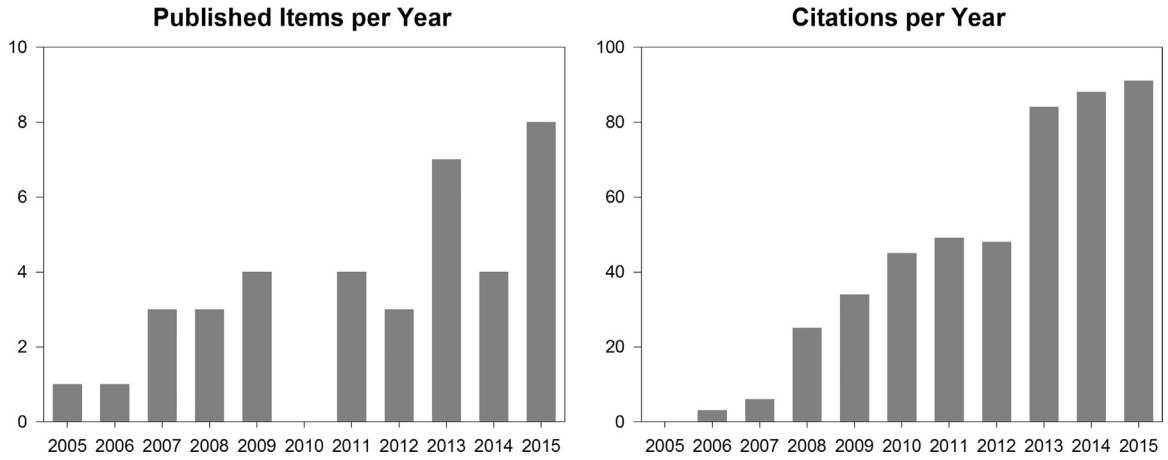

Fig. 3. Citation report created from ISI Web of Science through the search of "bioelectronic tongue" as topic; accessed on 1/12/2015.

as objective performance indicators regardless of the application.

– Joint confidence intervals: as previously stated, the usual approach when validating the performance of quantitative models starts with the graphical comparison of the predicted and actual values, which might be later followed by statistical tests on the slope and intercept. However, if these tests are independently carried out, the strong correlation between the estimated slope and intercept obtained by least squares calculations is ignored, potentially leading to erroneous conclusions (Lark, 1954). That is, a positive error might be accompanied by a negative error in the intercept (slope >1, intercept <0), and *vice versa* (Fig. 2B). To address this issue, the calculation of joint confidence intervals for the intercept and the slope has been proposed as an alternative (Martínez et al., 2002).

2.4. Commercial devices

Despite the great variety of electronic noses commercially available and produced by more than 20 companies (Wilson and Baietto, 2009), the commercial availability of ETs is limited.

A case-in-point are the devices offered by *Alpha Mos* in France, arguably the best known company in this field, which is currently commercializing four electronic noses, one electronic tongue and one electronic eye. Other examples are the companies *Insent* (Intelligent Sensor Technology Inc.; Japan) and *McScience* (Korea), which also commercialize different ETs. The latter has been supplying different ETs since 1993. Although it has only one ET in its catalogue, this is the result of the evolution of the previous models: three devices currently discontinued, which led to the fourth version, available since 2007.

All these devices are potentiometry-based, and to the best of authors' knowledge, BioETs or ETs based on other transduction principles are not being commercialized yet, despite some attempts (Winquist, 2008).

3. BioETs in water and food analysis

A literature search employing the term "bioelectronic tongue" demonstrates a steady increase of the number of publications since 2005, when the term BioET was first used (Fig. 3). More significant is the increase in the number of citations that those publications have been receiving. Besides, there is a huge number of publications in which the term is not being used, falling under the generic name of ET or taste sensor/chip depending on the

Table 4
Relevant applications employing the BioET concept in water and food analysis.

Application	Principle of detection	Data processing	System description	Ref.
Applications in water analysis				
Quantification of insecticides: paraoxon and carbofuran mixtures	Amp	ANNs	Array of four enzymatic sensors based on AChE inhibition	(Bachmann et al., 2000; Bachmann and Schmid, 1999)
Detection of pesticides and phenols in wastewater samples	Amp	PCA	Miniaturized 8-channel array combining multiple enzymes immobilized onto carbon and platinum working electrodes	(Solná et al., 2005)
Quantification of pesticides: dichlorvos and carbofuran mixtures	Amp	ANNs	Array of three enzymatic sensors based on AChE inhibition	(Cortina et al., 2008)
Quantification of pesticides: dichlorvos and methylparaoxon mixtures	Amp	ANNs	Array of three enzymatic sensors based on AChE inhibition, incorporated in a FIA system	(Valdés-Ramírez et al., 2009)
Quantification of pesticides: chlorpyriphos-oxon, chlorfenvinphos and azinphos-methyl oxon	Amp	ANNs	Array of two enzymatic sensors based on AChE inhibition. Simplified one-step method that involves measuring the slope of inhibition	(Alonso et al., 2012)
Determination of six organophosphates pesticides: dichlorvos, malaoxon, chlorpyrifos-oxon, chlorpyrifosmethyl-oxon, chlorfenvinphos and pirimiphos-methyl-oxon	CAmp	ANNs	Array of six enzymatic sensors based on AChE inhibition, incorporated in an automated system (Fig. 4)	(Crew et al., 2011)
Classification of pesticides residues based on three groups (carbamates, pyrethroids, and organophosphates), including up to 28 compounds	Pot	ANNs	Array of cellular sensors based on BERA, using the electrophysiological responses of three cultured cell lines	(Ferentinos et al., 2013)
Quantification of phenolic compounds: phenol, catechol and *m*-cresol	Amp	ANNs	Array of five Tyr-based enzymatic sensors incorporated in a FIA system	(Trojanowicz et al., 1999)
Quantification of phenolic compounds: phenol, catechol and *m*-cresol	LSV	ANNs	Single Tyr-based enzymatic sensor incorporated in a SIA system	(Gutés et al., 2005)
Quantification of phenolic compounds: catechol and 4-chlorophenol mixtures	Amp	PLS	Single Tyr-based enzymatic sensor incorporated in a FIA system	(Dock et al., 2005)
Quantification of phenolic compounds in binary mixtures: phenol/chlorophenol, cathecol/phenol, cresol/chlorocresol and phenol/cresol	LSV	PLS-1	Array of two Tyr- and Lac-based enzymatic sensors	(Freire et al., 2003)
Quantification of phenolic compounds: catechol and caffeic acid mixtures in olive oil mill wastewater	Amp	ANNs	Single Lac-based enzymatic sensor	(Torrecilla et al., 2007)
Monitoring of the photo-degradation of phenolic compounds: catechol, *m*-cresol and guaiacol in artificial wastewater	CV	FFT + ANNs	Array of four (bio)sensors, including Tyr, Lac and Cu nanoparticles	(Cetó et al., 2015)
Quantification of Cu^{2+}, Cd^{2+} and Pb^{2+} mixtures	SWV	PLS, nPLS	Array of four gold electrodes modified with three peptides. Single gold electrode modified with the three peptides	(Chow et al., 2006; Ebrahimi et al., 2008)
Quantification of Pb^{2+}, Cd^{2+} and Zn^{2+} mixtures	AdSV	FFT + ANNs	Array of three peptide-modified electrodes	(Serrano et al., 2014)
Discrimination of wastewater based on its quality	Amp	PCA	Miniaturized 8-channel array combining multiple enzymes immobilized onto carbon and platinum working electrodes	(Tønning et al., 2005)
Evaluation of wastewater quality and prediction of several organic pollutant indexes	Amp	PCA, PLS	Two miniaturized 8-channel array combining multiple enzymes immobilized onto carbon and platinum working electrodes	(Czolkos et al., 2016)
Evaluation of BOD in synthetic industrial wastewaters	Amp	PLS, PCA	Array of seven biosensors based on different semi-specific and universal microorganisms immobilized onto a Clark-type electrode	(Raud and Kikas, 2013)
Evaluation of COD in water samples	Generated current	ANNs	MFC-based biosensing	(Feng et al., 2013b)
Identification of specific chemical pollutants present in water samples: glucose, starch, acetate and butyrate	Generated current	ANNs	MFC-based biosensing	(Feng et al., 2013a)
Identification of specific chemical pollutants present in water samples: aldicarb, dimethyl-methylphosphonate and bisphenol-A	Generated current	ANNs	MFC-based biosensing	(King et al., 2014)
Applications in food analysis				
Quantification of glycoalkaloids: α-solanine and α-chaconine mixtures	Amp	ANNs	Array of two enzymatic sensors based on AChE inhibition. Simplified one-step method that involves measuring the slope of inhibition	(Espinoza et al., 2014)
Quantification of pesticides in milk: chlorpyriphos-oxon and malaoxon mixtures	Amp	ANNs	Array of two enzymatic sensors based on AChE inhibition, incorporated in a FIA system	(Mishra et al., 2015)
Quantification of antibiotics in urine, serum and milk: tetracycline and cefixime mixtures	SWV	PCA, ANNs	Single gold SPE modified with gold-nanoparticles and a self-assembled monolayer (SAM) of cysteine	(Asadollahi-Baboli and Mani-Varnosfaderani, 2014)
Quantification of phenolic compounds: catechol, caffeic acid and catechin mixtures in wine	CV	CI/ + ANNs	Array of four (bio)sensors, including Tyr, Lac and Cu nanoparticles	(Cetó et al., 2012b)
Quantification of phenolic compounds: ferulic, gallic and sinapic acids mixtures in beer	CV	Int + ANNs, PCA	Array of four (bio)sensors, including Tyr, Lac and Cu nanoparticles	(Cetó et al., 2013b)
Quantification of total phenolic content in wines and sparkling wines	CV	FFT/Int + ANNs, PCA	Array of four (bio)sensors, including Tyr, Lac and Cu nanoparticles	(Cetó et al., 2014b; Cetó et al.,

Table 4 (*continued*)

Application	Principle of detection	Data processing	System description	Ref.
				2012a)
Quantification of total phenolic content in wines	CV	*Kernels*/DWT+PLS/ANNs	Array of twelve (bio)sensors, including Tyr, Lac and several electron mediators	(Cetó et al., 2014a)
Monitoring the ageing of beers	CV	*Kernels*+PCA/LDA	Array of three Tyr-based enzymatic sensors	(Ghasemi-Varnamkhasti et al., 2012)
Discrimination of phenolic compounds and grape varieties	CV	*Kernels*+PCA	Array of three (bio)sensors modified with Tyr, Lac and $LuPc_2$ Array of six (bio)sensors modified with GOx and Tyr, plus electron mediators	(Medina-Plaza et al., 2014; Medina-Plaza et al., 2015)
Determination of propionaldehyde	Amp	PLS	Disposable enzymatic SPE using aldehyde dehydrogenase	(Rojas et al., 2004)
Determination of glucose and ascorbic acid in fruit juice samples	LSV	ANNs	Array of three biosensors containing GOx and different metallic catalysts, incorporated in a SIA system	(Gutés et al., 2006)
Determination of ethanol and glucose mixtures	Amp	ANNs	Array of two amperometric microbial sensors based on the immobilization of *Gluconobacter oxydans* and *Pichia methanolica* cells	(Lobanov et al., 2001)
Determination of glucose, ascorbic acid and uric acid mixtures	CV	ANNs	Single gold-nanoparticle GOx-based biosensor	(Torrecilla et al., 2008)
Classification of beer samples	CV	FFT+LDA	Array of six electrodes incorporating a GOx-based enzymatic sensor	(Cetó et al., 2013c)
Quantification of lysine in feed samples	Pot	PCR, PLS, ANNs	Array of eight ISEs incorporating a lysine oxidase-based enzymatic sensor Array of two ISEs incorporating a lysine oxidase-based enzymatic sensor, integrated in a FIA system	(García-Villar et al., 2001; García-Villar et al., 2003)
Detection of *Salmonella typhimurium* in pork samples	EIS	PLS	Immunosensor based on the immobilization of anti-*Salmonella* antibodies on the surface of an interdigitated gold microelectrode	(Kim et al., 2013)
Quantification of acetate, L-lactate and succinate mixtures	Amp	PLS	Single microbial sensor based on the immobilization of *Alcaligenes eutrophus* KT02 bacteria cells on an oxygen electrode, and integrated in a flow-through system	(Plegge et al., 2000)

AdSV: Differential pulse adsorptive stripping voltammetry, Amp: amperometry at fixed potential, CAmp: chronoamperometry, CV: cyclic voltammetry, DPV: differential pulse voltammetry, EIS: electrochemical impedance spectroscopy, LSV: linear sweep voltammetry, Pot: potentiometry, SWV: square wave voltammetry.
ANNs: artificial neural networks, CI: causal index, DWT: discrete wavelet transform, FFT: fast Fourier transform, Int: windowed slicing integral, LDA: linear discriminant analysis, PCA: principal component analysis, PCR: principal component regression, PLS: partial least-squares regression.

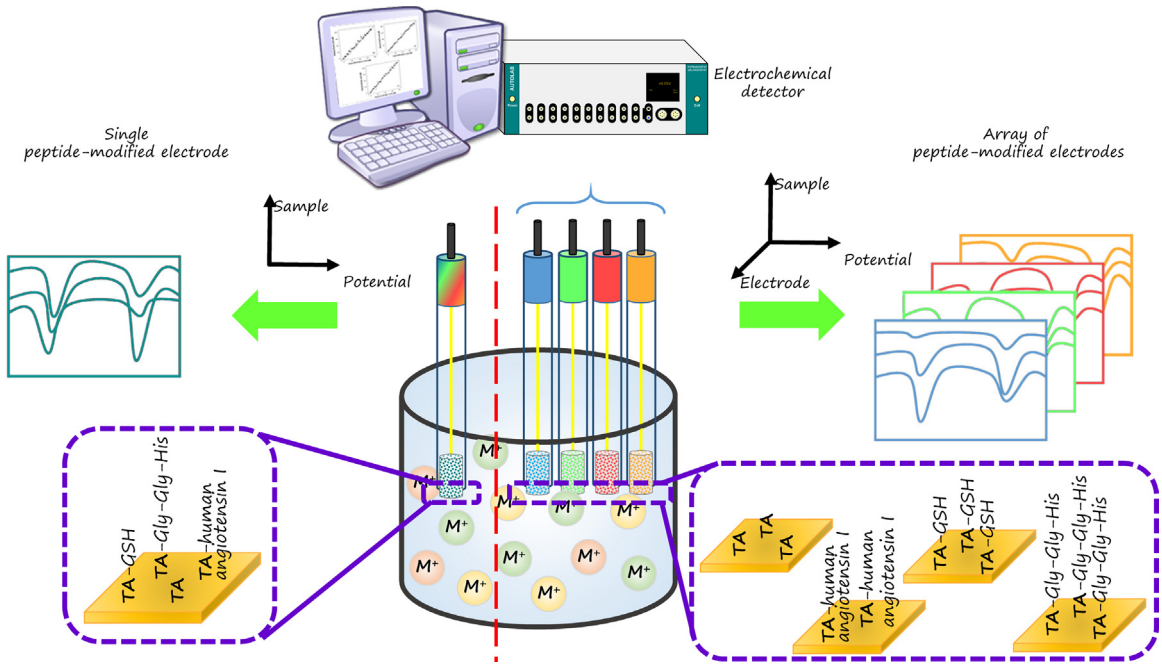

Fig. 4. Scheme of the approach used by Ebrahimi et al. (2008) to demonstrate the improved performance of an array of sensors compared to the use of a single sensor. To this aim, four gold electrodes were modified each one with a different peptide, and their response compared to the performance of a single gold electrode modified with the four peptides.

region (Ciosek and Wroblewski, 2007), or simply described as the combination of some sensor systems combined with modelling tools.

Many variants of BioETs have already been reported in the literature, and after an extensive search, the most relevant applications in water, food and beverages analysis will be described in the next sections. A brief description of those has also been summarized in Table 4.

Even though systems based on a single biosensor instead of an array are not properly considered as BioET according to the IUPAC definition (Vlasov et al., 2005), some of them follow the same principles described above, in our opinion deserving to be included in this section. For instance, recent work from Ebrahimi *et al.* demonstrated the improved performance of an array of peptide-modified sensors compared to the use of a single sensor modified with multiple peptides in the determination of metals in water (Fig. 4) (Ebrahimi et al., 2008). In that work, the authors emphasize the greater information content of the generated

$$AChE:$$

$$thiocholine\ ester \longrightarrow thiocholine + acid$$

$$2thiocholine \xrightarrow[anode]{} dithiocholine + 2e^- + 2H^+$$

$$Tyr:$$

$$monophenol \xrightarrow{1/2\ O_2} o\text{-}diphenol \underset{cathode}{\overset{1/2\ O_2}{\rightleftarrows}} o\text{-}quinone + 2e^- + 2H^+$$

$$Lac:$$

$$phenols \xrightarrow{O_2} phenoxyradicals \xrightarrow{O_2} quinones$$

$$quinone + 2e^- + 2H^+ \xrightarrow[cathode]{} phenols$$

$$GOx:$$

$$\beta\text{-}glucose \xrightarrow{O_2} gluconolactone + H_2O_2$$

$$H_2O_2 \xrightarrow[anode]{} 2H^+ + 2e^- + O_2$$

Fig. 5. Summary of the enzymatic reactions of AChE, Tyr, Lac and GOx, enzymes commonly used in the design of arrays of amperometric biosensors.

multiway data, but without scorning the merits of a single sensor.

3.1. Water analysis

Pesticide detection in drinking water is an important area of BioETs application. This has been accomplished by means of enzymatic inhibition, using cholinesterases and other enzymes (Fig. 5) (Sassolas et al., 2012). In this area, the first multi-biosensor system, reported by Bachmann *et al.*, was used for the simultaneous detection and discrimination of binary organophosphate and carbamate mixtures (Bachmann et al., 2000; Bachmann and Schmid, 1999). The system was based on an array of amperometric biosensors with different types of native or recombinant acetylcholinesterase (AChE) enzymes as biological receptors, and ANNs as the chemometric tool. In the first application (Bachmann and Schmid, 1999), paraoxon and carbofuran mixtures were successfully evaluated in the 0–20 μg/L range (pM level); whereas in the second one (Bachmann et al., 2000), malaoxon and paraoxon mixtures were also considered, albeit over a narrower range of 0–5 μg/L (pM level).

Similarly, Cortina et al. developed an array of screen-printed electrodes (SPEs) modified with wild-type and two genetically-modified AChE enzymes for the simultaneous determination of dichlorvos and carbofuran mixtures (Cortina et al., 2008). Interestingly, results predicted by the ANN model were much better than those obtained by direct interpolation of the measurements into the calibration plot, due to the counterbalance of the interfering effects (e.g. 92–116% *vs.* 566–962% for the recovery yields). That is, actually demonstrating the benefits derived from the usage of the chemometric model. Further automation of the system by the integration of the biosensors to a flow injection analysis (FIA) system improved the reproducibility and speed of analysis (Valdés-Ramírez et al., 2009).

All the previously described approaches were based on chronoamperometric measurements that reached a steady-state response used to calculate the percentage of inhibition. More recently, Alonso et al. have proposed a one-step method that involves measuring the slope of inhibition (Alonso et al., 2012), from where the irreversible inhibition rate is calculated. To demonstrate the capabilities of their method, an array of three AChE-based biosensors was evaluated towards chlorpyriphos-oxon, chlorfenvinphos and azinphos-methyl oxon insecticides, demonstrating a linear relation between the slope of inhibition and the individual concentrations of each pesticide. Furthermore, the same sensor array in combination with ANNs was used to quantify mixtures of pesticides in water samples.

Crew *et al.* went a step further and presented a portable analytical system that integrated a six AChE-based enzymatic biosensors array in a novel automated instrument incorporating a neural network program (Fig. 6) (Crew et al., 2011). The system was successfully evaluated by performing the analysis of six organophosphate pesticides at the nM to μM concentration range, in less than 6 min. Furthermore, the system was also validated towards different sample matrices (including water, food and vegetable extracts), showing no detrimental matrix effects in any of those scenarios.

Fig. 6. Prototype of the BioET system developed by Crew et al. (2011) for the in-field detection of pesticides, both in water and food extracts; the system is powered from a car battery via the lighter socket. Images have been provided by Adrian Crew and John Hart.

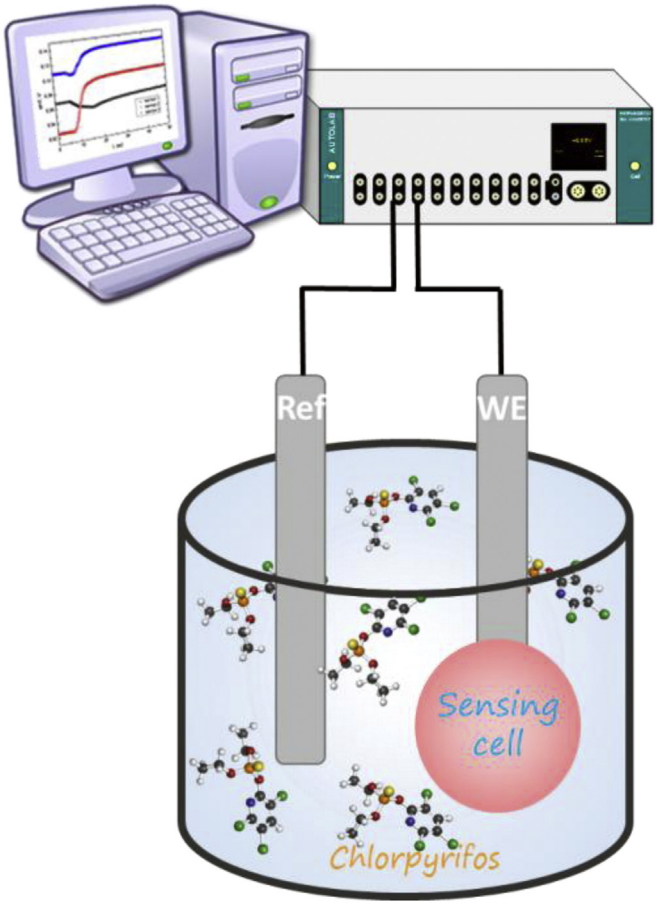

Fig. 7. Scheme of the BERA approach, based on potentiometrically measuring changes in the electric properties of immobilized cells induced by the interaction with the analyte.

In a more recent work, Ferentinos *et al.* used a cellular biosensor based on the bioelectric recognition assay (BERA) for the classification of pesticide groups (Ferentinos et al., 2013). BERA couples live functional cells immobilized in a gel matrix with a sensor system able to measure changes in their electric properties (Kintzios et al., 2001; Kintzios, 2007), producing a unique electrical potential pattern as a result of the cell-analyte interaction (Fig. 7). Electrophysiological responses of three cultured cell lines were evaluated, by means of an ANN model, to classify carbamates, pyrethroids, and organophosphates.

Several BioETs have also been developed for the electrochemical detection of phenolic compounds, being mainly based on tyrosinase (Tyr) and laccase (Lac) enzymes as bioreceptors (Fig. 5) (Arribas et al., 2012).

Phenolic compounds are widely used in the industry as chemical intermediates or antioxidants, additives to gasoline or lubricants, disinfectants, tanning agents, photographic developers or in the production of drugs and pesticides (Mukherjee et al., 2013). Besides industrial sources, large quantities of phenol-polluted waters are also formed from e.g. the production of olive oil (olive oil mill wastewater) in the main olive oil producing countries of the Mediterranean region (Gianfreda et al., 2006). The first reported approach in this field is the work of Trojanowicz et al., who developed an array of five Tyr sensors to quantify phenolic compounds using a flow-injection system (Trojanowicz et al., 1999). The biosensors were prepared by immobilizing the enzyme on platinum disk electrodes with different membranes to provide different levels of selectivity. Concretely, mixtures of phenol, catechol and *m*-cresol were tested at the μM level, and the biosensors steady-state responses were modelled by means of ANNs, which exhibited good correlation for catechol, but performed poorly for *m*-cresol. A trend that followed the sequence of sensitivities to these species of almost all biosensors examined.

Following the same idea, Gutés et al. used a single graphite-epoxy biocomposite bulk-modified with Tyr and a sequential injection analysis (SIA) system to detect the same phenolic compounds (Fig. 8), but using the whole voltammogram for modelling purposes rather than the steady-state responses (Gutés et al., 2005). In this way, a significant improvement on the modelling performance (from correlation coefficients between expected and predicted values of 0.88, 0.96 and 0.67 reported by Trojanowicz et al. to 0.998, 0.997 and 0.993 for phenol, catechol and *m*-cresol, respectively) was achieved due to the richness of the data afforded by the system.

Likewise, Dock *et al.* demonstrated that the dynamic responses

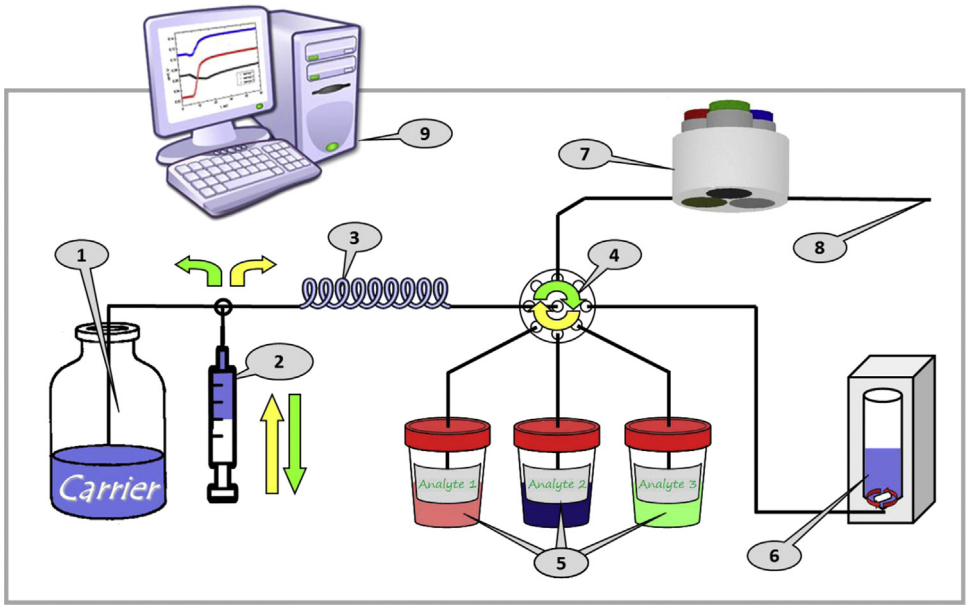

Fig. 8. Scheme of the SIA system employed by Gutés *et al.* (1) buffer/carrier reservoir; (2) bi directional microburette; (3) holding coil; (4) multi-way valve; (5) stock solutions of analytes; (6) mixing cell; (7) electrochemical cell; (8) waste; (9) computer to control the system. Adapted from Kirsanov et al. (2014), with permission from Elsevier.

of a single-Tyr biosensor in FIA conditions, were rich enough to allow the quantitative determination of catechol and 4-chlorophenol binary mixtures (Dock et al., 2005). For each sample measurement, 260 current values were registered upon polarization of the Tyr-modified graphite electrode at -50 mV. These data were used to build the response model by means of PLS. It is interesting to highlight the correction algorithm used to correctly compensate for biosensor ageing as well as for poor reproducibility in biosensor preparations (e.g. when employing a new batch of enzyme).

Another interesting work, reported by Freire et al., shows an array of two carbon-fiber electrodes modified with Lac and Tyr enzymes (Freire et al., 2003). In this case, the array was first characterized towards five phenolic compounds (catechol, phenol, chlorophenol, cresol and chlorocresol), and later applied to the resolution of four binary mixtures by PLS. Similarly, Torrecilla et al. combined the steady-state responses of a single-Lac biosensor with ANNs, as the modelling tool, to determine catechol and caffeic acid in olive oil mill wastewater (Torrecilla et al., 2007).

Recently, Cetó et al. reported the application of a voltammetric (bio)sensor array for the simultaneous monitoring of catechol, *m*-cresol and guaiacol in wastewater (Cetó et al., 2015). In this case, voltammetric responses of three composite electrodes bulk-modified with Tyr, Lac or copper nanoparticles plus a bare graphite electrode were first compressed by means of FFT, using ANNs for building the quantitative prediction model. The system was applied to monitor the photo-degradation of the three phenolic pollutants (Fig. 9).

BioETs, based on peptide-modified electrodes (Chow and Gooding, 2006; Pavan and Berti, 2012), have also been developed for the detection and quantification of metal ions. Chow and Ebrahimi et al. simultaneously quantified Cu^{2+}, Cd^{2+} and Pb^{2+} at the μM level in water samples by means of an array of four gold electrodes functionalized with self-assembled D,L-6,8-thioctic acid (TA), where three of them were further modified with the peptides Gly–Gly–His, glutathione (GSH) and human angiotensin I (Fig. 4) (Chow et al., 2006; Ebrahimi et al., 2008). As already stated, the most significant contribution of their work is that highlights the importance of designing experiments that generate multiway data (sample × variable 1 × variable 2 × … × variable *n*).

In the same line, Serrano et al. recently proposed the use of pH as an additional variable to enrich the departure data (sample × potential × sensor × pH) and to improve the performance of the generated model (Serrano et al., 2014); which is a promising field to be explored. In that work, GSH and its fragments Cys-Gly and γ-Glu-Cys were covalently bound to aryl diazonium salts electrografted onto the surface of graphite-epoxy composite electrodes, and the peptide sensors were used for the simultaneous determination of Cd^{2+}, Pb^{2+} and Zn^{2+} at the ppb level (0–1.5 μM). Despite the usage of quatrilinear data did not result in a significant improvement compared to the results obtained from the trilinear data set, as could be expected from the increase of the data complexity, authors reported a significant reduction in analysis time and an improvement on BioET performance compared to previous reported works.

Another interesting application of ETs and BioETs is their use in the characterization of wastewater quality. This was first studied by Tønning et al. who explored the capabilities of a miniaturized array of eight platinum SPEs (Figs. 10 and 11) for the discrimination of wastewater quality (Tønning et al., 2005). Seven of those

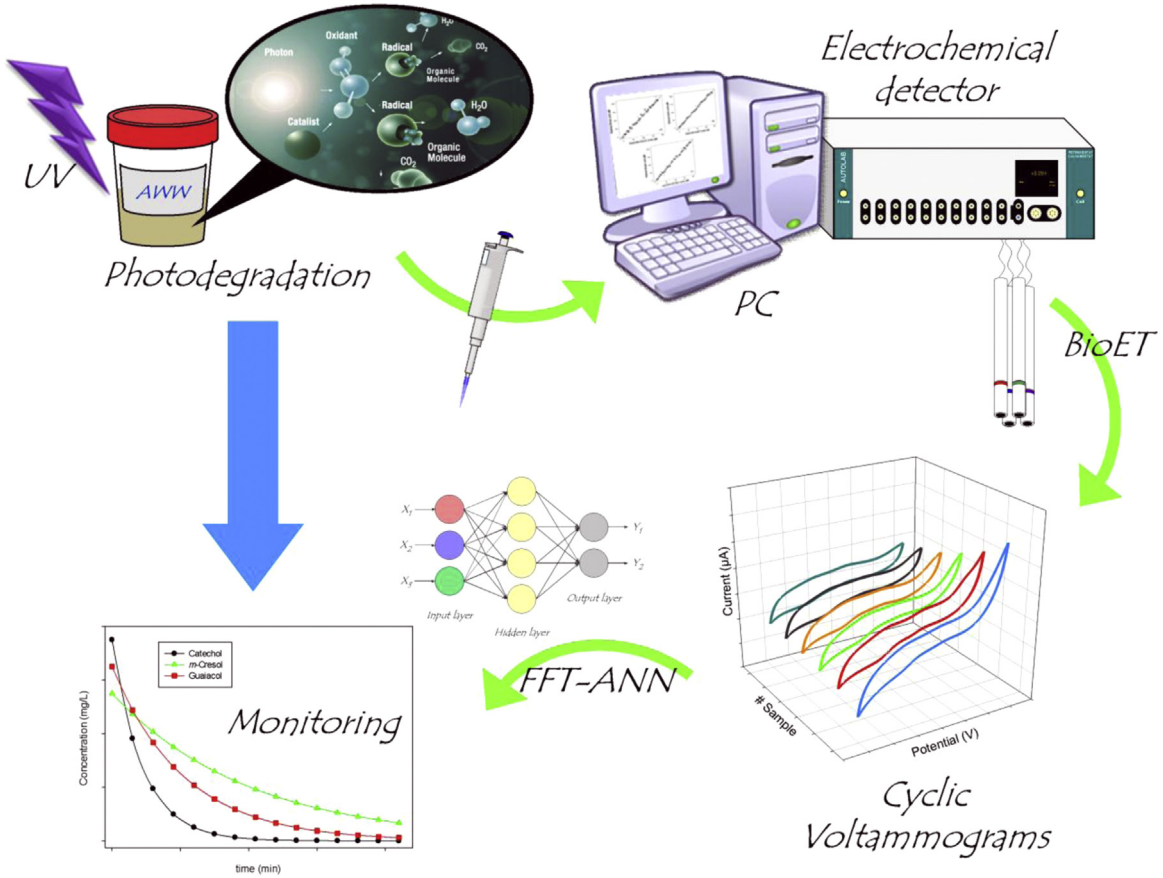

Fig. 9. Scheme of the experimental setup used by Cetó et al. for the photodegradation and monitoring of phenolic compounds in artificial wastewater (AWW). Phenols under study were oxidised using a photo-Fenton process: aliquots were taken and individual phenolic concentrations were predicted employing an already built ANN model. Reprinted from Cetó et al. (2015), with permission from John Wiley and Sons.

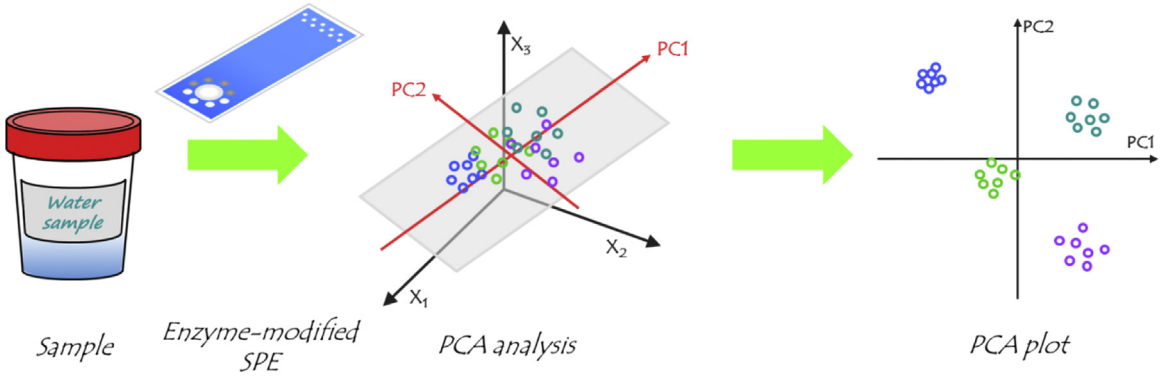

Fig. 10. Scheme of the approach followed by Tønning et al. (2005) for the qualitative evaluation of wastewater quality. Eight platinum SPEs, featuring a miniaturized array, were enzymatically modified and applied to the analysis of wastewater. The obtained responses were processed by PCA, resulting in the clustering of the data in different groups.

electrodes were enzymatically modified with Tyr, horseradish peroxidise (HRP), AChE and butyrylcholinesterase (BChE). Chronoamperometric measurements were drift-corrected and analyzed by means of PCA, resulting in the clustering of four wastewaters samples: untreated, alarm, alert and normal (Fig. 10).

In a further contribution to the topic by Solná et al., an amperometric array of eight screen-printed (bio)sensors was developed for the detection of pesticides and phenols (Solná et al., 2005). The beauty of the approach lied in the miniaturized design of the array (Fig. 11) and the combination of multiple enzymes; concretely, AChE and BChE, Tyr, HRP, soybean peroxidase, and cellobiose dehydrogenase were immobilized onto carbon and platinum working electrodes. The whole system was first characterized towards model phenolic and pesticide compounds, achieving detection limits in the nM and μM ranges for pesticides and phenols, respectively. Later, the system was evaluated on wastewater samples from two industrial sources (namely, pulp and paper, and pesticide industries), allowing discrimination based on their origin (Fig. 10).

More recently, these two miniaturized BioETs were combined and applied towards the prediction of wastewater quality at different purification stages in a wastewater treatment plant (Czolkos et al., 2016). The two systems were incorporated in a FIA system and used to predict several organic pollutant indexes commonly used to assess wastewater treatment processes, including Microtox®, algae test, chemical oxygen demand (COD), biochemical oxygen demand (BOD) and total organic carbon (TOC).

In the same direction, Raud and Kikas proposed the usage of an array of seven bacterium-modified Clark-type electrodes for the determination of the BOD in complex industrial wastewaters (Raud and Kikas, 2013). Firstly, the performance of each biosensor was individually evaluated using synthetic samples; whereas later, modelling of the obtained responses allowed samples discrimination by PCA and correct quantification of BOD by PLS.

Recently, Feng et al. have demonstrated that the combination of microbial fuel cells (MFCs, Fig. 12) and ANNs is a promising tool for water quality monitoring since ANNs can unveil the complex relationship between water quality and MFCs output, and overcomes the problems with manual correlation of BOD or COD values and MFC responses (e.g. maximum current outputs). Combining a time series analysis model and ANNs, the authors successfully predicted the influent COD concentration (Feng et al., 2013b). In another study, MFCs were used for the identification of specific chemical pollutants present in water samples. As a proof of concept, four readily degradable substrates were tested, including two fermentable (glucose and starch) and two non-fermentable chemicals (acetate and butyrate) (Feng et al., 2013a). Likewise, King et al. evaluated the performance of a MFC-based biosensing

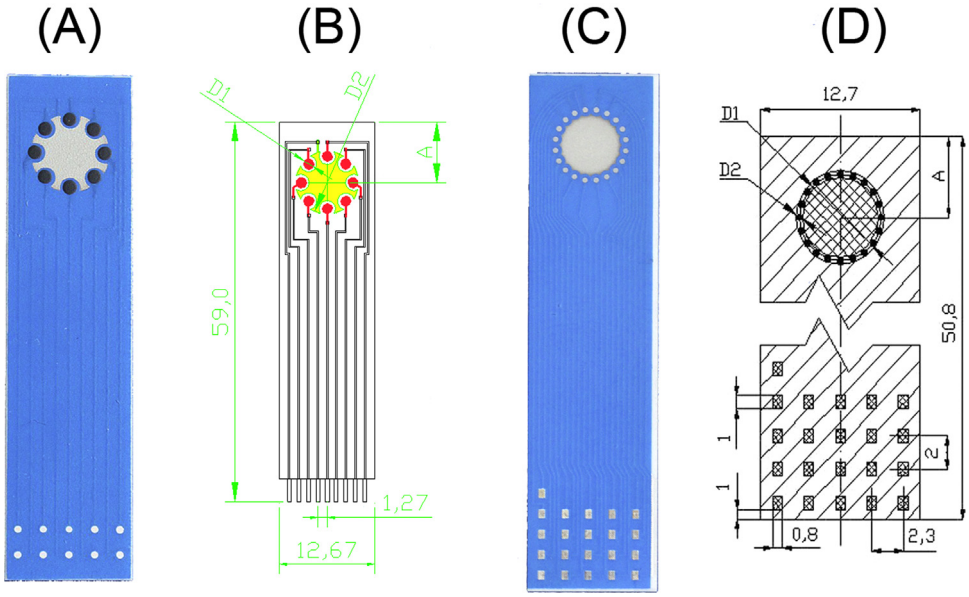

Fig. 11. Reproduction of the (A,B) 8-channel and (C,D) 20-channel SPEs manufactured by BVT Technologies. Images reproduced with the agreement of BVT.

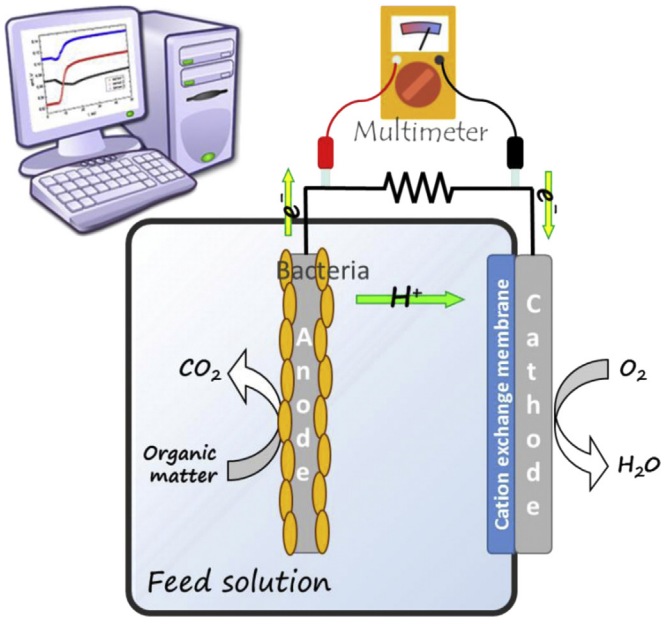

Fig. 12. Scheme of the basic components of a single-chamber MFC (Feng et al., 2013b).

system for the detection of three organic pollutants: aldicarb, dimethyl-methylphosphonate and bisphenol-A (King et al., 2014). Recorded readings of the MFCs were first parameterized, and calculated metrics were used as input into an ANN model which permitted accurate determination of both the concentration and identity of the industrial chemicals. Moreover, ANNs were also useful for samples in which the target chemicals were mixed together.

3.2. Food and beverage analysis

BioETs have also been applied to the detection of pesticides in food samples. The above described AChE-based enzymatic biosensors array by Crew et al. (Fig. 6) was also applied to food matrices (Crew et al., 2011). Matrix effects were evaluated with food extracts by extraction of pesticides from a broad range of raw foods with a non-toxic solvent and reconstitution in a methanolic phosphate buffer solution. The BioET was then validated with spiked samples, showing no false positive nor false negative results.

Espinoza et al. recently reported the detection of α-solanine and α-chaconine, two poison glycoalkaloids found in potatoes, using AChE-based sensors (Espinoza et al., 2014). Amperometric measurements and responses modelling were carried out as already described for Alonso et al. (Alonso et al., 2012); lowering the detection down to 50 ppb (58 fM).

In more recent work, Mishra et al. reported the usage of an automated flow-based biosensor for the detection of trace levels of pesticides in milk (Mishra et al., 2015). The system combines two AChE-modified biosensors and ANNs for the quantification of chlorpyriphos-oxon and malaoxon mixtures at sub-nM levels.

In turn, Asadollahi-Baboli et al. achieved the simultaneous determination of tetracycline and cefixime antibiotics in the 10^{-5}–10^{-3} M range (Asadollahi-Baboli and Mani-Varnosfaderani, 2014). The sensing part was comprised by a gold SPE modified with gold-nanoparticles and a self-assembled monolayer (SAM) of cysteine. Samples were analysed by square wave voltammetry (SWV), and the obtained responses were pre-processed by PCA for data reduction and modelled by means of ANNs. Furthermore, the biosensor was validated in urine, serum and milk samples.

As introduced in the previous section, BioETs for phenolic compounds analysis is one of the applications that has gained attention. Analysis of phenolic compounds content is especially relevant to wine and, to a lesser extent, beer analysis, due to contribution of phenolics to the wine and beer sensorial features (e.g. colour, body and astringency) (Ribéreau-Gayon et al., 2006), and their well-known antioxidant capacity, acting as free radical scavengers and inhibitors of lipoprotein oxidation (Sánchez-Moreno et al., 1999). Cetó et al. reported the application of a BioET in the analysis of individual phenolics in wine (Cetó et al., 2012b) and beer (Cetó et al., 2013b), resolving ternary mixtures of catechol, caffeic acid and catechin in wine, or ferulic, gallic and sinapic acids in beer. The study also involved the qualitative discrimination of up to ten phenolic compounds in spiked wine samples (Cetó et al., 2012a). Furthermore, the same approach was successfully used to tackle the determination of total phenolic indexes in wine (Cetó et al., 2012a) and sparkling wine (Cetó et al., 2014b). Voltammetric responses from an array of four bulk-modified (bio)sensors were registered and the data compressed using methods such as FFT, and modelled by means of ANNs (Fig. 13).

In a more qualitative approach, Ghasemi et al. reported the application of a BioET, including three enzymatic biosensors based on Tyr and phthalocyanines as electron mediators, to monitor beer

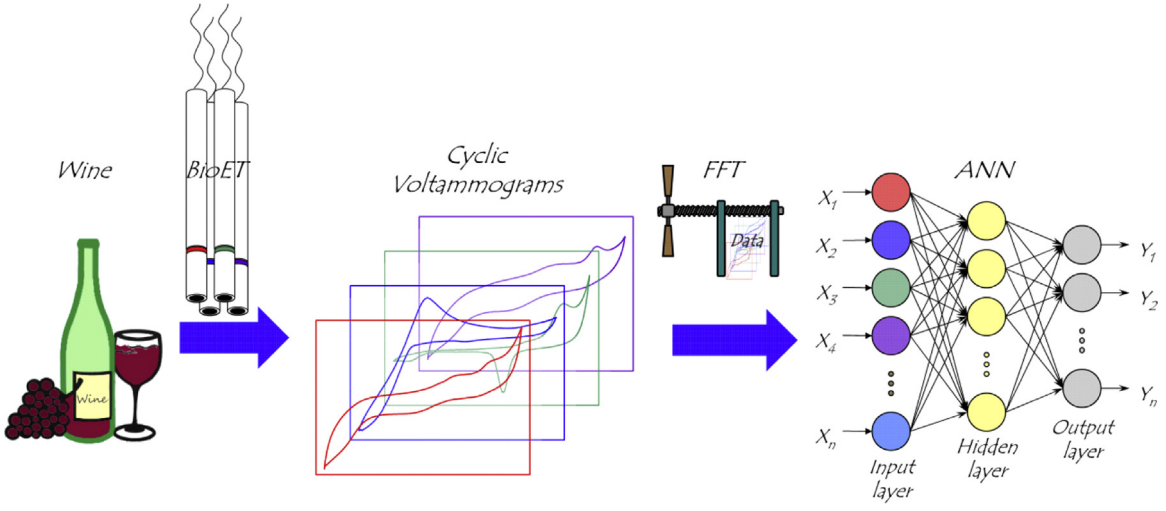

Fig. 13. Scheme of the approach reported by Cetó et al. for the determination of phenolic compounds in wine samples. Voltammetric signals were compressed employing FFT and the obtained coefficients were taken as input into an ANN model. Reprinted from Cetó et al. (2012a), with permission from Elsevier.

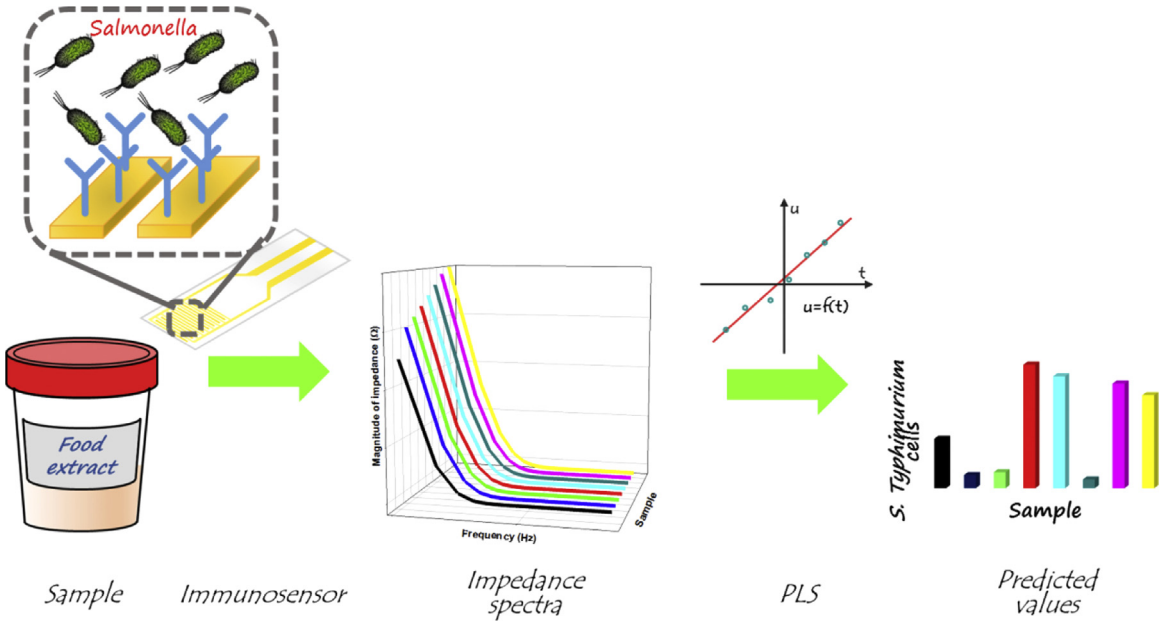

Fig. 14. Scheme of the approach reported by Kim et al. (2013) for the detection of *Salmonella typhimurium* based on an impedimetric immunosensor prepared by the immobilization of anti-*Salmonella typhimurium* antibody on an interdigitated gold electrode. The immunosensor responses were modelled by means of PLS, which permitted the quantification of the pathogen.

ageing based on the changes in flavonoid levels (Ghasemi-Varnamkhasti et al., 2012). To simulate the long storage periods, beer samples were stored in an oven at 40 °C. The voltammetric responses for four beer types were measured with the (bio)sensor array, compressed employing "kernels" method and modelled by means of LDA to allow their discrimination.

Along the same line, Medina-Plaza et al. proposed two systems for the qualitative discrimination of phenolic compounds and grapes of different varieties (Medina-Plaza et al., 2014; Medina-Plaza et al., 2015). The former was a nanostructured voltammetric multi-sensor system based on phenol oxidases (Tyr and Lac) incorporated into an arachidic acid Langmuir-Blodgett film, which also contained lutetium bisphthalocyanine ($LuPc_2$) as electron mediator. This BioET was employed for the discrimination of six phenolic antioxidants, and five grape varieties based on their phenolic content. The second system was an array of six SPEs modified with carbon, platinum, gold, graphene, Prussian blue and nickel oxide nanoparticles, and glucose oxidase (GOx) or Tyr cross-linked using glutaraldehyde. The electron mediators provided a variety of responses (an approach previously used by Gutés et al. (2006)) that allowed the discrimination of grape varieties by means of PCA analysis.

Another interesting application of BioETs is the analysis of saccharides, especially in the food and beverage industry, due to quality, storage, nutrition and safety standpoints. The levels of certain carbohydrates, like lactose or glucose, affect intolerance conditions or diabetes. The presence of unwanted carbohydrates can alter the manufacturing process, as well as indicate microbial contamination (e.g. yeasts) or improper processing (e.g. overheating). Besides, in the case of raw materials that have variable sugar content, like fruit juice or wine, their levels can influence the quality of the finished product and should therefore be monitored.

In an effort to demonstrate the capabilities of microbial sensors as analytical devices, Lobanov et al. employed two amperometric biosensors, based on the immobilization of *Gluconobacter oxydans* and *Pichia methanolica* cells, to quantify ethanol and glucose mixtures at the mM level (Lobanov et al., 2001). ANNs were used to successfully counterbalance the lack of selectivity of these microbial sensors.

As previously introduced, Gutés et al. combined three metallic catalysts and GOx to develop an array of biosensors for glucose that featured cross-response towards oxidizable compounds acting as interferents (e.g. ascorbic acid) (Gutés et al., 2006). The idea behind this approach was to correctly quantify glucose in real samples based on the correction of interferents by ANNs. In this way, quantification of glucose and ascorbic acid present in real fruit juices was achieved, without sample pre-treatment, after building the prediction model with standard solutions prepared automatically by a SIA system (Fig. 8).

Likewise, Torrecilla et al. reported the simultaneous quantification of glucose and the common interferents, ascorbic and uric acids, by processing the data from a voltammetric biosensor, based on GOx immobilized onto a colloidal gold-modified gold disk electrode, with ANNs as the modelling tool (Torrecilla et al., 2008).

The incorporation of an enzymatic glucose sensor into an array of non-specific voltammetric sensors was proposed by Cetó et al. to discriminate between craft and commercial beers (Cetó et al., 2013c): craft beers are bottled with some sugar and yeast to promote a second fermentation that produces CO_2 in the bottle, and thus the excess of non-fermented sugar may indicate a craft-made beer (McKay et al., 2010). Successful classification of beer samples was achieved after data modelling by means of LDA.

Apart from amperometric (bio)sensors, potentiometric or impedimetric (bio)sensors have also been used for BioETs. García-Villar et al. reported the application of a potentiometric BioET for the determination of lysine in feed samples (García-Villar et al., 2001). To this aim, the sensor array comprised a lysine biosensor, based on a lysine oxidase membrane assembled on an NH_4^+ electrode, plus seven cationic ion selective electrodes (ISEs; NH_4^+, K^+, Na^+, Ca^{2+}, Mg^{2+}, Li^+ and H^+) aimed at correcting the lack of biosensor selectivity towards other cations with the chemometric model. For data processing, different strategies were used, and the best results were obtained with PLS and PCA-ANN models. In order to improve the previous results, a second system comprising only a lysine biosensor and an NH_4^+ sensor incorporated in a flow system was then developed (García-Villar et al., 2003). Quantification of lysine at the mM level in sample mixtures was achieved with an acceptable accuracy.

Up to now, all the described approaches found in the literature have mainly focused on enzymatic sensors. In a significant contribution to the field, Kim et al. have recently reported the development of an impedimetric immunosensor, based on the immobilization of anti-*Salmonella* antibodies on the surface of an interdigitated microelectrode, for the quantification of *Salmonella typhimurium* (Fig. 14) (Kim et al., 2013). Estimation of *S. typhimurium* cell numbers in phosphate buffer saline (PBS) samples with univariate regression analysis produced poor linear regression and prediction performance; where best regression results led to an RMSE of 2.08 Log CFU/mL and R^2 of only 0.48. To improve these results, impedimetric responses were modelled by means of PLS regression, allowing the successful detection of less than 10^3 CFU/mL of *S. typhimurium* in PBS and pork samples with an RMSE down to 1.02 Log CFU/mL and $R^2 > 0.85$.

4. Summary and conclusions

There is a strong demand for simple and efficient sensing devices that allow the continuous, simultaneous and selective monitoring of several key compounds on different fields. In this regards, chemometrics has emerged as a key tool to complement the evolution of existing analytical technologies and foster the appearance of new ones. Particularly, the combination of chemometrics with chemical sensors led to the concept of ETs over 20 years ago. Since then, ETs have been successfully applied to the analysis of diverse samples in a plethora of scenarios (Ciosek and Wroblewski, 2007; del Valle, 2010).

At the same time, biosensors have demonstrated their utility in a wide variety of applications due to their ability to quickly, simply, and cost-effectively gather information (Bănică, 2012). However, despite the higher selectivity and specificity of biosensors compared to chemosensors, they still show certain cross-sensitivity (e.g. affinity of enzymes not only for a single compound, but towards a family of them) and suffer undesired matrix effects.

Several approaches exploiting the incorporation of biosensors in ETs have been reported in the last decade. This approach, known as BioET, has demonstrated improved performance compared to “conventional” ETs or the usage of individual biosensors, and consequently, allows to spawn new application fields. BioETs provide superior performance by combining the capabilities of ETs to derive meaning from complex or imprecise data, and the high selectivity and specificity of biosensors. The result is a powerful tool that exploits chemometrics to solve the interference problems of biosensors, and biosensors to solve selectivity problems in ETs.

This field is still in its infancy but the advantages of the BioET approach are already apparent; e.g. low-cost, ease of use, portability and fast response, among others. Another attractive feature of these devices is the possibility of tuning the mode of operation depending on the desired application (i.e. quantitative/qualitative analysis, prediction of total or individual indexes, classification/discrimination of samples, etc.) and the ability to correlate subjective or non-chemical indexes with the recorded data, e.g. to artificially reproduce the descriptors perceived by a sensory panel. Moreover, (Bio)ETs can overcome limitations found with classical approaches in (bio)sensor research, for example allowing usage without any sample pretreatment and thus representing an alternative to conventional analytical methods.

However, there are many technical challenges faced by today’s (bio)sensor manufacturing, and overcoming those will help to solve contemporary (Bio)ET technology problems. Reproducibility, drift, and the transfer of properties from one lot of sensors to another, are only the first issues to be dealt with. Although these issues are mainly related to the sensors themselves and not specific of (Bio)ETs, the higher complexity of the approach (e.g. cross-sensitivity of the sensors, dimensionality of the generated data and usage of a more complex model) exacerbates the problem.

Despite the great variety of applications reported, where (Bio)ETs are starting to prove their usefulness as quality control devices or for process monitoring purposes, particularly suitable for screening analysis, there is a conspicuous lack of commercial devices. However, a few prototype systems have been developed, and are ready to undergo commercialization, e.g. (Crew et al., 2011; Winquist, 2008).

Lastly, it has to be taken into consideration that (Bio)ETs do not intend to replace biosensors, but to spawn their applications.

Overall, our aim was to illustrate the capabilities of BioETs by providing an overview of the most significant contributions reported in the field of water and food analysis. In addition, a description of the key concepts related to ETs and the usage of the different chemometric tools was provided for a better understanding.

5. Future perspectives

A range of different electrochemical sensor arrays have been designed, with an emphasis on potentiometric ISEs or voltammetric electrodes. However, the usage of other types of sensors such as impedimetric or quartz crystal microbalance (EQCM) ones, offers huge opportunities. Perhaps even more promising is the combination of different types of sensors based on different transduction principles (hybrid ETs, data fusion) either using different types of electrochemical sensors (e.g. combination of potentiometric and amperometric ones), or even sensors based on different detection techniques (e.g. electrochemical and optical ones). In this regards, the fusion of the responses of an ET with an electronic nose and/or an electronic eye may improve the recognition capabilities of such a biomimetic system, exactly as happens with the biological system.

Obviously, the development of new (bio)sensors arrays not only considers the transduction principle, but also the recognition element. As shown in Table 4, most of the reported BioETs are based on the usage of enzymes as recognition elements. In this direction, the usage of an array of sensors based on antibodies, aptamers or DNA opens a fascinating wide range of possibilities. However, apart from those defined biological recognition elements many other systems can be designed. For example, Dong et al. went a step further and developed a bioelectronic nose based on brain–machine interface technology for odour detection by *in vivo* electrophysiological measurements of an olfactory bulb (Dong et al., 2013).

On the other side, since ETs can be considered as the coupling of two parts: the sensor array plus the chemometric tools, many possibilities arise from the development of the latter. Especially since the advances in computing allow the obtaining, recording and processing of higher data sets, but at the expense of increased complexity which also hinders implementation. In this context, multiway approaches have demonstrated to provide data with greater information content. The challenges here are the development of systems that lead to high multi-dimensional data (e.g. through the usage of pH or dynamic profiles as additional variable), and of more advanced chemometric tools that can take advantage of data multidimensionality.

Lastly, efforts should not only be directed to the development of novel systems or their application to unexplored scenarios, but also to the improvement of existing ones. There are key factors that require further research to achieve wider use of BioETs. First, thorough characterization of sensor reproducibility and drifts over long usage periods is needed, as well as the development of strategies for their counterbalancing upon modelling. Second, due to the considerable effort in constructing a robust model (huge number of samples required plus optimization of the chemometric

models), frequent recalibration is problematic; e.g. when using different instruments, working under differing environmental factors from those used to build the model or using disposable sensors. To overcome such problematic, further studies on the usage of transfer methods are required (Feudale et al., 2002; Pereira et al., 2008).

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Appendix A. Qualitative metrics

After building the confusion matrix (Table 3), the classification rate (Eq. (1)), sensitivity (Eq. (2)) and specificity (Eq. (3)) values are calculated according the following equations:

$$\frac{\sum_{i=1}^{n} \mathrm{TP}_i}{\sum_{i=1}^{n} \mathrm{TP}_i + \mathrm{FP}_i} \tag{1}$$

$$\frac{1}{n}\sum_{i=1}^{n} \frac{\mathrm{TP}_i}{\mathrm{TP}_i + \mathrm{FN}_i} \tag{2}$$

$$\frac{1}{n}\sum_{i=1}^{n} \frac{\mathrm{TN}_i}{\mathrm{TN}_i + \mathrm{FP}_i} \tag{3}$$

where n corresponds to the number of samples.

Appendix B. Quantitative metrics

- RMSE
  The root mean square error is calculated according to Eq. (4):

$$\mathrm{RMSE} = \sqrt{\frac{\sum_{ij} (y_{ij} - \hat{y}_{ij})^2}{l \cdot n - 1}} \tag{4}$$

  where n corresponds to the number of samples, l to the number of analytes, and $y/\hat{y}$ to the predicted and actual values (residual values).
- RPD *and* RER
  Both the RPD and RER statistics are calculated as a ratio of the standard error of prediction (SEP), and accordingly, require its calculation. Unfortunately, there is not a universal agreement about how to calculate it (Fearn, 2002), but the simplest way is according to Eq. (5):

$$SEP = \sqrt{\frac{\sum d_i^2}{n}} \tag{5}$$

  where n corresponds to the number of samples and d to the difference between the predicted and actual values (d, Eq. (6)) for each of the samples (i).

$$d_i = y_i - \hat{y}_i \tag{6}$$

  From it, the ratio of standard error of performance to standard deviation (RPD, Eq. (7)) is calculated as the ratio of the standard deviation of the target values to the SEP:

$$\mathrm{RPD} = \frac{s}{\mathrm{SEP}} \tag{7}$$

  where $\bar{y}$ and s are the mean and standard deviation of the target values, respectively (Eqs. (8) and (9)).

$$\bar{y} = \frac{\sum \hat{y}_i}{N} \tag{8}$$

$$s = \sqrt{\frac{\sum (y_i - \bar{y})^2}{n - 1}} \tag{9}$$

  and the ratio error ratio (RER, Eq. 10) is calculated as the ratio of the range of the target values to the SEP:

$$\mathrm{RER} = \frac{R}{\mathrm{SEP}} \tag{10}$$

  where R is the range of the target values, namely, the difference between the maximum and minimum values.
- *Joint confidence intervals*

The elliptical joint confidence intervals can be calculated according to the following Eq. (11):

$$n(b - \hat{b})^2 + 2S(b - \hat{b})(m - \hat{m}) + Q(m - \hat{m})^2 = 2Fs^2 \tag{11}$$

where n corresponds to the number of samples, b and m to the intercept and slope calculated from the regression (Eqs. (19) and (20)) and F is the critical value for the F-distribution at the desired level of significance (α) with 2 and N-2 degrees of freedom ($F_{1-\alpha,(2,N-2)}$). Other values are calculated according to Eqs (12–18):

$$S = \sum x \tag{12}$$

$$Q = \sum x^2 \tag{13}$$

$$Y = \sum y \tag{14}$$

$$L = \sum y^2 \tag{15}$$

$$P = \sum xy \tag{16}$$

$$\Delta = nQ - S^2 \tag{17}$$

$$s^2 = \frac{1}{n-2}\left(L - \frac{Y^2}{n} - \frac{\Delta}{n}\hat{m}^2\right) \tag{18}$$

$$\hat{m} = \frac{\mathrm{nP} - \mathrm{SY}}{\Delta} \tag{19}$$

$$\hat{b} = \frac{\mathrm{QY} - \mathrm{SP}}{\Delta} \tag{20}$$

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