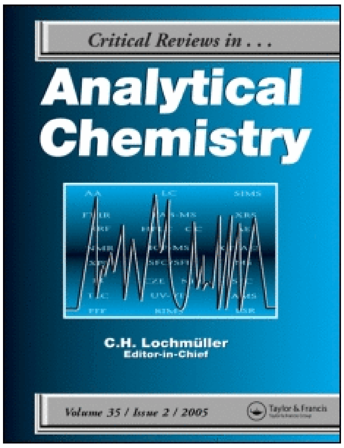

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Chemometrics in Electroanalytical Chemistry

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Chemometrics in Electroanalytical Chemistry

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The use of chemometrics in electroanalytical chemistry is not as popular as in spectroscopy, although recently, application of these methods for mathematical resolution of overlapping signals, calibration and model identification have been increasing. Self-modelling curve resolution and multivariate analysis have been shown to be very powerful for in the analysis of electroanalytical data, especially for multianalyte calibration and modelling in multicomponent dynamic systems. In this paper, an overview on the application of chemometrics to electroanalytical data is presented, with special attention to the contributions of the last decade.

Keywords artificial neural networks, chemometrics, deconvolution, multicomponent systems, multivariate analysis, partial least squares, soft-modelling, voltammetry

INTRODUCTION

Chemometrics is a chemical discipline that uses mathematics, statistics, and formal logic to (a) either design or select optimal experimental procedures; (b) provide maximum relevant chemical information by analyzing chemical data; and (c) obtain knowledge about chemical systems (1). Among the disciplines intimately related to analytical chemistry, chemometrics has been probably the one with a more continuous steady growth during the last years, as biannual reports in *Analytical Chemistry* show (2–5).

In an excellent (and yet classical) paper Brown and Bear critically reviewed the use of chemometric techniques in electrochemistry (6). These authors reviewed more than 100 relevant contributions in the field and stated, among other conclusions, that: (i) “the portion of papers in electroanalytical chemistry reporting the use of chemometrics appears to be lower than that observed in analytical chemistry as a whole”, and (ii) “much progress has been made in applying chemometrics to electrochemical problems, but remains a tremendous potential for advancement.” Brown and Bear expected a substantial growth in multivariate calibration because studies using techniques such as Multiple Linear Regression (MLR) and Partial Least Squares (PLS) regression showed that modern chemometric techniques were beginning to permeate all areas of electroanalytical chemistry. Moreover, they were also expecting the expansion of pattern recognition in electrochemistry.

More recently, this journal showed again its interest to promote Chemometrics through two tutorial articles on linear algebra (7) and factor analysis (8), which are the basis of a lot of chemometric techniques of interest in Electroanalytical Chemistry. During recent years, several reviews, tutorials and overviews have focused attention on different aspects of chemometric applications in electroanalytical chemistry (see, for instance, 9–13), illustrating the research community’s great interest in the subject and the potential for future applications. Among them, applications of chemometrics to electrochemical sensors, sensor arrays, and electronic tongues have received significant attention during last years (12, 13).

Despite the variety and increased numbers of recent papers, the above mentioned statements (6) are still valid because application of chemometrics to electroanalytical chemistry is relatively scarce compared to applications of chemometrics in spectroscopy and, more recently, image analysis (4, 5).

This apparent, or real, lack of interest in the extensive use of chemometrics to solve electrochemical problems could arise paradoxically from the intimate relationship between mathematics and electroanalytical chemistry. In this discipline the foundamental corpus of knowledge concerns: (i) the formulation of an hypothetical physicochemical picture of the electrochemical processes, the corresponding joint transport phenomena, and the nature of the measurements made; (ii) the analytical or numerical solution of the mathematical formulation outlined according to the corresponding previous model and, in the most favourable cases; (iii) the interpretation of the electroanalytical data in terms of a proper physicochemical picture of the processes taking place and/or the determination of concentrations, constants, parameters or whatever. This general approach is usually designated as hard-modelling, and it is the common

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approach used in electrochemical investigations, found in literature, and probably felt by majority of electrochemists as the real and rigorous approach.

In many cases, however, the postulation of a theoretical physicochemical model is very difficult because the electrode process, the transport phenomena, the perturbation provoked by the excitation signal, or all of them, are rather complex. In such cases, and depending on the kind of information required, the lack of a hard model leads to greater interest in other types of approaches that can provide information about the systems under study. This alternative (and complementary) approach can be provided by Chemometrics, and it is based on extracting results and/or identificating models from numerical and statistical analysis of the data, instead of fitting the parameters of an a priori assumed theoretical model to the experimental data. This new approach is sometimes denoted as soft-modelling to distinguish it clearly from the classical hard-modelling approach (6).

Chemometrics can be applied to different steps of the electroanalytical process or with different objectives. Among the different steps, we can mention: (i) experimental design and optimization of relevant experimental and instrumental parameters, (ii) preparation and transformation of data for further data treatments, (iii) data exploration and sample classification, and (iv) concentration determination, calibration, and model identification. A particular case of this last section concerns modelling of dynamic multicomponent systems.

In the present review, we attempt to give a brief overview of the application of Chemometrics, in particular of multivariate analysis techniques and soft-modelling, to electroanalytical data. The review is done from an experimental electroanalytical point of view, more than from a chemometrical one, with the aim of providing useful information for the electroanalytical community and to promote the use of chemometrics in this field. With this in mind, we will pay special attention to the contributions of the last decade not covered by other previous reviews, especially reference (6).

EXPERIMENTAL DESIGN AND OPTIMIZATION

The term "experimental design" is usually used in two contexts. The first one is to describe the set of experiments carried out with the intention of developing a model (e.g., a regression model or an ANOVA model); but, it is also used in the context of optimization of products or processes in order to determine in an efficient way the set of conditions that are required to obtain a proper product or process (1). We will refer to this term in the second meaning. This means one aims to: (i) understand the effect of the factors (the variables that are changed in a controlled way to study their effect on the process), and (ii) model the relationship between responses and factors, all with a minimum of experiments and efforts.

Optimization of experimental conditions and/or instrumental parameters in order to reach the most satisfactory results is one of the applications of chemometrics to electroanalytical determinations covered in this review. In recent examples, experimental design strategies were used to optimize variables of Adsorptive Stripping Voltammetry (AdSV) methods for the determination of a variety of analytes. AdSV, especially using differential-pulse or square-wave modes, is a very useful technique but, because of the lack of specificity in the adsorptive accumulation process before the stripping step, the analytical response depends on many experimental factors (pH, buffer composition and concentration, supporting electrolyte, complexing agent), instrumental ones (deposition potential and time, pulse amplitude, frequency, step potential, . . .) and operational ones (stirring rate, cell geometry, . . .). Because of that, screening designs and optimization designs of these parameters are highly recommended.

Arcos et al. reported the determination of inorganic ions such as Ni, by using dimethylglyoxime (14, 15), the determination of both Cr(III) and Cr(VI) by a variety of ligands in different samples (16–19), the determination of Ga (20); and the determination of pharmaceutical compounds such as indomethacin and acemethacin (21), rifamycin (22), and rifampicin (23, 24). Herrero et al. determined three phenolic compounds by a continuous flow system with electrochemical detection (25). They used Full Factorial Designs and Central Composite Designs for response surface modelling and optimization. Moreover, the use of robust regression methods allows them the elimination of anomalous points.

Pinzauti et al. have specialized in the development and set-up of drug electroanalysis by experimental design (26). Plackett-Burman, D-Optimal and Doehlert designs have been widely used for screening tests. They determined Rufloxacin in tablets, human plasma and urine (27), the antiulcer drug Omeprazole (28), the quinolone antibacterial agent Cinoxacin (29), Kynurenic acid (30) and Nimesulide (31, 32).

Other recent electroanalytical determinations using experimental designs include the determination of trace metal ions in different samples: Mo(VI) in plants (33), Hg(II) in foodstuffs (34), Cd(II) (35) and Pb(II) (36) in natural waters. Additional applications include the determination of glyphosate (37) and metallothioneins in polychaetes (38, 39). Also, the study of strategies for constructing a global multivariate calibration model that includes calibration samples measured by electroanalytical means over time on different days has been explored because of great interest in routine analysis (40).

DATA PREPARATION AND TRANSFORMATION

The presence of noise due to capacitive currents, instrumental artifacts and parasite currents is very difficult to prevent in any measurement of electrode processes, usually of a Faradaic nature. This is a characteristic, ambiguous and tedious problem often encountered in the analysis of electroanalytical data. Minimizing capacitive currents has been one of the main reasons for the development of many relevant electroanalytical techniques such as those based on the application of potential pulses or alternating currents (41). In conjunction with more sophisticated techniques, significant efforts have been aimed at outliers detection and noise elimination, baseline subtraction, smoothing and compressing data using statistical and numerical tools, all without considering at that time that all these operations could be considered Chemometrics. The electroanalytical literature is full of references proposing different signal processing treatments to obtain a secondary data set where it is easier to estimate characteristic parameters (for instance, peak potentials and peak heights) (42) or easier to perform further data treatment operations such as deconvolution (43). For these kinds of signal processing operations, classical methods such as Savitzky-Golay, Kalman Filtering and the Fast Fourier Transform have been widely used and referenced (6). The Kalman Filtering approach will be discussed in more detail in a later section.

Recently, Wavelet Transformation (WT) has emerged as a powerful new tool that is the focus of great attention (44). The WT offers the possibility to use not only the intensity values of the signal, but also peak widths, slopes of selected portions, degree of smoothness, more or less evident discontinuities, and many other shape aspects of the response signal in order to achieve the information sought (45). Among other applications, the WT has been used recently pre-processing before applying more powerful multivariate techniques (45, 46). For example, transformation of electroanalytical data sets of Pb and Tl mixtures to the WT-domain allowed removing baseline effects, reducing noise and compressing the data thus facilitating the application of several multivariate calibration techniques (46). It seems that transformation in the wavelet domain could be a future usual practice in the electroanalytical field.

DATA EXPLORATION AND SAMPLE CLASSIFICATION

The techniques considered under this title provide a way of visualizing variation within large multivariate data sets as an end in itself or as a pre-processing step to discriminate information before building calibration or classification models. Principal components analysis (PCA) is the main tool for this purpose, and it can be implimented through a number of algorithms, the most common being nonlinear iterative partial least squares (NIPALS) and singular values decomposition (SVD). As an example to illustrate its use on electroanalytical data, PCA has been very recently used for rapid screening of cyclic voltammetry (CV) and square wave voltammetry (SWV) measurements to model cork-wine interactions in order to determine if the corks were able to contaminate a bottle of wine (47). PCA and cluster analysis dendrograms were also used to identify clusters of similar samples for classification of 55 different untreated beverages, including wines, beers, coffees, milk and fruit juices, after SWV measurements at Pt electrodes (48).

The method of PCA, as well as some other multivariate analysis techniques, seems to be extremelly useful techniques for use in conjunction with multi-sensor arrays (electronic tongues) (49, 50) for screening and monitoring a great variety of analytes, including some microorganisms, in many different samples (51–62) and for selection of conducting electroactive polymers (CEPs) for sensor arrays development (63).

CONCENTRATION DETERMINATION AND CALIBRATION

The greatest progress in applying chemometrics to electroanalytical determinations has been in the analytical resolution of complex systems. These applications include several specific tasks such as, for instance, (i) the determination, by means of deconvolution, of mixtures of analytes, that cannot be physically isolated, giving highly overlapping signals, (ii) calibration, and (iii) chemical model identification in complex dynamic systems.

From a very practical point of view we can consider two main approaches for solving the overlapping signal problem. In the first approach, the simplest (and usual) way is to deconvolute the electroanalytical signal (usually a voltammogram) contributed by the different analytes, and then perform a simple calibration on the deconvolved signals using peak heights or peak areas. In this approach, that can be denoted as a *one-way* approach, the voltammograms are analyzed individually, one by one, so data can be considered as vectors.

In the second approach, that can be denoted as a two-way approach, the data is collected and analyzed as a whole, so a data matrix is exhaustively analyzed to get the proper information.

One-Way Approach

Literature shows that several techniques can be used for signal deconvolution, independently of the type of signal (optical, electrochemical or whatever), and that the choice of the most proper approach for each problem is not a trivial task. For this reason, in many papers several deconvolution techniques are applied to the same data sets and further compared.

Many authors stress the importance of having preknowledge of the studied system or sample for the successful application of any deconvolution procedure. Knowing the peak shapes before deconvolution is not a very restrictive condition since in many cases they can be measured in a preliminary determination or assay. Baseline effects can also be determined in advance and included in the model. Usually, a much more severe restriction is the need to specify in advance the number of components in the sample or the system, i.e., the number of individual components in which the signal must be deconvoluted. This number cannot be assumed to be known in general, and the larger it is the more ambiguous the results (64).

One other critical point on deconvolution is the assumption of linearity of the signal, i.e., that the experimental signal (very usually a current) is the sum of the individual contributions of each analyte or component. This assumption, which is obviously a major aspect of spectroscopic data (recorded inside the region where Beer-Lambert's law is observed to hold true), is not necessarily true in electrochemical measurements because of the involvement of interfacial phenomena in the measurements.

In the field of electroanalytical chemistry, deconvolution has been performed by means of several approaches. The use of some relevant approaches is briefly described in the following.

Kalman Filter. An especially relevant approach in this field is the Kalman Filter technique (KF) because of its efficiency, especially in conjunction with high-resolution techniques such as SWV (65–67). The potential of the KF and of several modifications to the basic KF algorithm, such as the adaptive KF (68), were exhaustively studied by Brown and coworkers in the eighties, and a very sound theoretical and practical basis is available (6, 65–69).

The main limitation of the KF, as with other deconvolution methods, is the assumption of linearity in the experimental signal. On the other hand, the KF has shown to be a very powerful and versatile tool for solving electroanalytical problems. Through its use (above mentioned) in signal processing tasks (see also section V.B. in ref. (6)), the KF has been demonstrated to be suitable for parameter estimation (see section III.B. in ref. (6)). However, we have not found new relevant contributions for such application from those previously reported (6).

Fourier Transform. Still within this relatively simple one-way approach, other methods have been applied for the resolution of overlapping peaks. Fourier Transform methods have been extensively used (see section V.A in (6)). However, a significant number of recent Fourier Transform-based applications have been devoted to processing of electrochemical signals but without an analytical subject. A relatively common practice in electroanalytical literature is the comparison of new deconvolution approaches with deconvolution by the Fast Fourier Transform (FFT), taking the FFT as a sort of reference method to which the new ones are compared (43, 70–73).

As mentioned previously for the KF, the FFT is also a very versatile method used in electroanalytical chemistry for other tasks besides deconvolution. For examlpe, Pizeta et al. (72) have used the FFT for resolution enhancement of adsorption peaks in differential pulse polarography (DPP).

Signals Ratio Methods and Wavelet Transform. The signals ratio method (SRM) is an alternative simple approach for deconvolution of voltammetric signals (74–76). In SRM, applied to DPP, the ratio of pseudo-DPP signals are obtained dividing the multianalyte DP-polarogram with individual DP-polarograms of a single analyte. A minor analyte could be resolved from a 200-fold excess presence of other analytes with very close peak potentials (75). Very recently, SRM has been combined with the WT for the resolution of overlapped simulated and experimental SWV data (77), thus taking advantage of the recent popular use of the WT for resolving overlapped signals and its realibility for resolving simulated overlapped spectra.

Recently the derivative WT was developed for resolving overlapped signals in multicomponent analysis (78). The derivative WT is much better than the conventional numerical methods in resolving practical signals with low signal-to-noise ratio, particularly in the case when the degree of overlapped between different signals is high and high order derivatives are required for the further resolution.

Maximum Entropy Method. There are some other useful techniques for deconvolution, although at the moment some of them are practically not used in electroanalytical applications. This is the case of Maximum Entropy methods (MEM). MEM have been successfully applied, among many other applications, to restoration, reconstruction and deconvolution in NMR spectroscopy (79, 80), deconvolution in electrospray mass spectrometry (81) and in mass spectra of high-mass biomolecules (82), Small-Angle X-ray Scattering measurements and Image Reconstruction (83), deconvolution of x-ray photoelectron spectra (84), and deconvolution of simulated ideal 3-peak chromatograms, 15-peak heptane storage column profile, and Pioneer Venus chromatographic data (85).

Inside the field of electrochemical measurements or intimately related ones, MEM have been very scarcely applied. It can be reported its use in deconvolution of images obtained by Atomic Force and Scanning Tunneling Microscopy (86), deconvolution of dielectric and impedance data (87), and analysis of electrochemical noise (88, 89).

At the best of our knowledge, no applications of MEM to typical electroanalytical problems have been reported. This is certainly surprising because, from the literature reviewed for this article, it seems that MEM can be ideal for those cases where prior knowledge of peak shape can be used effectively and prior knowledge of the number of peaks is not required.

Two-Way Approach

The other main approach (that we have denoted as the *two-way* approach) considers a series of experiments, e.g., the experimental data as a whole, without explicitly treating the individual signals, voltammogram by voltammogram. This is the typical case when the multivariate analysis term is used.

For the most usual case of voltammetry, the fundamental starting point is the arrangement of the data as a matrix of currents $\boldsymbol{I}$ (nR, nC), where nR indicates the number of rows as the number of recorded voltammograms (of different samples, or of the same system but at some different conditions of any relevant variable), and nC indicates the number of columns, for example, potentials scanned during the current measurements. The basic goal of the different multivariate analysis methods is to decompose mathematically the experimental current data matrix $\boldsymbol{I}$ into a product of two matrices (or vectors, depending on the case) containing the information of concentrations ($\boldsymbol{C}$) and of the individual voltammograms ($\boldsymbol{V}$). This decomposition is based on the assumption that the measured instrumental responses are bilinear and can be expressed as $\boldsymbol{I} = \boldsymbol{C}\,\boldsymbol{V} + \boldsymbol{X}$, where $\boldsymbol{X}$ is a residual matrix containing the variance not explained by $\boldsymbol{C}$ and $\boldsymbol{V}$**.**

Depending on the mathematical details of the decomposition of matrix $\boldsymbol{I}$ and the algorithms used, different multivariate calibration methods can be defined (1, 90, 91).

Multivariate calibration is the collective term used for the development of a quantitative model for the reliable prediction of properties of interest from a number of predictor variables. The classical example is the spectroscopic analysis (e.g., UV, IR, NIR, XRF, NMR) of a mixture in order to measure the concentration of one or more of its constituents. Using the entire range spectral information may, in principle, lead to better predictions than using only characteristic parameters (e.g., maxima intensities). Among these techniques, because of their relevance in the application to electroanalytical data, multiple linear regression (MLR), principal components regression (PCR), classical least squares (CLS), partial least squares (PLS), non-linear PLS and inverse least squares (ILS) will be mentioned. Among all the mentioned techniques, the mostly commonly used calibration method in the electroanalytical chemistry field is PLS. Because of that we focus especial attention to this technique.

Partial Least Squares. This technique has been widely explained in literature, including some tutorial articles (92, 93). There is a great number of PLS applications to electroanalytical data described in the literature, although not so many as in Spectroscopy. Table 1 summarizes, in cronological order, some representative and recent (majority from 1994) examples of PLS. A review of Table 1 shows that PLS has been applied mainly to voltammetric data, either without or with a previous preconcentration step, and that the great versatility of PLS has allowed it to be used to determine different types of analytes.

Herrero, Ortiz et al. have been very active in the application of PLS for metal trace analysis by DPP and stripping voltammetry (101, 103, 104, 106, 107) as well as in electrochemical (amperometric) detection of phenolic compounds (110). The resolution by PLS of the strongly overlapping DPASV peaks of Tl^+ and Pb^{2+} has been one of the typical examples in this field (94). Even when an interfering background current is present, PLS regression was successfully applied to the simultaneous determination of Tl and Pb by ASV (103). The presence of a significant baseline that overlaps Tl peak, together with the overlapping Tl and Pb signals, were both suitably modeled by PLS regression. A similar satisfactory result was achieved in the determination of Cu in the presence of interfering Fe (106). In a series of papers, Herrero et al. (101, 104, 107) solved properly the simultaneous

TABLE 1
Application of partial least squares (PLS) method to electroanalytical data

Technique	Application	Ref.
DPASV	Determination of Tl and Pb	94
PSA (at Au electrode)	Determination of As in the presence of Cu and Sn	95
DPP	Determination of furaltadone, furazolidone and nitrofurantoin	96
DPV	Determination of 2-(3)-t-butyl-4-methoxyphenol and propyl gallate	97
NPP, DPP	Determination of furazolidone and furaltadone	98
DPP	Determination of sulfadiazine, sulfamerazine and sulfamethazine	99
SWV, SWAdSV	Determination of sulphamethoxypyridazine and trimethoprim in veterinary formulations	100
DPP	Determination of Cu, Pb, Cd and Zn	101
LSV	Determination of indomethacin and acemethacin	102
ASV	Determination of Tl and Pb	103
DPP	Determination of Pb, Cd and Sn(IV)	104
LSV, CV, DC, DPP	Determination of propylgallate, butylated hydroxyanisole and butylated hydroxytoluene	105
DPASV	Determination of Cu in the presence of Fe	106
DPP	Variable selection for the determination of benzaldehyde, and of Cu, Pb, Cd and Zn	107
DPASV	Variable selection for the determination of the binary mixtures Tl/Pb and Cu/Fe(III)	107
SWV, DPV	Determination of paraquat and diquat	108
DPAdSV	Speciation of Cr (determination of Cr(III) and Cr(VI))	109, 111
FIA-ED	Determination of 4-nitrophenol, phenol and p-cresol	110
DPV	Determination of the anti-inflammatory drugs indomethacin, acemethacin, piroxicam and tenoxicam	112
LSV	Determination of mixtures of vapours (ethanol, acetaldehyde, acetylene, SO_2, NO_2, NO, O_3)	113
DPAdSV	Determination of Al and Cr(VI)	114
DPV	Determination of nordihydroguaiaretic acid	115
DC, DPV, SWV	Determination of tocopherols in vegetable oils	116
NPP (at UME array)	Monitoring of Staphylococcus aureus population	117
NPP (at UME array)	Monitoring of *Escherichia coli* ATCC 13706 and *Pseudomonas aeruginosa* ATCC 27853 population	118
CV	Determination of cysteine, tyrosine and tryptophan	119
DPAdSV	Determination of In	120

determination of several cations (Pb, Cd, Zn, Pb, Sn) using both DPP and DPASV. In one of these papers (107), a genetic algorithm (GA) was successfully applied as a variable selection method in the PLS regression of DPP data.

Arcos et al. used PLS in the AdSV determination (and speciation) of Cr species (109, 111, 114), of In (120) and of some anti-inflammatory drugs of pharmaceutical interest (102, 112). Thus, a PLS regression method was proposed for the resolution of strongly overlapping peaks from mixtures of Indomethacin and Acemethacin by using the full voltammogram (102). The application of a GA to select some of the predictor variables allowed to reduce by up to one-tenth the number of experimental variables, but did not diminish the prediction capabilities of the PLS model constructed with these selected variables. The relative error was <2% when concentrations of several mixtures were calculated.

Galeano, Guiberteau et al. have been also very active in this field. They used PLS in the determination of several organics (96, 98, 99), antioxidants (105, 115), Diquat and Paraquat (108) and tocopherols in vegetable oil samples (116). Antioxidants have been also analyzed by other groups (97), as well as pharmaceutical active products (100), aminoacids (119) and mixtures of vapours (113), PLS has been also used for microbiological analysis through the use of UME arrays (117, 118).

Artificial Neural Networks (ANN). A very different approach for calibration is based on the use of artificial neural networks (ANN). ANNs are machine learning tools capable of learning any continuous function, suitable for modelling either linear or non-linear systems, and is of of significant interest in analytical chemistry (121). A special characteristic of ANNs is that they can produce a very large number of different models of the same system. This means that ANNs can be very difficult to optimize, thus requiring a lot of time to reach a good calibration model, although GA implementation has increased the efficience in the optimization (122). Despite these difficulties, ANNs are being used increasingly in electroanalytical determinations, as Table 2 shows.

TABLE 2
Application of artificial neural networks (ANN) method to electroanalytical data

Technique	Application	Refs.
DPASV	Determination of Pb, Cd, Tl and In	123
ASV	Determination of Cu, Zn, Cd and Pb	124
DPV	Monitoring of freshness of milk (by an electronic tongue)	125
DPAdSV	Determination of Cu	126
LSV, DPP	Determination of adenine and cytosine	127
DPAdSV	Determination of Cu and Mo	128
DuPSV	Determination of ethanol, fructose and glucose	129
SWV	Determination of vitamins B6 and B12 in pharmaceutical preparations	130
DPAdSV	Determination of Cu	131
DPSV	Determination of ethanol, methanol, fructose and glucose	132
SWV	Determination of nalidixic acid and its metabolite 7-hydroxymethylnalidixic acid	133

Techniques: LSV, Linear Sweep Voltammetry; DPV, Differential Pulse Voltammetry, DuPSV, Dual Pulse Staircase Voltammetry, SWV, Square Wave Voltammety; DPP, Differential Puse Polarography; ASV, Anodic Stripping Voltammetry; DPAdSV, Differential Pulse Adsorptive Stripping Voltammetry.

Cladera et al. (123) used MLR- and ANN-based methods to resolve highly overlapping DPASV signals of binary, ternary and quaternary mixtures of Pb, Tl, In and Cd. Different network architectures were studied using the back propagation algorithm. Chan et al. (124) investigated multimetal systems under conditions with intermetallic compounds formation. Using simulated data, modeled after complex interactions experimentally observed in samples containing Cu and Zn, it was demonstrated that networks containing two layers of neurons (a non-linear hidden layer and a linear output layer) can be trained to calculate concentrations under a variety of complicated situations. These include, but are not limited to, cases where the response of the intermetallic is observed as a shoulder of one of the pure metals and cases where the response of the intermetallic is not observed in the potential window. In addition, the network described above was trained for the determination of Cu, Pb, Cd, and Zn in a concentration range where all responses were complicated by intermetallic compounds formation (1–500 ppb). Khayamian et al. proposed PC-ANN methods for the AdSV determination of Cu through Cu-PAN (126) and Cu-xylenol orange complexes (131), and of Mo and Cu through their cupferron complexes (128). Bessant et al. (129, 132) used Dual Pulse Staircase Voltammetry (DPSV) and a combination of pulsed electrochemical detection and staircase voltammetry for the simultaneous quantification of four aliphatic compounds (ethanol, methanol, fructose and glucose), mixed in varying concentrations, by an optimized ANN using an elitist GA. The best average root-mean-square errors achieved when testing with unseen validation data were 5.03%, 7.72%, 3.29% and 4.00% for maxima analyte concentrations of ethanol, methanol, fructose and glucose responses. This work represents an important step forward because DPSV data is notoriously difficult to calibrate due to complex electrode-analyte interactions, and had not previous been shown to be amenable to quaternary mixtures.

Winquist et al. (125) described an electronic tongue which consists of a reference electrode, an auxiliary electrode and five wires of different metals (Au, Ir, Pd, Pt and Rh) as working electrodes for monitoring of freshness of milk by means of pulse voltammetry. The electronic tongue was used to follow the deterioration of the quality of milk due to microbial growth when milk is stored at room temperature. The data obtained were treated with PCA and the deterioration process could clearly be followed in the diagrams. To make models for predictions, projections to latent structure and ANNs were used. When they had been trained, both models could satisfactorily predict the course of bacterial growth in the milk samples. Cukrowska et al. (127) used ANNs for the evaluation of LSV and DPP signals, with errors in all cases below 6%. Authors claim that the method is quite general and can be used for analysis of other biological important substances without their previous separation. Hernández et al. (130) used SWV, with glassy carbon electrode, together with ANNs for determining B6 and B12 vitamins. The calibration set was built with several artificial samples

TABLE 3
Comparison of different multivariate analysis techniques as applied to electroanalytical data

Chemometrical techniques	Electrochemical techniques	Application	Reference
MLR/PLS	DPASV	Study of influence of pH and Ca in metals/ fulvics interactions	134
CLS/PLS/PCR	AdSV	Determination of synthetic colorants	135
CLS/ILS/KF	SWASV	Determination of Pb, Cd, In and Tl	136
CLS/PLS/PCR/MLR	DPP, NPP	Determination of Pb, Cd, Cu, Ni and V	137
CLS/PLS/PCR/MLR	ASV	Determination of Pb, Cd, Cu and Zn (comparison with ICP/MS)	138
PLS/NL-PLS/PCR	CV	Determination of tryptophan in feed samples	139
PLS/NL-PLS/PCR/MLR/ANN	DuPSV	Determination of ethanol, fructose and glucose	140
PLS/PCR	CV	Determination of cysteine, tyrosine and tryptophan	141
PLS/ANN	DPV	Determination of catechol and hydroquinone at C fiber electrode	142
PLS/ANN	DC, DPP	Determination of atrazine/simazine and terbutryn/prometryn	143
CLS/PLS/PCR	LSV	Determination of synthetic food antioxidants	144
CLS/PLS/PCR/MLR	DPSV	Determination of chlorpromazine and promethazine hydrochlorides	145
CLS/PLS/PCR/MLR	DPSV	Determination of five nitro-substituted aromatic compounds	146
PLS/PCR	ASV	Determination of Pb, Cd, In and Tl	147
CLS/PLS/MCR-ALS	ASV	Determination of Pb, Cd, In and Tl	148
PLS/PCR/ANN	ASV	Determination of Pb and Tl	149
PLS/PCR	DPSV	Determination of paracetamol and phenobarbital in pharmaceuticals	150
CLS/PCR/PLS/KF/ANN	DPSV	Determination of parathion, fenitrothion and parathion	151
PCR/PLS/GA-PLS/ANN	DPV	Determination of cysteine, tyrosine and tryptophan	152
CLS/PCR/PLS/ANN	DPV	Determination of propoxur, isoprocarb, carbaryl and carbofuran	153
HPCR/HPLS/CPCR/MBPLS	ACV	Determination of brightener in industrial Cu electroplating baths	154
PLS/ANN	CV	Determination of isoniazid and hydrazyne	155
PLS/ANN	DPV	Determination of vitamins C, B6 and PP in pharmaceuticals	156

Electroanalytical Techniques: ACV, Alternating Current Voltammetry; LSV, Linear Sweep Voltammetry; CV, Cyclic Voltammetry; DPV, Differential Pulse Voltammetry, DuPSV, Dual Pulse Staircase Voltammetry; DPSV, Differential Pulse Stripping Voltammetry; DPASV, Differential Pulse Anodic Stripping Voltammetry; DC, Sampled Direct Current Polarography, NPP, Normal Pulse Polarography; DPP, Differential Puse Polarography; ASV, Anodic Stripping Voltammetry; AdSV, Adsorptive Stripping Voltammetry; SWASV, Square Wave Anodic Stripping Voltammetry

Chemometrical Techniques: CLS, classical least squares; CPCR, consensus principal components regression, PCR; HPCR, Hierarchical principal component regression; HPLS hierarchical partial least squares; MBPLS, Multiblock partial least squares; MLR, multivariate linear resolution; PLS, partial least squares; NL-PLS, non-linear partial least squares; PCR, principal components regression, ILS, inverse least squares; ANN, artificial neural networks; KF, Kalman filter; GA-PLS, genetic algorithn partial least squares.

containing both active ingredients and excipients. Deviations from linearity were observed for both analytes. It is probably due to interactions among the electroactive components and competition by the electrode surface, a fact that supports the use of ANNs. Recoveries, when analyzing a nine sample validation set, of 100.2 and 96.4 were calculated for B6 and B12, respectively. Comercial samples were analyzed with reasonably good results.

Nalidixic acid (NA) and its main metabolite, 7-hydroxymethylnalidixic acid (OH-NA), were simultaneously determined in urine by Guiberteau et al. (133) by applying ANNs to their SWV signals. The recovery values are between 91 and 109% for NA and between 82 and 112% for OH-NA, these results being better than the results obtained by PLS calibration.

Combined Use of Different Techniques. What is more frequently found in literature is the comparison and evaluation of several calibration techniques. Table 3 summarizes some of the comparative studies. Again, the simultaneous voltammetric determination of several metal ions, especially Pb, Cd, In and Tl, has been performed by a great number of chemometric techniques and the respective results compared (136–138, 147–149). Also concerning heavy metal ions, von Tuempling et al. (134) studied the effects of pH, Ca and fulvic acid (FA) levels in natural waters on the interactions of heavy metals (Cd, Cu, Zn) with FA as measured by DPASV. Experimental data were analyzed by MLR and PLS regression. The PLS model yielded smaller relative errors (of 9.7, 6.0, and 58% for Cd, Zn, and Cu, respectively) than the MLR model (with relative errors of 12, 9, and 65%).

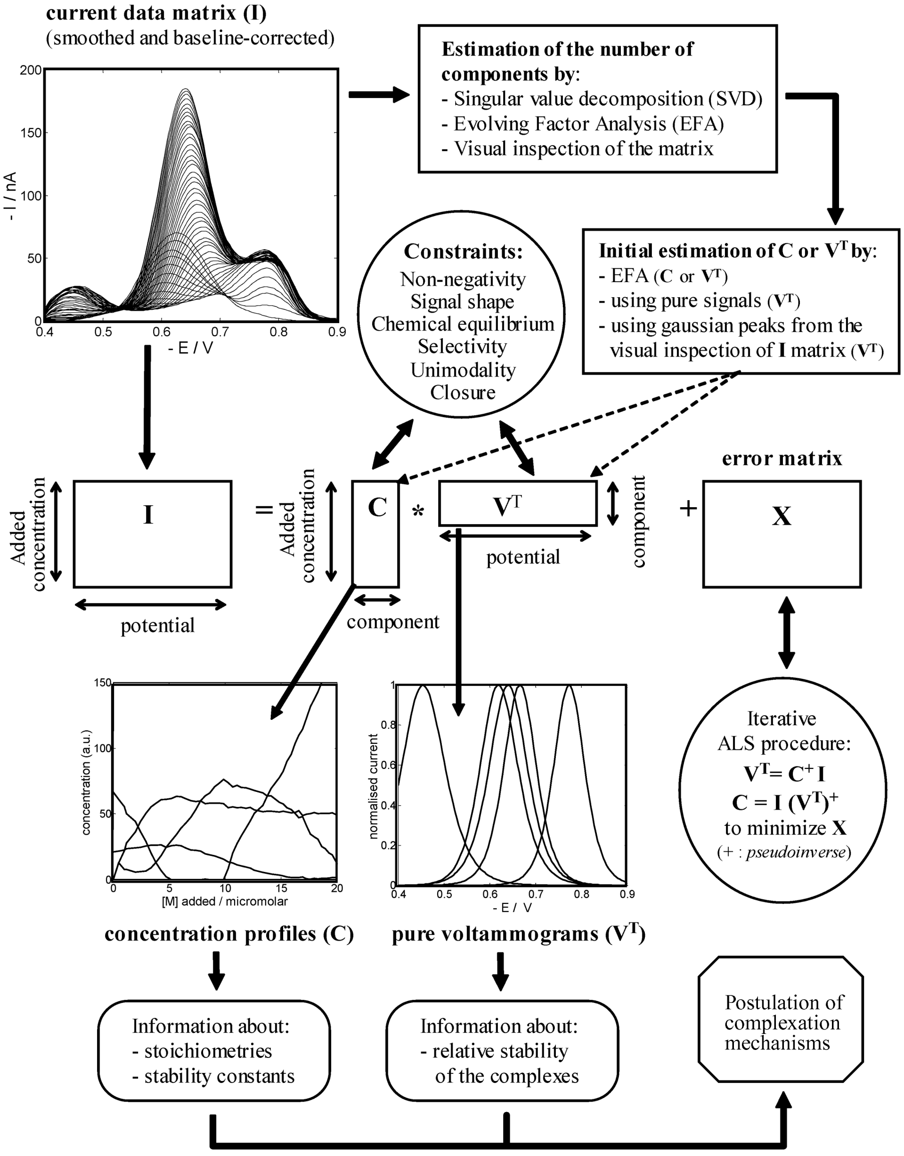

FIG. 1. Flowchart of the MCR-ALS procedure applied to voltammetric data.

The rest of applications summarized in Table 3 are referred to a miscellaneous of compounds and problems, including the determination of oxidizable aminoacids (139, 141, 152), antipsychotic drugs (145), active compounds in pharmaceuticals as paracetamol (150), antituberculosis drugs (155), vitamines (156), pesticides (151, 153), herbicides of the 1,3,5-triazine family (143), synthetic colorants (135), synthetic food antioxidants (144), aromatic compounds (142, 146), and ethanol, fructose and glucose (140), and a brightener compound in industrial Cu electroplating baths (154).

CHEMICAL MODEL IDENTIFICATION

Multivariate Curve Resolution with Alternating Least Squares (MCR-ALS)

The application of chemometrics to electroanalytical data with the aim of resolving dynamic multicomponent systems (such as metal complexation equilibria) is rather scarce and very recent, especially compared to its use in spectroscopic data. At the best of our knowledge, the first application of factor analysis to polarographic data was over 30 years ago (157). Later, factor analysis was used for the determination of the number of species in solution for simulated polarographic data sets of the Cd-Cl, Bi-Cl and Cd-SCN systems, and for experimental data sets of Cd-Cl and Cu-morpholine systems (158). Simeon et al. (159) applied several Factor Analysis techniques (160) to DPASV data of Pb and Cd solutions, while Kankare et al. to spectroelectrochemical data of a thin film of poly(3-methylthiophene) (161).

Multivariate Curve Resolution with Alternating Least Squares (MCR-ALS), a technique developed by Tauler et al. (162, 163), was shown to be a very powerful tool for the spectroscopic study of metal complex equilibria. Later, the method was adapted for metal complexation studies by voltammetry, and some modifications were introduced in order to adapt it to the characteristics of voltammetric data. Figure 1 shows a schematic flow-chart of MCR-ALS as applied to voltammetric data.

The main advantage of MCR-ALS in the study dynamic multicomponent systems, compared to PCR, PLS and other techniques, is that MCR-ALS allows one to decompose the experimental current data matrix (Figure 2) into a matrix that contains the information of the concentration profiles (Figure 3) and another matrix containing the individual voltammograms (Figure 4). From the first matrix (Figure 3) it is possible to deduce information of the evolution of the different species during the experiment and the stoichiometries. From the second matrix (Figure 4), it is possible to deduce information about the characteristics of the involved processes. From the combined analysis of both matrices an electrochemical scheme can be proposed and, from that, a complexation model containing speciation information can be deduced.

To obtain chemically meaningful results, not just mathematically satisfactory solutions, some constraints during the ALS-optimisation must be imposed. The constraints usually applied in spectroscopic studies are: (i) non-negativity of concentrations, (ii) non-negativity of the signals, (iii) unimodality of the concentrations, (iv) unimodality of the signals, (v) selectivity (presence in parts of the experiment of only some of the species), and (vi) closure (the sum of the concentrations of the metal ion or the ligand, depending on the experimental design, remains constant).

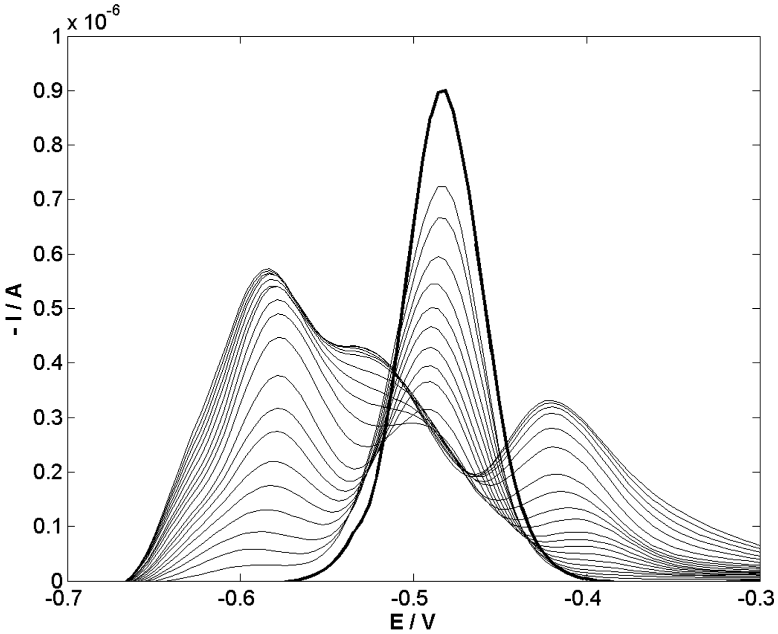

FIG. 2. Differential pulse polarograms measured during the titration of a 1.0 10^{-4} mol l^{-1} Pb(II) solution with glutathione (GSH) at pH 5.5 (maleic/maleate buffer, 0.01 mol l^{-1} in maleate ion). The signal obtained in the absence of GSH is denoted with a thicker line.

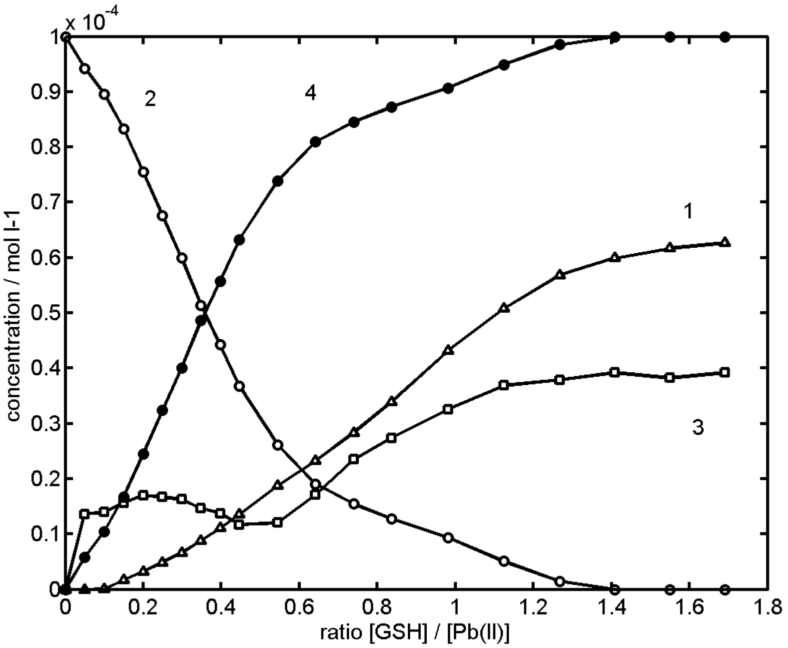

FIG. 3. Concentration profiles obtained from the data matrix shown in Figure 2 when MCR-ALS is applied using the constraints of non-negativity (signals and concentrations), closure (for components 2 and 4 only) and signal shape (asymmetric logistic function applied to all signals). Components 2 and 4 are associated to the reduction of free Pb(II)-ion and Pb(II) bound to glutathione (GSH), respectively, whereas components 1 and 3 are associated to the oxidation of the mercury of the electrode induced by the formation of Hg-GSH complexes. In the graph, concentrations of components 1 and 3 (not restricted by closure) are expressed in arbitrary units.

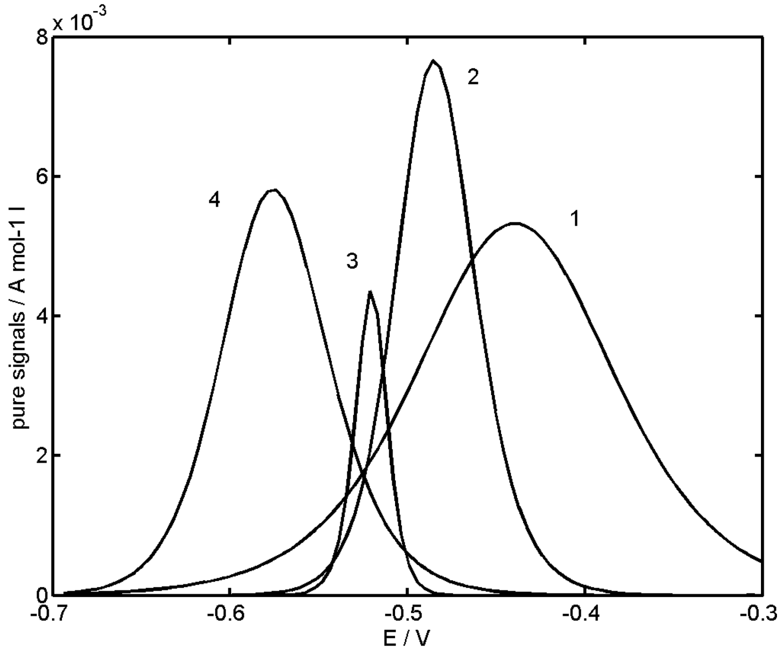

FIG. 4. Pure voltammograms obtained from the MCR-ALS analysis of the data in Figure 2, corresponding to the components 1–4, which are described in Figure 3.

TABLE 4
Summary of the different metal complex systems studied by the combined use of voltammetric techniques and multivariate curve resolution by alternating least squares optimisation (MCR-ALS)

Systems	Techniques	Comments	References
Zn-GSH	NPP, RPP, DPP	Speciation	165
Cu–Tannic Acid	DPP	Presence of intermediate Cu(I) complexes	166
Cd-Zn-FT, Cd-{Zn-MT}	SWV, DPP	Metal mixed system (exchange experiments)	167,173,176
Cd-1,10-phenanthroline, Zn-GSH	NPP, RPP, DPP	Implementation of a chemical equilibrium constraint	168
Cd-glycine, Pb-glycine	NPP, RPP, DPP	Successive and labile weak complexes	169
Pb-GSH	DPP	Interference of anodic signals of Hg electrode	170
Zn-glycine	DCP, DPP	Both electrochemically labile and inert complexes	171
Cd-Cys-Gly, Cd-γ-Glu-Cys	DPP	Analysis of single and augmented matrices	172
Cd-PC_2	DPV	Cd complexation model for phytochelatin PC_2	174
Cd – Humic Acid	DPASV	Detection of two types of complexation	175
Cd-FT, Zn-FT	DPP, EXAFS	Comparison voltammetry/MCR-ALS *vs*. spectroscopy	177
Zn-Cys-Gly, Zn-γ-Glu-Cys	DPP	Analysis of single and augmented matrices	178
Cd-Zn-α- and β-MT domains	DPP	Metal exchange properties of α- and β-MT domains	179
Cd-PC_3,Zn-PC_3,Cd-Zn-PC_3	DPP	Complexation models for phytochelatin PC_3	180
Cys-containing compounds	ED-HPLC	Amperometric vs. Voltammetric/MCR-ALS detection	181

Compounds: GSH, glutathione; FT, {56-61} C-terminal fragment of the mammalian metallothionein: Lys-Cys-Thr-Cys-Cys-Ala; PC_2, phytochelatin (γ-Glu-Cys)$_2$Gly; PC_3, phytochelatin (γ-Glu-Cys)$_3$Gly; Zn-MT, Zn-containing mammalian metallothionein; α- and β-MT domains, α- and β-domains of mammalian metallothioneins.

Techniques: DCP, Direct Current Polarography; DPP, Differential Puse Polarography; DPV, Differential Puse Voltmmetry; ED-HPLC, Electrochemical detection in HPLC; EXAFS, Extended X-ray Absorption Fine Structure Spectroscopy; NPP, Normal Pulse Polarography; RPP, Reverse Pulse Polarography, SWV, Square Wave Voltammetry.

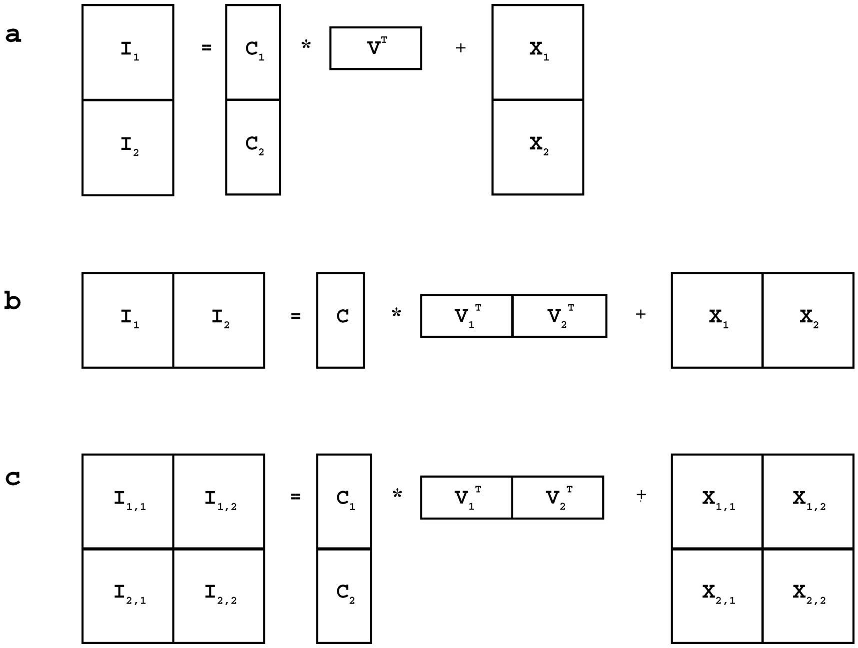

FIG. 5. Different combinations of data sets to perform MCR-ALS: (a) column-wise augmented data matrix (measurements under the same conditions in different experiments); (b) row-wise augmented data matrix (different types of measurement along the same experiment); and (c) column- and row-wise augmented data matrix (different measurements for each different experiment).

Due to the characteristics of voltammetric data, an additional constraint has been implemented: (vii) the peak-shape constraint, which takes into account the expected shape of the signal produced by the used technique and its proper parametric equation.

Later, a second additional constraint was imposed to take advantage of the available information for some systems, including (viii) chemical equilibrium constraints for systems with successive metal complexes.

The resolution power of the method is greatly enhanced by simultaneous analysis of several matrices obtained using either different techniques or experiments for the same system. As an example, data analysis can be performed using augmented column- or row-wise matrices such as those shown in Figure 5.

The main drawback of MCR-ALS as applied to metal complexation studies by voltammetry is that the mathematical decomposition is based on the assumption that the measured current is linear with respect to the species concentration. This hypothesis can be true, but it is not necessarily the case. As a consequence, strictly speaking, MCR-ALS can only be applied to linear systems. However, it was demonstrated that satisfactory results can be reached even with some lack of linearity (164). Table 4 summarizes some of the metal complex systems investigated with the MCR-ALS approach from 2000. Previous studies were summarized elsewhere (10).

Artificial Neural Network

More recently, a complementary approach was presented that in principle does not suffer from the limitations due to a lack of linearity. Cukrowski et al. have evaluated ANNs and various experimental designs for refinement of experimental polarographic data from metal-ligand equilibria studies of either fully inert (kinetically slow) metal complexes (182) or for fully dynamic (labile) metal complexes (183). It was demonstrated that properly designed ANNs can provide accurate values of stability constants, with absolute errors in the range of 0.05 log unit or smaller (for labile systems) or below 0.02 log unit (for inert systems).

The major interest of this approach is the possibility of studying highly non-linear systems. This can be the case, for instance, in the analysis of dynamic (labile) metal systems with small and weak complexing ligands.

CONCLUSIONS

Nowadays, chemometrics is essential to exploiting the extraordinary potential of modern analytical instruments. This has been widely demonstrated with different types of signals, especially of a spectroscopic nature. Electroanalytical chemistry cannot ignore this dominant trend. Modern electrochemical instrumentation provides reliable and reproducible data that are the basis of analytical methods with very low quantitation limits. The combined use of these methods with the proper chemometrical tools can increase their capabilities. Although some of the expectations by Brown and Bear have been realized, as for instance the intensive application of PLS, there still remains a tremendous potential for advancement in applying chemometrics to electroanalytical data. We hope this review will help to promote the use of chemometrics in electroanalytical chemistry.

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NOMENCLATURE

ACV	Alternating Current Voltammetry
AdSV	Adsorptive Stripping Voltammetry
ANN	Artificial Neural Networks
ASV	Anodic Stripping Voltammetry
CLS	Classical Least Squares
CPCR	Consensus Principal Components Regression
Cupferron	benzene, N-hydroxy-N-nitroso
CV	Cyclic Voltammetry
DC	Sampled Direct Current Polarography
DPAdSV	Differential Pulse Adsorptive Stripping Voltammetry
DPASV	Differential Pulse Anodic Stripping Voltammetry
DPP	Differential Pulse Polarography
DuPSV	Dual Pulse Staircase Voltammetry
DPV	Differential Pulse Voltammetry
ED-HPLC	Electrochemical Detection in Liquid Chromatography
EXAFS	Extended X-ray Absorption Fine Structure Spectroscopy
FA	Factor Analysis
FFT	Fast Fourier Transform
FIA-ED	Flow Injection Analysis – Electrochemical (Amperometric) Detection
GA	Genetic Algorithm
GA-PLS	Genetic Algorithm Partial Least Squares
HPCR	Hierarchical Principal Components Regression
HPLS	Hierarchical Partial Least Squares
ILS	Inverse Least Squares
KF	Kalman Filtering
LSV	Linear Sweep Voltammetry
MBPLS	Multiblock Partial Least Squares
MCR-ALS	Multivariate Curve Resolution with Alternating Least Squares
MEM	Maximum Entropy Methods
MLR	Multiple Linear Regression
NIPALS	Nonlinear Iterative Partial Least Squares
NLPLS	Non-linear Partial Least Squares
NPP	Normal Pulse Polarography
PCA	Principal Components Analysis
PCR	Principal Components Regression
PLS	Partial Least Squares

PSA	Potentiometric Stripping Analysis
SVD	Singular Values Decomposition
SRM	Signals Ratio Method
SWAdSV	Square Wave Adsorptive Stripping Voltammetry
SWASV	Square Wave Anodic Stripping Voltammetry
SWV	Square Wave Voltammetry
UME	Ultramicroelectrode
WT	Wavelet Transformation

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