- Speciation analysis by HPLC-CVG

- Trace-level analysis of organic contaminants

- Multivariate calibration methods

Second-order and higher-order multivariate calibration methods applied to non-multilinear data using different algorithms

A.C. Olivieri, G.M. Escandar, A. Muñoz de la Peña

We discuss and evaluate the current state of second-order and higher-order multivariate calibration methods devoted to the determination of compounds in non-multilinear data systems. We examine possible causes of multilinearity deviations:

(1) a non-linear relationship between signal and analyte concentration;

(2) a signal for a given sample that is non-multilinear; and,

(3) component profiles that are not constant across the different samples.

We discuss the advantages and the limitations of the algorithms available to cope with these different situations.

The review covers relevant analytical problems found in samples of environmental and biological interest, highlighting some significant examples, and evaluating the advantages and the limitations of the different algorithms available.

A.C. Olivieri*, G.M. Escandar,
Departamento de Química Analítica, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Instituto de Química de Rosario (CONICET), Suipacha 531, Rosario, S2002LRK, Argentina

A. Muñoz de la Peña
Departamento de Química Analítica, Facultad de Ciencias, Universidad de Extremadura, 06071 Badajoz, España

*Corresponding author.
Tel./Fax: +54 341 4372704;
E-mail:
aolivier@fbioyf.unr.edu.ar

1. Introduction

Chemometric analysis has gained widespread acceptance over the past two decades, responding to the need to study increasingly complex samples by improving existing analytical protocols. There is intensive research devoted to the development and the testing of multivariate algorithms applied to progressively more difficult chemical scenarios [1,2]. The main reason for this continuing interest is that second-order and higher-order data are able to deal with potential interferences in real samples, in contrast to both zero-order and first-order calibrations [3]. Potential interferences not included in the calibration set can be modeled, allowing us to quantify accurately the calibrated analytes, even in the presence of unknown constituents. The chemometric literature has coined the expression ''second-order advantage'' to describe the latter property [4], whose potential in multi-component analysis cannot be overestimated.

For the proper application of the available multivariate algorithms to second-order data, it is important to know whether specific relations exist between the profiles for the sample components along both data dimensions. In this context, a relevant property of the data is their multilinearity, because this property is assumed by the underlying models of some of the algorithms available. It may be briefly defined as the possibility of expressing a multi-way data array for a set of samples as a linear function of component concentrations and profiles in the various data dimensions. Second-order data complying with these requirements are called trilinear, third-order data are called quadrilinear, etc.

Models with trilinear structure are:
- parallel factor analysis (PARAFAC) [5];
- several versions of alternating trilinear decomposition (ATLD) [6] e.g.:
  - self-weighted ATLD (SWATLD) [7];
  - penalized ATLD (PATLD) [8];
  - generalized rank annihilation (GRAM) [9]; and,

- ■ direct trilinear decomposition (DTLD) [10]; and,
- bilinear least-squares combined with residual bilinearization (BLLS/RBL) [11,12].

  For third-order data, suitable quadrilinear models are:
- PARAFAC;
- trilinear least-squares (TLLS) with residual trilinearization (RTL) [13]; and,
- alternating penalty quadrilinear decomposition (APQLD) [14].

  However, models allowing for deviations of multilinearity in one way or another are:
- PARAFAC2 (a variant of PARAFAC that allows profile variations in one of the data dimensions from sample to sample) [15];
- PARALIND (PARAFAC for linearly dependent systems) [16];
- multivariate curve resolution coupled to ALS (MCR-ALS) [17];
- non-bilinear rank annihilation (NBRA) [18];
- BLLS extended to linearly dependent systems [19];
- unfolded partial least-squares (U-PLS) [20];
- multi-way PLS (N-PLS) [21];
- non-linear kernel-PLS [22]; and,
- artificial neural networks (ANN) [23,24].

To achieve the second-order advantage, BLLS, PLS and ANN should be combined with RBL [25–30] or with RTL [13], if they are to be applied to third-order data.

Independent component analysis (ICA) is able to process unfolded second-order data, whether they are trilinear or deviate from trilinearity (e.g., the Rayleigh dispersion, which is observed in fluorescence matrix spectroscopy, and may thus be considered in this group) [31].

In the next section, we explain the concept of multilinearity, and detail possible causes of deviations from the multilinear situation, with emphasis on the specific algorithms that can be applied in each case.

The sections thereafter discuss examples in the literature where these deviations have been detected and solved.

Finally, we devote a section to the special case of linear dependency in component profiles, whose status regarding multilinearity is somewhat controversial.

2. Multilinear systems

In this discussion, we focus on second-order data, which are the employed most in analytical applications to date, although the considerations can be extended to higher data dimensions. When second-order data are processed for a set of samples, it is important whether the three-dimensional array built with these data complies or not with the so-called trilinearity condition. The latter establishes that the three-way data array built with a set of second-order signals can be modeled through the following expression:

$$X_{ijk} = \sum_{i=1}^{N} a_{in}b_{jn}c_{kn} + E_{ijk} \qquad (1)$$

where N is the total number of chemical constituents generating the measured signal, a_{in} is the relative concentration or score of component n in the i-th sample, and b_{jn} and c_{kn} are the intensities in the instrumental channels (or data dimensions) j and k, respectively. The values of E_{ijk} are the elements of the three-dimensional array E, representing the residual error, and having the same dimensions as X. The column vector $\mathbf{a}_n$ is collected in the scores matrix $\mathbf{A}$, while vectors $\mathbf{b}_n$ and $\mathbf{c}_n$ are collected in the loading matrices $\mathbf{B}$ and $\mathbf{C}$ (usually $\mathbf{b}_n$ and $\mathbf{c}_n$ are normalized to unit length).

The above principle can be formulated in a less mathematical way. A three-dimensional array will be trilinear provided the following requirements are verified:

(1) the signal is linearly related to the analyte concentration;
(2) the signal for a given sample is bilinear; and,
(3) the component profiles are constant across the different samples.

The first point simply means that the maximum signal, measured for a pure component at selected values of the sensors in each of the two data dimensions, is directly proportional to the component concentration.

The second requirement implies that a single component data matrix can be decomposed into the product of two vectors, each containing the component profile in one of the two data dimensions. A familiar example of bilinear data is an excitation-emission fluorescence matrix, which decomposes into the excitation and the emission spectrum for a given fluorescent component. By contrast, tandem mass-spectrometric (MS^2) data are not bilinear, because each fragment of a single compound has a specific MS pattern in the second MS dimension, making it impossible to describe the MS^2 data in terms of one MS profile in each dimension.

Finally, the third requirement implies that the shape of the profiles in all dimensions for a given component must be the same, with intensity variations being due only to different concentrations in different samples.

When the three-way array of second-order data is trilinear, trilinear models PARAFAC, ATLD (and its variants), GRAM and DTLD can be conveniently applied, since their internal structure is that of Equation (1). Usually, the component profiles are amenable to physical interpretation, since they correspond to spectra, chromatograms or kinetic evolutions of pure components, depending on the type of second-order data registered.

In going from second-order to third-order data, the requisites for quadrilinearity are analogous to those commented upon above, except that the signal for a single sample in requisite No. 2 should be trilinear instead of bilinear. More complex data arrays can of course

be imagined, for which data multilinearity can be defined by generalizing the above considerations.

3. Non-multilinear systems

When a three-way data array deviates from the multi-linearity condition, because one (or more) of the three requirements is (or are) violated, other non-multilinear algorithms should be applied. The selection of the proper algorithm, in turn, depends on the specific cause provoking loss of multilinearity. Table 1 provides a convenient summary, although we discuss full details below.

3.1. Non-linear relationship between signal and analyte concentration

This phenomenon occurs in certain kinetic-spectroscopic systems. In this case, various analytical procedures are possible. One of them involves applying any of the tri-linear models commented upon in Section 2.

Usually, the analytical results from the trilinear models are obtained by interpolation of the analyte score in the test sample into the calibration graph obtained by regressing the analyte scores in the calibration samples against their nominal concentrations, the result being called the pseudo-univariate analyte calibration graph.

In non-linear cases, a non-linear pseudo-univariate calibration graph will be obtained, because the non-linearity will be transmitted to the relation between scores and concentrations. If an appropriate non-linear expression can be found (e.g., a polynomial expression) to model this relation, the analyte calibration and the prediction can be carried out with the calibration graph fitted to the non-linear expression. This resource was employed to determine malonaldehyde in olive-oil samples, in the presence of the background signal of the olive oil, processing with PARAFAC third-order data [the temporal evolution of excitation-emission fluorescence matrices (EEFMs) during the reaction of the analyte with dimethylamine] [32]. The reaction product, 1,4-disub-stituted-1,4-dihydropyridine-3,5-dicarbaldehyde, is a highly fluorescent compound, whose emission intensity bears a non-linear relationship to the analyte concentration. The calibration graph of PARAFAC scores *versus* malonaldehide concentration could be modeled by means of a second-degree polynomial expression. This allowed the prediction of the analyte concentration in a complex background, in spite of the non-linear behavior and in the presence of uncalibrated interferences. The latter data were also processed using several ANN models, based on the combination of unfolded principal component analysis (U-PCA), RTL and radial basis functions, with similar analytical results [32].

Second-order data for the same reaction (in the form of EEFMs collected at a fixed reaction time) were recently processed by a non-linear PLS model (kernel-PLS) combined with RBL [30]. Neural-network models or kernel projections are more flexible than those that employ simple non-linear expressions to fit the response-concentration curve. They constitute universal non-linear approximators, and are useful when it is impossible to find an equation modeling the non-linearity present in a given system.

Three additional experimental systems were studied by resorting to the combination of ANNs with post-training residual bilinearization, including:

(1) the determination of two pharmaceuticals, lorata-dine and pseudoephedrine, in the presence of unexpected excipients, by absorbance-pH matrix measurements;

(2) the quantitation of iron(II) by its catalytic effect on the kinetics of the bromate oxidation of a colorant in the presence of bromocresol blue, a second interfering organic dye; and,

(3) the analysis of the antibiotic amoxicillin by photoinduced EEFMs in the presence of the fluorescent anti-inflammatory salicylate as interference [33,34]; non-linear kernel-PLS/RBL [30] was also recently applied to this system.

Table 1. Characteristics of three-dimensional arrays

	Linear signal-concentration analyte relationship	Signal bilinearity	Profile constancy	Applicable algorithm
Trilinear systems	Yes	Yes	Yes	PARAFAC, ATLD variants, GRAM, DTLD
Non-trilinear systems	No	Yes	Yes	Non-linear PARAFAC Non-linear PLS/RBL ANN/RBL
	Yes	Yes	No	MCR-ALS PARAFAC2 PLS/RBL
	Yes	No	Yes	PLS

A few other applications of neural networks to non-linear second-order data are known, but, in none of them was the second-order advantage exploited. They are:

(1) the kinetic spectrophotometric determination of carbamate pesticides [35];
(2) the correlation of two-dimensional nuclear magnetic resonance spectra to the composition and properties of oil samples [36]; and,
(3) the monitoring of fermentation processes [37].

3.2. Non-multilinear signal for a single sample

In this case, the requirement of ''equal profiles in all dimensions and all samples for a given component'' is not fulfilled. This phenomenon occurs in the case of data that are not intrinsically trilinear (e.g., MS^2 matrices). This is because the mass spectra of the fragments (obtained in the second MS dimension) depend on the position (and therefore the structure) of the fragment in the mass spectrum of the mother compound (obtained in the first MS dimension). In this way, a given component will display various different profiles in one of the data dimensions, violating the above-mentioned principle. To process this type of second-order data successfully, flexible non-trilinear algorithms are required (e.g., U-PLS or N-PLS).

A pertinent example is the simultaneous determination of the three isomers, 2-ethyl, 3-ethyl and 4-ethyl pyridine, through MS^2 data processed with both U-PLS and N-PLS [38]. No reports appear to have been published using MS^2 second-order data achieving the second-order advantage. This would require, in principle, the corresponding PLS approach to be coupled to RBL to quantify an analyte successfully in the presence of uncalibrated interferences.

3.3. Non-constant component profiles

Another case of violation of the multilinearity is when component profiles are not constant in one (or more) dimension modes from sample to sample. There are several different cases of this common phenomenon, which we discus below in the following sub-sections.

3.3.1. One of the dimensions is the retention time

The most prolific area of interest in which non-constant profiles have been observed is chromatography. Retention times usually vary from run to run due to changes in the temperature profile, the flow, the sample matrix and the injection. An indication of the growing interest in this field is the recent publication of several reviews on multi-dimensional chromatographic analysis and their chemometric processing {e.g., quantitative chromatographic determinations based on N-way calibration strategies were reviewed by Ortiz and Sarabia [39]}.

Stoll et al. [40] have reviewed systems resolved by two-dimensional liquid chromatography (LC), including considerations related to the use of diode-array detection (DAD) or MS detectors and appropriate chemometric data analysis.

Skov et al. described the advantages of multi-dimensional chromatography (i.e. the importance of multi-channel detectors to solve overlapping issues). They discuss how to solve common problems (e.g., retention-time shifts) [41,42].

Wasim and Brereton described methods for decomposing two-dimensional LC-DAD and LC-nuclear magnetic resonance (NMR) chromatograms [43].

There are basically two strategies for dealing with the phenomenon of varying retention times:

(1) One alternative for processing multi-dimensional chromatographic data is to restore the multilinearity, removing the effect introduced by sample-to-sample retention-time shifts. This activity is generally known as chromatographic alignment, and some effort has been made in the recent years to improve methods for properly aligning chromatograms.
(2) A second alternative is to process the multi-dimensional chromatograms with algorithms allowing for varying retention-time profiles across samples (e.g., MCR-ALS and PARAFAC2). In some cases, PLS/RBL has also been found to be useful in this regard, although its general applicability is still in doubt.

3.3.1.1. Use of aligned chromatograms. There are numerous alignment algorithms that have been applied in different systems [44–48]. Synchronization methods for multi-dimensional chromatographic data [49] and for complex, highly variable LC-MS data sets were recently reviewed [50].

Prazen et al. introduced rank alignment to correct the time shift in bidimensional chromatography based on PCA of an augmented data matrix [51,52].

Nielsen et al. introduced the correlation optimized warping (COW) algorithm for the alignment of two chromatographic profiles by piecewise linear stretching and compression of the time axis of one of the profiles [44].

Bylund et al. applied a modified COW algorithm for time alignment of LC-MS data before successful PARAFAC modeling of both simulated data and a real standard mixture of peptides [46].

Retention-time shifts in two-dimensional separations can occur in both chromatographic dimensions, creating the need for new methods to align the data [53,54].

Quantitative analysis using two-dimensional gas chromatography (GC) with a flame-ionization detector was reported for six essential oil markers in full perfumes [55]. The results of conventional integration with those

obtained using PARAFAC, PARAFAC2 and N-PLS were compared.

To solve retention-time shifts, Wasim and Brereton employed a correlation-optimized shifting based on the so-called inner-product correlation to the local selections [44]. Although traditional integration produced slightly better results with respect to accuracy and precision, multi-way analysis methods were far superior in terms of speed and possibilities for automation.

Fraga developed a chemometric approach to the quantification, in environmental samples, of unresolved target-analyte signals (triethyl phosphate and 1,4-dithiacyclohexane) in a GC-selected ion monitoring (GC-SIM) mass spectrometer [56]. While an unskewing algorithm was used to correct the retention-time differences within a single GC-SIM data matrix caused by using a scanning mass spectrometer, rank alignment corrected the run-to-run retention-time difference between a sample GC-SIM data matrix and a standard addition GC-SIM data matrix. GRAM was then applied to quantify the target analytes.

PARAFAC was applied to LC-ESI-MS (ESI = electrospray ionization) data for screening unknown metabolites of citalopram, an antidepressant drug, in urine samples [57]. Curve resolution was used for deconvolution of the LC-MS data followed by peak alignment, and the preprocessed data were then used for metabolite-pattern recognition using PARAFAC. A combination of data from positive and negative ionization enhanced the identification of metabolites and new unreported metabolites were found and characterized by LC-MS^2 and accurate mass measurements.

GC-GC-time-of-flight (TOF)-MS coupled with chemometric analysis (PCA followed by PARAFAC) were used to identify chemical differences in metabolite extracts isolated from yeast cells either metabolizing glucose by fermentation or metabolizing ethanol by respiration, providing a reliable ratio of the metabolite concentrations [58]. In cases where it was necessary, a high-speed peak-matching algorithm for retention-time alignment was applied [59].

Recently, U-PLS and N-PLS combined with RBL were applied to the determination of the polycyclic aromatic hydrocarbons (PAHs) benzo[b]fluoranthene and benzo[k]fluoranthene in the presence of benzo[j]fluoranthene as interference, based on LC fluorescence emission matrices [60]. A new alignment procedure, which is able to take into account the presence of potential interferences, was developed, based on the decomposition of a three-way array composed of a test and a reference-data matrix using a suitably initialized and constrained PARAFAC model [60].

Resorcinol and phenol, and pesticides oxamyl and methomyl were determined in river-water and waste-water samples by coupling HPLC with DAD and the algorithms GRAM, PARAFAC and MCR-ALS [61]. Before

data processing with GRAM and PARAFAC, a time-shift correction aligned the peaks using iterative target transformation factor analysis (ITTFA) [46]. Although the three algorithms provided similar mean predictions, MCR-ALS was the most robust to cope with the time shift.

PARAFAC was used for the analysis of HPLC-DAD data for binary mixtures of two anesthetic drugs, lidocaine and prilocaine, with both zero and low chromatographic resolution [62]. DAD data from three different cases were studied. In one experiment, the analysis was carried out without a chromatographic column; instead, a back-pressure tube connected between the autosampler and the detector provided pressure for the pump to work against. In the remaining cases, a chromatographic column was employed, and a varying amount of acetonitrile in the mobile phase provided the different separations. In the first case, small shifts in the retention time of the single peak were observed in all samples, and thus corrections were made to the shifts for a successful prediction.

Three synthetic mixtures (p-chlorobenzoic acid/benzoic acid, uracil/pyruvic acid, and fumaric acid/maleic acid/phenyl phosphoric acid), each containing a different target analyte (p-chlorobenzoic acid, uracil, and fumaric acid, respectively) were analyzed by two-dimensional LC data using an in-house LC×LC analyzer that coupled an anion-exchange column with a reversed-phase column connected to a UV-absorbance detector [63]. The resulting unresolved target-analyte signals were then analyzed by standard addition with GRAM and PARAFAC. GRAM followed by PARAFAC refinement was shown to produce better results than using each method separately. Because, in some cases, rank alignment did not correct the run-to-run retention-time shifts of the LC×LC data, the authors introduced a new alignment method. It involved incrementally applying a time-shift correction to the LC×LC data followed by GRAM and then PARAFAC analysis. The right shift provided the best data fit between the PARAFAC data and the raw data.

PARAFAC and BLLS were applied to the determination of five pesticides (simazine, carbaryl, carbendazim, methyl thiophanate and dimethoate) and two metabolites (phthalimide and 3,5-dichloroaniline) in wine samples by HPLC-DAD [64]. Rank alignment was employed to correct the effects of time shifts. Use of constraints or choice of an appropriate initialization procedure for PARAFAC was necessary in some situations to provide better results, and, although these tools are very useful, they should be optimized. However, although BLLS presents the advantages of not requiring initialization and constraints, the knowledge of all components in the calibration samples is required for application of this method. In the cases analyzed, BLLS presented results that were of the same quality as

PARAFAC in five cases, but, in two other situations, only PARAFAC enabled analyte quantitation.

HPLC-DAD coupled with the ATLD algorithm determined levodopa, carbidopa and methyldopa simultaneously in human plasma samples [65]. While selection of the retention-time domain for each analyte avoided collinearity problems, the second-order chromatographic standardization [51] was applied to align the data sets and to obtain better analytical figures of merit.

HPLC-DAD and PARAFAC were applied for the simultaneous determination of four aflatoxins in a set of spiked and naturally-contaminated pistachio nuts in the presence of matrix interferences [66]. The effect of retention-time shifts was corrected by rank alignment [51].

3.3.1.2. Use of unaligned chromatograms. In this subsection, we review papers where raw chromatographic data were directly processed by suitable algorithms, which allowed for varying retention-time profiles in different experiments. However, in some cases, minor time shifts in selected chromatographic regions allowed direct trilinear analysis of the multi-dimensional chromatograms. For example, metabolomic analysis was carried out from third-order LC-LC-DAD data processed by PARAFAC, including quantitative analysis of selected compounds [67]. The entire chromatogram was partitioned into small sections, in which the data were apparently quadrilinear.

Also, in the quantification of sulfamethoxypyridazine, sulfamethoxazole and sulfadimethoxine in porcine kidney by HPLC-DAD and PARAFAC [68], no significant retention-time shifts were observed.

Agrochemicals in both synthetic and spiked environmental wastewaters and sediment samples were evaluated by LC-DAD data recorded using two types of columns [69], with promising (although not ideal) results when applying MCR-ALS, due to co-elution problems and matrix interferences. In a subsequent work, the authors improved results by coupling the chromatographic run to an MS detector in scan mode [70]. Finally, using coupled LC-DAD-MS data, all problems were successfully resolved by MCR-ALS and quantitation errors were below 12% [71].

LC with DAD detection and MCR-ALS was also applied for the quantitation of:
(1) nine phenolic acids in synthetic samples and strawberry samples [72];
(2) three synthetic dyes in non-alcoholic beverages [73];
(3) seven non-steroidal anti-inflammatory drugs and anticonvulsant carbamazepine in river water and wastewater [74];
(4) nine β-blockers and two analgesics (paracetamol and phenazone) in river water [74];
(5) pesticides in water samples [76]; and,
(6) four phenolic acids in olive oil [77].

In some of these cases, MCR-ALS showed better predictive ability than U-PLS/RBL [73] and PARAFAC2 [77].

U-PLS/RBL was applied to LC-DAD data for the simultaneous determination of eight tetracyclines in wastewaters [78]. The use of a latent variable structure provided predictive results that were comparable to MCR-ALS.

Six sulfamides were extracted from kidney and analyzed by HPLC-DAD and PARAFAC2 [79], and nine components of reserpine (a common antihypertensive) tablets were determined by MCR-ALS applied to capillary electrophoresis-DAD data [80].

MCR-ALS and PLS were compared for the resolution of co-eluted peaks of pyrocatechol, dopamine and epinephrine in LC with electrochemical detection [81]. Voltammetric detection coupled to MCR-ALS was preferred for high analyte concentrations, whereas amperometric detection combined with PLS was more adequate at lower levels.

HPLC with attenuated total reflection-FTIR detection was implemented for the determination of carbohydrates, alcohols and organic acids in red wine. Where co-elution was detected, MCR-ALS was successfully employed for quantitative analysis [82].

István et al. analyzed the capabilities of some chemometric algorithms for the eluent-elimination problem in HPLC-IR spectroscopy [83]. When the elution profiles of the eluent were not the same from sample to sample, the simple use of MCR-ALS, PARAFAC or PARAFAC2 did not yield acceptable results. A method named objective subtraction of solvent spectrum with iterative use of PARAFAC2 (OSSS-IU-PARAFAC2) was therefore introduced and adequately retrieved the analyte profiles in both simulated and real HPLC-IR data sets.

Ten PAHs were determined in aqueous samples, six of which correspond to heavy PAHs, in the presence of two interferences, processing second-order data from LC-fluorescence detection [84]. The second-order data were obtained in a short time with a chromatographic system operating in isocratic mode. Although both MCR-ALS and PARAFAC2 were able to overcome the problem of the presence of unexpected interferences, the superiority of MCR-ALS to resolve this complex system successfully was demonstrated.

Coupling of fluorescence emission-retention-time matrices with the MCR-ALS algorithm allowed the determination of the following marker-pteridin pathological urine samples, even in the presence of interferences: neopterin, biopterin, pterin, xanthopterin and isoxanthopterin. Baseline correction was applied to reduce the large drift caused by interferences, but no time-shift alignments were necessary. The method allowed calculation of pteridine/creatinine ratios in urine samples from children with different pathologies [85].

Retention-time shifts are less likely to occur in multi-dimensional GC experiments. However, some authors reported better results with non-trilinear algorithms. GRAM and MCR-ALS were used in conjunction with GC-MS data for the quantification of four unsaturated fatty acids in the presence of interfering components [86]. Unlike MCR-ALS, a retention-time shift correction on GC profiles was necessary for GRAM [51]. Amigo et al. showed the potential of PARAFAC2 for solving common GC-MS problems, using GC-MS data from wine samples to illustrate the solutions [87].

It was demonstrated that two-dimensional GC coupled to TOF-MS (GC×GC/TOF-MS) provides retention times on two chromatographic columns, and a complete mass spectrum for each component within an environmental mixture. These are trilinear data compatible with chemometric calibration techniques (e.g., TLD and PARAFAC) [88]. It was determined that PARAFAC performed a better deconvolution than TLD. A standard-addition method was performed on one of the deconvoluted analytes of interest to demonstrate the utility of PARAFAC for quantification without the need for retention-time alignment between sample and standard data sets. This approach also eliminated the need for fully selective mass channel ions for deconvolution; however, some selectivity is required in each dimension for the algorithm to be successful.

Both aligned and unaligned emission fluorescence-LC retention-time data matrices were probed for the determination of eight fluoroquinolones in samples with and without interferences [89]. PARAFAC and N-PLS/RBL yielded good results for all the investigated systems, provided they were fed with suitably pre-processed data, particularly in what concerns the alignment of the chromatographic profiles in the retention-time dimension. MCR-ALS also produced reasonably accurate results, even if raw data were processed. However, extensive spectral overlapping seriously affected the MCR-ALS predictions in one of the systems.

3.3.2. One of the dimensions is pH or reaction time.
In experiments in which one of the data dimensions is a pH gradient or a reaction time for kinetic data, the pH or temporal profiles may vary from sample to sample due to a variety of reasons (e.g., irreproducibility in the pH gradient generation, and temperature changes between runs). This type of data can be therefore conveniently handled by MCR-ALS or PARAFAC2, two multivariate algorithms allowing for varying component profiles along one of the data dimensions (pH or reaction time). However, PLS or RBL strategies would also cope with such multilinearity deviations.

An enzymatic reaction, carried out in a reverse stopped-flow-injection system and monitored by UV-vis spectroscopy, was proposed for the determination of levodopa and carbidopa in pharmaceuticals, using MCR-ALS as the chemometric tool [90].

A flow-injection chemiluminescent method, based on the different rates of the reaction of codeine and noscapine in an $Ru(bpy)_3^{2+}$-Ce(IV) system, was developed for the simultaneous determination of these compounds in pharmaceutical preparations [91]. Because the concentration of sulfuric acid has a different influence on the chemiluminescent intensity of the compounds, a three-way data structure given by sulfuric-acid concentration, time and samples was constructed and followed by N-PLS regression, which does not strictly require the trilinearity condition.

Carneiro et al. carried out the quantitation of ascorbic and acetylsalicylic acids in pharmaceutical samples using a flow-injection analysis system with pH gradient, a DAD detector and MCR-ALS [92].

Antihypertensor nifedipine was determined in pharmaceutical formulations by acquiring UV-vis spectra as function of the time of the alkaline hydrolysis reaction in dimethylsulfoxide [93]. The fact that a better model fit of the three-way data structures obtained was found with PARAFAC2 with respect to PARAFAC suggested that the experimental data sets had deviations from trilinearity. Applying a kinetic spectrophotometric method, the same authors quantified other antihypertensor, diltiazem, in pharmaceuticals applying both PARAFAC2 and MCR-ALS [94].

3.3.3. Analyte-background interactions.
In the presence of analyte-background interactions, analytical spectral changes occur from sample to sample (e.g., in second-order EEFM data). U-PLS/RBL has been used for the determination of antibiotic tetracycline and anti-inflammatory salicylate, in both cases in the presence of human serum, where significant analyte background interactions occurred, as the interaction of the analyte with the serum proteins modified their spectral fluorescence properties [28], and in the presence of other usually co-administered drugs as interferences.

3.3.4. Inner-filter effect.
In luminescence spectroscopy, the inner-filter phenomenon may occur when a sample component significantly absorbs radiation from the light source of the instrument or the emission of an analyte. Reflection on the inner-filter effect leads to the conclusion that, in a given set of samples, emission and excitation profiles for the affected analytes vary from sample to sample, in not only intensity but also shape. This is usually because the spectral overlapping (between the absorption of the component producing the inner-filter effect and the emission/excitation peaks of the analyte) varies across the analyte band. It is this property that makes conventional second-order multivariate methodologies inapplicable to this particular

case, because most of them are designed to recover unique component profiles (excitation and emission).

MCR-ALS cannot be applied to augmented data matrices with these properties, because this algorithm can take into account only changes in spectral or time profiles in one of the data dimensions. In these situations, only U-PLS/RBL (and presumably also N-PLS/RBL) can be applied if the second-order advantage is to be achieved, as was recently demonstrated with mixtures of pesticides [95] and PAHs [96], in the latter case containing chrysene (the analyte of interest) and benzo[*a*]-pyrene (which produced a strong inner-filter effect across the useful wavelength range).

4. Linearly dependent profiles

We discuss the question of profiles that are linearly dependent in this section, because their multilinearity is somewhat uncertain, as discussed below.

4.1. Kinetic or pH profiles

Linear dependency occurs when one or more sample components obey a certain closure relationship, implying that they are mutually correlated. For example, if two species are components of an acid-base pair, or are the reagent and the product of a chemical reaction, then the sum of their concentrations will be constant in the corresponding dimension (pH or reaction time, respectively). These correlated profiles are known are linearly dependent. Correlations of this type may produce data matrices with a rank lower than the number of chemically responsive components {i.e. a rank-deficient matrix, a situation also known as ''rank overlap'' [97,98]}.

These linearly dependent profiles pose special challenges to trilinear algorithms, because three-dimensional arrays may not be uniquely resolved by the trilinear models. This led some authors to consider this phenomenon as an additional cause of trilinearity loss. In fact, an algorithm named non-bilinear rank annihilation was developed for handling cases of second-order analytical problems in which one of the data dimensions was the pH [18]. The name of the algorithm itself implies that the authors believed the signal to be non-bilinear, and hence a set of samples to be non-trilinear.

In these cases, each of the species separately fulfils the trilinearity condition, and, although the overall signal follows Equation (1), the uniqueness property of the model is lost. As a result, PARAFAC (and other trilinear models as well) will present a problem associated with a multiplicity of local minima during the least-squares fitting phase, with many different solutions lacking physical interpretability.

However, the problem can be solved by subjecting PARAFAC to restrictions, e.g.:

(1) initialization with values as close as possible to the global minimum; and,
(2) forcing the elements of the scores and the loadings to be non-negative (or unimodal and non-negative, if they are of chromatographic origin).

Others are to employ:
(1) PARALIND, which operates in a similar way to PARAFAC, but incorporates in the model the linear dependency among profiles; or,
(2) MCR-ALS, which regularly includes initialization and restrictions of the type discussed above.

Flexible models based on the PLS/RBL philosophy are still more convenient, as they can be applied without any modification with respect to the original algorithm.

Recent examples are the determinations of antibiotics in human-urine samples, in which the second-order advantage was achieved in the presence of the fluorescent signal of the biological background, processing with U-PLS/RBL kinetic spectrophotometric data [99] and pH-gradient data [100]. In the first case, the kinetic evolution of UV-vis absorption spectra of amoxicillin in the presence of copper(II) was used as the analytical signal [99], and, in the second case, several fluoroquinolones, ciprofloxacin, norfloxacin and ofloxacin were determined in human-urine samples based on flow-injection pH-modulated synchronous fluorescence data matrices [100].

An additional experimental set was also analyzed, by resorting to PLS/RBL, in a case in which linear dependency was due to pH equilibria [27]. The analytes were sodium benzoate and sodium sorbate in fruit-juice samples, and each analyte has two species that are related by proton-transfer reactions. The U-PLS/RBL method allowed circumvention of some of the challenges posed by this linearly dependent system on second-order multivariate calibration.

BLLS was modified to take into account acid-base species, and was applied to the analysis of ascorbic acid in fruit juices by spectral-pH data [19]. Subsequently, the algorithm was employed for the quantification of four dyes in juices via a flow system [101]. Linear dependencies in the pH dimension and strong spectral overlapping made it impossible to analyze these data using MCR-ALS and PARAFAC.

Tetracycline, chlortetracycline and oxytetracycline were determined in surface-water samples from photochemical-induced fluorescence excitation emission matrices, modeled with BLLS and PARAFAC [102]. In addition to significant overlapping of the analyte spectra, strong collinearity in tetracycline and oxytetracycline excitation spectra was detected. It was confirmed that BLLS yielded better predictions than PARAFAC, indicating the ability of BLLS to take into account high collinearities in the data.

4.2. Equal profiles in one of the data dimensions

Finally, the problem presented by the high (or even complete) overlapping of profiles in one of the data dimensions can be regarded as a special case of linear dependency. However, it is more serious than the linear dependency discussed above, for reasons discussed below. It occurs when the spectral or temporal profiles are virtually identical in all samples, reducing the selectivity in the affected dimension to zero.

It is worth distinguishing two main cases of this type of extreme overlapping in one dimension:
(1) when it occurs between calibrated analytes; and,
(2) when it takes place between a calibrated analyte and an interference.

PARAFAC and other trilinear models cannot be applied to any of these two cases, even after imposing suitable initialization and restriction conditions. The first case could be conveniently solved by U-PLS/RBL, exploiting the selectivity in one of the data dimensions, in order to distinguish the analytes. However, in the second case, PLS/RBL will fail, because the RBL technique will be unable to distinguish between analyte and interference. Nevertheless, this second case is the most interesting from the analytical point of view, since it constitutes the field of activity of the second-order advantage, one of the central objectives of the second-order multivariate work. Hence, this special case of linear dependency poses more severe challenges to second-order multivariate algorithms, whether they are trilinear (e.g., PARAFAC) or not (PLS/RBL).

Among the algorithms capable of achieving the second-order advantage, the only two that can solve this interesting problem are MCR-ALS and PARALIND. The MCR-ALS model does so by decomposing an augmented data matrix, built by placing matrices for different samples adjacent to each other, in such a way that the augmentation mode is the one affected by the profile overlapping. As a result, the null selectivity in the affected dimension is recovered in the augmented dimension. However, in the PARALIND model, the linear dependency is already incorporated into the structural model, allowing some components to have identical profiles in one dimension but different profiles in the other. None of the remaining algorithms may be able to solve the problem.

Experimentally, this situation is encountered when a chemical reaction generates a single responsive product from a series of analytes. Although the kinetics of each reaction may differ from analyte to analyte, the spectrum of the common product is identical for all analytes [103].

Another important case under consideration is when using as an analytical signal channel the time decay of the luminescent signal of complexes formed by lanthanide ions and several sample components. Since the emission of radiation arises from the complex ion, the excitation spectra may differ (due to the different structure of the ligands), but the emission spectra will be identical, and the decay times will, in general, be very similar. An example of this case is the determination of fluoroquinolones in human serum in the presence of the interferent salicylate using lanthanide-sensitized excitation-time decay luminescence data and MCR-ALS [104].

Very recently, second-order signals presenting this phenomenon were measured for the time evolution of chemiluminescence spectra [105]. In this case, the

Table 2. Second-order and third-order experimental data		
Data order	**Experimental data[a]**	**Selected references**
Second	Excitation-emission fluorescence	[32–34]
	Excitation-emission phosphorescence	[106]
	Kinetic-DAD or fluorescence	[33,35,90,91,93,94,99,103]
	pH-DAD or fluorescence	[18,33,92,100]
	Lanthanide luminescence-time decay	[104]
	Chemiluminescence-time evolution	[105]
	Phosphorescence-time decay	[107]
	HPLC- DAD detection	[61–69,71–79]
	HPLC- fast-fluorescence detection	[60,84,85,89]
	HPLC- MS detection	[57,58,70,71]
	HPLC-electrochemical detection	[81]
	HPLC-IR detection	[82,83]
	GC-MS detection	[86–88]
	CE-DAD detection	[80]
	CE-MS detection	[108]
	MS^2	[38]
Third	Kinetic-excitation-emission fluorescence	[32]
	Excitation-emission phosphorescence-time decay	[109]

[a]HPLC, High-performance liquid chromatography; CE, Capillary electrophoresis; DAD, Diode-array detection; GC, Gas chromatography; MS, Mass spectrometry.

spectra were identical, with the selectivity provided by the time-evolution dimension. A variant of U-PLS/RBL was also proposed and compared with MCR-ALS [105].

As a summary of the above information, Table 2 lists the second-order and higher-order instrumental data available to the analyst and already employed in different analytical applications.

References

[1] G.M. Escandar, N.M. Faber, H.C. Goicoechea, A. Muñoz de la Peña, A.C. Olivieri, R.J. Poppi, Trends Anal. Chem. 26 (2007) 752.
[2] R. Bro, Crit. Rev. Anal. Chem. 36 (2006) 279.
[3] A.C. Olivieri, Anal. Chem. 80 (2008) 5713.
[4] K.S. Booksh, B.R. Kowalski, Anal. Chem. 66 (1994) 782A.
[5] R. Bro, Chemom. Intell. Lab. Syst. 38 (1997) 149.
[6] H.L. Wu, M. Shibukawa, K. Oguma, J. Chemometrics 12 (1998) 1.
[7] Z.P. Chen, H.L. Wu, J.H. Jiang, Y. Li, R.Q. Yu, Chemom. Intell. Lab. Syst. 52 (2000) 75.
[8] A.L. Xia, H.L. Wu, D.M. Fang, Y.J. Ding, L.Q. Hu, R.Q. Yu, J. Chemometrics 19 (2005) 65.
[9] E. Sanchez, B.R. Kowalski, Anal. Chem. 58 (1986) 496.
[10] E. Sanchez, B.R. Kowalski, J. Chemometrics 1 (1990) 29.
[11] M. Linder, R. Sundberg, Chemom. Intell. Lab. Syst. 42 (1998) 159.
[12] M. Linder, R. Sundberg, J. Chemometrics 16 (2002) 12.
[13] J.A. Arancibia, A.C. Olivieri, D. Bohoyo Gil, A. Espinosa Mansilla, I. Durán Merás, A. Muñoz de la Peña, Chemom. Intell. Lab. System 80 (2006) 77.
[14] A.L. Xia, H.L. Wu, S.F. Li, S.H. Zhu, L.Q. Hu, R.Q. Yu, J. Chemometrics 21 (2007) 133.
[15] H.A.L. Kiers, J.M.F. Ten Berge, R. Bro, J. Chemometrics 13 (1999) 275.
[16] M. Bahram, R. Bro, Anal. Chim. Acta 584 (2007) 397.
[17] R. Tauler, Chemom. Intell. Lab. Syst. 30 (1995) 133.
[18] M.M. Reis, S.P. Gurden, A.K. Smilde, M.M.C. Ferreira, Anal. Chim. Acta 422 (2000) 21.
[19] H.C. Goicoechea, A.C. Olivieri, Appl. Spectrosc. 59 (2005) 926.
[20] S. Wold, P. Geladi, K. Esbensen, J. Öhman, J. Chemometrics 1 (1987) 41.
[21] R. Bro, J. Chemometrics 10 (1996) 47.
[22] T. Czekaj, W. Wu, B. Walczak, J. Chemometrics 19 (2005) 341.
[23] S. Haykin, Neural Networks. A Comprehensive Foundation, 2nd Edition., Prentice-Hall, Upper Saddle River, NJ, USA, 1999.
[24] F. Marini, R. Bucci, A.L. Magri, A.D. Magri, Microchem. J. 88 (2008) 178.
[25] J. Öhman, P. Geladi, S. Wold, J. Chemometrics 4 (1990) 79.
[26] V.A. Lozano, G.A. Ibañez, A.C. Olivieri, Anal. Chim. Acta 610 (2008) 186.
[27] A.C. Olivieri, J. Chemometrics 19 (2005) 253.
[28] M.J. Culzoni, H.C. Goicoechea, A.P. Pagani, M.A. Cabezón, A.C. Olivieri, Analyst (Cambridge, UK) 131 (2006) 718.
[29] A. García Reiriz, P.C. Damiani, M.J. Culzoni, H.C. Goicoechea, A.C. Olivieri, Chemom. Intell. Lab. Syst. 92 (2008) 61.
[30] A. García Reiriz, P.C. Damiani, A.C. Olivieri, Chemom. Intell. Lab. Syst. 100 (2010) 127.
[31] D.J.R. Bouveresse, H. Benabid, D.N. Rutledge, Anal. Chim. Acta 589 (2007) 216.
[32] A. García Reiriz, P.C. Damiani, A.C. Olivieri, F. Cañada Cañada, A. Muñoz de la Peña, Anal. Chem. 80 (2008) 7248.
[33] M.J. Culzoni, P.C. Damiani, A. García Reiriz, H.C. Goicoechea, A.C. Olivieri, Analyst (Cambridge, UK) 132 (2007) 654.
[34] A. García Reiriz, P.C. Damiani, A.C. Olivieri, Anal. Chim. Acta 588 (2007) 192.
[35] Y. Ni, C. Huang, S. Kokot, Chemom Intell. Lab. Syst. 38 (2004) 177.
[36] T. Vaananen, H. Koskela, Y. Hiltunen, M. Ala Korpela, J. Chem. Inf. Comp. Sci. 42 (2002) 1343.
[37] J.A. Lopes, J.C. Menezes, Anal. Chim. Acta 515 (2004) 101.
[38] C.G. Zampronio, S.P. Gurden, L.A. Moraes, M.N. Eberlin, A.K. Smilde, R.J. Poppi, Analyst (Cambridge, UK) 127 (2002) 1054.
[39] M.C. Ortiz, L. Sarabia, J. Chromatogr., A 1158 (2007) 94.
[40] D.R. Stoll, X. Li, X. Wang, P.W. Carr, S.E.G. Porter, S.C. Rutan, J. Chromatogr., A 1168 (2007) 3.
[41] T. Skov, R. Bro, Anal. Bioanal. Chem. 390 (2008) 281.
[42] J.M. Amigo, T. Skov, R. Bro, Chem. Rev. 110 (2010) 4582.
[43] M. Wasim, R.G. Brereton, J. Chem. Inf. Model. 46 (2006) 1143.
[44] J.O. Ramsey, J. ten Berge, G.P.H. Styan, Psychometrika 49 (1984) 403.
[45] N.P.V. Nielsen, J.M. Carstensen, J. Smedsgaard, J. Chromatogr., A 805 (1998) 17.
[46] E. Comas, R.A. Gimeno, J. Ferré, R.M. Marcé, F. Borrull, F.X. Rius, Anal. Chim. Acta 470 (2002) 163.
[47] D. Bylund, R. Danielsson, G. Malmquist, K.E. Markides, J. Chromatogr., A 961 (2002) 237.
[48] T. Skov, J.C. Hoggard, R. Bro, R.E. Synovec, J. Chromatogr., A 1216 (2009) 4020.
[49] R.J.O. Torgrip, E. Alm, K.M. Åberg, Bioanal. Rev. 1 (2010) 105.
[50] C. Christin, H.C.J. Hoefsloot, A.K. Smilde, F. Suits, R. Bischoff, P.L. Horvatovich, J. Proteome Res. 9 (2010) 1483.
[51] B.J. Prazen, R.E. Synovec, B.R. Kowalski, Anal. Chem. 70 (1998) 218.
[52] C.G. Fraga, B.J. Prazen, R.E. Synovec, Anal. Chem. 73 (2001) 5833.
[53] K.M. Pierce, L.F. Wood, B.W. Wright, R.E. Synovec, Anal. Chem. 77 (2005) 7735.
[54] K.J. Johnson, B.J. Prazen, D.C. Young, R.E. Synovec, J. Sep. Sci. 27 (2004) 410.
[55] V.G. van Mispelaar, A.C. Tas, A.K. Smilde, P.J. Schoenmakers, A.C. van Asten, J. Chromatogr., A 1019 (2003) 15.
[56] C.G. Fraga, J. Chromatogr., A 1019 (2003) 31.
[57] H. Idborg, P.O. Edlund, S.P. Jacobsson, Rapid Commun. Mass Spectrom. 18 (2004) 944.
[58] R.E. Mohler, K.M. Dombek, J.C. Hoggard, E.T. Young, R.E. Synovec, Anal. Chem. 78 (2006) 2700.
[59] K.J. Johnson, B.W. Wright, K.H. Jarman, R.E. Synovec, J. Chromatogr., A 996 (2003) 141.
[60] S.A. Bortolato, J.A. Arancibia, G.M. Escandar, A.C. Olivieri, Chemom. Intell. Lab. Syst. 101 (2010) 30.
[61] E. Comas, R.A. Gimeno, J. Ferré, R.M. Marcé, F. Borrull, F.X. Rius, J. Chromatogr., A 1035 (2004) 195.
[62] K. Wiberg, S.P. Jacobsson, Anal. Chim. Acta 514 (2004) 203.
[63] C.G. Fraga, C.A. Corley, J. Chromatogr., A 1096 (2005) 40.

[64] J.W.B. Braga, C.B.G. Bottoli, I.C.S.F. Jardim, H.C. Goicoechea, A.C. Olivieri, R.P. Poppi, J. Chromatogr., A 1148 (2007) 200.

[65] S.F. Li, H.L. Wu, Y.J. Yu, Y.N. Li, J.F. Nie, H.Y. Fu, R.Q. Yu, Talanta 81 (2010) 805.

[66] M. Vosougha, M. Bayata, A. Salemi, Anal. Chim. Acta 663 (2010) 11.

[67] S.E.G. Porter, D.R. Stoll, S.C. Rutan, P.W. Carr, J.D. Cohen, Anal. Chem. 78 (2006) 5559.

[68] I. García, L. Sarabia, M. Cruz Ortiz, J.M. Aldama, Analyst (Cambridge, UK) 129 (2004) 766.

[69] E.P. Trepat, A. Hildebrandt, D. Barceló, S. Lacorte, R. Tauler, Chemom. Intell. Lab. Syst. 74 (2004) 293.

[70] E.P. Trepat, S. Lacorte, R. Tauler, J. Chromatogr., A 1096 (2005) 111.

[71] E.P. Trepat, R. Tauler, J. Chromatogr., A 1131 (2006) 85.

[72] S. Mas, G. Fonrodona, R. Tauler, J. Barbosa, Talanta 71 (2007) 1455.

[73] M.J. Culzoni, A.V. Schenone, N.E. Llamas, M. Garrido, M.S. Di Nezio, B.S. Fernández Band, H.C. Goicoechea, J. Chromatogr., A 1216 (2009) 7063.

[74] M.D. Gil García, F. Cañada Cañada, M.J. Culzoni, L. Vera Candioti, G.G. Siano, H.C. Goicoechea, M. Martínez Galera, J. Chromatogr., A 1216 (2009) 5489.

[75] M. Martínez Galera, M.D. Gil García, M.J. Culzoni, H.C. Goicoechea, J. Chromatogr., A 1217 (2010) 2042.

[76] R.M. Maggio, P.C. Damiani, A.C. Olivieri, Talanta 83 (2011) 1173.

[77] F. Marini, A. D'Aloise, R. Bucci, F. Buiarelli, A.L. Magrì, A.D. Magrì, Chemom. Intell. Lab. Syst., in press, doi: 10.1016/j.chemolab.2010.05.006.

[78] M.D. Gil García, M.J. Culzoni, M.M. De Zan, R. Santiago Valverde, M. Martínez Galera, H.C. Goicoechea, J. Chromatogr., A 1179 (2008) 115.

[79] I. García, M.C. Ortiz, L. Sarabia, J.M. Aldama, Anal. Chim. Acta 587 (2007) 222.

[80] F. Zhang, H. Li, Electrophoresis 26 (2005) 1692.

[81] O. González García, C. Ariño, J.M. Díaz Cruz, M. Esteban, Chemom. Intell. Lab. Syst. 93 (2008) 49.

[82] A. Edelmann, J. Diewok, J. Rodriguez Baena, B. Lendl, Anal. Bioanal. Chem. 376 (2003) 92.

[83] K. István, R. Rajkó, G. Keresztury, J. Chromatogr., A 1104 (2006) 154.

[84] S.A. Bortolato, J.A. Arancibia, G.M. Escandar, Anal. Chem. 81 (2009) 8074.

[85] A. Mancha de Llanos, M.M. de Zan, M.J. Culzoni, A. Espinosa Mansilla, F. Cañada Cañada, A. Muñoz de la Peña, H.C. Goicoechea, Anal. Bioanal. Chem., in press, doi: 10.1007/s00216-010-4071-3.

[86] M. Vosough, A. Salemi, Talanta 73 (2007) 30.

[87] J.M. Amigo, T. Skov, R. Bro, J. Coello, S. Maspoch, Trends Anal. Chem. 27 (2008) 714.

[88] A.E. Sinha, C.G. Fraga, B.J. Prazen, R.E. Synovec, J. Chromatogr., A 1027 (2004) 269.

[89] F. Cañada Cañada, J.A. Arancibia, G.M. Escandar, G.A. Ibañez, A. Espinosa Mansilla, A. Muñoz de la Peña, A.C. Olivieri, J. Chromatogr., A. 1216 (2009) 4868.

[90] M. Grünhut, M. Garrido, M.E. Centurión, B.S. Fernández Band, Anal. Chim. Acta 673 (2010) 33.

[91] B. Rezaei, T. Khayamian, A. Mokhtari, J. Pharm. Biomed. Anal. 49 (2009) 234.

[92] R.L. Carneiro, J. Willian, B. Braga, R.J. Poppi, R. Tauler, Analyst (Cambridge, UK) 133 (2008) 774.

[93] J.M.M. Leitão, J.C.G. Esteves da Silva, Anal. Chim. Acta 559 (2006) 271.

[94] J.M.M. Leitão, J.C.G. Esteves da Silva, Chemom. Intell. Lab. Syst. 89 (2007) 90.

[95] G.N. Piccirilli, G.M. Escandar, Analyst (Cambridge, UK) 131 (2006) 1012.

[96] D. Bohoyo Gil, A. Muñoz de la Peña, J.A. Arancibia, G.M. Escandar, A.C. Olivieri, Anal. Chem. 78 (2006) 8051.

[97] A.K. Smilde, Y. Wang, B.R. Kowalski, J. Chemometrics 8 (1994) 21.

[98] A.K. Smilde, R. Tauler, J. Saurina, R. Bro, Anal. Chim. Acta 398 (1999) 237.

[99] A.G. García Reiriz, P.C. Damiani, A.C. Olivieri, Talanta 71 (2007) 806.

[100] M.D. Borraccetti, P.C. Damiani, A.C. Olivieri, Analyst (Cambridge, UK) 134 (2009) 1682.

[101] N.R. Marsili, A. Lista, B.S. Fernández Band, H.C. Goicoechea, A.C. Olivieri, Analyst (Cambridge, UK) 130 (2005) 1291.

[102] R. Santiago Valverde, M.D. Gil García, M. Martínez Galera, H.C. Goicoechea, Talanta 70 (2006) 774.

[103] M.J. Culzoni, H.C. Goicoechea, G.A. Ibañez, V.A. Lozano, N.R. Marsili, A.C. Olivieri, A.P. Pagani, Anal. Chim. Acta 614 (2008) 46.

[104] V.A. Lozano, R. Tauler, G.A. Ibañez, A.C. Olivieri, Talanta 77 (2009) 1715.

[105] A.C. Olivieri, G.A. Ibañez, V.A. Lozano, Anal. Chem. 82 (2010) 4510.

[106] J.A. Arancibia, G.M. Escandar, Anal. Chim. Acta 584 (2007) 287.

[107] A. Muñoz de la Peña, N. Mora Diez, D. Bohoyo Gil, E. Cano Carranza, J. Fluoresc. 19 (2009) 345.

[108] F. Benavente, B. Andón, E. Giménez, A.C. Olivieri, J. Barbosa, V. Sanz-Nebot, Electrophoresis 29 (2008) 4355.

[109] H.C. Goicoechea, S. Yu, A.C. Olivieri, A.D. Campiglia, Anal. Chem. 77 (2005) 2608.