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Recent Applications of First- and Second-Order Multivariate Calibration to Analytical Chemistry

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This report reviews recent literature on the application of multivariate calibration techniques to both first- and second-order data, aimed at the analytical determination of analytes of interest or sample properties in a variety of industrial, pharmaceutical, food, and environmental samples, including examples of process control. The most used data processing tools are briefly described, with emphasis on the advantages that can be obtained by applying specific combinations of multivariate data and algorithms. The main focus is on works devoted to first-order data (i.e., spectra, chromatograms, etc.) combined with partial least-squares regression, which has become the standard for this type of analytical research. A brief discussion on recent work on second-order data and algorithms is also included, as this field is rapidly growing, although at present it does not show, the general applicability of the first-order counterparts.

Classical analytical calibration is based on fully selective instrumental signals (1). Any foreign component producing a signal under the same experimental conditions as the analyte constitutes an interference and leads to bias in its determination (2). The presence of interferences calls for the use of complementary techniques, such as sample pretreatment or cleanup, to remove the interferences before analyte determination; masking the interference effect, leaving the analyte signal as the only measured one; or physical separation of the analyte and the use of chromatography, capillary electrophoresis, etc.

There are instances where these approaches would not work for a variety of reasons, such as cost, time, or simply because none of them can free the analyte from the interference. In these cases, a valid alternative is the measurement and processing of multiple signals, some of which are only partially selective regarding the analyte of interest. The whole subject started when near-IR (NIR) spectroscopy was applied to the determination of components of intact materials, such as protein in seeds (3). NIR spectra are composed of the superposition of many different signals arising from the several constituents (most of them possibly unknown) of the sample. The subsequent development of multivariate techniques for processing these data led to the outburst of myriad of algorithms, starting the discipline of chemometrics in the 1960s (4).

To place classical and multivariate calibration in a broader scenario, a consistent nomenclature of different data types is required. One possibility is to employ the concept of "order," widely used in analytical chemistry (5, 6). The order is a tensorial property of the data measured for a single sample; scalars are zeroth-order tensors; thus, univariate calibration is also known as zeroth-order. If spectra (or other unidimensional vectors/sample) are measured, the calibration becomes first-order. Increasing the number of data dimensions/sample leads to correspondingly complex data structures, which give rise to second- and higher-order multivariate calibration. An alternative nomenclature is based on the number of ways, which is the number of modes of a data array for a group of samples (7). In this context, univariate calibration is based on one-way data, first-order calibration on two-way data, etc. In what follows, the concept of order is used, because it is more familiar to analytical chemists and linked to the expression "second-order advantage," popular in the analytical community (8). Figure 1 pictorially shows the relationship among data orders.

First-order multivariate calibration is mainly dominated by partial least-squares (PLS) regression, a technique developed around 1970 by Hermann Wold and coworkers, particularly his son Svandte Wold (4). PLS suitably combines two characteristics, which makes it appealing for NIR analysis of complex materials: an inverse calibration phase, in which concentration information is regressed onto signals rather than signals onto concentrations, and dimensionality reduction, a technique that adequately compresses a data matrix of size samples × hundreds (or thousands) of variables (wavelengths) into a much smaller matrix of size samples × a small number of so-called latent variables. The latter number is close to the number of chemically responsive components in the spectral region of interest.

Today PLS is the most applied first-order multivariate calibration method, with the exception of nonlinear analytical systems, for which algorithms such as artificial neural networks or support vector machines appear to be preferable (9). Concerning the analyzed data, they include not only spectra, i.e., NIR, mid-IR (MIR), UV-Vis absorption, and luminescence, but other type of vectorial signals as well, such as chromatograms, electrochemical data (voltammograms), and responses associated with arrays of sensors (electronic tongues or noses) or sensometric parameters.

First-order multivariate calibration demands preparing a sufficiently representative set of calibration samples. All chemical components expected to be found in future test samples should be present in the calibration set, leading in

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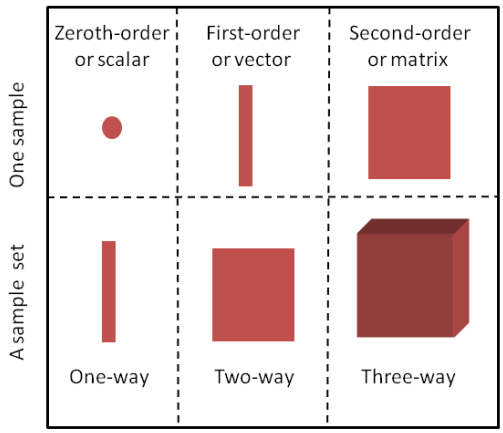

Figure 1. Pictorial representation of different data types, from zeroth- to second-order, for a single sample and a set of samples, giving rise to various analytical orders.

certain cases to the collection of a large number of training samples. The latter problem may be greatly alleviated if second- or higher-order signals can be measured/sample (5, 6) because in this case the relevant algorithms are able to separate the contribution of the interferences from that of the analyte. This property is known as second-order advantage (8) and permits the building of considerably simpler calibration sets, sometimes simply composed of a handful of pure analyte samples.

Progress in the application of first- and second-order multivariate calibration that has taken place in recent years is reviewed here, with emphasis on experimental analytical work.

First-Order Multivariate Calibration Algorithms

The first step in the multivariate processing of first-order data is to build a reference data set with the recorded signals for as many samples as required to span the chemical variability expected in future samples, and the reference values of the analyte concentrations or properties of samples (10). The various algorithms are designed to correlate the recorded signals with the concentrations, so that a model is produced that can then be applied to signals for an unknown sample in order to predict its analyte content or property value.

Collection of spectra (or other vectorial signals) leads to the building of a calibration matrix of signals. Usually this matrix has many more signal values than samples, since instruments deliver measurements at a large number of sensors, and signals may be correlated, because some samples may have similar composition. This poses some challenges to first-order calibration algorithms, with the result than some of them are of limited applicability and have been surpassed with the advent of more powerful tools.

The simplest first-order algorithm is classical least-squares (CLS), which resorts to two basic chemical laws: the direct proportionality between signal and concentration, and the additivity of signals of the sample components. CLS belongs to a group of methods known as direct because they are based on the assumption that signals are proportional to concentrations. To be able to apply CLS, however, one needs to know all the components in the calibration set of samples and their concentrations, something that is not possible for complex or natural samples and seriously limits its applicability (10).

Inverse methods are preferable to overcome this problem because by assuming that concentration is linearly related to signal, they are able to build a calibration model, ignoring the concentrations of most sample components except for a handful of analytes of interest, or even a single one. Figure 2 illustrates a group of NIR spectra collected for a set of seeds, intended to calibrate for the determination of fat, humidity, protein, and starch. Only inverse methods can be applied for this purpose.

The simplest version of this type of algorithms is inverse least-squares (10), which, however, has a major drawback: it requires having fewer sensors than samples. This calls for complex procedures for sensor selection, with the result that important information has to be removed from the calibration signals.

Two popular algorithms for processing full-sensor first-order data using inverse calibration are principal component regression (PCR) and PLS (10, 11). The first step in these methodologies is to decompose the calibration data matrix in the so-called latent variables: loadings and scores. They are called "latent" (meaning occult), as opposed as "explicit," which are the raw instrumental variables. The decomposition is accomplished using an algorithm whose aim is obtaining loadings and scores representing as much as possible the spectral variance in the calibration matrix (PCR), and at the same time, the maximal correlation between signals and the concentrations of an analyte of interest in each of the calibration samples (PLS; 10). The latter characteristic has made PLS the de facto standard for first-order multivariate calibration. One should note that there are two PLS versions: PLS-1, which focuses on a single analyte at a time and seems to be the preferred variant because the model is optimized towards a given analyte; and PLS-2, which allows one to calibrate for several analytes simultaneously, but is used less often (4).

The raw data matrix is sometimes subjected to a mathematical pretreatment procedure to remove spectral variations due to artifacts or physical phenomena but not sample chemical composition (11). This is particularly important in NIR spectroscopy analysis of solid or semisolid materials, where dispersion phenomena may be unrelated to the measured property. Good accounts on the subject can be found in the literature (11). In the case of chromatographic data, the application of PLS requires that the elution profiles of different samples are first aligned or synchronized, because this phenomenon is not related to the chemical composition of samples. Otherwise, the method will not work or an unnecessary number of latent variables will be needed to compensate for shifts, broadenings, and peak shape changes among chromatograms.

As explained above, PLS is a linear regression method. It may cope with slight deviations of linearity in the signal-concentration relationship by including additional latent variables. However, it cannot be applied to strongly nonlinear problems, where one must resort to truly nonlinear algorithms, such as artificial neural networks, support vector machines, radial basis function networks (9), or nonlinear PLS versions (12).

Second-Order Multivariate Calibration Algorithms

It is not the purpose of the present work to discuss the many available second-order algorithms, although a brief account will

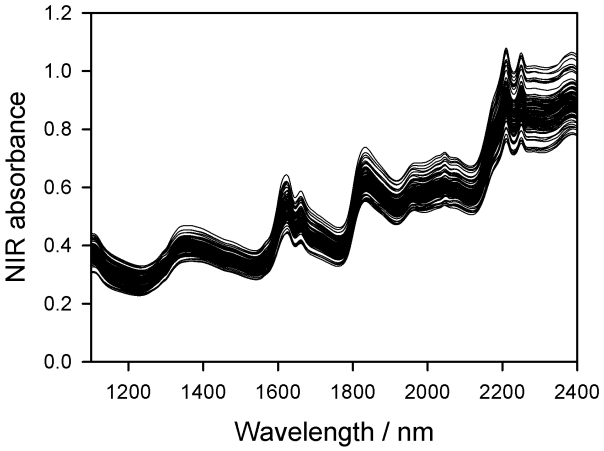

Figure 2. A set of NIR spectra collected for 100 samples of sunflower seeds, which can be used to build a first-order multivariate model for the determination of fat, humidity, protein, and starch. None of the wavelengths is specific for performing any of these determinations, but the multivariate model is able to provide a suitable answer.

be given. One group of methods comprises the so-called trilinear algorithms, which require the data to fulfill the condition of trilinearity. This basically implies that the constituent signals are proportional to concentrations, and their profiles along both instrumental modes are unique and equal for all samples (13).

The most popular trilinear algorithm is parallel factor analysis (PARAFAC; 14), which has become the algorithm of choice due to its efficiency, robustness, ability to process multiple samples, and availability of constraints to be applied during the modeling phase, which aids in reaching physically interpretable results (14). PARAFAC achieves the second-order advantage, often leading to uniquely defined models in which the contribution of the potential interferences and the analytes to the total signal are adequately decomposed.

When component profiles change from sample to sample (e.g., chromatograms), PARAFAC cannot be applied, and nontrilinear algorithms are needed, with the most popular alternative being multivariate curve resolution-alternating least-squares (MCR-ALS; 15). In the so-called extended mode (16), the latter operates by decomposing an augmented data matrix created from the set of signals. Decomposition is achieved through ALS under a series of sensible constraints, which provide physical interpretability to the final solution and limit their possible number. MCR-ALS needs initial estimates of component profiles, which can be efficiently computed using several methods (17, 18).

Figure 3 shows the difference between PARAFAC, which builds a three-way data structure with the individual data matrixes and assumes a trilinear model for decomposition, and MCR-ALS, which constructs an augmented data matrix in a given direction and assumes a bilinear model for decomposition.

For additional analytical systems deviating from the trilinear model, latent-variable regression methods may be useful, such as unfolded and multidimensional PLS (U-PLS and N-PLS, respectively; 19, 20). Here the achievement of the second-order advantage is a post-calibration activity, a procedure called residual bilinearization (RBL), which separates the portion of the signal explained by calibration from the contribution of the interferences. The result is the flexible U-PLS/RBL and N-PLS/RBL methods (21, 22).

Table 1 provides a summary of second-order algorithms, and Figure 4 shows a three-dimensional plot of an excitation-emission fluorescence matrix for a sample of an antibiotic. The latter can be quantitated in human urine even in the presence of a fluorescent background from the biological matrix, illustrating the achievement of the second-order advantage.

Software for Multivariate Calibration

A variety of free software is available on the internet from a large number of sources. One example is the Multivariate Calibration 1 (MVC1, www.iquir-conicet/decargas/mvcl.rar) toolbox (23), which employs a useful MATLAB graphical user interface for making data loading and manipulation easy without knowledge of MATLAB programming.

For second-order calibration, the most-used software is freely available as MATLAB codes, including useful graphical interfaces, as shown in Table 2 (24–26). Almost no commercial software exists, which indicates that second-order analysis is still in its infancy regarding its popularity among analytical chemists.

First-Order Multivariate Calibration Examples

The number of literature references available for review is too large to be thoroughly reviewed here. We have thus selected a representative number of references published in recent years, with emphasis on covering several different research areas. In the cited papers, PLS has been applied for data processing, in many cases along with other first-order multivariate variants for comparison, including nonlinear techniques, such as artificial neural networks. Our view is that PLS is the de facto standard for these analyses, and that only in cases of strong nonlinearities is it justified to move to alternative methodologies.

Food Analysis

Probably because of historic reasons, spectroscopy/multivariate calibration has been widely used for food analysis, with NIR/PLS-based calibrations already established in official documents (27). Hence, this area of application occupies a prominent place in the present review.

NIR spectroscopy is ubiquitous in the analysis of dairy products. Coupled to spectral pretreatment and PLS or other chemometric models, it was used to measure fat, protein, and carbohydrate in milk powder samples (28), fat, protein, lactose, urea, and somatic cell count in milk (29), and fat, dry matter, protein, and fat/dry matter contents in cheeses (30).

Beverages can be conveniently analyzed by IR spectroscopy/PLS. In wines and related samples, MIR/PLS was used to determine tartaric, malic, lactic, succinic, citric, and acetic acids (31), and several anthocyanins (32). NIR spectroscopy/PLS allowed the measurement of haloanisoles and halophenols, responsible for musty taint defects in barrel-aged red wines (600 wines of different aging time and from four different geographic zones), with reference values obtained by GC/MS (33), and calcium, potassium, magnesium, phosphorus, sodium, sulfur, iron, boron, and manganese (34). In the case of juices, glucose, fructose, and sucrose were determined in

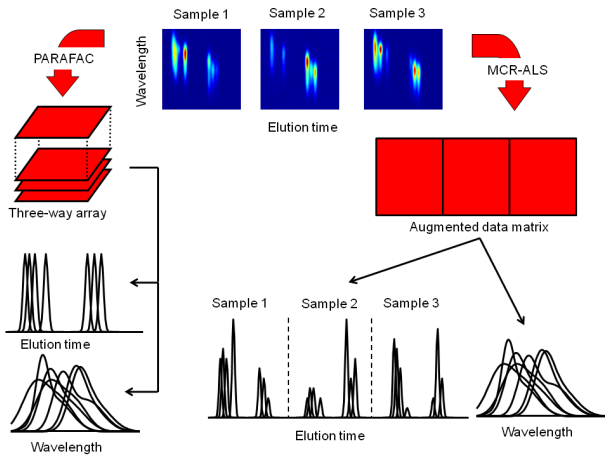

Figure 3. Schematic representation of the main second-order algorithms. From a set of data matrixes (in this case, chromatographic elution time-spectral matrixes), PARAFAC builds a three-way array, which is decomposed into spectral and elution profiles of individual sample components (elution profiles are assumed to be identical in all samples if the trilinear model holds). MCR-ALS, on the other hand, builds an augmented data matrix, which is decomposed into spectral and augmented elution profiles of sample components using a bilinear model. The latter better reflects the variability of chromatograms from sample to sample.

bayberry juice by NIR spectroscopy/PLS (35). The sensorial attributes acidity, bitterness, flavor, cleanliness, body, and overall quality of coffees were assessed by NIR spectroscopy/PLS (36).

Food adulteration has been the subject of several papers. Olive oils possibly adulterated with different vegetable oils were analyzed using NIR spectroscopy/PLS (37, 38). Soya bean products, widely used in the animal feed industry as a protein-based feed ingredient, were checked for adulteration with melamine using NIR spectroscopy/PLS to detect the latter in dehulled soya, soya hulls, and toasted soya (39). The fraudulent addition of barley to roasted and ground coffee samples was identified and quantitated (40). Added sugar, total soluble solids, and real juice content in fresh and commercial mango juice were measured by MIR spectroscopy/PLS to predict the adulteration of mango juice by added sugar (41).

Interesting developments involve an NIR spectroscopy/PLS study of microbial contamination. Microbial spoilage was detected on Atlantic salmon (*Salmo salar*) by a PLS model that predicts the number of bacteria that would be present after 9 days of storage (42). Also, aflatoxin B1 was measured in red chili powder (43) and the fungal toxins fumonisin B1 and B2 in corn meal (44).

Comparatively less-used are PLS-processed Raman and UV-Vis spectral data. Some Raman examples that deserve to be cited are the determination of fat in liquid homogenized milk (45), furazoline and malachite green in fish samples (using the surface-enhanced Raman mode; 46), sulfonamide residues in muscle-building foods (47), and glucose in sport drinks by visible micro-Raman spectroscopy/PLS (48). Based on UV-Vis spectroscopy data, the following determinations were reported: caramel in spirits (cachaca, whiskies, and brandies) aged in oak casks (49); cobalt and nickel in water, food, and geological certified reference materials after ionic liquid-based dispersive liquid–liquid microextraction and complexation with 1-(2-pyridylazo)-2-naphthol (50); two herbicides (atrazine and cyanazine) in rice, mealie, soybean, pear, apple, cauliflower, and cabbage after reaction with *p*-aminoacetophenone (51); the dyes Allura Red, Sunset Yellow, and tartrazine in powdered soft drinks (52); and monosodium glutamate, guanosine-5′-monophosphate, and inosine-5′-monophosphate in stock cube samples without any previous extraction step using stopped flow injection analysis (FIA; 53).

Kinetic UV-Vis spectroscopic data, i.e., time profiles at a single wavelength, have been used, via PLS calibration, for food analysis. The dyes Amaranth, Ponceau 4R, Sunset Yellow, tartrazine, and Brilliant Blue were determined in fruit juices, tea, and jellies by oxidation with iron(III) acid solution, followed by reaction of the generated iron(II) with hexacyanoferrate(III) to yield Prussian blue. Several algorithms besides PLS were used, including nonlinear methods (54). Acesulfame-K, sodium cyclamate, and saccharin sodium were measured in artificial sweeteners relying on the kinetic differences in the analyte oxidations by $KMnO_4$ (55).

Electrochemical data processed with PLS usually correspond to promising devices, such as electronic tongues, which are arrays of partially selective electrodes based on voltammetric or other techniques. They provided determination of polyphenols in wine (56), and theaflavins and thearubigins in black tea (57), in both cases including data pretreatment and comparison with nonlinear methods. Similar systems were proposed for measuring chloride, nitrite, and nitrate in minced meat (58) and fructose and glucose in soft drinks, in the latter case using a potentiometric electronic tongue containing 36 lipo/polymeric membranes (59).

Chromatographic data showing partial peak resolution is being gradually incorporated into multivariate calibration protocols. PLS usually allows coping with coeluting chromatograms, successfully predicting individual analyte concentrations or sample properties. For example, beer sensorial parameters, such as bitterness and grain taste, were predicted from unresolved GC/MS data (60), and pine nuts and Pecorino in Pesto Genovese by headspace sorptive extraction and GC/MS data (61). The content of olive oil in blends was assessed from GC/MS (62) and HPLC (63) profiles of triacylglycerol, and from GC–flame ionization detection profiles of fatty acids methyl esters (64). Protein HPLC profiles with UV-Vis detection were used to control the types of milk used in the elaboration of dairy products and to detect adulterations in milk mixtures and cheeses (65).

Miscellaneous techniques include visible light scattering for measuring fat and total protein in milk (66), impedance spectroscopy for salt content in minced meats, cured hams, and pork loins (67); time domain reflectometry for water content in extra virgin olive oils (68); differential scanning calorimetry for fatty acid composition (palmitic, stearic, oleic, and linoleic acids, saturated, mono- and polyunsaturated, oleic/linoleic and unsaturated/saturated ratios) in vegetable oils (69); NMR spectroscopy for organic acids (acetic, citric, lactic, malic, pyruvic, and succinic) in beer (70); fluorescence spectroscopy for riboflavin and the aromatic amino acids tryptophan, tyrosine, and phenylalanine in beer (71); and matrix-assisted laser desorption ionization-time of flight-MS for quantitation of bacterial spoilage in milk and pork meat (72).

Table 1. Description of usual algorithms used for processing second-order data

Algorithm	Brief description
PARAFAC	Assumes a trilinear model for the data array built with a set of second-order signals, i.e., an element (i,j,k) is the sum of contributions of the form ($a_i \times b_j \times c_k$), where a_i is the relative concentration of a component in the ith. sample, and b_j, and c_k are the values of the instrumental profiles at the jth., kth. channel in each data mode. Values of a_i are employed for analyte quantitation using a pseudo-univariate calibration graph.
MCR-ALS	Places I data matrixes (size $J \times K$) on top of each other along one of the data modes, and assumes that the augmented matrix follows a bilinear model, i.e., a matrix element (m,k) is the sum of contributions of the form ($a_m \times b_k$), where a_m describes the profile for each sample in the augmented mode, and b_k in the common mode (m runs from 1 to $I \times J$). For analyte quantitation, areas under each sample profile in the augmented mode are computed and used to build a pseudo-univariate calibration graph.
PLS/RBL	After calibrating a PLS model, the interference signals in the test sample are assumed to follow a bilinear model, i.e., an element (j,k) of the interference matrix is the sum of contributions of the form ($y_j \times z_k$), where y_j, and z_k are abstract loadings in each mode. Analyte scores are produced by modeling the residuals of the fit of the test sample data array to the bilinear model, hence the name residual bilinearization. In U-PLS, data arrays are unfolded into vectors; in N-PLS, the original data structure is maintained.

Pharmaceutical and Biomedical Analyses

Of particular interest to the pharmaceutical industry is the combination of multivariate calibration to NIR, MIR, and Raman spectroscopies, because they allow for the nondestructive analysis of intact pharmaceutical forms (73–75). This includes the determination of both active pharmaceutical ingredients and excipients, which can be performed remotely through optical fibers. The results are often comparable to those obtained by official HPLC methods, and are being incorporated into official protocols (76).

As examples, hydrochlorothiazide was determined in powdered pharmaceutical samples (77); chondroitin, glucosamine, and methyl sulfonyl methane in tablets (78); amoxicillin in powdered drugs (79) and oral suspensions (80); ranitidine during the manufacturing process (in granulates and cores) and in the final step (in coated tablets) (81); azithromycin in tablets (82); and particle size distribution in paracetamol powders (83), all using the successful combination NIR spectroscopy/PLS. Glucose, fructose, and maltose were measured in depilatory formulations without any sample pretreatment, based on MIR spectroscopy/PLS, with results similar to HPLC with online IR detection (84). Attenuated total reflectance-Fourier transformed MIR and Raman spectra allowed detection of the presence of acetaminophen in over-the-counter pharmaceutical formulations (85).

Raman spectroscopy is also suitable for QC assays and to identify polymorphic forms or monitor phase changes in pharmaceutical products. Coupled to PLS, it allowed in situ anhydrate concentration measurements during the crystallization and phase transition processes of citric acid in water (86).

A recently introduced technique for nondestructive characterization of pharmaceutical materials is the collection of hyperspectral data; NIR or Raman spectra are collected for many different pixels in the surface of a solid, and a chemical image is produced, reflecting the component distribution using PLS. The model can be built on the average spectrum of the images (first-order data), and can be used to predict bulk concentrations in unknown images (from new image average spectra) or concentrations at a pixel level (from new individual pixel spectra), which provides chemical distribution maps. This helped to quantitate piroxicam polymorphs (87) and carbamazepine by NIR spectroscopy-CI (88) and to evaluate atorvastatin calcium formulations by Raman spectroscopy-CI (89).

Additional pharmaceutically relevant data have been processed by PLS, such as thermogravimetric profiles for the resolution of paracetamol and codeine phosphate (90) and TLC-densitometric data for atenolol, chlorthalidone, and their degradation products (91). For completeness, we include the PCR/PLS processing of UV-Vis data for simultaneous determinations in multicomponent pharmaceutical forms after dissolution, such as mixtures of ambroxol and doxycycline (92); aspirin, paracetamol, caffeine, and chlorphenamine (93); paracetamol, ibuprofen, and caffeine (94); two antiparkinsonians (95); paracetamol, propiphenazone, caffeine, and thiamine (96); diprophylline, guaiphenesin, methylparaben, and propylparaben or clobutinol, orciprenaline, saccharin sodium, and sodium benzoate (97); chlorpheniramine maleate and phenylpropanolamine hydrochloride with ibuprofen and caffeine or propyphenazone (98); and dienogest and estradiol valerate in sugar-coated tablets (99).

For some pharmaceutical mixtures of simple composition, the basic CLS algorithm was shown to be useful, as in the UV-Vis spectroscopic study of binary, ternary, and quaternary mixtures of the water-soluble vitamins thiamine, pyridoxine, riboflavin, and cyanocobalamin (100), and in the determination of ezetimibe and simvastatin in bulk powder, laboratory-prepared mixtures, and a combined dosage form (101). The results were compared with those provided by PCR and PLS.

In the biomedical field, NIR spectroscopy data have been applied for direct in situ analysis in complex biological systems. In this context, the noninvasive glucose monitoring in blood using NIR or MIR spectroscopy with PLS is perhaps the single most important contribution of the combination of spectroscopy and chemometrics to biomedical analysis because of its impact in the monitoring of diabetic patients (102–104). Despite the efforts devoted to this project in recent decades, however, the final aim appears to be elusive (105).

Following earlier ideas on the application of IR spectroscopy combined with multivariate techniques for the rapid screening of clinically relevant parameters in human blood (106), there has been a recent revival of the subject. Promising research works are the determination of albumin, immunoglobulin, total globulin, and albumin/globulin by MIR spectroscopy/PLS (107), glucose, glucose-6-phosphate, and pyruvate by NIR spectroscopy/PLS (108), and glucose, human serum albumin,

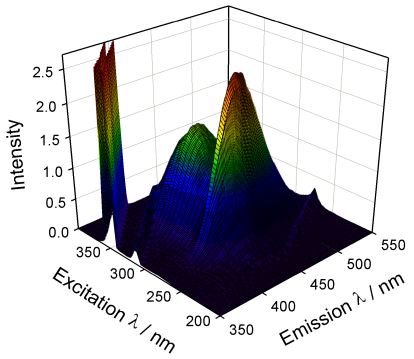

Figure 4. Three-dimensional surface showing the fluorescence emission intensity of a urinary antibiotic as a function of emission and excitation wavelengths. From these second-order data, it is possible to quantitate the concentration of the antibiotic in a biological fluid, such as urine, even in the presence of uncalibrated interferences (for example, the urine background constituents or other pharmaceuticals). The vertical scale is in arbitrary fluorescence intensity units.

and γ-globulin by NIR spectroscopy/PLS (109). The results may find applications in the rapid screening of clinical parameters of blood samples in the microliter range.

NIR spectroscopy/PLS has also enabled the determination of triglycerides and high-density lipoprotein in rat plasma (110), and fish sperm DNA in solution after adsorption preconcentration (111). Dispersive NIR Raman spectroscopy has been applied for diagnosing toxoplasmosis by quantitating anti-*Toxoplasma gondii* antibodies in blood sera from domestic cats, with results comparable to ELISA (112).

Industrial and Miscellaneous Applications

There are many examples of multivariate calibration with impact on industrial fields. The driving force has been replacement of classical analytical methodologies by techniques capable of producing reliable results in a short time, with simple equipment, and amenable to automation. A nice example is the estimation of the octane number in fuels, a measure of the resistance to autoignition in internal combustion engines. The most common type of octane rating is the Research Octane Number (RON), determined by running the fuel in a test engine with a variable compression ratio under controlled conditions and comparing the results with those for mixtures of iso-octane (RON = 100) and *n*-heptane (RON = 0). NIR spectroscopy/PLS allows for an accurate measurement of octane number in a much simpler and faster way than with the engine method (113).

Other relevant fuel properties can be adequately measured using the PLS-assisted analysis of the following indicated data: (a) in diesels, flash point and cetane number (114) and quality parameters (115) by NIR spectroscopy, residual oil by fluorescence (116), ethanol, and specific gravity by distillation curves (117), and vegetable oils and fats adulterants by LC with UV-Vis detection (118); (b) in biodiesels, methyl ester content by NIR spectroscopy (119), density, kinematic viscosity, methanol, and water content by MIR spectroscopy (120), and adulteration with vegetable oil by NIR and MIR spectroscopies (121); (c) in gasolines, blending control by NIR spectroscopy (122), adulteration with diesel oil, kerosene, turpentine spirit, or thinner by MIR spectroscopy (123); and pyrolytic diene values by UV-Vis spectroscopy (124); (d) fatty acid methyl ester in jet fuel by MS (125); (e) constituents of heavy fuel oil by ^{1}H NMR spectroscopy (126); and (f) adulteration of ethanol fuel with methanol by MIR spectroscopy (127).

Additional determinations of industrial relevance are the total acid number (128), quality (129), and sulfur content (130) of crude oil, glucose and ethanol in bioethanol (131), butene in ethylene/propylene/1-butene terpolymers (132) by MIR spectroscopy, saturates, aromatics, resins, and asphaltenes in crude oil by fluorescence spectroscopy (133), nickel and chromium in steel by laser UV spectroscopy (134), and 11 pesticides in agrochemical formulations by a NIR spectroscopy/PLS-based QC with results comparable to HPLC (135). In a typical real-time NIR spectroscopy/PLS application, the natural antimalarial artemisinin was determined in dried leaves of *Artemisia annua* L. using a hand-held device (136).

Some environmentally related analytical determinations conducted with the aid of PLS are the determination of the pesticide mixtures parathion-methyl, chlorpyrifos-methyl and vinclozolin, parathion-ethyl, chlorpyrifos and triadimefon, and endosulfan sulfate and carbophenothion by GC (137); Fe(III), Al(III), and Zr(IV) in water samples by kinetic-potentiometric data (138); monitoring of trace elements in estuarine sediments by NIR/MIR (139) and X-ray fluorescence spectroscopy (140) and in water samples by UV-Vis spectroscopy (141); carbamate pesticides in waters by UV-Vis data using FIA (142, 143); anions in water using a voltammetric electronic tongue (144) and UV-Vis data (145); phenol derivatives in air by fluorescence spectroscopy (146); and the pesticides aminocarb and carbaryl in vegetables and waters by kinetic-spectroscopic data based on their differential oxidation rates with potassium ferricyanide (147).

Process Control

Industrial process control is a relevant field for pharmaceutical and other industrial applications. The classical approach to handling process control through univariate-control charting techniques, such as the Shewart approach, suffers from several drawbacks. In the presence of complex relationships and correlations among process variables, the simple graphical methods cannot be used as performance indicators based on independent assumptions. To overcome these problems, PLS has been proposed to optimize the quality of products made in process industries with a large number of process and quality variables (148).

Specifically in the pharmaceutical industry, process analytical technology (PAT) was proposed by the U.S. Food and Drug Administration to develop more technically and scientifically rigorous production processes (149). NIR spectroscopy is one of the most useful spectroscopic techniques for applying the PAT concepts to analysis of pharmaceutical products, because of its ability to measure a number of physical and chemical properties of samples, and its suitability for online and inline measurements. Some of the better known uses of NIR spectroscopy in the production of solid pharmaceutical forms include chemical raw material identification, blend uniformity assessment, granulation monitoring, roller compaction monitoring, drying end-point determination, and coating end-point and uniformity determinations.

As examples, we mention development of a fast and reliable

Table 2. Software for first- and second-order calibration

Name	Main algorithm(s)	Ref.	Web page
The N-way toolbox	PARAFAC	14	http://www.models.life.ku.dk/algorithms
	U-PLS		
	N-PLS		
MCR graphical interface	MCR-ALS	24	http://www.mcrals.info/
GUIPRO graphical interface	MCR-ALS	25	http://personal.ecu.edu/gemperlinep
MVC2 graphical interface	PARAFAC	26	www.iquir-conicet/decargas/mvcl2.rar
	U-PLS/RBL		
	N-PLS/RBL		

QC system by building different quantitative calibrations of a pharmaceutical key quality parameters, which allowed derivation of a general classification model capturing the overall product grade (150), and development of fast and noninvasive quantitative methods for real-time prediction of critical quality attributes of pharmaceutical granulates (active principle content, pH, moisture, flowability, angle of repose, and particle size; 151).

Second-Order Multivariate Calibration Examples

This field has been dominated in the past by matrix data, such as chromatography with spectral detection and excitation-emission fluorescence matrix (EEFM) spectroscopy. EEFMs have a number of advantages: (a) they can be easily measured in most modern spectrofluorometers, and with the advent of fast-scanning monochromators or multiwavelength charge-coupling detectors they can be recorded in a very short time; (b) fluorescence signals are highly selective and sensitive, allowing low LODs to be reached for the analytes of interest; and (c) the specific data structure of an EEFM is very simple because excitation and emission spectra for each sample component do not vary from sample to sample. This latter aspect is important when compared with other second-order signals, for which at least one of the component profiles suffers important changes for different experimental runs, such as chromatograms, pH gradients, or kinetic profiles. Recent applications in this field involve the development of luminescent signals on solid surfaces, either in a batch mode or as a detecting system for FIA, for example, nylon membranes in batch mode (152–154), molecularly imprinted polymers (155), C18 particles (156), and nylon powder (157, 158) as sensing phases for FIA systems. For recent reviews on the subject, *see* refs. 5, 6, and 159.

Second-order data can also be produced by connecting two instruments, each of which provides a data mode to the finally collected data. This is called hyphenation and has given rise to a large number of second-order data methods. For example, if chromatography is followed by UV-Vis detection with a diode array device, a fast-scanning spectrofluorometer or a mass spectrometer, then second-order data are obtained in which one data mode is the elution direction and the second is the spectral direction. These data pose some challenges to data processing algorithms, mainly because the elution profiles are not constant from run to run. This demands two alternative solutions: correcting for the temporal changes by synchronizing the chromatograms (160–162), or applying a calibration methodology that is able to model the elution profile changes, such as MCR-ALS (163).

Second-order LC with diode array detector has been profusely used to analyze complex samples of different origins, mostly in the presence of unexpected interferences, i.e., achieving the second-order advantage. Some recent examples from the prolific research group of Hunan University, China, are the following determinations: 11 antihypertensives in isocratic mode in only 10 min (164); 12 quinolones in honey (165); atrazine, ametryn, and prometryne in soil, river sediment, and wastewater (166); and levodopa, carbidopa, and methyldopa in human plasma samples (167).

When spectrofluorometric detection is used in chromatographic analysis, lower LODs are possible, as in the following determinations using MCR-ALS as the processing algorithm: 10 polycyclic aromatic hydrocarbons in waters (168), and the marker pteridins neopterin, biopterin, pterin, xanthopterin, and isoxanthopterin in urine samples (169). When determining eight fluoroquinolones in urine by HPLC coupled to fast scanning fluorescence detection, on the other hand, PARAFAC was used after isocratic chromatographic development (170). In all of these cases, the second-order advantage had to be exploited because the test samples contained unexpected interferences.

Two-dimensional GC-GC and FID constitutes an additional possibility for second-order data generation, as reported for the quantitative analysis of essential oils in perfume using MCR-ALS (171), and for gasoline analyses using N-PLS (172, 173).

Conclusions

Multivariate calibration is a powerful tool available to the analytical chemist. It allows determination of a variety of analytes or properties in a wide range of sample types, from pharmaceuticals to foodstuff, and from fuels to natural waters. The processed data are mainly of spectroscopic origin, although other techniques, such as chromatography, MS, and electrochemistry, are gradually being incorporated. It is likely that the present trend will continue in the future, as instrumental advances add new dimensions to the data and chemometricians uncover new algorithmic data processing techniques.

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References

(1) Danzer, K., & Currie, L.A. (1998) *Pure Appl. Chem*. **70**, 993–1014. http://dx.doi.org/10.1351/pac199870040993

(2) Van der Linden, W.E. (1989) *Pure Appl. Chem*. **61**, 91–95. http://dx.doi.org/10.1351/pac198961010091

(3) Burns, D.A., & Ciurczak, E.W. (2008) *Handbook of Near-*

Infrared Analysis, 3rd Ed., Practical Spectroscopy Series, Vol. 35, CRC Press, Boca Raton, FL

(4) Wold, S., Sjöström, M., & Eriksson, L. (2001) *Chemometr. Intell. Lab.* **58**, 109–130. http://dx.doi.org/10.1016/S0169-7439(01)00155-1

(5) Olivieri, A.C. (2012) *Anal. Methods* **4**, 1876–1886. http://dx.doi.org/10.1039/c2ay25064k

(6) Escandar, G.M., Faber, N.M., Goicoechea, H.C., Muñoz de la Peña, A., Olivieri, A.C., & Poppi, R.J. (2007) *Trends Anal. Chem.* **26**, 752–765. http://dx.doi.org/10.1016/j.trac.2007.04.006

(7) Smilde, A., Bro, R., & Geladi, P. (2004) *Multi-Way Analysis with Applications in the Chemical Sciences*, John Wiley & Sons, Chichester, UK. http://dx.doi.org/10.1002/0470012110

(8) Booksh, K.S., & Kowalski, B.R. (1994) *Anal. Chem*. **66**, 782A–791A. http://dx.doi.org/10.1021/ac00087a022

(9) Haykin, S. (1999) *Neural Networks, A Comprehensive Foundation*, 2nd. Ed., Prentice-Hall, Upper Saddle River, NJ

(10) Haaland, D.M., & Thomas, E.V. (1988) *Anal. Chem*. **60**, 1193–1202. http://dx.doi.org/10.1021/ac00162a020

(11) Massart, D.L., Vandeginste, B.G.M., Buydens, L.M.C., De Jong, S., Lewi, P.J., & Smeyers-Verbeke, J. (1997) *Handbook of Chemometrics and Qualimetrics*, Elsevier, Amsterdam, The Netherlands

(12) Czekaj, T., Wu, W., & Walczak, B. (2005) *J. Chemometrics.* **19**, 341–354. http://dx.doi.org/10.1002/cem.937

(13) Olivieri, A.C., Escandar, G.M., & Muñoz de la Peña, A. (2011) *Trends Anal. Chem*. **30**, 607–617. http://dx.doi.org/10.1016/j.trac.2010.11.018

(14) Bro, R. (1997) *Chemometr. Intell. Lab.* **38**, 149–171. http://dx.doi.org/10.1016/S0169-7439(97)00032-4

(15) Tauler, R. (1995) *Chemometr. Intell. Lab.* **30**, 133–146. http://dx.doi.org/10.1016/0169-7439(95)00047-X

(16) Tauler, R., Maeder M., & de Juan, A. (2009) in *Comprehensive Chemometrics*, Vol. 2, S. Brown, R. Tauler, & B. Walczak (Eds), Elsevier, Oxford, UK, pp 473–505. http://dx.doi.org/10.1016/B978-044452701-1.00055-7

(17) Windig, W., & Guilment, J. (1991) *Anal. Chem*. **63**, 1425–1432. http://dx.doi.org/10.1021/ac00014a016

(18) Antunes, M.C., Simao, J.E.J., Duarte, A.C., & Tauler, R. (2002) *Analyst* **127**, 809–817. http://dx.doi.org/10.1039/b200243b

(19) Wold, S., Geladi, P., Esbensen, K., & Øhman, J. (1987) *J. Chemometrics* **1**, 41–56. http://dx.doi.org/10.1002/cem.1180010107

(20) Bro, R. (1996) *J. Chemometrics* **10**, 47–61. http://dx.doi.org/10.1002/(SICI)1099-128X(199601)10:1<47::AID-CEM400>3.0.CO;2-C

(21) Öhman, J., Geladi, P., & Wold, S. (1990) *J. Chemometrics* **4**, 79–90. http://dx.doi.org/10.1002/cem.1180040109

(22) Olivieri, A.C. (2005) *J. Chemometrics* **19**, 253–265. http://dx.doi.org/10.1002/cem.927

(23) Olivieri, A.C., Goicoechea, H.C., & Iñón, F.A. (2004) *Chemometr. Intell. Lab.* **73**, 189–197. http://dx.doi.org/10.1016/j.chemolab.2004.03.004

(24) Jaumot, J., Gargallo, R., de Juan, A., & Tauler, R. (2005) *Chemometr. Intell. Lab. Syst*. **76**, 101–110. http://dx.doi.org/10.1016/j.chemolab.2004.12.007

(25) Gemperline, P.J., & Cash, E. (2003) *Anal. Chem*. **75**, 4236–4243. http://dx.doi.org/10.1021/ac034301d

(26) Olivieri, A.C., Wu, H.L., & Yu, R.Q. (2009) *Chemometr. Intell. Lab. Syst*. **96**, 246–251. http://dx.doi.org/10.1016/j.chemolab.2009.02.005

(27) *Second Committee Draft of a Recommendation on Protein Measuring Instruments for Cereal Grain and Oil Seeds* (2010) International Organization of Legal Metrology, Bureau International de Métrologie Légale, Paris, France

(28) Wu, D., He, Y., & Feng, S. (2008) *Anal. Chim. Acta* **610**, 232–242. http://dx.doi.org/10.1016/j.aca.2008.01.056

(29) Melfsen, A., Hartung, E., & Haeussermann, A. (2012) *J. Near Infrared Spectrosc.* **20**, 477–482. http://dx.doi.org/10.1255/jnirs.1009

(30) Oca, M.L., Ortiz, M.C., Sarabia, L.A., Gredilla, A.E., & Delgado, D. (2012) *Talanta* **99**, 558–565. http://dx.doi.org/10.1016/j.talanta.2012.06.035

(31) Regmi, U., Palma, M., & Barroso, C.G. (2012) *Anal. Chim. Acta* **732**, 137–144. http://dx.doi.org/10.1016/j.aca.2011.11.009

(32) Romera-Fernandez, M., Berrueta, L.A., Garmon-Lobato, S., Gallo, B., Vicente, F., & Moreda, J.M. (2012) *Talanta* **88**, 303–310. http://dx.doi.org/10.1016/j.talanta.2011.10.045

(33) Garde-Cerdán, T., Lorenzo, C., Zalacain, A., Alonso G.L., & Salinas, M.R. (2012) *LWT-Food Sci. Technol*. **46**, 401–405

(34) Cozzolino, D., Kwiatkowski, M.J., Dambergs, R.G., Cynkar, W.U., Janik, L.J., Skouroumounis, G., & Gishen, M. (2008) *Talanta* **74**, 711–716. http://dx.doi.org/10.1016/j.talanta.2007.06.045

(35) Xie, L., Ye, X., Liu D., & Ying, Y. (2009) *Food Chem.* **114**, 1135–1140. http://dx.doi.org/10.1016/j.foodchem.2008.10.076

(36) Ribeiro, J.S., Ferreira, M.M.C., & Salva, T.J.G. (2011) *Talanta* **83**, 1352–1358. http://dx.doi.org/10.1016/j.talanta.2010.11.001

(37) Maggio, R.M., Cerretani, L., Chiavaro, E., Kaufman T.S., & Bendini, A. (2010) *Food Control* **21**, 890–895. http://dx.doi.org/10.1016/j.foodcont.2009.12.006

(38) Rohman, A., & Che Mana, Y.B. (2010) *Food Res. Int.* **43**, 886–892. http://dx.doi.org/10.1016/j.foodres.2009.12.006

(39) Haughey, S.A., Graham, S.F., Cancouët, E., & Elliott, C.T. (2012) *Food Chem.* **136**, 1557–1561. http://dx.doi.org/10.1016/j.foodchem.2011.11.136)

(40) Ebrahimi-Najafabadi, H., Leardi, R., Oliveri, P., Casolino, M.C., Jalali-Heravi, M., & Lanteri, S. (2012) *Talanta* **99**, 175–179. http://dx.doi.org/10.1016/j.talanta.2012.05.036

(41) Jha, S.N., & Gunasekaran, S. (2010) *J. Food Eng.* **101**, 337–342. http://dx.doi.org/10.1016/j.jfoodeng.2010.07.019

(42) Tito, N.B., Rodemann, T., & Powell, S.M. (2012) *Food Microbiol.* **32**, 431–436. http://dx.doi.org/10.1016/j.fm.2012.07.009

(43) Tripathi S., & Mishra, H.N. (2009) *Food Control* **20**, 840–846. http://dx.doi.org/10.1016/j.foodcont.2008.11.003

(44) Gaspardo, B., Del Zotto, S., Torelli, E., Cividino, S.R., Firrao, G., Della Riccia, G., & Stefanon, B. (2012) *Food Chem.* **135**, 1608–1612. http://dx.doi.org/10.1016/j.foodchem.2012.06.078

(45) El-Abassy, R.M., Eravuchira, P.J., Donfack, P., von der Kammer, B., & Materny, A. (2011) *Vib. Spectrosc.* **56**, 3–8. http://dx.doi.org/10.1016/j.vibspec.2010.07.001

(46) Zhang, Y., Huang, Y., Zhai, F., Du, R., Liu, Y., & Lai, K. (2012) *Food Chem.* **135**, 845–850. http://dx.doi.org/10.1016/j.foodchem.2012.04.082

(47) Lai, K., Zhai, F., Zhang, Y., Wang, X., Rasco, B.A., & Huang, Y. (2011) *Sens. Instrumen. Food Qual. Safety* **5**, 91–96. http://dx.doi.org/10.1007/s11694-011-9115-7

(48) Delfino, I., Camerlingo, C., Portaccio, M., Della Ventura, B., Mita, L., Mita, D.G., & Lepore, M. (2011) *Food Chem.* **127**, 735–742. http://dx.doi.org/10.1016/j.foodchem.2011.01.007

(49) Boscolo, M., Andrade-Sobrinho, L.G., Lima-Neto, B.S., Franco, D.W., & Castro Ferreira, M.M. (2002) *J. AOAC Int.* **85**, 744–750

(50) Khani, R., & Shemirani, F. (2013) *Food Anal. Methods* **6**, 386–394. http://dx.doi.org/10.1007/s12161-012-9449-8

(51) Zhang, G., & Pan, J. (2011) *Spectrochim. Acta A* **78**, 238–242. http://dx.doi.org/10.1016/j.saa.2010.09.028

(52) Al-Degs, Y.S. (2009) *Food Chem.* **117**, 485–490. http://dx.doi.org/10.1016/j.foodchem.2009.04.097

(53) Acebal, C.C., Lista, A.G., & Fernández Band, B.S. (2008)

Food Chem. **106**, 811–815. http://dx.doi.org/10.1016/j.foodchem.2007.06.009
(54) Ni, Y., Wang, Y., & Kokot, S. (2009) *Talanta* **78**, 432–441. http://dx.doi.org/10.1016/j.talanta.2008.11.035
(55) Ni, Y., Xiao, W., & Kokot, S. (2009) *Food Chem.* **113**, 1339–1345. http://dx.doi.org/10.1016/j.foodchem.2008.08.068
(56) Cetó, X., Gutiérrez, J.M. , Gutiérrez, M., Céspedes, F., Capdevila, J., Mínguez, S., Jiménez-Jorquera, C., & del Valle, M. (2012) *Anal. Chim. Acta* **732**, 172–179. http://dx.doi.org/10.1016/j.aca.2012.02.026
(57) Ghosh, A., Tudu, B., Tamuly, P., Bhattacharyya, N., & Bandyopadhyay R. (2012) *Chemometr. Intell. Lab.* **116**, 57–66. http://dx.doi.org/10.1016/j.chemolab.2012.04.010
(58) Campos, I., Masot, R., Alcañiz, M., Gil, L., Soto, J., Vivancos, J.L., García-Breijo, E., Labrador, R.H., Barat, J.M., & Martínez-Mañez, R. (2010) *Sensor. Actuat. B* **149**, 71–78. http://dx.doi.org/10.1016/j.snb.2010.06.028
(59) Dias, L.G., Peres, A.M., Barcelos, T.P., Sá Morais, J., & Machado, A.A.S.C. (2011) *Sensor. Actuat. B* **154**, 111–118. http://dx.doi.org/10.1016/j.snb.2010.01.005
(60) da Silva, G.A., Maretto, D.A., Bolini, H.M.A., Teófilo, R.F., Augusto, F., & Poppi, R.J. (2012) *Food Chem.* **134**, 1673–1681. http://dx.doi.org/10.1016/j.foodchem.2012.03.080
(61) Zunin, P., Leardi, R., & Boggia, R. (2009) *J. AOAC Int.* **92**, 1526–1530
(62) Ruiz-Samblás, C., Marini, F., Cuadros-Rodríguez, L., & González-Casado, A. (2012) *J. Chromatogr. B* **910**, 71–77. http://dx.doi.org/10.1016/j.jchromb.2012.01.026
(63) de la Mata-Espinosa, P., Bosque-Sendra, J.M., Bro, R., & Cuadros-Rodriguez, L. (2011) *Talanta* **85**, 177–182. http://dx.doi.org/10.1016/j.talanta.2011.03.049
(64) Monfreda, M., Gobbi, L., & Grippa, A. (2012) *Food Chem.* **134**, 2283–2290. http://dx.doi.org/10.1016/j.foodchem.2012.03.122
(65) Rodríguez, N., Ortiz, M.C., Sarabia, L., & Gredilla, E. (2010) *Talanta* **81**, 255–264. http://dx.doi.org/10.1016/j.talanta.2009.11.067
(66) Bogomolov, A., Dietrich, S., Boldrini, B., & Kessler, R.W. (2012) *Food Chem*. **134**, 412–418. http://dx.doi.org/10.1016/j.foodchem.2012.02.077
(67) Masot, R., Alcañiz, M., Fuentes, A., Schmidt, F.C., Barat, J. M., Gil, L., Baigts, D., Martínez-Máñez, R., & Soto, J. (2010*) Sensor. Actuat. A* **158**, 217–223. http://dx.doi.org/10.1016/j.sna.2010.01.010
(68) Ragni, L., Berardinelli, A., Cevoli, C., & Valli, E. (2012) *J. Food Eng.* **111**, 66–72. http://dx.doi.org/10.1016/j.jfoodeng.2012.01.028
(69) Cerretani, L., Maggio, R.M., Barnaba, C., Gallina Toschi, T., & Chiavaro, E. (2011) *Food Chem.* **127**, 1899–1904. http://dx.doi.org/10.1016/j.foodchem.2011.02.041
(70) Rodrigues, J.E.A., Erny, G.L., Barros, A.S., Esteves, V.I., Brandão, T., Ferreira, A.A., Cabrita, E., & Gil, A.M. (2010) *Anal. Chim. Acta* **674**, 166–175. http://dx.doi.org/10.1016/j.aca.2010.06.029
(71) Sikorska, E., Gliszczynska-Swiglo, A., Insinska-Rak, M., Khmelinskii, I., De Keukeleired, D., & Sikorski, M. (2008) *Anal. Chim. Acta* **613**, 207–217. http://dx.doi.org/10.1016/j.aca.2008.02.063
(72) Nicolaou, N., Xu, Y., & Goodacre, R. (2012) *Anal. Chem.* **84**, 5951–5958. http://dx.doi.org/10.1021/ac300582d
(73) Luypaert, J., Massart, D.L., & Heyden, Y.V. (2007) *Talanta* **72**, 865–883. http://dx.doi.org/10.1016/j.talanta.2006.12.023
(74) Jamrógiewicz, M. (2012) *J. Pharm. Biomed. Anal.* **66**, 1–10. http://dx.doi.org/10.1016/j.jpba.2012.03.009
(75) Strachan, C.J., Rades, T., Gordon, K.C., & Rantanen, J. (2007) *J. Pharm. Pharmacol*. **59**, 179–192. http://dx.doi.org/10.1211/jpp.59.2.0005
(76) *U.S. Pharmacopeia* (2012) U.S. Pharmacopeial Convention, Rockville, MD, Chapter USP-1119
(77) Ferreira, M.H., Braga, J.W.B., & Sena, M.M. (2013) *Microchem. J.* **109**, 158–164. http://dx.doi.org/10.1016/j.microc.2012.03.008.
(78) El-Gindy, A., Attia, K.A.S., Nassar, M.W., Seda, H.H.A., & Al-Shabrawi, M. (2012) *J. AOAC Int.* **95**, 1035–1042. http://dx.doi.org/10.5740/jaoacint.11-301
(79) Qu, N., Zhu, M., Mi, H., Dou, Y., & Ren, Y. (2008) *Spectrochim. Acta A* **70**, 1146–1151. http://dx.doi.org/10.1016/j.saa.2007.10.036
(80) Silva, M.A.M., Ferreira, M.H., Braga, J.W.B., & Sena, M.M. (2012) *Talanta* **89**, 342–351. http://dx.doi.org/10.1016/j.talanta.2011.12.039
(81) Rosa, S.S., Barata, P.A., Martins, J.M., & Menezes, J.C. (2008) *Talanta* **75**, 725–733. http://dx.doi.org/10.1016/j.talanta.2007.12.008
(82) Li, P., Du, G., Cai, W., & Shao X. (2012) *J. Pharm. Biomed. Anal.* **70**, 288–294. http://dx.doi.org/10.1016/j.jpba.2012.07.013
(83) Sarraguça, M.C., Cruz, A.V., Amaral, H.R., Costa, P.C., & Lopes, J.A. (2011) *Anal. Bioanal. Chem.* **399**, 2137–2147. http://dx.doi.org/10.1007/s00216-010-4230-6
(84) Cascant, M., Kuligowski, J., Garrigues, S., & de la Guardia, M. (2011) *Talanta* **85**, 1721–1729. http://dx.doi.org/10.1016/j.talanta.2011.06.040
(85) Komsta, L., Czarnik-Matusewicz, H., Szostak, R., Gumieniczek, A. Pietraš, R., Skibiński, R., & Inglot, T. (2011) *J. AOAC Int.* **94**, 743–749
(86) Chen, Z.-P., Fevotte, G., Caillet, A., Littlejohn, D., & Morris, J. (2008) *Anal. Chem.* **80**, 6658–6665. http://dx.doi.org/10.1021/ac800987m
(87) de Carvalho Rocha, W.F., Sabin, G.P., Março, P.H., & Poppi, R.J. (2011) *Chemometr. Intell. Lab.* **106**, 198–204
(88) Sabin, G.P., de Carvalho Rocha, W.F., & Poppi, R.J. (2011) *Microchem. J.* **99**, 542–547. http://dx.doi.org/10.1016/j.microc.2011.07.007
(89) Breitkreitz, M.C., Sabin, G.P., Polla, G., & Poppi, R.J. (2013) *J. Pharm. Biomed. Anal.* **73**, 3–12. http://dx.doi.org/10.1016/j.jpba.2012.03.054
(90) Khanmohammadia, M., Soleimania, M., Morovvata, F., Bagheri Garmarudia, A., Khalafbeigic, M., & Ghasemia, K. (2012) *Thermochim. Acta* **530**, 128–132
(91) Abdelwahab, N.S. (2010) *Anal. Methods* **2**, 1994–2001. http://dx.doi.org/10.1016/j.tca.2011.12.009
(92) Hadad, G.M., El-Gindy, A., & Mahmoud, W.M.M. (2008) *Spectrochim. Acta A* **70**, 655–663. http://dx.doi.org/10.1016/j.saa.2007.08.016
(93) Mo, A.C., Soponar, F., Medvedovici, A., & Sârbu, C. (2010) *Anal. Lett.* **43**, 804–813. http://dx.doi.org/10.1080/00032710903486260
(94) Khoshayand, M.R., Abdollahi, H., Shariatpanahi, M., Saadatfard, A., & Mohammadia, A. (2008) *Spectrochim. Acta A* **70**, 491–499. http://dx.doi.org/10.1016/j.saa.2007.07.033
(95) Grünhut, M., Centurión, M.E., & Fernández Band, B.S. (2007) *Anal. Lett.* **40**, 2016–2031. http://dx.doi.org/10.1080/00032710701486249
(96) Dinc¸ E., Baleanuc, D., Ioele, G., De Luca, M., & Ragno, G. (2008) *J. Pharm. Biomed. Anal.* **48**, 1471–1475. http://dx.doi.org/10.1016/j.jpba.2008.09.035
(97) Hadad, G.M., El-Gindy, A., & Mahmoud, W.M.M. (2008) *J. AOAC Int.* **91**, 39–51
(98) Hadad, G.M., El-Gindy, A., & Mahmoud, W.M.M. (2007) *J. AOAC Int.* **90**, 957–970
(99) Aglayan, M.G., Palabiyik, I.M., & Onur, F. (2010) *J. AOAC Int.,* **93**, 862–868
(100) Mohamed, A.M.I., Mohamed, H.A., Mohamed, N.A., & El-

Zahery, M.R. (2011) *J. AOAC Int.* **94**, 467–481. http://dx.doi.org/10.5740/jaoacint.9-493

(101) Lotfy, H.M., Alamein, A.M.A., & Hegazy, M.A.M. (2010) *J. AOAC Int.* **93**, 1844–1855.

(102) Ferrante do Amaral, C.E., & Wolf, B. (2008) *Med. Eng. Phys.* **30**, 541–549. http://dx.doi.org/10.1016/j.medengphy.2007.06.003

(103) Chuah, Z.-M., Paramesran, R., Thambiratnam, K., & Poh, S.-C. (2010) *Chemometr. Intell. Lab.* **104**, 347–351. http://dx.doi.org/10.1016/j.chemolab.2010.08.015

(104) Li, Q.-B., Li, L.-N., & Zhang, G.-J. (2010) *Infrared Phys. Technol.* **53**, 410–417. http://dx.doi.org/10.1016/j.infrared.2010.07.012

(105) Pickup, J.C., Hussain, F., Evans, N.D., & Sachedina, N. (2005) *Biosens. Bioelectron*. **20**, 1897–1902. http://dx.doi.org/10.1016/j.bios.2004.08.016

(106) Heise, H.M., Marbach, R., Koschinsky, Th., & Gries, F.A. (1994) *Appl. Spectrosc*. **48**, 85–95. http://dx.doi.org/10.1366/0003702944027598

(107) Perez-Guaita, D., Ventura-Gayete, J., Pérez-Rambla, C., Sancho-Andreu, M., Garrigues, S., & de la Guardia, M. (2012) *Anal. Bioanal. Chem*. **404**, 649–656. http://dx.doi.org/10.1007/s00216-012-6030-7

(108) Liu, L., & Arnold. M.A. (2009) *Anal. Bioanal. Chem.* **393**, 669–677. http://dx.doi.org/10.1007/s00216-008-2475-0

(109) Kasemsumran, S., Du, Y.P., Murayama, K., Huehn, M., & Ozaki, Y. (2004) *Anal. Chim. Acta* **512**, 223–230. http://dx.doi.org/10.1016/j.aca.2004.02.045

(110) de Oliveira Neves, A.C., de Araújo, A.A., Silva, B.L., Valderrama, P., Henrique Março, P., & Gomes de Lima, K.M. (2012) *J. Pharm. Biomed. Anal.* **66***,* 252–257. http://dx.doi.org/10.1016/j.jpba.2012.03.023

(111) Yang, Y., Tu, J., Cai, W., & Shao, X. (2012) *Talanta* **99**, 871–874. http://dx.doi.org/10.1016/j.talanta.2012.07.049).

(112) Duarte, J., Pacheco, M.T.T., Machado, R.Z., Zângaro, R.A., & Silveira, Jr, L., & Villaverde, A.B. (2010) *J. Biomed. Opt.* **15**, 047002–047007. http://dx.doi.org/10.1117/1.3463006

(113) Boschetti, C.E., & Olivieri, A.C. (2004) *J. Near Infrared Spectrosc*. **12**, 85–91. http://dx.doi.org/10.1255/jnirs.411

(114) Alves, J.C.L., Henriques, C.B., & Poppi, R.J. (2012) *Fuel* **97**, 710–717. http://dx.doi.org/10.1016/j.fuel.2012.03.016

(115) Alves, J.C.L., & Poppi, R.J. (2012) *J. Near Infrared Spectrosc.* **20***,* 419–425. http://dx.doi.org/10.1255/jnirs.1012

(116) Corgozinho, C.N.C., Pasa, V.M.D., & Barbeira, P.J.S. (2008) *Talanta* **76**, 479–484. http://dx.doi.org/10.1016/j.talanta.2008.03.003

(117) Aleme, H.G., & Barbeira, P.J.S. (2012) *Energy Fuels* **26**, 5769–5774. http://dx.doi 10.1021/ef3008757

(118) Paiva Brandão, L.F., Batista Braga, J.W., & Ziani Suarez, P.A. (2012) *J. Chromatogr. A* **1225,** 150– 157. http://dx.doi.org/10.1016/j.chroma.2011.12.076

(119) Baptista, P., Felizardo, P., Menezes, J.C., & Neiva Correia, M.J. (2008) *Anal. Chim. Acta* **607**, 153–159. http://dx.doi.org/10.1016/j.aca.2007.11.044

(120) Flôres Ferrão, M., de Souza Viera, M., Panta Pazos, R.E., Fachini, D., Gerbase, A.E., & Marder, L. (2011) *Fuel* **90**, 701–706. http://dx.doi.org/10.1016/j.fuel.2010.09.016

(121) Gaydou, V., Kister, J., & Dupuy, N. (2011) *Chemometr. Intell. Lab.* **106**, 190–197. http://dx.doi.org/10.1016/j.chemolab.2010.05.002

(122) Martínez, E., Huertas, S., Ménez, H., Peña, J.L., & Alcalde A. (2008) *J. Near Infrared Spectrosc.* **16***,* 297–303. http://dx.doi.org/10.1255/jnirs.791

(123) Teixeira, L.S.G., Oliveira, F.S., dos Santos, H.C., Cordeiro, P.W.L., & Almeida, S.Q. (2008) *Fuel* **87**, 346–352. http://dx.doi.org/10.1016/j.fuel.2007.05.016

(124) Hilgemann, M., Nascimento, P.C., Dias, D., Guterres, M.V., Stringhini, F.M., de Carvalho, L.M., & Bohrer, D. (2011) *J. Petrol. Sci. Eng.* **78**, 283–287. http://dx.doi.org/10.1016/j.petrol.2011.03.001

(125) Eide, I., Neverdal, G., & Westad, F. (2010) *Energy Fuels* **24**, 3661–3664. http://dx.doi.org/10.1021/ef100274c

(126) Nielsen, K.E., Dittmer, J., Malmendal, A., & Nielsen, N.C. (2008) *Energy Fuels* **22***,* 4070–4076. http://dx.doi.org/10.1021/ef800539g

(127) Carneiro, H.S.P., Medeiros, A.R.B., Oliveira, F.C.C., Aguiar G.H.M., Rubim, J.C., & Suarez, P.A.Z. (2008) *Energy Fuels* **22**, 2767–2770. http://dx.doi.org/10.1021/ef8000218

(128) Jingyan, L., Xiaoli, C., & Songbai, T. (2012) *Energy Fuels* **26**, 5633–5637. http://dx.doi10.1021/ef3002372

(129) Abbas, O., Rebufa, C., Dupuy, N., Permanyer, A., & Kister, J. (2012) *Fuel* **98**, 5–14. http://dx.doi.org/10.1016/j.fuel.2012.03.045

(130) Müller, A.L.H., Sogari Picoloto, R., Azevedo Mello, P., Flores Ferrão, M., Pereira dos Santos, M.F., Lourenço Guimarães, R.C., Müller, E.I., & Moraes Flores, E.M. (2012) *Spectrochim. Acta A* **89**, 82– 87. http://dx.doi.org/10.1016/j.saa.2011.12.001

(131) Liebmann, B., Friedl, A., & Varmuza, K. (2009) *Anal. Chim. Acta* **642**, 171–178. http://dx.doi.org/10.1016/j.aca.2008.10.069

(132) Marengo, E., Longo, V., Bobba, M., Robotti, E., Zerbinati, O., & Di Martino, S. (2009) *Talanta* **77**, 1111–1119. http://dx.doi.org/10.1016/j.talanta.2008.08.030

(133) Pantoja, P.A., Lopez-Gejo, J., Le Roux, G.A.C., Quina, F.H., & Nascimento, C.A.O. (2011) *Energy Fuels* **25**, 3598–3604. http://dx.doi.org/10.1021/ef200567x

(134) Barbieri Gonzaga, F., & Pasquini, C. (2012) *Spectrochim. Acta B* **69**, 20–24

(135) Armenta, S., Garrigues, S., & de la Guardia, M. (2008) *J. Near Infrared Spec.* **16**, 129–137. http://dx.doi.org/10.1255/jnirs.767

(136) Camps, C., Toussirot, M., Quennoz, M., & Simonnet X. (2011) *J. Near Infrared Spectrosc.* **19***,* 191–198. http://dx.doi.org/10.1255/jnirs.927

(137) Gil García, M.D., Martínez Galera, M., Pablos Espada, M. del C., Garrido Frenich, A., & Martínez Vidal, J.L. (2000) *J. AOAC Int.* **83**, 1068–1075

(138) Karimi, M.A., Ardakani, M.M., Ardakani, R.B., Mashhadizadeh, M.H., Zandmonfared, M.R., & Tadayon, M. (2010) *J. AOAC Int.* **93**, 327–334

(139) Moros, J., Fernández-Ortiz de Vallejuelo, S., Gredilla A., de Diego, A., Madariaga, J.M., Garrigues, S., & de la Guardia, M. (2009) *Environ. Sci. Technol.* **43**, 9314–9320. http://dx.doi.org/10.1021/es9005898

(140) Moros, J., Gredilla, A., Fernández-Ortiz de Vallejuelo, S., de Diego, A., Madariaga, J.M., Garrigues, S., & de la Guardia, M. (2010) *Talanta* **82**, 1254–1260. http://dx.doi.org/10.1016/j.talanta.2010.06.047

(141) Ghasemi, J.B., & Zolfonoun, E. (2010) *Talanta* **80**, 1191–1197. http://dx.doi.org/10.1016/j.talanta.2009.09.007

(142) Chu, N., & Fan, S. (2009) *Spectrochim. Acta A* **74**, 1173–1181. http://dx.doi.org/10.1016/j.saa.2009.09.030

(143) Ostra, M., Ubide, C., & Zuriarrain, J. (2007) *Anal. Chim. Acta* **584**, 228–235. http://dx.doi.org/10.1016/j.aca.2006.11.028

(144) Winquist, F., Olsson, J., & Eriksson, M. (2011) *Anal. Chim. Acta* **683**, 192–197. http://dx.doi.org/10.1016/j.aca.2010.10.027

(145) Sarlak, N., & Anizadeh, M. (2011) *Sensor. Actuat. B* **160**, 644–649. http://dx.doi.org/10.1016/j.snb.2011.08.042

(146) Pistonesi, M.F., Di Nezio, M.S., Centurión, M.E., Lista, A.G., Fragoso, W.D., Pontes, M.J.C., Araújo, M.C.U., & Fernández Band, B.S. (2010) *Talanta* **83**, 320–323. http://dx.doi.org/10.1016/j.talanta.2010.09.027

(147) Ni, Y., Xiao, W., & Kokot, S. (2009) *J. Hazard. Mater.* **168**, 1239–1245. http://dx.doi.org/10.1016/j.jhazmat.2009.03.003

(148) Song, K., Jang, P.Y., Cho, Y., & Juun, C.H. (2002) *IIE Trans.* **34**,881–890

(149) U.S. Food and Drug Administration (2004) *Guidance for Industry: PAT–A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, Rockville, MD

(150) Märk, J., Andre, M., Karner, M., & Huck, C.W. (2010) *Eur. J. Pharm. Biopharm.* **76**, 320–327. http://dx.doi.org/10.1016/j.ejpb.2010.06.015

(151) Rosas, J.G., Blanco, M., Gonzalez , J.M., & Alcala, M. (2012) *Talanta* **97**, 163–170. http://dx.doi.org/10.1016/j.talanta.2012.04.012

(152) Bortolato, S.A., Arancibia, J.A., & Escandar, G.M. (2008) *Anal. Chim. Acta* **613**, 218–227. http://dx.doi.org/10.1016/j.aca.2008.03.004

(153) Bortolato, S.A., Arancibia, J.A., & Escandar, G.M. (2008) *Anal. Chem*. **80**, 8276–8286. http://dx.doi.org/10.1021/ac801458a

(154) Chiarandini, J.P., & Escandar, G.M. (2012) *Anal. Bioanal. Chem*. **402**, 2221–2225. http://dx.doi.org/10.1007/s00216-011-5682-z

(155) Valero-Navarro, A., Damiani, P.C., Fernández-Sánchez, J.F., Segura-Carretero, A., & Fernández-Gutiérrez, A. (2009) *Talanta* **78**, 57–65. http://dx.doi.org/10.1016/j.talanta.2008.10.045

(156) Bortolato, S.A., Arancibia, J.A., & Escandar, G.M. (2011) *Environ. Sci. Technol.* **45**, 1513–1520. http://dx.doi.org/10.1021/es102811h

(157) Piccirilli, G., & Escandar, G.M. (2007) *Anal. Chim. Acta* **601**, 196–203. http://dx.doi.org/10.1016/j.aca.2007.08.028

(158) Piccirilli, G., & Escandar, G.M. (2009) *Anal. Chim. Acta* **646**, 90–96. http://dx.doi.org/10.1016/j.aca.2009.05.033

(159) Andersen, C.M., & Bro, R. (2003) *J. Chemometrics* **17**, 200–215. http://dx.doi.org/10.1002/cem.790

(160) Amigo, J.M., Skov, T., & Bro, R. (2010) *Chem. Rev*. **110**, 4582–4605. http://dx.doi.org/10.1021/cr900394n

(161) Pierce, K.M., Hoggard, J.C., Mohler, R.E., & Synovec, R.E. (2008) *J. Chromatogr. A* **1184**, 341–352. http://dx.doi.org/10.1016/j.chroma.2007.07.059

(162) Skov, T., van den Berg, F., Tomasi, G., & Bro, R. (2006) *J. Chemometrics* **20**, 484–497. http://dx.doi.org/10.1002/cem.1031

(163) Hantao, L.W., Aleme, H.G., Pedroso, M.P., Sabin, G.P., Poppi, R.J., & Augusto, F. (2012) *Anal. Chim. Acta* **731**, 11–23. http://dx.doi.org/10.1016/j.aca.2012.04.003

(164) Zhao, J., Wu, H.-L., Niu, J.-F., Yu, Y.-J., Yu, L.-L., Kang, C., Li, Q., Zhang, X.-H., & Yu, R.-Q. (2012) *J. Chromatogr. B* **902**, 96–107. http://dx.doi.org/10.1016/j.jchromb.2012.06.032

(165) Yu, Y-J., Wu, H.-L., Shao, S.-Z., Kang, C., Zhao, J., Wang, Y., Zhu, S.-H., & Yu, R.-Q. (2011) *Talanta* **85**, 1549–1559. http://dx.doi.org/10.1016/j.talanta.2011.06.044

(166) Li, Y.-N., Wu, H.-L., Qing, X.-D., Li, Q., Li, S.-F., Fu, H.-Y., Yu, Y.-J., & Yu, R.-Q. (2010) *Anal. Chim. Acta* **678**, 26–33. http://dx.doi.org/10.1016/j.aca.2010.08.007

(167) Li, S.-F., Wu, H.-L., Yu, Y.-J., Li, Y.-N., Nie, J.-F., Fu, H.-Y., & Yu, R.-Q. (2010) *Talanta* **81**, 805–812. http://dx.doi.org/10.1016/j.talanta.2010.01.019

(168) Bortolato, S.A., Arancibia, J.A., & Escandar, G.M. (2009) *Anal. Chem*. **81**, 8074–8084. http://dx.doi.org/10.1021/ac901272b

(169) Mancha de Llanos, A., de Zan, M.M., Culzoni, M.J., Espinosa Mansilla, A., Cañada Cañada, F., Muñoz de la Peña, A., & Goicoechea, H.C. (2011) *Anal. Bioanal. Chem*. **399**, 2123–2135. http://dx.doi.org/10.1007/s00216-010-4071-3

(170) Cañada-Cañada, F., Arancibia, J.A., Escandar, G.M., Ibañez, G.A., Espinosa Mansilla, A., Muñoz de la Peña, A., & Olivieri, A.C. (2009) *J. Chromatogr. A* **1216**, 4868–4876. http://dx.doi.org/10.1016/j.chroma.2009.04.033

(171) de Godoy, L.A.F., Wang, L., Pedroso, M., Poppi, R.J., & Augusto, F. (2011) *Anal. Chim. Acta* **699**, 120–125. http://dx.doi.org/10.1016/j.aca.2011.05.003

(172) de Godoy, L.A.F., Pedroso, M.P., Ferreira, E.C., Augusto, F., & Poppi, R.J. (2011) *J. Chromatogr. A* **1218**, 1663–1667. http://dx.doi.org/10.1016/j.chroma.2011.01.056

(173) Pedroso, M.P., de Godoy, L.A.F., Ferreira, E.C., Poppi, R.J., & Augusto, F. (2008) *J. Chromatogr. A* **1201**, 176–182. http://dx.doi.org/10.1016/j.chroma.2011.01.056