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A review of multivariate calibration methods applied to biomedical analysis

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Abstract

The determination of the contents of therapeutic drugs, metabolites and other important biomedical analytes in biological samples is usually performed by using high-performance liquid chromatography (HPLC). Modern multivariate calibration methods constitute an attractive alternative, even when they are applied to intrinsically unselective spectroscopic or electrochemical signals. First-order (i.e., vectorized) data are conveniently analyzed with classical chemometric tools such as partial least-squares (PLS). Certain analytical problems require more sophisticated models, such as artificial neural networks (ANNs), which are especially able to cope with non-linearities in the data structure. Finally, models based on the acquisition and processing of second- or higher-order data (i.e., matrices or higher dimensional data arrays) present the phenomenon known as "second-order advantage", which permits quantitation of calibrated analytes in the presence of interferents. The latter models show immense potentialities in the field of biomedical analysis. Pertinent literature examples are reviewed.
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1. Introduction

High-performance liquid chromatography (HPLC) with either ultraviolet, fluorescence or mass spectrometric detection is regularly employed to analyze the content of therapeutic drugs and their metabolites in biological fluids [1,2]. Other techniques such as capillary electrophoresis [3], optical biosensors [4], enzyme electrode amperometry [5], immunoassays [6], chemiluminescence [7], homogeneous substrate-labeled fluorescence [8] and fluorescence polarization [9] have also been extensively used for the investigation of analytes in blood, urine and other biological fluids.

Alternatively, multivariate calibration methods are being successfully applied to instrumental data of a variety of sources, mainly spectroscopic, in order to construct predictive models for selected analytes in biomedical samples, starting from rather unselective signals. Linear calibration models are generally preferred, because they are simple to apply and amenable to straightforward physico-chemical interpretation. Many regression methods which are intrinsically linear have been proposed for multicomponent analysis, among which the most popular one is partial least-squares (PLS). The latter enjoys this privileged place due to the performance of its calibration models, to the availability of software, and to the easiness of its implementation [10–15]. PLS shows several important advantages: 1) it employs full spectral data, a feature critical for the resolution of complex multi-analyte mixtures, 2) analytical procedures can be carried out in a short time, usually with no sample clean-up or physical separation, and 3) its calibration models ignore the concentrations of all other components except a selected analyte in the studied samples. For all the above reasons, PLS is especially suitable for the therapeutic drug determination in biological fluids, which often presents a complex, high absorbing background, severely overlapped with those from the analytes. Several recent articles highlight the potentiality and applicability of multivariate calibration methods in different areas [16–19].

Various alternative methods based on the useful net analyte signal (NAS) concept have also been described in the field of

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bioanalysis [15,21], and presented as alternatives to PLS. They are able to select spectral regions by estimating a moving-window error indicator function (ELF), built upon information from the NAS regression plot (NASRP) for each particular sample [22].

Special attention is deserved by high-order data, which have been recently introduced and applied in different analytical chemistry fields. These data are provided by many modem instruments, and are particularly useful for multicomponent analysis in complex samples. Specifically, second-order data, in which each sample produces a data matrix, are gaining widespread analytical acceptance [23,24]. The interest in this type of data is derived from a special property of a three-way data array (obtained when second-order data for a set of samples are grouped into a three-dimensional array): its decomposition is often unique. This allows concentrations and spectral profiles of individual sample components to be extracted directly, permitting correction for uncalibrated sample constituents. The property, coined into the name *second-order advantage* [24,25], has an immense potential in multi-component analysis. Three-way data are available to the analyst by implementing hyphenated instrumental techniques, although they can also be produced in a single instrument, such as excitation-emission fluorescence matrices in a spectrofluorometer and absorbance-time measurements in a diode array detector [23]. In the latter case, the analytical signal may be modulated by a reaction time or by a pH gradient.

High-order data can be analyzed with models such as generalized rank annihilation method (GRAM) [26,27], multivariate curve resolution-alternating least-squares (MCR-ALS) [28–31], parallel factor analysis (PARAFAC) [32–34], non-bilinear rank annihilation (NBRA) [35] and bilinear least-squares (BLLS), a recently introduced method in the second-order calibration scenario [36–38]. From the analytical point of view, the interesting fact is all of them exploit the second-order advantage. In contrast, the popular multi-way partial least-squares (NPLS) method is available for application to second-order data [39], and although it preserves the matrix data structure, it is not able to achieve the second-order advantage.

In the present Review, the theories of the most employed multivariate calibration models for first- and higher-order data will be presented. Finally, an overview of several applications in the biomedical field will be discussed.

2. Theory

2.1. Data orders

The various types of instrumental data have been classified on the basis on tensor algebra [40–42]. Within this scheme, when a given instrument produces a single instrumental response for a chemical sample, this datum is a scalar or zeroth-order tensor. Vector data for each sample belong to the first-order type: for example, absorption or emission spectra [UV-visible spectrophotometry, spectrofluorimetry, infrared, near-infrared (NIR), etc.], electrochemical scans (voltammograms, chrono-amperograms), nuclear magnetic resonance spectra, etc.

When two first-order instruments are coupled in tandem (e.g., GC-MS, MS-MS, etc.), the order increases from first- to second-order. The latter can also be produced using a single instrument: examples are a spectrofluorometer registering excitation-emission matrices (EEMs) or a diode-array spectrophotometer where a chemical reaction takes place. The data order can be further increased to three if, for example, EEMs are registered as a function of time.

Table 1 summarizes the classification scheme, including information which will be clear below.

2.2. Zeroth-order data

Zeroth-order data are usually fitted to a straight line by least-squares, a procedure known as univariate calibration [43], and requiring full selectivity for the analyte of interest. In the event that other sources respond, this signal should be constant, in order to be eliminated by a background correction or modeled by an intercept. When this is not the case, i.e., the responses are intrinsically unselective, a different approach, either instrumental or mathematical, is required.

2.3. First-order data

First-order data belong to the multivariate domain, and are processed by suitable first-order multivariate calibration procedures. The central idea of all of these methodologies is to compensate for the lack of total selectivity of the analyzed signals, using efficient mathematical algorithms to extract the portion of the overall signal which can be employed to predict the concentration of a particular sample component.

The available arsenal of first-order methodologies can be classified depending on whether the calibration model is classical or inverse [11]. The classical model assumes that instrumental data are a function of analyte concentration. The specific model for a test sample can be written as follows,

Table 1
Classification of data by their tensorial properties, and typical methods for data analysis

Classification	Order of single sample data	Sample data set	Typical method	Second-order advantage
Univariate	Zeroth-order	One-way	Linear regression	No
	First-order	Two-way	PCR, PLS, NAP, OSC	No
	Higher-order unfolded to first-order	Two-way	Unfold-PCR	No
			Unfold-PLS	No
	Second-order	Three-way	PARAFAC	Yes
Multivariate			GRAM	Yes
			BLLS	Yes
			SWATLD	Yes
			NPLS	No
	Third-order	Four-way	PARAFAC	Yes
			TLLS	Yes
			NPLS	No

provided both linearity and additivity hold for the various sample components:

$$\boldsymbol{y} = \mathbf{S}\boldsymbol{x}. \tag{1}$$

In Eq. (l), $\boldsymbol{y}$ (a vector of size $J \times 1$) is the test sample spectrum measured at J selected wavelengths, $\boldsymbol{x}$ (a vector of size $N \times 1$) contains the predicted concentrations of the N constituents, and $\mathbf{S}$ (a matrix of size $J \times N$) is a spectral matrix whose columns are the sensitivities of the N analytes at the J wavelengths. The latter one is either measured (if standards for all pure components are available) or estimated from the analysis of calibration mixtures:

$$\mathbf{Y} = \mathbf{X}\mathbf{S}^{\mathrm{T}}. \tag{2}$$

In the latter equation, $\mathbf{Y}$ (a matrix of sizes $I \times J$) contains the spectra for I calibration samples measured at the J wavelengths, $\mathbf{X}$ (a matrix of sizes $I \times N$) contains the reference concentrations of the N constituents in the I mixtures, and the superscript 'T' denotes transposition. This multivariate technique is known as classical least-squares (CLS). The applicability is rather limited, because it requires concentration information of all contributing species for proper calibration through Eq. (2), or knowledge of the pure spectra for concentration prediction by Eq. (1) [11].

In many calibration situations, an approach different than CLS is needed, simply because identifying all sample components is impractical or virtually impossible. Inverse models may conveniently solve these problems by assuming that the analyte concentration is a function of the response [12]. A multivariate inverse model for the test sample can be written as:

$$y = \boldsymbol{x}^{\mathrm{T}}\boldsymbol{b} \tag{3}$$

where y (a scalar) is the predicted concentration of the analyte of interest, $\boldsymbol{x}$ is the test sample spectrum (a vector of size $J \times 1$) and $\boldsymbol{b}$ (a vector of size $J \times 1$) contains J regression coefficients associated to the particular analyte being investigated. The value of J is generally greater than the number of training samples I, and therefore the calibration step requires to solve an underdetermined system of equations, requiring a drastic reduction in the number of sensors in order to apply least-squares for estimating the regression vector $\boldsymbol{b}$. Inverse least-squares (ILS), also called multiple linear regression (MLR), is a technique combining variable selection (to obtain an overdetermined system of equations) and least-squares [11]. In this method, calibration is carried out with the information provided by I mixtures whose spectra are recorded at J sensors (with $I > J$), and $\boldsymbol{b}$ is obtained from:

$$\boldsymbol{y} = \mathbf{X}\boldsymbol{b} \tag{4}$$

where $\boldsymbol{y}$ (a vector of size $I \times 1$) holds the reference concentrations and $\mathbf{X}$ (a matrix of size $I \times J$) is the corresponding calibration spectra.

Many algorithms exist for efficiently selecting the best subset of sensors for implementing ILS. Since the number of all possible combinations which may be employed for calibration can be exceedingly large, the selection is made by sensible algorithmic procedures, such as generalized simulated annealing (GSA), artificial neural networks (ANN) or genetic algorithms (GA) [44–46].

A popular alternative to ILS is to employ "scores" (linear combinations of the original variables) instead of the original responses, and then regress the reference concentrations on a limited number of scores. In the technique known as principal component regression (PCR), the scores are computed by projection onto the space spanned by a reduced number of eigenvectors of the square matrix ($\mathbf{X}^{\mathrm{T}}\mathbf{X}$). These loading vectors are selected in such a way that they explain a significant portion of the overall spectral variance displayed by the calibration spectra. Specifically, the scores are found by following these sequential steps: 1) obtaining the first A significant eigenvectors of the square matrix ($\mathbf{X}^{\mathrm{T}}\mathbf{X}$) (which define a loading matrix $\mathbf{P}$ of size $J \times A$), and 2) projecting the data matrix $\mathbf{X}$ onto the space spanned by $\mathbf{P}$ [11]:

$$\mathbf{T} = \mathbf{X}\mathbf{P}. \tag{5}$$

Hence, the size of the calibration score matrix $\mathbf{T}$ is ($I \times A$). The operation described by Eq. (5) compresses the information contained in $\mathbf{X}$ into a significantly smaller matrix, allowing to apply an inverse calibration procedure which involves the scores instead of the original variables:

$$\boldsymbol{y} = \mathbf{T}\boldsymbol{v} + \boldsymbol{e} \tag{6}$$

where $\boldsymbol{v}$ (size $A \times 1$) is the vector of regression coefficients and $\boldsymbol{e}$ is a vector of residuals not fitted by the inverse calibration model, The vector $\boldsymbol{v}$, required for subsequent prediction on new samples, is easily recovered from the least-squares solution to Eq. (6), since the problem becomes overdetermined, because A is in practice significantly smaller than I:

$$\boldsymbol{v} = \mathbf{T}^{+}\boldsymbol{y} \tag{7}$$

where $\mathbf{T}^{+} = (\mathbf{T}^{\mathrm{T}}\mathbf{T})^{-1}\mathbf{T}^{\mathrm{T}}$ is the so-called pseudo-inverse of $\mathbf{T}$, easily obtained since the columns of $\mathbf{T}$ are orthogonal.

Prediction proceeds as in the ILS method:

$$\boldsymbol{y} = t^{\mathrm{T}}\boldsymbol{v} \tag{8}$$

except that the information contained in $\boldsymbol{x}$ is replaced by the new sample scores t, where [11]:

$$t = \boldsymbol{x}\mathbf{P} \tag{9}$$

This philosophy leads to the so-called "full-spectrum" methods of which PCR and also PLS regression are the prime examples [11]. In fact, the latter has become the de facto standard in chemometrics, because of the availability of software and the ease of its implementation. PLS operates in similar manner in comparison with PCR. The main difference lies in the compression of the information contained in $\mathbf{X}$, i.e., the analogous of Eq. (5). In PLS this compression is made using the full calibration data, including instrumental signals ($\mathbf{X}$ matrix) and concentrations ($\mathbf{y}$ vector). An iterative PLS algorithm provides two types of loadings, contained in the matrices $\mathbf{W}$ (weight loadings) and $\mathbf{P}$ (loadings), both of size $J \times A$, which help to explain the maximum covariance between

signal and analyte concentration. The calibration scores are found by the following projection:

$$\mathbf{T} = \mathbf{XW}\left(\mathbf{P}^{\mathrm{T}}\mathbf{W}\right)^{-1}. \tag{10}$$

The calibration step is inverse, and identical to PCR. Once the regression coefficients are found, they are employed to predict the analyte concentration through Eq. (8), with the new sample scores found by an equation analogous to Eq. (10):

$$t = \left(\mathbf{W}^{\mathrm{T}}\mathbf{P}\right)^{-1}\mathbf{W}^{\mathrm{T}}\boldsymbol{x}. \tag{11}$$

A problem which is common to most factor-based multivariate methodologies is the estimation of the optimum number of factors (A) to be employed for future predictions. The most popular procedure to estimate A is cross-validation [11]. Briefly, during cross-validation, from a given set of I calibration spectra, a PLS model is built using $(I-1)$ spectra. Using this model, the concentration of the sample left out during the calibration is predicted. This process is repeated a total of I times, until each sample has been left out once. The sum of squared prediction errors for all calibration samples, or PRESS$=\sum(y_{i,\mathrm{act}}-y_{i,\mathrm{pred}})^2$ is calculated each time a new factor is added to the PLS model. The optimum number of factors is estimated by computing the ratios $F(A)$=PRESS($A<A^*$)/PRESS(A) (where A is a trial number of factors and A^* corresponds to the minimum PRESS), and selecting the number of factors leading to a probability of less than 75% that $F>1$ [11].

The arsenal of first-order methods has been complemented in recent years by the introduction of methods for filtering or preprocessing the raw instrumental data, producing new data sets in which the correlation between signal and concentration of particular analytes is enhanced. Pertinent examples of this are net analyte preprocessing (NAP) [15] and orthogonal signal correction (OSC) [47].

2.4. Second- and higher-order data

If a sample produces second- or higher-order data, then the multivariate strategies are also known as multi-way techniques. Data for a single sample are contained in a multidimensional array (either a matrix, or a higher-order array). In general, various components contribute to the overall matrix signal $\mathbf{M}$ (of size $J\times K$), and in the most interesting scenario the latter can be written as:

$$\mathbf{M} = \mathbf{XZY}^{\mathrm{T}} \tag{12}$$

where $\mathbf{X}$ is a matrix ($J\times N$) collecting the profiles of N components at the J sensors spanned by the first dimension of $\mathbf{M}$, $\mathbf{Y}$ is a matrix ($K\times N$) whose columns are the profiles at the K sensors spanned by the second data dimension, and $\mathbf{Z}$ is a diagonal ($N\times N$) matrix whose diagonal elements are the component concentrations (all off-diagonal elements are zero). The columns of the so-called *loading* matrices $\mathbf{X}$ and $\mathbf{Y}$ are usually normalized to unit length, in which case $\mathbf{Z}$ contains only relative concentrations. Due to the special form of Eq. (12), the model is called *trilinear*.

If matrix data for a group of samples are joined in the third dimension, then a three-dimensional array is obtained (called a 'three-way' array), and the methods employed for analyzing them are called three-way methods. A mathematical model for such an array is not easily written using standard matrix notation, but can be simply understood in terms of individual three-way elements. If the three-way array $\underline{F}$ (of size $I\times J\times K$, I being the number of samples) has general $\underline{F}_{ijk}$ elements, and provided the trilinear model is valid, each of these elements can be written as:

$$\underline{F}ijk = \sum_{n=1}^{N} \mathbf{X}_{in}\mathbf{Z}_{nn}\mathbf{Y}_{jn} + \underline{E}ijk \tag{13}$$

where $\underline{E}_{ijk}$ are the elements of an error array $\bar{E}$ of the same dimensions as $\underline{F}$. A popular algorithm for processing thee-way data is parallel factor analysis (PARAFAC) [23]. The latter method fits Eq. (13), often in a unique manner, using an alternating least-squares (ALS) procedure, providing the profiles in both dimensions for all sample components, as well as the scores or relative concentrations, the latter ones contained in the $\mathbf{Z}$ matrix. From this matrix, the nth column corresponding to a given analyte can be isolated, and the scores corresponding to the calibration samples are regressed against reference analyte concentrations, in a pseudo-univariate fashion. Interpolation of the new sample score into the latter graph allows to predict the analyte concentration. Since the decomposition of Eq. (13) is unique, profiles and scores are directly extracted from the three-way data, regardless of whether uncalibrated components occur in the new samples. This constitutes the basis of the important second-order advantage.

We collect in Table 1 a brief nomenclature summary, in order to avoid a common confusion which may arise from the proliferation of data orders.

Second-order multivariate calibration methods are of great interest because many instruments produce data that following the trilinear model [48–50]. Other appropriate techniques for analyzing these data are the generalized rank annihilation method (GRAM) [40], bilinear least-squares (BLLS) [36] and multivariate curve resolution-alternating least-squares (MCR-ALS) [51]. Bilinear data are of great importance to the analysis of complex mixtures, because they permit quantification even in the presence of unsuspected sample constituents, which give rise to second-order advantage [40]. Hence, even when second-order multivariate calibration may be viewed as a natural extension of its first-order counterpart, the change between these two orders is revolutionary rather than evolutionary.

There are few literature reports on third-order calibration methods, useful when a sample produces a three-way array, and the set formed by joining a samples set is an $I\times J\times K\times L$ four-way array characterized by four indexes: I is the number of samples, and J, K and L are the numbers of sensors in the corresponding data dimensions. Suitable methods for processing this information are PARAFAC and trilinear least-squares (TLLS) [52].

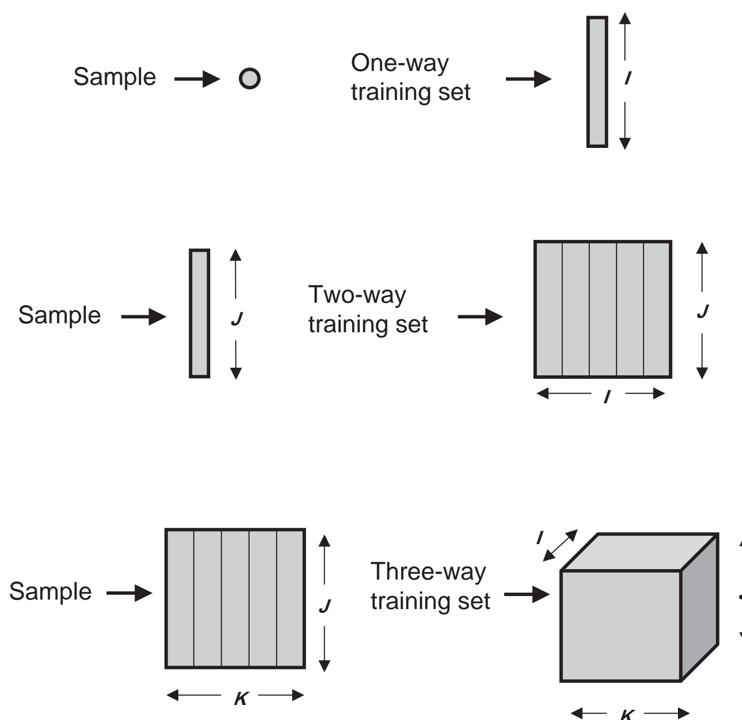

Fig. 1. Representation of data of various orders and of the calibration sets obtained when joining data sets.

An alternative which is sometimes employed is to rearrange the higher-order data arrays into vectors, and then apply a first-order method. This procedure leads, for example, to unfold-PCR and unfold-PLS [53]. A promising alternative to these unfolding methods is NPLS [39], a genuine N-way method. However, neither NPLS nor the unfolded versions of PCR or PLS are able to achieve the second-order advantage.

A summary of data orders, uni- and multivariate models, and adherence to the second-order advantage, is given in Table 1. Fig. 1 shows, in turn, a pictorial representation of data of various orders, as well as the nomenclature of the corresponding training sets.

3. Application to biomedical analysis

3.1. Synthetic mixtures

Before their application to real samples, several chemometric methods have been previously optimized and explored on suitable sets of artificial samples. The latter are prepared in the laboratory in order to simulate (sometimes only partially) natural matrices. In several of these cases, the samples are basically obtained by dissolving the analytes in adequate solvents. Some examples are reviewed below.

A near-infrared method combined with PLS regression was reported for determining serum proteins (albumin and IgG) in phosphate buffer solutions [54]. A fluorescence method applying multivariate calibration in real serum samples was also developed for determining the same proteins (see below).

A spectrophotometric method has been described and applied to resolve binary synthetic mixtures of the corticosteroid dexamethasone and the antibiotic polymyxin B. Absorption spectra of these compounds were used to optimize the spectral data set by applying PLS and PCR algorithms [55].

The simultaneous spectrophotometric determination of vitamins belonging to the B complex (folic acid, thiamin, riboflavin, and pyridoxal) has been described using the PLS method [56,57]. Satisfactory results were obtained in all of the laboratory-made analyzed samples.

Several works have employed multivariate calibration for the determination of metal ions in both synthetic and commercial dialysis fluids. Kargosha and Sarrafi developed a method for the simultaneous determination of calcium and magnesium in dialysis fluids using PCR and PLS algorithms [58]. The method was based on the reaction between the analytes and eriochrome black T at pH 10.1. The samples were analyzed with good precision, corroborating that other components, frequently added to dosage forms, do not cause a serious interference.

A method for the quantitation of zinc, copper and manganese in dialysis fluids, based on their complex formation with 1-(2-pyridylazo)-2-naphthol (PAN), was developed [59]. CLS was compared with PCR and PLS, concluding that all of these multivariate algorithms showed similar results.

Binary and ternary mixtures of different metal ions [Zn(II), Ni(II), Pb(II), Co(II) and Cd(II)] were analyzed by a ligand substitution kinetic method and PARAFAC [60].Three-way data matrices were generated by acquisition of UV-visible spectra as a function of: 1) the reaction time of a substitution reaction between the metal complex with 4-(2-pyridylazo) resorcinol (PAR) and EDTA, and 2) different relative concen-

trations of the metal ions in the micromolar concentration range.

Differences between the luminescence lifetimes of EDTA–lanthanides–protein complexes were exploited by analyzing mixtures of anhydrase, human serum albumin (HSA) and γ-globulin. PLS regression analysis was used to determine HSA and γ-globulin in binary mixtures, without previous separation at the concentration ranges typically found in clinical tests of human blood serum [61].

The monitoring of free chlorine in dialysis fluids using a calorimetric method and PLS was investigated [62], based on the use of *N*,*N*′-diethyl-*p*-phenylenediamine (DPD). The results were compared with those obtained from the current univariate DPD-method, which uses a single wavelength detection at 515 nm. The multivariate approach showed better performance, because it was able to model the influence of the high ionic strengths of the saline matrices on the equilibrium among the DPD species.

Finally, a new method for quantifying adrenaline and noradrenaline in mixtures of catecholamine standards was described by Nikolajsen et al. [63]. The method gains selectivity from the different rates at which the fluorescing 3,5,64-trihydroxyindole derivatives (lutines) of the catecholamines are formed and degraded to adrenaline and noradrenaline. Fluorescence surfaces were measured at consecutive time points for every sample, creating a four-way data array. Quantitative information was obtained by two-component four-way PARAFAC and also by NPLS, with very similar results. The authors expect the method to be suitable for the determination of catecholamines in real urine samples.

3.2. Real biological samples

Although working with synthetic samples is a first approximation to solve multi-component cases, analytical methods are frequently required to work in situations which are far from ideal. Real samples, especially those related to biological systems, may show high viscosity and/or ionic strength, or contain interfering species, high protein concentrations, etc. Therefore, in recent years, multivariate calibration methods have been gaining importance in the resolution of complex multicomponent mixtures, such as serum, plasma, urine and biological tissues.

Chemometric methods have been mainly developed for spectroscopic data, for a variety of reasons. On one hand, traditional chemometric analysis began by the need of exploiting heavily overlapped NIR spectra for quantitative purposes. On the other, spectroscopic data are, in general, less selective than other data sources due to severe signal overlapping, immediately calling for suitable chemometric tools. Consequently most of the work cited below concern the application of chemometrics to spectral data, although occasionally other data types (i.e., electrochemical) have also been studied.

3.2.1. UV-visible spectrophotometry

The simultaneous spectrophotometric resolution of copper (II) and zinc (II) using 2-carboxyl-2-hydroxy-5-sulfoformazylbenzene in blood serum by using a modified version of PLS has been reported [64]. Likewise, the resolution of quaternary mixtures formed by iron, cobalt, nickel and copper using UV-visible spectrophotometric data was accomplished in biological materials (dogfish liver, pig kidney and bovine liver) [65]. The method is based on the absorption produced by the complexes formed between the cited ions and 1,5-bis(di-2-pyridylmethylene) thiocarbonohydrazide (DPTH). A comparative study of the results obtained by using PCR and PLS for absorbance, first-derivative and second-derivative data is presented, and the authors concluded that best recovery values were obtained by the PLS method.

A flow-injection analysis of five chlorophenols (priority pollutants) in urine samples using spectrophotometric data and PLS was developed [66]. PLS calibration of spectrophotometric data has been applied to the determination of theophylline (a xanthine bronchodilator) in blood serum [67]. A comparison of this method with an immunofluorescent polarization technique revealed no significant differences in their prediction abilities. This work also included the analyses of potential interferences. Studies in the presence of triglycerides, bilirubin, hemoglobin and caffeine showed that only the latter was able to interfere, as with other theophylline monitoring techniques.

Spectrophotometry (in the first-derivative mode) and PLS were also combined for the simultaneous determination of triamterene (a diuretic drug) and leucovorin in serum and urine [68]. The absorption spectra of samples of biological fluids, spiked with either one or both pharmaceuticals, were used to perform the optimization of the calibration matrices by PLS. It is important to point out that the analysis could be successfully carried out without sample pretreatment.

The determination of orotic acid in urine, useful for the diagnosis of disorders on the urea cycle and hereditary orotic aciduria, was performed by capillary zone electrophoresis with diode array detection [69]. Due to small disturbances by matrix-co-migrants, chemometric procedures (target transformation factor analysis, fixed size moving window-evolving factor analysis, orthogonal projection approach and fixed size moving window-target transformation factor analysis) had to be applied when the orotic acid concentration was 10 μmol l^{-1}.

Second-order calibrations of multivariate spectroscopic-kinetic data in the visible region were proposed to improve the Jaffé method for creatinine assay [70]. Quantitative determinations of creatinine using PARAFAC and direct trilinear decomposition (DTLD), performed on synthetic mixtures containing bilirubin, glucose, and albumin, confirmed that second-order calibration is useful for creatinine determination in human serum.

3.2.2. Mid- and near-infrared spectroscopy

Different authors have evaluated the application of chemometric algorithms to infrared data, with especial attention to near-infrared spectroscopy [71–75].

The determination of glucose in blood deserves a prominent place in the present review, because it is the base of non-invasive tools which could be efficiently employed in the war against diabetes, mainly by using NIR spectroscopy.

Khalil has reviewed infrared optical methods (NIR transmission and reflectance, NIR Chronoscopic measurements, spatially resolved diffuse reflectance, NIR frequency domain reflectance, polarimetry, Raman scattering, NIR photoacoustic spectroscopy) employed for non-invasive glucose measurements, with emphasis on multivariate chemometric techniques for data analysis [76]. McNichols and Coté reviewed optical glucose sensing including calibration and data processing methods useful for optical techniques [77], and Koschinsky and Heinemann published an article devoted to both technical and clinical aspects of glucose sensors [78].

Critical to the accurate measurement of glucose are the product engineering and the multivariate algorithms. From the point of view of NIR spectral properties, glucose molecules are similar to water, and hence a major problem in the optics and software design is to clearly distinguish the target molecule from the intense water background. In the simplest device, the light source shines NIR radiation into the skin, and the reflected light is analyzed by a spectrometer and processed by an algorithm to yield the blood glucose content. Prototypes are being considered for the approval of the US Food and Drug Administration (FDA) [116].

Since 1990, numerous researches were devoted to the determination of glucose by both near- and mid-infrared spectroscopies in water matrices, plasma, whole blood and different tissues using chemometric tools (PLS, PCR and ANNs) [79–100].

Lewis et al. developed an on-line, non-invasive method for the determination of glucose in cell culture media, via NIR spectroscopy [101], using a unique fiber optic coupling method and a commercial Fourier transform infrared (FT-IR) spectrometer. This system was the first of its kind and integrates a completely non-invasive optical probe to measure glucose concentrations within cell culture media, in situ. PLS regression was used to extract the analyte-dependent information and to build a multivariate calibration model.

In 2004, Du et al. published a novel chemometric method: region orthogonal signal correction (ROSC), in order to pretreat NIR spectra of blood glucose measured in vivo [102]. Moving window-PLS (MWPLS) regression was used to select NIR regions informative of glucose. The obtained results demonstrated that ROSC-pre-treated spectra, either including whole spectra or informative regions selected by MWPLS, provided very good performance of the PLS models.

MWPLS was also employed to determine the concentrations of human serum albumin, γ-globulin and glucose by using NIR spectroscopy [103,104]. The procedure was proposed to search for the optimized combinations of informative regions (spectral intervals) considered containing useful information for building PLS models.

Very recently [105], Schrader et al. have described a suitable optical set-up for the in vivo non-invasive NIR measurement of glucose in the human eye. A chemometric (PLS) study of NIR aqueous glucose spectra with concentrations of l0–350 mg/dl furnished in a calibration model which was able to predict physiological glucose concentrations. Even though the medically desired prediction error (less than 10 mg/dl) was not reached, the results were very promising, and show the feasibility of in vivo determination of glucose in the human eye.

Hall and Pollard determined total protein, albumin, globulins, and urea in unmodified human serum using NIR spectroscopy [106]. The distinctive NIR spectra of the individual protein fractions allowed unique spectroscopic models to be derived for each fraction, using MLR, while a PLS regression analysis was necessary to fully extract the relevant spectral information for urea.

Multicomponent assays for blood substrates, including glucose, proteins, triglycerides, cholesterol, urea and uric acid in human plasma by using mid- and near-infrared spectroscopies and PLS calibration were developed by Heise et al. [107,108]. The results were compared with those obtained by the official standard methods. They concluded that while in several cases the standard prediction errors were in the clinically accepted range, in other cases these errors were higher, and therefore the proposed methods are only suitable for screening purposes.

Results for the analysis of several blood substrates (protein, cholesterol and triglycerides) in human blood plasma using PLS multivariate calibration and short-wave NIR were presented by Bittner et al. [109]. Whereas the relative mean-squared prediction error for total protein using short wave NIR data was comparable with previous results using conventional NIR spectroscopy, the errors found for total cholesterol and triglycerides were nearly a factor of two worse for this study.

A multicomponent assay of proteins, glucose, cholesterol, triglycerides and urea was presented for human plasma using mid-infrared spectra recorded in the attenuated total reflection mode [110]. PLS was used for multivariate calibration based on spectral intervals in the fingerprint region, selected for optimum prediction and modelling.

The potential for noninvasive determinations of glucose, lactate and ammonia in cell culture media was investigated through NIR spectroscopy [111]. PLS regression was used to build a multivariate model based on NIR spectra and reference values. An independent calibration was performed with aqueous mixtures of glucose, lactate, ammonia, glutamate and glutamine. Finally, a calibration using a combination of spectra from cell culture media samples and aqueous mixtures was performed. The results indicated that a selective calibration model can be produced by combining data from samples of different type.

Berger et al. demonstrated the use of NIR Raman spectroscopy to measure the concentration of many serum constituents (glucose, cholesterol, urea, and other analytes) in serum and whole blood samples using PLS [112].

Biomedical samples have been studied by combining second derivative of IR spectra with chemometric methods using glass substrates [113]. These analyses involved the determination of serum triglycerides, fetal lung maturity (through measurements of amniotic fluid lecithin/sphingomyelin—L/S ratios), and the classification of synovial fluid for the differential diagnosis of arthritis. The IR methods for serum triglyceride analysis and the determination of amniotic fluid L/S ratios were calibrated using a PLS algorithm. The classifi-

cation of the synovial fluid spectra was carried out using a feature extraction method (optimal spectral region selection algorithm) and linear discriminant analysis (LDA).

Heise et al. evaluated the quantification of urea, creatinine, uric acid, phosphate, and sulfate in urine, using mid-infrared attenuated total reflection spectroscopy and PLS calibration [114].The limitations of the multicomponent assay and the potential of fiber optic measurements were discussed.

The quantitative analysis of triglycerides in human plasma was done using near-infrared spectroscopy by da Costa Filho and Poppi [115]. The applied multivariate techniques (PLS, MLR and ANN) showed similar performance, although MLR was preferred because of its easy implementation.

Non-invasive analysis of ethanol in blood can be done by NIR measurements combined with suitable chemometric algorithms. Recent subject studies show that these instruments measure alcohol more accurately than state-of-the-art breath alcohol analyzers [116].

NIR spectroscopy was used to measure the somatic cell count (SCC) content of cow milk [117]. The calibration for log(SCC) was performed using PLS regression and different spectral data. It was found that SCC determination by NIR milk spectra is based on SCC-related changes in milk composition, and the most significant factors simultaneously influencing milk spectra with the increase in SCC were the alteration of proteins and the changes in ionic concentration.

An adaptive calibration procedure was used by Rhiel et al. to build selective multivariate calibration models for the measurement of glucose, lactate, glutamine, and ammonia in undiluted serum-based cell culture media [118]. This procedure removes metabolism-induced covariance between these analytes in a series of calibration samples collected during the cultivation of PC-3 human prostate cancer cells. PLS calibration models were generated from both full NIR spectra and optimized spectral ranges. Similar analytical performance was achieved, and with fewer model factors, when the optimized spectral range was used. The results demonstrated that NIR spectroscopy can be effectively used in the off-line measurement of important nutrients (glucose and glutamine) and by-products (lactate and ammonia) in a serum-based animal cell culture medium.

Lafrance et al. evaluated NlR as a technique for lactate analysis in plasma (in vitro) [119] and from exercising humans (in vivo) [120]. Calibration of the lactate concentration by NIR was made using PLS. The results suggest that NIR may provide a valuable tool to assess in vivo physiological status for both research and clinical needs.

A subject which accompanies a discussion based on NIR spectra is the so-called calibration transfer, which refers to the transfer of multivariate calibrations between different NIR instruments or to the maintenance of a given calibration in time [121,122]. As expected regulatory authorities have recently moved towards this issue [123]. There are several important reasons to implement a transference of models: a) when sample pre-treatment is carried out, such as extraction or clean-up, b) because of the need to transport a calibration model previously built on a given instrument, to a second instrument, c) when changes on the instrument over time (for example wavelength shift) take place, and d) when variations between samples from different production batches are observed.

When multivariate calibration is applied, especially in the first-order domain, an enormous amount of calibration samples are sometimes required in order to contemplate the large number of variability sources which are present in biological materials [20,67,88]. It is in this scenario where model transfer plays an important role, because of the possibility of using this information in order to analyze new samples, obtained in new conditions, without the need of building the calibration model again.

Among the most popular methods for calibration transfer, the following can be cited: direct standardization (DS) [124], piecewise direct standardization (PDS) [124], OSC [125], ANN [126], wavelet analysis [127] and guided model re-optimization (GMR) [122]. PDS is probably the best solution for complex systems. It builds a multivariate model between the response of a sample measured at the jth wavelength in situation A and the corresponding window (a selected region) of the response obtained on situation B. The regression coefficients are located in a transformation matrix $\mathbf{F}$ according to:

$$\mathbf{X}_{\mathrm{A}} = \mathbf{X}_{\mathrm{B}}\mathbf{F} \qquad (14)$$

where $\mathbf{X}_{\mathrm{A}}$ and $\mathbf{X}_{\mathrm{B}}$ are the response matrices of the standardization samples obtained from the primary and secondary situations (A and B), respectively. Once the transformation matrix is estimated, the response vector of a new sample $\boldsymbol{x}_{\mathrm{B}}$ is projected onto the original measurement space so that its property values can be predicted with the old model:

$$\boldsymbol{x}_{\mathrm{A}} = \mathbf{F}\boldsymbol{x}_{\mathrm{B}}. \qquad (15)$$

The relevant matrix $\mathbf{F}$ is usually estimated by means of PCR or PLS regression in order to obtain a least-squares solution.

Literature reports examples of application of multivariate calibration standardization on the bioanalytical field, which are almost exclusively related with the determination of glucose and other compounds in serum samples by FT-NIR spectrometry. In these cases, samples measured in a secondary spectrophotometer are quantified by using the calibration data previously obtained with a primary instrument [122,128–130].

3.2.3. Spectrofluorimetry

Since fluorescence spectroscopy shows the advantages of both high sensitivity and simplicity, it has found extensive use in the determination of analytes at low concentrations. However, it is noteworthy that only few works have been published regarding the use of direct spectrofluorimetric methods for the analysis of compounds in biological samples. This is due to the frequently observed overlapping between the intense fluorescence emission from human urine or serum and the investigated compounds, which precludes their direct spectrofluorimetric quantification. With the advent of chemometric tools, this problem was solved in several important

cases. The pioneering works were devoted to the use of first-order calibration: Durán Merás et al. performed the fluorimetric determination of the antibacterial nalidixic acid and 7-hydroxymethylnalidixic in urine by PLS and PCR multivariate calibration [131].

PLS regression of fluorimetric data for the determination of the diuretic triamterene in urine was successfully developed [132]. The simultaneous determination of salicylic acid and diflusinal in human serum has been performed by synchronous fluorimetry in combination with PLS multivariate calibration [133]. The method is based on the fluorescence of these compounds in chloroform containing 1% (v/v) acetic acid. Serum samples are treated with trichloroacetic acid too remove the proteins, and both compounds are extracted in chloroform—l% (v/v) acetic acid prior to the determination.

The spectrofluorimetric determinations of two anti-inflammatory drugs (naproxen and salicylate) in serum [134], and of naproxen, salicylic acid and acetylsalicylic acid have been carried out by using PLS multivariate calibration [135].

The simultaneous resolution of naproxen–salicylic acid mixtures in serum and naproxen–salicylic acid–salicyluric acid mixtures in urine was accomplished and employed for a discussion of the relative advantages of the applied both first-(PLS) and second-order multivariate calibration of fluorescence data [136]. In this case, the analysis of second-order data was performed using excitation-emission matrices, in combination with chemometric software such as GRAM (in the iteratively reweighted version called IRGRAM), parallel factor analysis (PARAFAC) and self-weighted alternating trilinear decomposition (SWATLD), and the fluorescence signals were improved by the complexation of the studied compounds with β-cyclodextrin.

Another widely used anti-inflammatory, piroxicam, was spectrofluorimetrically determined in serum through the use of three-way fluorescence data and multivariate calibration performed with PARAFAC and SWATLD [137]. The method exploits the so-called second-order advantage of the three-way data, and was developed following two different procedures: internal standard addition and external calibration with standard solutions, which were compared and discussed.

Excitation-emission matrix fluorescence and multi-way analysis (PARAFAC and NPLS) were also accomplished for the direct determination of doxorubicin (a cytotoxic anthracycline antibiotic) in human plasma [138].

An original approach is presented for the spectrofluorimetric determination of the powerful anticonvulsant carbamazepine and its main metabolite (10,11-epoxide) in human serum [139]. The strategy consists in supporting both compounds on a nylon membrane, and subsequently determining them through a solid-surface fluorescence methodology combined with chemometric analysis. The algorithms applied were PARAFAC, SWATLD and NPLS. The results were compared with two-way calibration data analysed with PLS regression.

The overlapping between the fluorescence spectra for human serum and ibuprofen (the oldest of the newer non-steroidal anti-inflammatory drugs) is significant and, in principle, precludes the direct spectrofluorimetric determination of this drug. However, this problem was overcome by combining the property of β-CD of enhancing the low native fluorescence of ibuprofen with a suitable chemometric analysis. Specifically, second-order data analysis was performed on excitation-emission fluorescence matrices (EEMs) with the aid of the SWATLD algorithm [140].

Ternary mixtures of fluoroquinolones (norfloxacin, ofloxacin and enoxacin) have been spectrofluorimetrically determined in human urine samples by application of a PLS model [141]. The method is based on the native fluorescence of these compounds in the presence of the surfactant sodium dodecyl sulfate at pH = 4.

In a recent work, the analytical performances of two second-order algorithms, the novel BLLS and the popular PARAFAC, were compared as regards fluorescence data recorded for the determination of ciprofloxacin (a fluoroquinolone antibiotic) in urine [38].

The simultaneous determination of two serum proteins (albumin and IgG) in real serum samples using spectrofluorimetry and multivariate calibration was attempted by Wiberg et al. [142]. The results obtained showed reasonable content predictions for both albumin and IgG, although in a few cases interfering fluorescence from other serum proteins was detected.

Very recently, four-way fluorescence data recorded by following the kinetic evolution of excitation-emission fluorescence matrices (EEMs) have been analyzed by PARAFAC and trilinear least-squares (TLLS) algorithms [52]. They were applied to the simultaneous determination of the components of the anticancer combination of methotrexate and leucovorin in human urine samples. Both analytes were converted into highly fluorescent compounds by oxidation with potassium permanganate, and the kinetic of the reaction was continuously monitored by recording full EEM of the samples at different reaction times. The excitation, emission and kinetic time profiles recovered by both chemometric techniques were in good agreement with experimental observations.

It should be mentioned that non-invasive screening of Type 2 diabetes is being performed by fluorescence measurements. In a similar way to the NIR devices discussed above, fluorescence spectroscopy allows one to measure advanced glycation end products (AGEs) in the dermis of a patient's forearm [116]. The concentration of AGEs in the dermis is an excellent indicator of cumulative hyperglycemic exposure and is highly correlated with the development of diabetes complications [143].

3.2.4. Electrochemistry

Reports on the use of chemometric techniques in biomedical analysis involving electrochemical data are not as abundant as its spectroscopic counterpart. In 2002, Pravdová et al. reviewed multivariate chemometric methods employed in electrochemistry, and applied to a wide variety of samples [144]. Most of them refer to the analysis of classification problems (in a variety of samples including foodstuffs, beverages, microbial species, explosive gases, etc.), generally performed by PCA and ANNs.

An amperometric glucose biosensor was developed by Kulys and Hansen [145]. The long-term stable biosensors were obtained using stabilized glucose oxidase and an array of biosensors. The application of a chemometric method permitted employment of the biosensor during more than 166 days at 35 °C and relative humidity 75%. The relative error of chemometric prediction was less than 5.4%, and the response changes less than 0.15% per week.

In several cases, chemometric tools were used with the purpose of optimizing the different analytical variables. In 1995, Furlanetto et al. [146] proposed an adsorptive stripping voltammetric method for the determination of rufloxacin in tablets, plasma and urine, using a multivariate strategy for the optimization of the experimental design.

A chemometric method was applied for determining quinolinic acid in human plasma and urine by differential pulse polarography. The variables involved in the applied procedure were evaluated by means of experimental design: a screening symmetric matrix and a central composite design [147].

An ionic-selective-electrode multisensor system and back-propagation ANN for the simultaneous determination of several cations and anions were successfully employed in a solution modelling human blood plasma [148].

An array of conducting polymer-coated microelectrodes was employed as an amperometric detector to analyze a range of proteins [149]. Protein identification and quantification were performed using PCA, soft independent modelling of class analogy (SIMCA), ordinary least-squares (OLS) and PLS. Individual proteins in a two component mixture were quantitatively analyzed with acceptable accuracy.

Lobanov et al. have applied ANNs to the analysis of ethanol–glucose mixtures by using two sensors based upon whole microbial cells [150]. Amperometric sensors were constructed using immobilized cells of either *Gluconobacter oxyduns* or *Pichia methanolica*. The bacterial cells of *G. oxydans* were sensitive to both substrates, while the yeast cells of *P. methanolica* oxidized only ethanol. Using a polynomial approximation, data from both of these sensors were processed to provide accurate estimates of glucose and ethanol over a concentration range of 1.0–8.0 mM. When data were processed using an artificial neural network, glucose and ethanol were accurately estimated over a range of 1.0–10.0 mM.

A voltammetric method based on the oxidation at a glassy carbon electrode was proposed for the simultaneous determination of two antipsychotic drugs (chlorpromazine hydrochloride and promethazine hydrochloride) [151]. Since the voltammetric peaks of these two drugs seriously overlap, they were interpreted with the aid of chemometric methods such as CLS, PCR and PLS. The proposed method was applied to determine these two drugs in a set of synthetic mixtures and blood samples, and, in general, satisfactory results were obtained.

An electrochemical approach for the determination of the antibacterial enrofloxacin in spiked canine urine was proposed. The method, based on adsorptive stripping voltammetry and PCR analysis, was developed in the presence of the enrofloxacin metabolite (ciprofloxacin) and yielded successful results [152].

An array of six potentiometric sensors, constituted by two creatinine biosensors and four ion-selective electrodes for potassium, sodium, ammonium and calcium, was employed to calibrate a multivariate model based on PLS for the response to creatinine [153]. The array was used for the analysis of creatinine in urine samples, and the results were compared with the classical clinical analysis.

Freire et al. developed a simple method for a rapid evaluation of mixtures of phenolic compounds (phenol/chlorophenol, cathecol/phenol, cresol/chlorocresol and phenol/cresol) using a dual amperometric device [154]. The approach is based on the difference between the sensitivity of lactase and tyrosinase for different phenolic compounds. A multichannel potentiostat is used to simultaneously monitor lactase- and tyrosinase-based biosensors, and the data are treated using the PLS algorithm. The results showed that the proposed methodology can be employed to the simultaneous determination of phenolic compounds in industrial, clinical or environmental samples.

Recently, Berrettoni et al. used home-made RVC (reticulated vitreous carbon) microelectrodes array to monitor bacterial loads, by coupling electrochemical with chemometric methods [155,156]. Normal pulse voltammograms (NPV) were recorded with the purpose of obtaining the growth curves of bacterial species: *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The electrochemical signals processed by PLS allowed to correlate the instrumental signals with the bacterial population.

3.2.5. Chromatography

Chemometric processing of chromatographic data has been mainly used with classification purposes, although some work has also been done on quantitative analysis. For example, studies of polychlorinated biphenyls in serum using gas chromatography were performed by Luotamo et al. [157]. Their results not only demonstrated that polychlorinated biphenyls can be used for classifying persons according to the source of exposure (occupational, accidental, or environmental), but also that PLS is suitable for the quantitation of polychlorinated biphenyl compounds in biological materials.

Principal component analysis (PCA) has also been used in the determination of the chromatographic peak purity, allowing, for example, for the analysis of synthetic binary mixtures of the local anaesthetic drugs lidocaine and prilocaine [158].

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