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Analytica Chimica Acta 348 (1997) 1–9

ANALYTICA CHIMICA ACTA

Calibration method choice by comparison of model basis functions to the theoretical instrumental response function

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Received 11 October 1996; received in revised form 18 November 1996; accepted 3 December 1996

Abstract

Sorting through the large array of calibration methods available for first and second order calibration is often a daunting task for initiates into the field of chemometrics. Justifying the selected method as the most appropriate one is even more difficult. Presented here is a justification for calibration method selection based on matching the model employed in the calibration method with the instrumental response function. This is applied to the disparate types of nonlinearities found in both first and second order calibration. Matching the calibration method to the instrumental response function is employed to parse the decision making process for choosing between branches in the first order parsimony tree. The different types of nonlinearities present in second order data and their implications on calibration model selection are discussed.

Keywords: Data structures; Multivariate calibration; Second-order calibration; Expert system; Method selection

1. Introduction

The advent of rapid, inexpensive computers has permitted the proliferation of computationally intensive calibration methods. Calibration by standard additions is possible for univariate, multivariate, and higher order data. Locally weighted regression (LWR), alternating conditional expectations (ACE), multivariate adaptive regression splines (MARS) have joined multiple linear regression (MLR), principal component regression (PCR), and partial least squares (PLS) as accepted multivariate calibration algorithms in the toolboxes of many practising chemometricians. Analysis of cubes and hyper-cubes of chemical data by linear models is commonplace; application of nonlinear models has just started to emerge.

Consequently, one must chose between many competing methods and algorithms for application to any particular calibration challenge. Although it is well known that certain calibration methods are inapplicable in some situations, and other methods are tailored to fill well defined niches, it is often a daunting challenge for many calibration method end-users to decide with confidence as to which calibration method to use in any given situation. The need to develop logical rules to aid in calibration method selection is imperative since, as technology progresses, technologists are moving closer to implementing multivariate and higher order sensors capable of self calibration. Ideally, these sensors should have access to the whole

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PII S0003-2670(96)00604-6

range of calibration methods and algorithms available to expert chemometricians. What remains is to construct an expert system capable of optimizing the decision making process.

Chemometricians have been moving closer to such an expert system. Data collections can be classified based on the number of dimensions in the physical data structure. For example, in one nomenclature system, an instrument that produces a matrix (second order tensor) of data per sample, e.g. an LC-UVDAS, is nominally considered a "second order" instrument and the instrumental output is "second order" data. In a competing, but equally valid, nomenclature system data are classified based on their structure in a data set to be simultaneously analyzed. Here, a data set garnered from analyzing multiple samples on an LC-UVDAS is considered "3-way:" chromatographic by spectroscopic by samples.

Esbensen, Wold, and Geladi employed the concept of ways and orders to comment on the relationship between data structure and information content [1]. This work permits discrimination among application of models of different orders for application to a particular problem. Gerristen et al. proposed an expert system that recommends calibration methods based on the knowledge of the system assumed and sought [2]. This permits discrimination between, say, the generalized standard addition method (GSAM) and a (non)-linear multivariate calibration method, but does not permit discrimination among a host of nonlinear calibration alternatives. Seasholtz and Kowalski presented a hierarchical decision tree for the selection of progressively complex multivariate models based on the Parsimony Principle [3]. This system is limited in the inability to decide between equivalent branches in the tree, e.g. LWR vs. ACE.

The next requirement for an automated expert system is to develop a methodology to aid in rapidly choosing the best method for calibration. By the Parsimony Principle, the best calibration method for future prediction accuracy and precision will be the one that employs the simplest model that fits the calibration data. If otherwise equivalent methods are required to model the data to arbitrary precision, the method that incorporates a basis set that best mimics the data will construct the simplest model. This approach has been employed in modified artificial neural networks, ChemNets [4]. Hence, many calibration method possibilities can be eliminated based on the knowledge that their basis models are not compatible with the theoretical instrument response function of the data collection. Comparison of the method basis model and instrumental response functions predicts the recommendations of Gerristen and Kowalski, help chose between branches in the Parsimony Principle decision tree, and can be extended to higher order calibration [5].

2. Zero-order (univariate) calibration

Calibration of zero-order, or univariate instrumentation is well understood and hence, serves as a good starting point for the comparison of instrument response functions and model bases. The instrumental response function, f(), of a univariate sensor can be generalized to

$$r = \mathrm{f}(c, e_1, e_2, \ldots) + \varepsilon \tag{1}$$

where r is the instrumental response to a sample of analyte concentration, c. The remaining variables, e_1 etc., describe the environment surrounding the sensor, be it interfering species or sample temperature. Any random errors associated with the collection and digitization of recorder data are collected into the error term, ε. Depending on the function form of f() in Eq. (1), one of a number of different calibration strategies will be dictated. These calibration strategies are not unique to univariate calibration but can be generalized and extended to multivariate and multimode calibration.

2.1. Linear calibration

In general, for univariate calibration, the environmental variables are controlled to remain constant among all samples in the calibration set and with the future unknown samples. Hence, the instrument response is assumed to be a function of only analyte concentration, $r = \mathrm{f}(c)$. If $\mathrm{f}(c)$ is linear with respect to changes in analyte concentration, a set of samples with analyte concentration $\mathbf{c}$ would give rise to a set of instrument responses $\mathbf{r}$ based on the model

$$\mathbf{r} = \mathbf{c}b + a + \varepsilon \tag{2}$$

where the environmental variables factor into sensitivity of the instrument, b, or the instrumental signal

offset, a. Calibration and prediction can be performed by estimating the parameters a and b in Eq. (2) after analyzing at least two standards of known concentration. If the instrument response is actually nonlinear with respect to analyte concentration or the unknown sample contains added species that produce an instrumental response that is different from the instrumental response of the calibration standards' matrix, prediction will be inaccurate.

2.2. Nonlinear calibration

If $f(c)$ is not linear with respect to changes in analyte concentration, that is $f(c)$ cannot be sufficiently modeled by a first order polynomial, a nonlinear calibration method must be employed. Here, one or more of three different strategies can be employed: transformations, curve fitting, and local linear models. A logarithmic linearizing transformation is common to convert nonlinear transmittance signals to linear absorbance data. The concept of employing local models is implicit in the notion of "linear dynamic range" and local models can be employed when global linearizing transformations are unavailable. If a linearizing transformation cannot be found and employing a series of local linear models is not acceptable, fitting a nonlinear function, e.g. a high order polynomial or cubic spline, to the instrumental responses from the calibration samples can be employed to model $f(c)$ and yield accurate predictions. As with linear calibration, if the unknown sample contains added species that yield an instrumental response different from the instrumental response of the calibration standards' matrix, prediction will be inaccurate.

2.3. Calibration by standard additions

The preceding calibration methods assume that any uncontrollable difference in the matrix of the unknown samples from that of the calibration standards does not change the function $f()$ in Eq. (1). These matrix effects prohibit construction of accurate external calibration models unless the matrix of each unknown sample can be reproduced in the external calibration set. In most cases, matrix effects prohibit accurate univariate calibration. Assuming that the changes in the instrumental response with respect to analyte concentration is linear, matrix effects will effectively change either the instrumental offset, a in Eq. (2), or the instrument sensitivity, b in Eq. (2). In the case of changing instrument sensitivity, quantitation is possible when the instrumental offset is 0, by employing the standard addition method (SAM) for calibration [6]. Calibration by SAM is inaccurate with any type of instrumental offset since it is impossible to distinguish the signal related to the instrumental offset from the signal derived from the analyte. Furthermore, if $f(c)$ is nonlinear and cannot be linearized by a global transformation, SAM should not be attempted due to the lack of robustness of nonlinear methods to extrapolation.

3. First-order (multivariate) calibration

A first order sensor is an array of zero-order sensors where each zero-order sensor responds uniquely to changes of its environment. Hence, the instrumental response function of an array of J univariate sensors, $\mathbf{r}$, can be expressed as

$$\mathbf{r}^T = [f_1(c, e_1, e_2, \ldots), f_2(c, e_1, e_2, \ldots), \ldots, f_J(c, e_1, e_2, \ldots)] + \varepsilon^T \quad (3)$$

Assuming that the function $f_j()$ is constant for all samples, a collection of I standards in a calibration set can hence be expressed as $I \times J$ matrix $\mathbf{R}$ by augmenting the instrument response vectors from the I standards,

$$\mathbf{R} = [\mathbf{r}_1|\mathbf{r}_2|\ldots|\mathbf{r}_I]^T + E \quad (4)$$

The power of first-order sensors lies in the ability to perform accurate calibration and prediction in the presence of multiple environmental factors (e.g. interfering chemical species) that elicit an instrumental response. By studying the functional form of each $f_j()$ and the interrelationship among the J $f_j()$s, the appropriate linear or nonlinear calibration methods can be determined. With all first order calibration methods, accurate calibration is contingent upon the existence of variance among each environmental factor in the calibration set.

3.1. Bilinear calibration

If each $f_j()$ that comprises $\mathbf{r}^T$ can be expressed as linear combinations of the input variables $c, e_1, e_2, \ldots$

then R_{ij} is determined by

$$R_{ij} = c_i b_{oj} + e_{1i} b_{1j} + e_{2i} b_{2j} + \ldots + E_{ij}$$
$$= [c_i, e_{1i}, e_{2i}, \ldots, 1]\mathbf{I}[b_{oj}, b_{1j}, \ldots, a]^T + E_{ij} \quad (5)$$

where the subscript i and j refers to the ith sample and jth sensor. The bold capital I, **I**, represents an appropriately dimensioned identity matrix. The matrix notation for the determination of R_{ij} from two vectors of input parameters, a vector of the analyte concentration and environmental factors and a vector of instrumental sensitivities, is in the "bilinear form" defined in mathematics and statistics.

Eq. (5) relates to multivariate regression as the bilinear model, $\mathbf{R} = \mathbf{CB}$, employed by multilinear regression (MLR) [7]. Eq. (5) is also of the same form as the decomposition of a response matrix into scores and loadings that is employed by principal component regression (PCR) and partial least squares regression (PLS), $\mathbf{R} = \mathbf{UV}^T$ [8]. Both PCR and PLS assume a relationship between the scores, **U**, and analyte concentration based on the linear model

$$\mathbf{c} = \mathbf{Ub} + \varepsilon \quad (6)$$

where then regression vector **b** in Eq. (6) has no relation with the matrix **B** in Eq. (5). PCR and PLS differ only in the manner in which they determine the scores and loadings in the decomposition of **R**.

3.2. Nonlinear calibration

Two strategies for calibration are common with nonlinear multivariate data. Global transformations or fitting of global models are employed by methods such as nonlinear principal components regression (NPCR) and nonlinear partial least squares (NPLS) [8,9], alternating conditional expectations (ACE) [10,11], and global linearizing transformation regression (GLT) [12]. Locally weighted regression (LWR) [13,14], and multivariate adaptive regression splines (MARS) [15,16] utilize local (non)linear curves to fit the data for optimal predictive ability. For comparison of the models employed in many of these methods, see Sekulic et al. [17] and Frank [18]. The search for the calibration method that will provide the best true predictive ability can be shortened with the aid of the parsimony principle in conjunction with comparing the form of the model basis function to the form of the instrumental response function.

The parsimony principle states that of two sufficient models, the one that is defined by fewer parameters will have the better predictive ability [13]. From this postulate, a hierarchy of increasingly complex calibration methods is constructed that branches at the advent of nonlinear calibration. A hierarchy does exist along the branches, e.g. LWR is more parsimonious than MARS since LWR is MARS constrained to use a local linear fit. However, the parsimony principle offers no insight as to which branch has the highest probability of containing the (most parsimonious) model that yields the optimal predictive ability.

The need to search every branch of the parsimony tree can be alleviated by recognizing that NPCR, NPLS, ACE, and GLT employ global models. If there is no, or very little, expectation that a simple global transformation would convert the data into a linear space, these methods are probably not the best bet. On the contrary, LWR, MARS employ local models to effect optimal calibration. In general, there are additional parameters associated with local models (e.g. optimizing the number of local samples or knots) so these methods would not be a parsimonious as an equivalent global model. Hence, it is predicted that the local methods will perform better when no global transformation to linearity exists and, based on the parsimony principle, the global methods will provide better predictive calibration models when either a global or local method is appropriate.

The accuracy of these predictions are supported by the results of a comparative study of 8 linear and nonlinear calibration methods on 6 different data sets [17]. The calibration methods are assessed based on cross validation and true prediction. Of the three data sets whose models were compared based on cross validation, the results are inconclusive. Linear calibration always failed, but the local or global models performed equivalently. With simulated IR emission data, where a complex but continuous transformation function exists, ACE slightly outperformed LWR and MARS on true prediction. LWR and MARS outperformed the other calibration alternatives for benzene and toluene prediction with an array of Taguchi gas sensors. In a separate study, GLT has difficulty handling a sharp discontinuity in the response of the sensors in the array [12]. In the final data set, linear,

local nonlinear, and global nonlinear models performed equivalently on prediction of oil content in soybean samples by NIR-reflectance. This data is purported to contain only slight nonlinearities. The lack of improvement witnessed by the nonlinear methods over linear calibration could be explained by the nonlinear methods incorporating equivalent amounts of noise and nonlinearities into the calibration model.

3.3. Calibration by generalized standard additions

As with univariate calibration, the presence of uncontrolled environmental factors that change the functional form of the instrumental response with respect to changes in analyte concentration prohibits the successful application of external calibration. To compensate for these matrix effects, the required variance of the contributing variables in $f_j()$ must be elicited by standard additions of every contributing species. This is known as the generalized standard addition method (GSAM) [19].

GSAM has numerous limitations, although it is more powerful than the univariate standard addition method. Like SAM, GSAM is an extrapolative method so linearity is assumed. GSAM also assumes the linear model of Eq. (5) with the exception that sensitivity of the instrument to the analyte, b_o, is a function of an environmental parameter that elicits no instrumental response on its own and that the instrumental offset, a, is zero. If any of these assumptions are violated, the situation is inappropriate for the GSAM.

4. Second-order (multimode) calibration

A second order instrument is produced from two first-order instruments working in tandem to produce a second-order tensor, a matrix, of data per sample analyzed. With second-order instrumentation, one instrument modulates the instrumental response of the second instrument. Examples of second-order instrumentation are chromatographic-spectroscopic systems and excitation–emission matrix spectrometers. The instrumental response for the ith, jth digitized channel of an instrumental response matrix, R_{ij} is generalized

$$R_{ij} = g_j(f_{ci}(c, e_1, e_2, \ldots), f_{e1i}(c, e_1, e_2, \ldots), \ldots) + E_{ij} \tag{7}$$

where e_1, e_2 generally refer to concentrations of other chemical species with signal profiles that overlap the signal of the analyte. Here, $f_{ci}()$ is the instrumental response function for the analyte at the ith digitized row of $\mathbf{R}$ (e.g. $f_{ci}()$ yields apparent analyte concentration at the detector on digitized time i with a chromatographic system). The function $f_{e1i}()$ and subsequent functions are analogous to $f_{ci}()$ except that they refer to the interferents. The function $g_j()$ is the detector response at the jth digitized channel and is analogous to $f_j()$ in Eq. (3).

It should be noted that not all second-order data is produced by the interaction of two first-order instruments. One order can be provided by the natural progression of a chemical reaction or physical process. For example, a chemical engineer might consider a batch reactor that is monitored by a multivariate sensor array to provide second-order data (the time evolution of temperature, pressure, color, etc.).

Often, second-order data is broadly classified as either bilinear or nonbilinear. This classification is based on the interrelationship between the instrument response functions that create the data for each sample analyzed. This binary classification applied to second-order data is insufficient as it does not allow for accurate prediction of the best model to employ for calibration and prediction. To accurately predict the most appropriate calibration model, the relationship of the instrument response functions between samples and the linearity of the instrument response function in each order must be considered.

4.1. Trilinear calibration

In the instance that each $f_{,i}()$ is a linear function of only the respective chemical species where, for example, $f_{ci}() = x_{0i}c$ and there is linear additivity of signal at the detector, Eq. (7) can be specified to

$$R_{ij} = [x_0, x_1, \ldots]_i \mathbf{D} [y_0, y_1, \ldots]_j^T + E_{ij} \tag{8a}$$

or

$$\mathbf{R} = \sum_{n=1}^{N} \mathbf{x}_n \mathbf{z}_n \mathbf{y}_n^T + \mathbf{E} \tag{8b}$$

Here, $[x_0, x_1, \ldots]_i$ specify the fraction of analyte that is present at the detector during instrumental state i, $[y_0, y_1, \ldots]_j$ specify the sensitivity of the detector's jth digitized channel to the chemical species. The concentrations of the chemical species present, $[c, e_1, \ldots]$, comprise the diagonal matrix, **D**. The vectors $\mathbf{x}_n$ and $\mathbf{y}_n$ present the instrumental profiles with respect to each of the two conjugated instruments for the nth chemical species. For a collection of K samples, the instrument response of the kth sample is

$$R_{ijk} = [x_0, x_1, \ldots]_i \mathbf{D}_k [y_0, y_1, \ldots]_j^T + E_{ijk} \tag{9a}$$

where **D** is a diagonal matrix of the species' concentrations in the kth sample, or

$$\mathbf{R}_k = \sum_{n=1}^{N} \mathbf{x}_n Z_{kn} \mathbf{y}_n^T + \mathbf{E}_k \tag{9b}$$

Eq. (8a) presents the construction of **R** in terms of the bilinear model familiar in mathematics and statistics, while Eq. (8b) presents the construction of **R** in terms of the bilinear parallel factor analysis (PARAFAC) model familiar in chemistry [20]. Of note is the fact that if a collection of second-order spectra have been constructed following the model of Eqs. (9a) and (9b), the data can be uniquely deconvolved into a set of arbitrarily scaled instrumental profiles for the N constituent species, $\mathbf{x}_n$s and $\mathbf{y}_n$s, and a set of relative concentrations among the K samples, the N columns of **Z**. Since the bilinear model is a valid description of the data and the integrated spectral intensity of the analyte increases linearly with respect to increases in analyte concentration, the collection of data is said to be trilinear.

The trilinear model is implicit in early rank annihilation methods where quantitation is based on ratioing the resolved spectral intensity from two samples, one standard and one unknown [21,22]. Modern methods based on the generalized eigenvalue–eigenvector problem [23,24] and iterative least squares [25] have employed the trilinear assumption. With trilinear data calibration can be accomplished with only one impure standard of known analyze concentration. Also, the instrument response functions in each order can be recovered.

4.2. Non-trilinear bilinear calibration

If the I $\mathrm{f}_{ci}()$s are nonlinear functions of just analyte concentration, the instrument response of each sample follows a bilinear model. However, the data is not trilinear as there is no linear relationship among the resolved spectral intensities for the analyte in each sample. There are two types of bilinear, but not trilinear, data that are encountered in analytical chemistry, one is interpretable with minor modifications to the calibration methods applied to trilinear data. With the other, calibration is more difficult.

4.2.1. Global non-trilinearities

When the concentration dependence for all channels in the collection of samples is a single monotonic function of analyte concentration, Eq. (7) can be specified to

$$R_{ijk} = [x_0, x_1, \ldots]_i \mathbf{D}_k [y_0, y_1, \ldots]_j^T + E_{ijk} \tag{10}$$

where $\mathbf{D}_k$ is a diagonal matrix with nonlinear functions of the analyte's and interferent's concentrations in the kth sample, $[\mathrm{f}_c(c), \mathrm{f}_{e1}(e_1), \ldots]_k$, along the diagonal. Note that Eq. (10) still is in the bilinear form with same instrumental profiles, $\mathbf{x}_n$ and $\mathbf{y}_n$ for all samples. This type of non-trilinear data differs from trilinear data only in the fact that there is no linear relationship between the analyte concentration in each sample and the relative resolved spectral intensity of the analyte in each sample, $\mathbf{z}_n$.

This type of concentration dependent nonlinearity has been observed in a chemically facilitated Donnan dialysis-spectroscopic based sensor for analysis of Cd(II) and Pb(II) [26]. Here, accurate calibration is possible if enough standards are collected to model $\mathrm{f}_c()$ as a function of resolved spectral intensity. The instrumental profiles are also recoverable.

4.2.2. Local non-trilinearities

In the previous example, the concentration dependent nonlinearity $\mathrm{g}_c()$ was constant among all I rows in each data matrix $\mathbf{R}_k$. Eq. (7) can be specified to

$$R_{ijk} = [x_0, x_1, \ldots]_i \mathbf{D}_k [y_0, y_1, \ldots]_j^T + E_{ijk} \tag{11}$$

where $\mathbf{D}_k$ is a diagonal matrix with nonlinear functions of the analyte's and interferent's concentrations in the kth sample, $[f_{ic}(c), f_{ie1}(e_1), \ldots]_k$, along the diagonal and $f_{ic}()$ is a different function of analyte concentration for each of the I samples. If the concentration dependent nonlinearity differs among the I rows in each $\mathbf{R}_k$ calibration is much more difficult.

The detrimental effects of this nonlinearity can best be illustrated with an example. Consider two 3×3 second-order instrument response matrices for the analyte where the first row is proportional to the analyte concentration, $f_{1c}(c) = c$, the second row is proportional to the square of analyte concentration, $f_{2c}(c) = c^2$, and the third row is proportional to the cube of analyte concentration, $f_{3c}(c) = c^3$. The second instrumental profile, $\mathbf{y}$, is defined by $y = [1, 2, 3]^T$. Two samples, one of unit and the other of twice unit concentration, would have instrumental response matrices of

$$\mathbf{R}_1 = \begin{bmatrix} 1*1 & 2*1 & 3*1 \\ 1*1^2 & 2*1^2 & 3*1^2 \\ 1*1^3 & 2*1^3 & 3*1^3 \end{bmatrix} = \begin{bmatrix} 1 & 2 & 3 \\ 1 & 2 & 3 \\ 1 & 2 & 3 \end{bmatrix} \tag{12a}$$

and

$$\mathbf{R}_2 = \begin{bmatrix} 1*2 & 2*2 & 3*2 \\ 1*2^2 & 2*2^2 & 3*2^2 \\ 1*2^3 & 2*2^3 & 3*2^3 \end{bmatrix} = \begin{bmatrix} 2 & 4 & 6 \\ 4 & 8 & 12 \\ 8 & 16 & 24 \end{bmatrix} \tag{12b}$$

Note that the second instrumental profile, $\mathbf{y}$, is identical for both samples, $[1, 2, 3]^T$; however the concentration dependent nonlinearity causes the effective first instrumental profile, $\mathbf{x}$, to differ from $\mathbf{R}_1$ to $\mathbf{R}_2$. With $\mathbf{R}_1$ $\mathbf{x}$ is effectively $[1, 1, 1]^T$, while with $\mathbf{R}_2$ $\mathbf{x}$ is effectively $[1, 2, 4]^T$. Consequently, the trilinear model cannot be applied to such collection of data.

When the analyte (and interferents) exhibits this type of nonlinearity quantitative calibration is not possible but self modeling curve resolution techniques such as evolving factor analysis (EFA) can be used to extract the spectral profiles of the analyte in each sample [27,28]. When just the interferents exhibit local concentration dependent nonlinearities, quantitative calibration is possible by way of the second-order standard addition method (see below). Such nonlinearities have been observed in, for example, pH-spectroscopic titrations with competing ligands.

4.3. Non-trilinear non-bilinear calibration

The bilinear model assumes that the instrument response is consistent, except for a scaling factor, throughout each order. That is, $g_j(f_{ci}(c)) = \alpha_j g_{j+1}(f_{ci}(c))$ for constant j all i and $g_j(f_{ci}(c)) = \alpha_i g_j(f_{ci+1}(c))$ for constant i and all j. If this condition does not hold, the bilinear model cannot be directly employed to extract the pure species profiles. There are two types of this nonlinearity that are often encountered in analytical chemistry. The first allows accurate calibration under special conditions with the bilinear model, the second requires that a data transformation be determined before the bilinear model be applied.

4.3.1. Apparent nonbilinearities

With instrumentation such as tandem-mass spectrometers and reaction kinetics–spectroscopic sensors, each species in the sample can form multiple distinct products upon interrogation by the first instrument in the hyphenated pair. Each of the distinct products has a unique instrumental profile in each of the two orders. This is the type of data that is traditionally considered "nonbilinear."

However, the bilinear model of Eqs. (8a) and (8b) and often the trilinear model of Eqs. (9a) and (9b) are applicable for calibration if allowance are made that consider the model linear with respect to the each subspecies formed not the initial species. Here, there will be an $f_i(c)$ for each subspecies formed. The number of subspecies formed per initial species ranges from 2 to 3 for reaction-kinetics based sensors to close to I for tandem-MS data.

The best calibration strategy to employ depends on the number of species formed per initial compound present in the calibration and unknown samples. With reaction-kinetics sensors, where the number of subspecies is small, variants of the trilinear model such as constrained Tuckers models [29,30] (relaxed PARAFAC models) and self modeling curve resolution based methods [31] have been successfully employed for calibration and spectral resolution. When the number of subspecies is large, as with tandem-MS, the non-bilinear rank annihilation method can be

employed for quantitation [32]. However, calibration by this method requires a pure standard of known concentration. Spectral resolution is not possible.

4.3.2. Inherent nonlinearities

If the instrumental response of the second instrument, the detector, is nonlinear the bilinear model of Eqs. (8a) and (8b) is not applicable. For most nonlinear detectors, three simplifying assumptions can be applied:

1. The non-linearity of the detector is a function of the total power impinging on the detector.
2. There is no interaction between the compounds at the detector.
3. The power a compound imparts on the detector is a monotonic function of the compound's concentration.

Assuming that the instrumental profiles of each species from the first of the two conjugated instruments is linear and additive with respect to changes in concentration, Eq. (7) can be specified to include a nonlinear detector response in the jth channel,

$$R_{ijk} = g_j([x_0, x_1, \ldots]_i \mathbf{D}_k [y_0, y_1, \ldots]_j^T) + E_{ijk} \qquad (13)$$

where $\mathbf{D}_k$ is a diagonal matrix of the analyte's and interferent's concentrations in the kth sample and Y_{jn} relates the concentration of the nth compound to the power imparted onto the detector. For spectroscopic applications Y_{jn} would be $\varepsilon_j b$, where ε_j is the molar absorbtivity at wavelength j and b is the optical pathlength.

Unfortunately, nonlinear data that is described by Eq. (13) cannot directly be used for calibration. Eq. (13) does not follow a bilinear model. This type of nonlinearity convolutes the intrinsic profiles of the compounds in each instrumental order and quantitative information is obscured as the instrumental response does not increase uniformly over all rows and columns with increasing analyte concentration. However, there is a bilinear model imbedded inside the function $g_j()$. If the inverse function to transform the $Jg_j()$s could be determined, Eqs. (9a) and (9b) would be applicable. Currently no calibration method has been published that explicitly tackles this problem, but an extension of global linearizing transformations to second-order data may provide an effective calibration strategy for unspecified nonlinearities.

4.4. Calibration by second-order standard additions

When the instrumental profiles of the analyte, the sensitivity of the instrument to the analyte, or the instrumental profiles of the interferents are dependent on the concentration of nonanalyte species in the samples, the trilinear model of Eqs. (9a) and (9b) are inappropriate to describe the instrumental response function for an arbitrary collection of samples and hence accurate calibration with an external calibration set is not possible. However, each sample does follow the bilinear model of Eqs. (8a) and (8b). The trilinear model is applicable if the samples in the calibration set and unknown samples are constrained to have the same concentrations of interfering species. Therefore, analyte quantitation is possible with a standard addition method.

The second-order standard addition method (SOSAM) has the advantage over GSAM that only standard additions of the analyte are required. SOSAM is applicable with both trilinear and multiple product second-order calibration where it has been applied to calibration of reaction kinetics-spectroscopic sensors [33]. Naturally, since standard additions are extrapolative, SOSAM is inappropriate for use with nonlinearities stemming from analyte concentration based nonlinearities.

5. Conclusions

Presented here has been a mathematical basis for choosing calibration models with first- and second-order chemical data. The next logical step would be to incorporate these results into a set of heuristic algorithms to aid users in model selection. For such an expert system to be of maximum value, what is needed is a set of diagnostic tools that automatically evaluates any set of data for nonlinearities and suggests the appropriate experimental design for the proper calibration model.

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