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A new and consistent parameter for measuring the quality of multivariate analytical methods: Generalized analytical sensitivity

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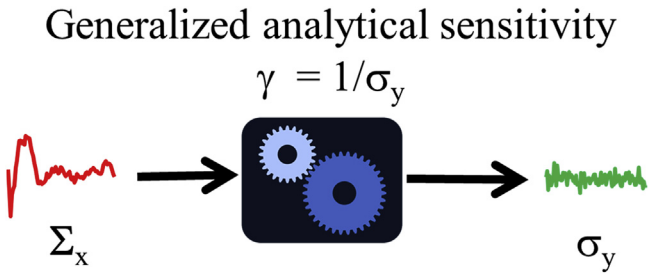
HIGHLIGHTS

- Sensitivity for various multivariate calibration methods is studied.
- Different error structures are considered.
- Generalized analytical sensitivity is proposed as a new figure of merit.
- The new parameter allows better comparison among calibration methods.

GRAPHICAL ABSTRACT



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ABSTRACT

Generalized analytical sensitivity (γ) is proposed as a new figure of merit, which can be estimated from a multivariate calibration data set. It can be confidently applied to compare different calibration methodologies, and helps to solve literature inconsistencies on the relationship between classical sensitivity and prediction error. In contrast to the classical plain sensitivity, γ incorporates the noise properties in its definition, and its inverse is well correlated with root mean square errors of prediction in the presence of general noise structures. The proposal is supported by studying simulated and experimental first-order multivariate calibration systems with various models, namely multiple linear regression, principal component regression (PCR) and maximum likelihood PCR (MLPCR). The simulations included instrumental noise of different types: independently and identically distributed (*iid*), correlated (pink) and proportional noise, while the experimental data carried noise which is clearly non-*iid*.

1. Introduction

Starting from the seminal work of Lorber [1], the estimation of analytical figures of merit in multivariate calibration has become an active research field in analytical chemistry. Some recent developments show the continuous interest in this area by the analytical community [2–7]. In particular, the derivation of a generalized expression for estimating the important sensitivity parameter in a general calibration scenario has been possible [3], with a twofold consequence. On one hand, the sensitivity has traditionally been considered as a good indicator for comparing methodologies in terms of analytical performance, thus any advance in the estimation of multivariate and multiway sensitivity is welcome [3]. On the other, knowledge of the sensitivity provides access to additional figures which depend on the latter, such as prediction uncertainty and detection capabilities [3,5].

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The classical definition of sensitivity is based on the idea of a signal change for a given change in analyte concentration [8]. This concept is valid in univariate calibration, where the sensitivity is numerically equal to the slope of the calibration graph [8]. It is also suitable in first-order multivariate calibration, provided 'signal' is replaced by 'net analyte signal' [1]. However, the analogous concept of net signal cannot be successfully extended to multiway calibration, for reasons already discussed [3].

It has been increasingly clear that a new definition of sensitivity was required, and this was possible in the framework of uncertainty propagation [3]. When the sensitivity is numerically defined as the ratio of signal to concentration uncertainties, a completely general expression can be derived, valid for univariate, first-order multivariate and higher-order multiway calibrations, including cases where the second-order advantage is achieved. This new definition is completely consistent with the classical univariate and first-order expressions, and is also in agreement with extensive noise addition simulations [3].

However, at the heart of the general sensitivity expression, derived from uncertainty propagation arguments, rests the assumption of a particular structure for the signal noise: it should be identically and independently distributed (*iid*). Operationally, a small amount of *iid* noise is numerically added to the test sample signal, and analyte concentration is predicted with its corresponding uncertainty (Fig. 1A). It is postulated that the small noise added to the signal is simply a probe to monitor the uncertainty propagation behavior, and should not necessarily reflect the real noise structure of the instrumental signals [3]. It should be noted that the small *iid* noise is only added to the test sample signal, keeping the calibration model precise. In this way, uncertainty only propagates from the instrumental signal for the test sample and not from the calibration signals or concentrations.

The question remains whether the sensitivity parameter is useful for one of its intended purposes, i.e., method performance comparison, in the case of real systems showing signal noise structures different than the ideal *iid*. In light of the presently discussed results, the answer is negative. In this report, an alternative figure of merit is proposed, which is better correlated with analytical performance and can be estimated only from the calibration data set. It is a generalization of the already known analytical sensitivity (γ) [9,10], here extended to any noise structure and calibration methodology [11]. The classical parameter γ, defined as the ratio between univariate calibration slope and standard measurement error, has been proposed for method comparison instead of the slope, because the former is independent

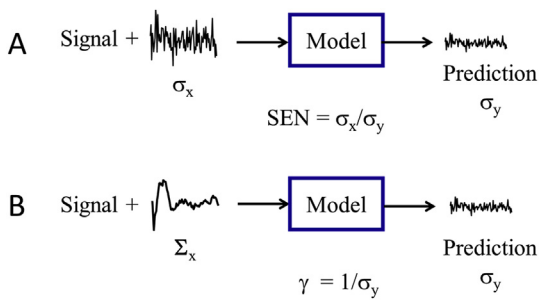

Fig. 1. Schematic representation of the uncertainty propagation approach to sensitivity analysis. A) *iid* noise (represented by its standard deviation σ_x) is introduced only in the test sample signal, keeping the model precise, and the sensitivity (SEN) is computed as the ratio of input signal noise to output concentration noise (σ_y). B) Real non-*iid* noise (represented by its error variance-covariance matrix Σ_x) is added only to the test signal, keeping the model precise, and the generalized analytical sensitivity (γ) is estimated as the inverse of the output concentration noise. See text for the meanings of σ_x, σ_y and Σ_x.

on the type of instrumental signal [9]. We generalize the definition of γ for multivariate methods, as the inverse of the concentration uncertainty generated by real noise propagation, and show it to be an excellent parameter for method comparison in the case of general noise structures. Fig. 1B adequately illustrates the presently proposed definition, noting that, as in Fig. 1A, the noise is only added to the instrumental signal for the test sample, keeping the calibration model precise, i.e., avoiding propagation from errors in calibration signals or concentrations.

To support our proposal, we use a set of simulated first-order data carrying *iid*, correlated and proportional noise, and also experimental data including non-*iid* noise. They were processed using the following multivariate tools: (1) multiple linear regression (MLR) [12] of signals for a few wavelengths, which were carefully selected with the aid of the successive projection algorithm (SPA) [13], (2) principal component regression (PCR) [14] and (3) maximum likelihood PCR (MLPCR) [15,16]. The purpose of using MLR was to assess the performance when calibration is built using a few wavelengths, which in principle presents significantly smaller sensitivity in comparison with full spectral latent methods such as PCR and MLPCR, yet sometimes producing comparable or even better analytical results [17,18]. On the other hand, MLPCR was applied because of its known ability to cope with noise structures other than the *iid* one [15,16], and to check whether this improved analytical ability is correlated with the corresponding numerical sensitivity value.

In sum, the present proposal has the following purposes: (1) providing a figure of merit which could be used to compare different calibration models with confidence, and derived only from the calibration data set, i.e., not requiring an independent set of samples for its estimation, and (2) solving inconsistencies in literature reports where calibration with a few sensors provided better analytical results but lower classical sensitivity.

2. Theory

2.1. Calibration methodologies

The theory behind MLR and PCR calibration is well known [12,14]. SPA and MLPCR are briefly described in the Supplementary Material. Partial least-squares (PLS) results are not shown, as they were almost identical to those furnished by PCR, but are included in the Supplementary Material.

In all cases, a calibration data matrix $\mathbf{X}$ (size $I \times J$, I = number of calibration samples, J = number of sensors or wavelengths) and a calibration concentration vector for the analyte of interest $\mathbf{y}_{cal}$ (size $I \times 1$) were submitted to the calibration phase with a given multivariate model. This yields the regression vector $\mathbf{b}$ (size $J \times 1$), which permits analyte quantitation through the usual predictive expression $\hat{y} = \mathbf{x}^T\mathbf{b}$ ($\mathbf{x}$ is the test sample spectrum, size $J \times 1$, the hat '^' implying predicted value).

2.2. Uncertainty propagation

In a recent work, Allegrini et al. presented a general scheme to estimate sample dependent prediction uncertainties in first-order multivariate calibration [19]. Because the *iid* hypothesis for measurement errors is not always valid for real data sets, new expressions were developed to take into account the specific noise structure. The overall prediction variance (σ_y^2) in multivariate models can be estimated by a sum of three contributing terms: (1) the variance from instrumental signals measured for the test sample, (2) the variance from instrumental signals measured for the calibration set of samples and (3) the variance in nominal concentrations of the analyte or property of interest [2,19]. The