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Multivariate calibration: applications to pharmaceutical analysis[1]

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Abstract

The principles of multivariate calibration (MC) are presented, with reference to the main objectives of this chemometrics technique: the reduction of the variance in the prediction of a response variable (generally, a chemical quantity) and the possibility of the determination of the response in complex matrices with no or limited sample preparation, as in the case of the determination of a drug in a medicament. In both cases MC uses the whole information in a spectrum (a series of predictors). The possibility of the improvement of the MC performances, eliminating some useless, noisy, predictors is shown. Variable selection has been performed using two original techniques: a stepwise elimination procedure, based on the normalised coefficients of the regression equation relating the response to the predictors and a technique based on iterative repetitions of the regression technique (partial least squares regression, PLS), each time by weighting the predictors by their normalised regression coefficient computed in the previous cycle. These strategies are illustrated by means of different data sets, a synthetic example and a real example where MC, applied to near infrared spectroscopy, is used in the analysis of a drug. In this case also the application of an original MC technique is shown, where a joint regression model is obtained for two different instruments.

Keywords: Multivariate calibration; Regression techniques; Useless variable elimination; Joint regression model

1. Introduction

The general procedure in chemical analysis is composed of two steps. In the first step some chemical and/or physical treatments, more or less complex, are used on the samples in order to obtain a system state where a measurable physical quantity is correlated univocally with the chemical quantity to be measured. The second step is the

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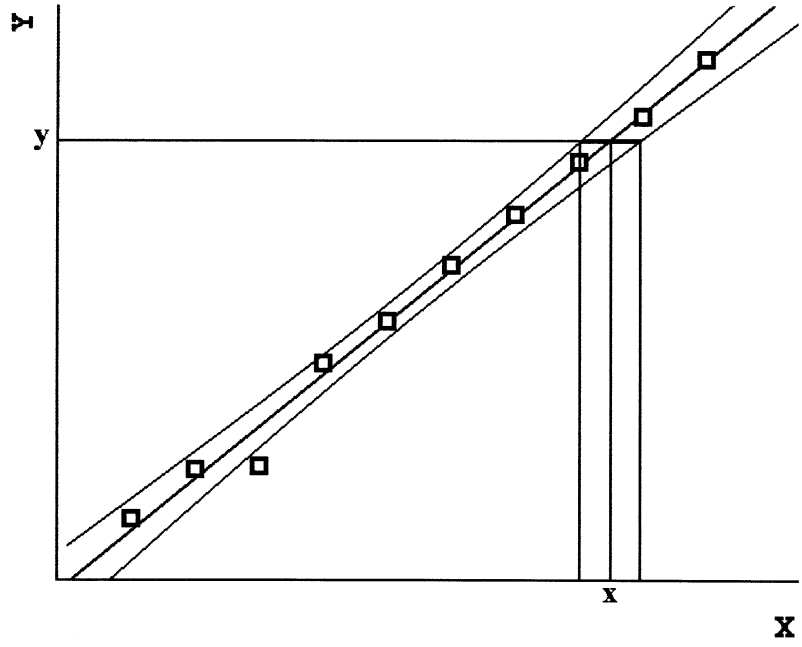

Fig. 1. Usual least squares regression line with the confidence hyperbole for the evaluation of the confidence interval of the unknown, x.

calibration one. The physical quantity is measured on a selected number of samples where the content of the analyte is known (standards); finally, the mathematical model relating the measured quantities with the corresponding chemical quantities, the regression function, is obtained.

Frequently this function is linear. In the usual procedure, under the assumption that the chemical quantity in the standards is known without error, the ordinary linear least squares regression is applied. The regression equation is obtained in the form:

$$y = a + bx \tag{1}$$

where y is the physical quantity, x is the chemical quantity, a and b are the regression coefficients, intercept and slope of the straight line.

In order to obtain the value of the unknown chemical quantity for a new sample, the inverse of Eq. (1) is used:

$$x = \frac{(y - a)}{b} \tag{2}$$

where y is the value of the physical quantity, obtained as the mean of M repetitions of the measure on the sample.

Error variance can be estimated from the experimental data. This variance is used to build a suitable (depending on the number of repetitions M) confidence hyperbole around the estimated regression line (Fig. 1); from this hyperbole the confidence interval of the unknown can be obtained.

In spectrophotometric determinations, the used physical quantity y is usually the maximum absorbance in the spectrum of the chemical component; when the error on the measurement of the physical quantity is constant, independent of its magnitude, the above choice corresponds to the minimum variance on the prediction of the chemical quantity. Fig. 2 shows as, for an idealised absorbance peak, the variance increases with the decreasing absorbance.

Multivariate calibration uses many physical quantities (predictors) to compute the value of the chemical quantity (response), with two main objectives:

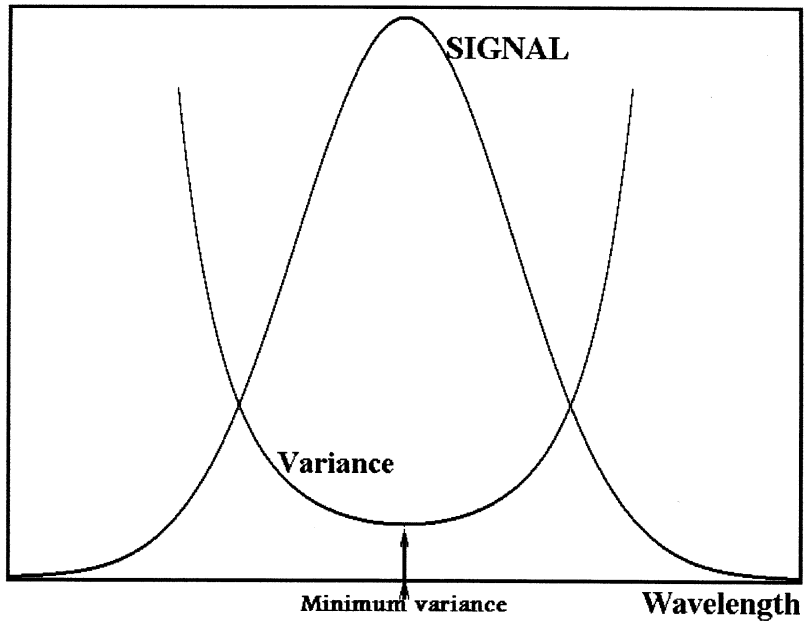

Fig. 2. Idealised peak with gaussian shape, and variance of the unknown as a function of the selected wavelength.

1. To predict the response with the minimum variance;
2. To eliminate (totally or partially) sample treatments: the state of the system must be such that a block of measurable physical quantities is correlated univocally with the chemical quantity.

The second objective corresponds to the majority of the applications of multivariate calibration, in the development of rapid analytical procedures for quality control with spectral techniques (often near infrared spectroscopy) of medicaments, foods, forage, or for the evaluation of physical properties of difficult or expensive direct determination (e.g. octane number).

Multivariate calibration uses the procedure of 'inverse calibration', in the sense that the equation that expresses the response as a function of the predictors

$$x = b_0 + b_1 y_1 + b_2 y_2 + ... + b_V y_V \quad (3)$$

is obtained directly in the calibration step. The term 'inverse' has the meaning of 'inverse of the usual procedure': really 'inverse calibration' is a direct calibration.

Because of this inversion, the nomenclature used is changed:

- y response, for a single sample
- x single predictor
- $\boldsymbol{x}$ vector of the V predictors measured on a single sample
- $\boldsymbol{y}$ vector of the response measured on N samples
- $\mathbf{X}$ matrix (V columns, N rows) of the V predictors measured on the N samples

Sometimes the symbol $\mathbf{X}$ is used to indicate the matrix of the predictors increased with a leading or tailing column of 1.Eq. (3) becomes:

$$y = b_0 + b_1 x_1 + b_2 x_2 + ... + b_V x_V \quad (4)$$

or in matrix form:

$$\boldsymbol{y} = \mathbf{X}\boldsymbol{b} \quad (5)$$

where $\boldsymbol{b}$ is the vector of the regression coefficients; a column of 1 added in $\mathbf{X}$ allows to include in the vector $\boldsymbol{b}$ also the intercept.

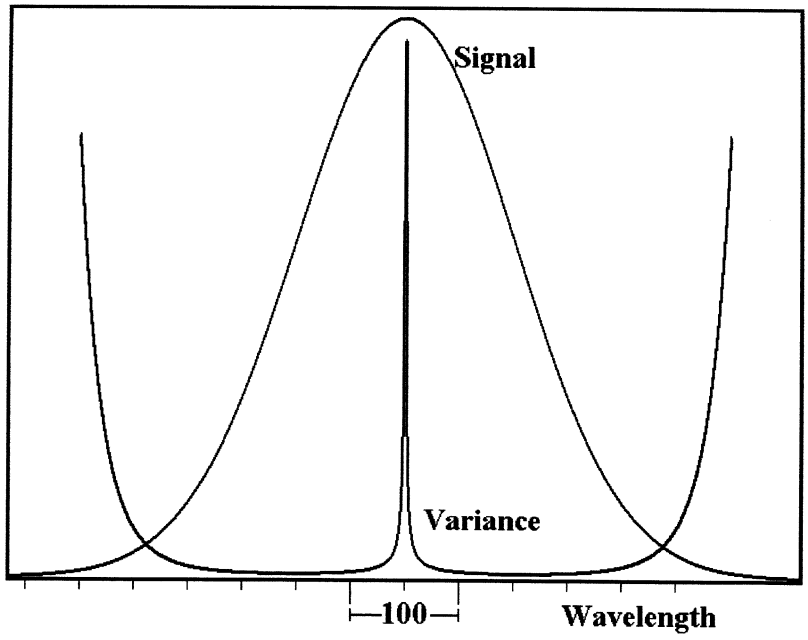

Fig. 3. Idealised peak and variance of the unknown in the case of multivariate calibration with wavelengths in a window centred around the peak maximum.

2. Decrease of the variance of the response

Only few lines are used here for this minor objective of multivariate calibration.

In the univariate calibration model, in the inverse form, simplified with intercept zero:

$$y = b_M x_M \tag{6}$$

the predictor x_M is the value of the peak absorbance, for which the regression coefficient b_M is minimum, so that the variance of the response is minimum (under the hypothesis that the variance of the predictor is independent of the wavelength):

$$\sigma_y^2 = b_M^2 \sigma_X^2 \tag{7}$$

When a different predictor $x_d < x_M$ is used, the regression coefficient is larger:

$$y = b_d x_d = b_M \frac{x_M}{x_d} x_d \tag{8}$$

and the variance of the response is also larger:

$$\sigma_y^2 = \left(b_M \frac{x_M}{x_d} \right)^2 \sigma_x^2 \tag{9}$$

When, around the absorbance peak, D more predictors are used, the regression equation becomes:

$$y = \frac{b_M x_M + \sum_{d=1}^{D} \left(b_M \frac{x_M}{x_d} \right) x_d}{D+1} \tag{10}$$

and, under the hypothesis of error independent on the predictors, response variance is:

$$\sigma_y^2 = \frac{b_M^2 \sigma_x^2 + \sum_{d=1}^{D} \left(b_M \frac{x_M}{x_d} \right)^2 \sigma_x^2}{(D+1)^2} \tag{11}$$

Fig. 3 shows, for the idealised peak, the effect of D on the variance of the response. As D increases, each predictor contributes to the estimate of the response both with useful information and with noise. For the first predictors (corresponding to wavelengths in the neighbourhood of the peak) the amount of useful information is much more than the amount of noise, so that the behaviour of the response variance is very similar to that computed for the repetition of a measurement D times, with the variance of the mean

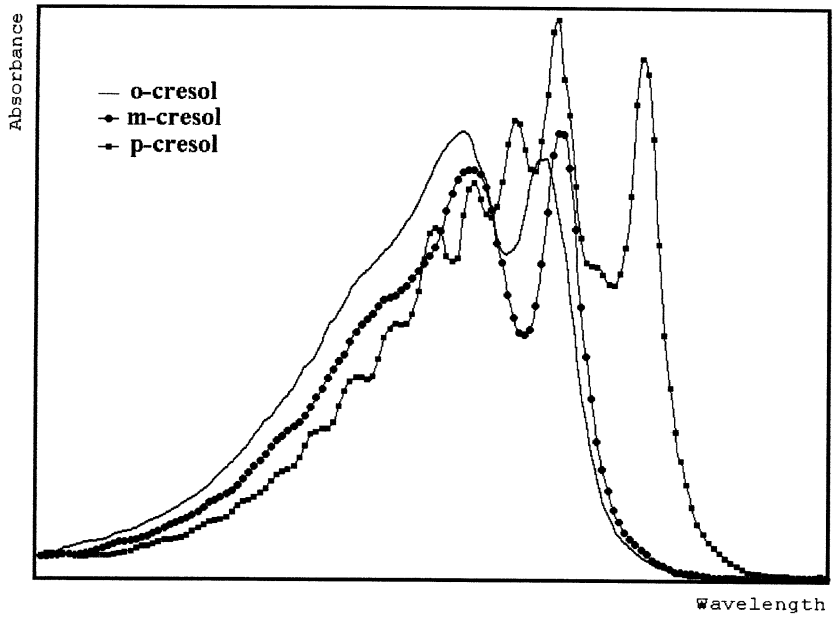

Fig. 4. UV spectra of cresols in the interval 240–300 nm.

decreasing with the increase of D. With larger windows first useful information and noise balance, so that the variance of the response is almost independent on D; then, when the windows contain also wavelengths with very small signal, very small useful information, the variance of the response increases.

A second advantage of the use of multivariate calibration with the wavelengths in a window of suitable amplitude centred around the peak is the relative insensitivity to the wavelength shift.

When only the peak signal is used, a wavelength shift always causes a diminution of the signal; on the contrary with multivariate calibration signal diminution due to the wavelengths that the shift moves away from the peak is balanced from the signal increase due to the wavelengths that the shift approaches to the peak.

So, multivariate calibration, with the use of all the measured information, and with a critical choice of the predictors, can produce more precise results without additional cost.

3. Determinations in complex matrices

3.1. Data

Three data sets are used here, to show the performances of multivariate calibration in the case of complex chemical systems.

The first data set, CRESOLS, has been obtained from data published by Carney and Sanford [1]; the UV spectra in the wavelength range from 240 to 300 nm, of the three isomeric cresols, roughly drawn from [1] and reported in Fig. 4, were used to compute the spectra of 50 mixtures with random concentrations of the three cresols. In the same wavelength interval, 440 equally spaced predictors describe each spectrum. A moderate gaussian noise has been added to the 50 spectra.

The second and the third data sets, UAB1 and UAB2, refer to the same 28 drug samples, analysed with two different instruments.

The pharmaceutical product used was Mentis®, a commercially available preparation from Laboratorios Menarini S.A. (Badalona, Spain) contain-

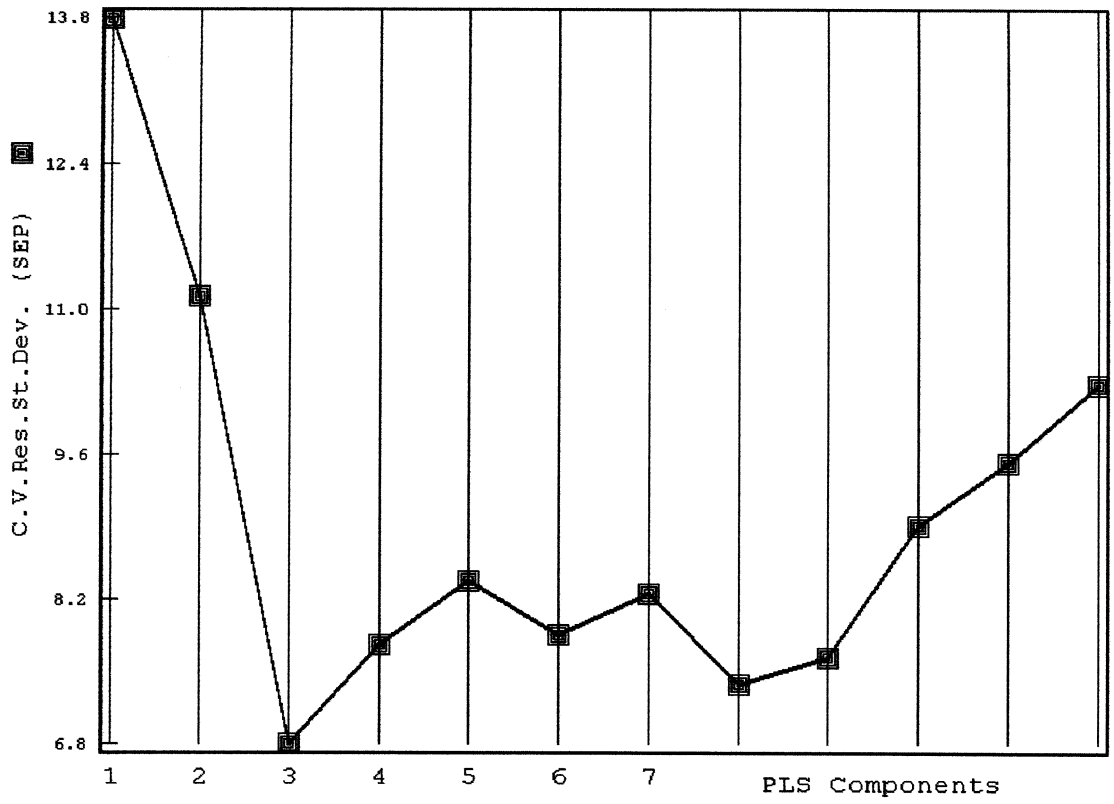

Fig. 5. Standard error of prediction as a function of the number of PLS latent variables; data set UAB1; 14 cancellation groups.

ing a nominal 880 mg g^{-1} of the active compound pirisudanol dimaleate, viz. butanedioic acid 2-(dimethylamino) ethyl [5-hydroxy-4-(hydroxymethyl)-6-methyl-3-pyridinyl]methyl ester. The preparation includes magnesium stearate, talc and colloidal silica intended to improve the stability and the mechanical properties of the mixture in dosing and encapsulation. Samples contain the active principle covering a range between 841.7 and 911.4 mg g^{-1}.

UAB1 set was recorded with an NIRSystems 6500 near infrared spectrometer equipped with a reflectance detector and spinning sample module.

UAB2 set was recorded with an NIRSystems 5000 near infrared spectrometer equipped with a reflectance detector and an AP6649 ANO4P fibre optic module for qualitative and quantitative analysis.

Each sample was used to record three spectra, each being the average of 50 scans over the range 1100–2500 nm. The average of the three spectra was used.

In both data sets, UAB1 and UAB2, only 350 equally spaced predictors have been used in data analysis. Additional information concerning these data can be found in [2].

3.2. Case of mixtures of known chemical components

In the case of a simple mixture of C chemical components, with known spectra, a system of C equations solves the analytical problem:

$$x_1 = k_{11}y_1 + k_{12}y_2 + k_{13}y_3$$
$$x_2 = k_{21}y_1 + k_{22}y_2 + k_{23}y_3$$
$$x_3 = k_{31}y_1 + k_{32}y_2 + k_{33}y_3 \quad (12)$$

where y_1, y_2 and y_3 are the concentrations of the three components of the mixture and x_1, x_2 and x_3

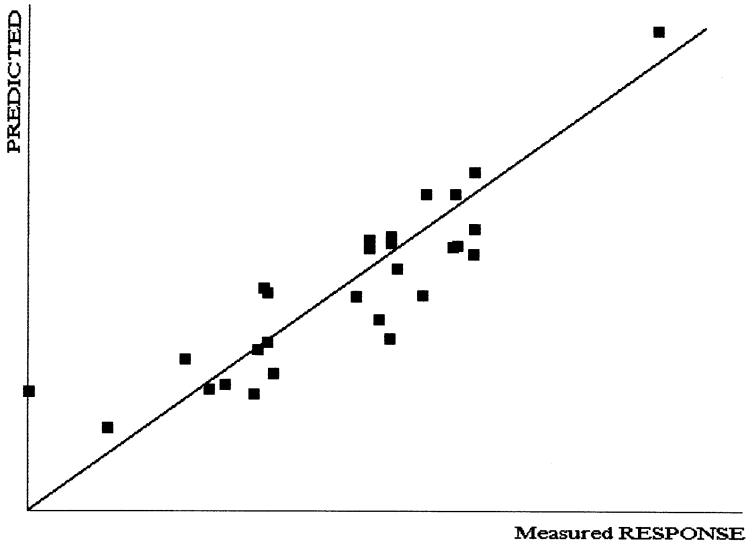

Fig. 6. Predicted versus measured response; data set UAB1; 14 cancellation groups; optimum regression model with three latent variables.

are the absorbance values measured for this sample at three selected wavelengths.

The absorbance coefficients $k_{\text{wavelength, component}}$ are obtained from the known spectra, at the same wavelengths. Carney and Sanford suggested for the example CRESOLS 272.8, 277.4 and 285.8 nm.

The system, here in matrix notation:

$$\boldsymbol{x} = \mathbf{K}\boldsymbol{y} \tag{13}$$

can be solved:

$$\mathbf{y} = \mathbf{K}^{-1}\mathbf{x} \tag{14}$$

when the matrix of the absorbance coefficients can be inverted. The quality of the final regression equation is measured by the determinant of matrix **K**.

This procedure can be indicated as classical multicomponent calibration.

3.3. Case of one component in matrix with interference

More frequently, and it is the general case in the determination of a drug in a medicament, or of a chemical component in a food, it is impossible to know the spectra of all chemical species, and there are also interactions and other effects that make it impossible to use the above procedure to obtain a regression equation for the unknown. In this case the typical procedures of multivariate calibration can be used.

Multivariate calibration born as the evolution of classical multicomponent calibration [3] and evolves [4–6] with the use of powerful regression techniques and with the availability of spectrophotometers able to produce as many as 1200 predictors for each spectrum.

Generally the original spectra undergo a pretreatment: first or second derivative, standard normal variate (SNV) transformation, i.e. row autoscaling (for each spectrum, subtraction of the mean value of the spectrum and division for its standard deviation), multiplicative scatter correction, Fourier transform, etc…

N samples are used in the calibration step. These samples are not standard samples in the usual meaning of the word, but generally they are real samples, representative of the problems, analysed with a reference technique, that often requires a complex treatment of separation. Because of the cost of the classical analysis, the samples for calibration are selected among a number of candidate samples. The choice of the sam-

ple subset is made by means of experimental design, generally performed on the principal components of the spectra of the candidate samples. Very useful strategies are D-optimum design for a quadratic regression model, and S-optimum design (space-filling design) that selects the samples in order to explore uniformly the space of the principal components.

The spectra **X** (original or transformed) and the response $\boldsymbol{y}$ for the N samples give a system of equations:

$$y_1 = a + b_1x_{11} + b_2x_{12} + ... + b_Vx_{1V}$$

$$y_2 = a + b_1x_{21} + b_2x_{12} + ... + b_Vx_{1V}$$

.....

$$y_{i1} = a + b_1x_{i1} + b_2x_{i2} + ... + b_Vx_{iV}$$

.....

$$y_N = a + b_1x_{N1} + b_2x_{N2} + ... + b_Vx_{NV} \quad (15)$$

that can not be solved directly because of the fact that generally the number V of predictors is larger than the number of samples, and also because of the very large correlation between predictors that causes a very large prediction error also in the case of NIR filter instruments, where ordinary least squares can frequently be used.

For these reasons multivariate calibration uses biased regression techniques, as principal component regression (PCR) or partial least squares regression (PLS) [7,8]. Biased regression techniques use a reduced part of the information in the predictors. In this way, they introduce a small bias in the result but they reduce the random error eliminating the noise associated with the discarded part of the information.

PCR starts with the computation of principal components (PC). Generally the predictors are centred; a multidimensional orthogonal rotation is performed from the original space of the predictors to the PC space. Principal components are non-correlated variables, linear combination of the original predictors, ordered according to their variance (eigenvalue). Always, from a lot of original predictors a small PC number (< 20) with significant variance is obtained (during an orthogonal rotation the number of variables does not change but, because of the very large correlation between the original predictors, the last PCs have variance zero). The 'scores' are the co-ordinates in the PC space; the 'loadings' are the coefficients of the predictors in the linear combination that gives the components.

PCR performs stepwise ordinary least squares regression (S-OLS) on the principal components. In each iteration of S-OLS, one of the PC is selected and added in the calibration model, until the introduction of a new component does not improve the result. The number of PC used defines the 'complexity' of the biased regression technique.

PLS works in a similar way, but the complexity is measured by the number of PLS components (latent variables) analogous to PC, and computed directly in PLS, instead of in a previous step as in PCR.

The complexity of a biased regression technique depends in principle on the chemical complexity of the problem, the number of chemical species whose concentration can change in the samples, and also (in the case of near infrared spectroscopy) on the physical structure of the sample. This is a very important feature of some samples typical of pharmaceutical analysis (e.g. tablets). Particle size can be selected as a response variable, instead of a chemical quantity, and determined by means of multivariate calibration.

The optimum complexity of a regression technique is obtained by means of predictive optimisation: some calibration samples are not used to build the regression model, and the model is used to predict the response for these left-out objects. Frequently, predictive optimisation is performed with the procedure of the 'cancellation groups'. Calibration samples are divided into cancellation groups, and the regression procedure is repeated as many times as the cancellation groups are. The limit of this procedure is known as leave-one-out, with only one object in each cancellation group. Each time the samples in one cancellation group are left-out; the regression equation is obtained with the other samples, and the response for the left-out samples is predicted. So, prediction is obtained for all the objects in the calibration set. The standard deviation of the prediction error is known as standard error of prediction (SEP). When the notation C.V. SEP is used it means that the cross

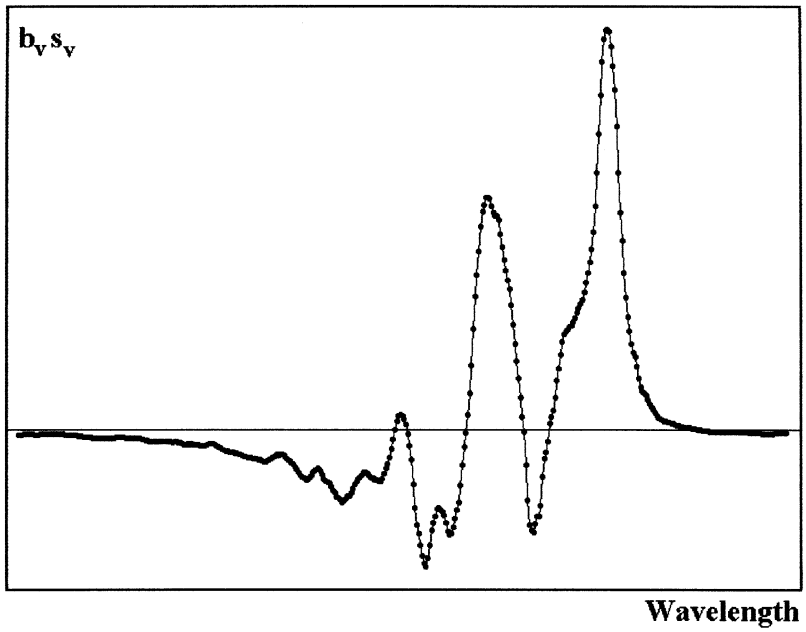

Fig. 7. Importance spectrum; data set CRESOLS; response: *p*-cresol; 10 cancellation groups, optimum regression model with three PLS latent variables.

validation procedure, based on cancellation groups, has been used. The minimisation of SEP is the criterion generally used to select the optimum model complexity, as shown in Fig. 5 for data set UAB1. The value of SEP corresponding to the optimum complexity is the measure of the performance of the analytical procedure. Details are usually shown as a plot of the predicted response versus the measured response, as in Fig. 6. This plot can reveal the presence of outliers and of non-linearity.

Both PCR and PLS give the regression equation as a function of the components; however it is easy to express the regression equation in terms of the original predictors (closed form). The regression coefficients of the closed form are a measure of the relevance of each predictor in the regression equation. A better measure is the 'importance' of the predictor, product between the regression coefficient and the standard deviation of the predictor in the calibration set.

Fig. 7 represents the 'spectrum' of the importance of the predictors, obtained for *p*-cresol, (data set CRESOLS) using PLS model with three latent variables.

A small standard deviation and a small regression coefficient indicate that the variation of the response caused by the variation of the predictor is very small, so small that possibly the predictor is not relevant. Its elimination can correspond to the elimination of noise and to an improvement of the regression model. The mean value of the predictor has no influence on the importance and on the result after elimination of the predictor, because its constant effect is balanced by a variation of the intercept. A back-wise procedure can be applied to refine the regression model, where each time the predictor with the minimum value of the importance is cancelled. Fig. 8 shows as the mean prediction error (analogous to SEP) changes during the elimination cycles. The final model, with only 70 predictors performs two times better than the original model with 440 predictors.

The same procedure, applied to data set UAB1, gives a refined regression model retaining only 20 predictors (Fig. 9a) with a mean error decrease from ~ 5.4 to 2.2.

3.4. Weighted predictors PLS (WP-PLS)

A different procedure to refine the PLS regression

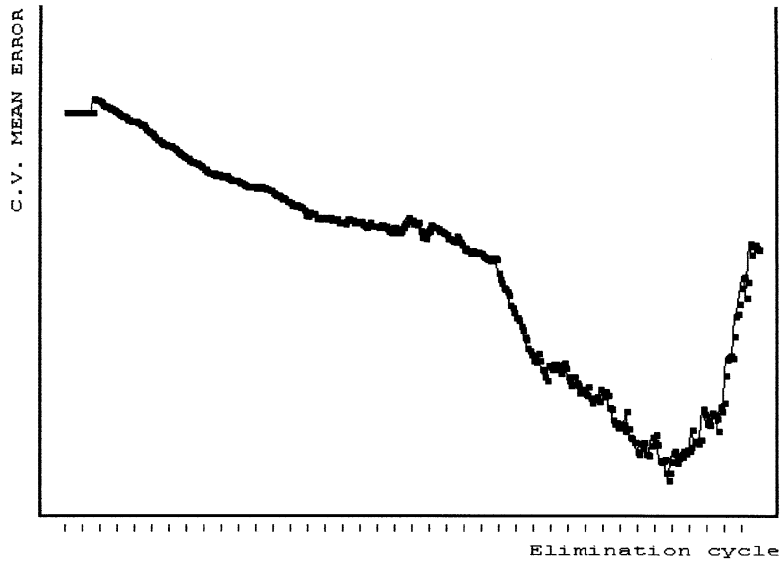

Fig. 8. C.V. mean error during the stepwise elimination of the predictors; in each elimination cycle the predictor with the smallest importance is cancelled. Data set CRESOLS, response: *p*-cresol.

model is the iterative re-weighted PLS technique [9]. Here after a first PLS regression, the predictor importance (computed for each variable as product between regression coefficient and standard deviation) is used to weight the predictors before to perform a second PLS regression. The importance obtained from the second calibration model is used to weight the predictors before the third regression, and so on.

With this repeated weighting procedure, non relevant predictors become so small that they are cancelled automatically by the number of digits allowed by the precision of data in the computing program (alternatively, a cut-off value can be used to eliminate predictors with importance less than the cut-off value).

Generally WP-PLS converges toward a model with a minimum number of predictors, and a value of SEP lower than the error obtained with all the predictors. The result with UAB1 is shown in Fig. 9(b). In this case WP-PLS retains only four predictors, and the prediction mean error is about 3.6. So, it seems that WP-PLS performs worse than the technique of back-wise elimination. However, it must be noticed that the real performance of a procedure must be evaluated in conditions of full-validation [10], i.e. on samples which have never been used in the development of the final model (complexity, number of retained predictors), and it is not the case of SEP values and mean prediction errors reported here, referred to the predictive optimisation. Moreover, back-wise elimination is a very long procedure, which makes it almost impossible to use full-validation. Finally, sometimes a minimum number of predictors, obtained at the expense of a slightly worse performance, can be preferable.

In other cases WP-PLS converges toward a minimum number of predictors but with an SEP greater than SEP obtained with all the predictors. This is the case of *o*-cresol and *m*-cresol (data set CRESOLS). This result is due to the extreme overlapping between the spectra of the two chemical components, which makes it necessary to use almost all the predictors for the optimum performances. In this example the back-wise elimination reduces the predictor number to only ~ 370, with a minimum improvement of the performance. WP-PLS retains ten predictors, in three groups of neighbours centred around the wavelengths selected by Carney and Sanford in their classical multicomponent strategy.

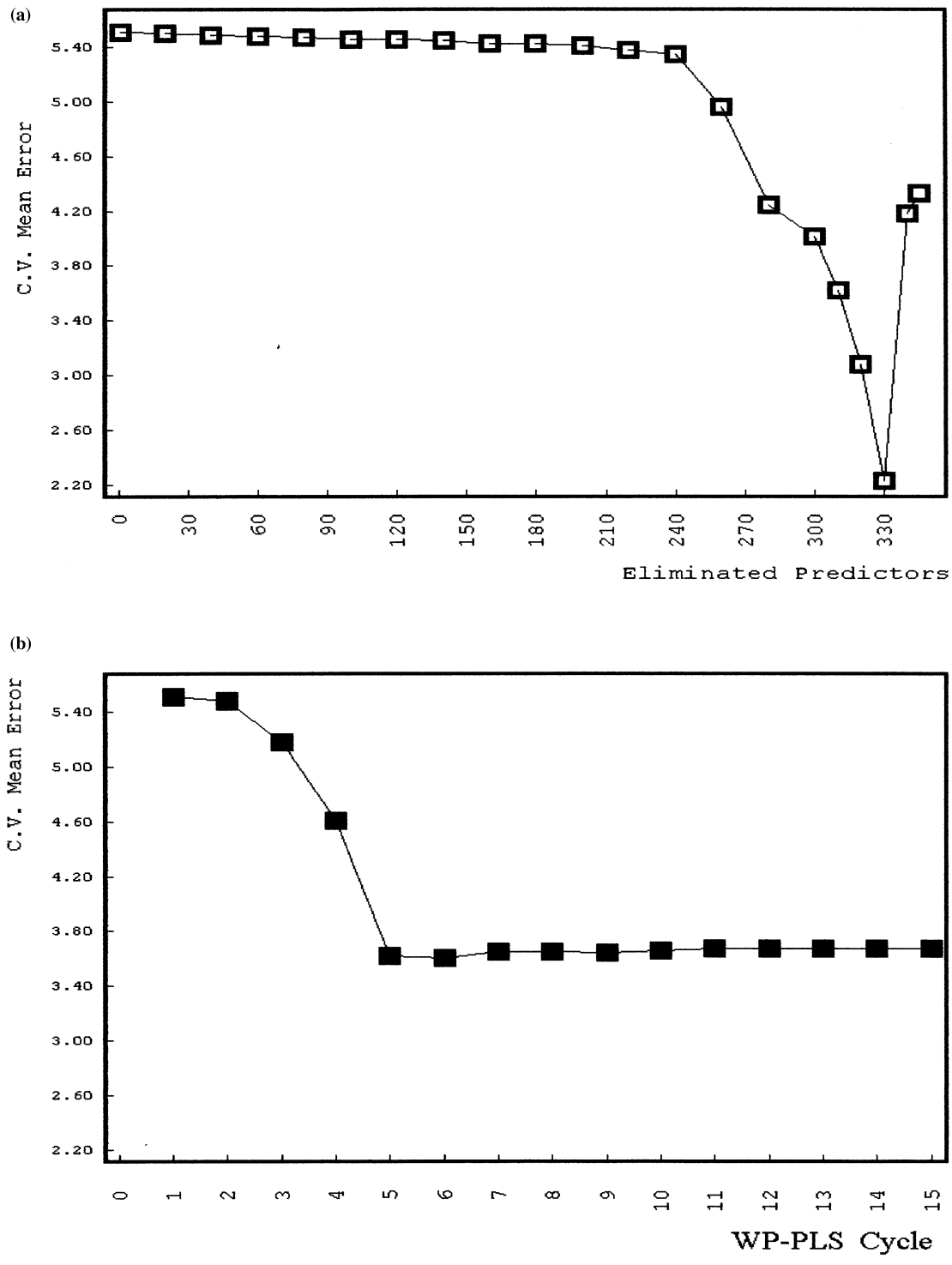

Fig. 9. Data set UAB1. (a) C.V. mean error in the stepwise elimination of predictors; (b) C.V. mean error in the cycles of WP-PLS.

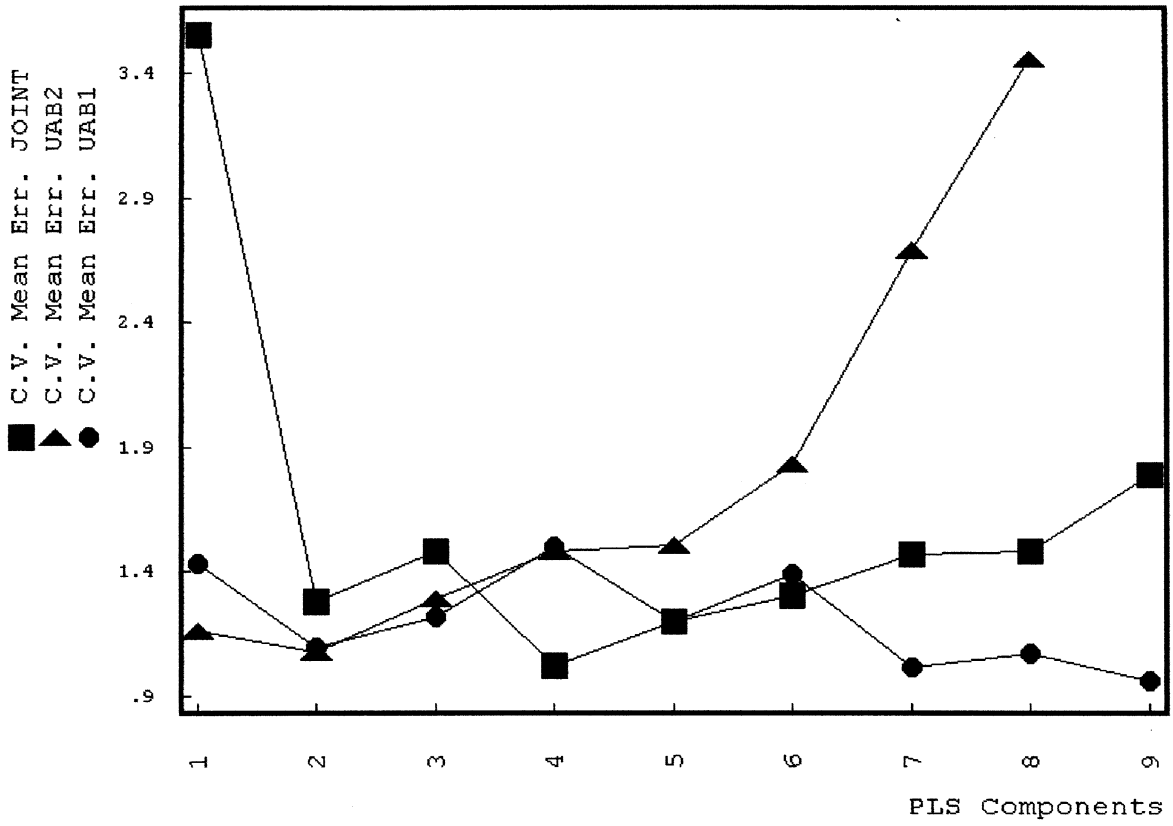

Fig. 10. Evaluation of optimum complexity for PLS regression with data sets UAB1 and UAB2 (12 samples) and for the joint regression model with the augmented data matrix (six samples from UAB1 and six samples from UAB2).

4. Joint PLS regression model for two instruments

Multivariate calibration with the PLS regression technique can also be applied in an unusual way to help in an important problem, that of two or more instruments used for the same analysis. Never two instruments are identical, and in NIR spectroscopy it is almost impossible to use the same regression equation with two different instruments. Several procedures have been developed to transfer the regression equation or the spectra from one instrument to another one.

Joint PLS regression [11] uses an augmented matrix of the predictors, here shown as a partitioned matrix:

$$\mathbf{X}_{AU} = \begin{vmatrix} \mathbf{X}_1 & 0 \\ 0 & \mathbf{X}_2 \end{vmatrix}$$

The augmented matrix results from four matrices. The first, $\mathbf{X}_1$, is the matrix of the predictors for the N_1 samples of the first instrument. $\mathbf{X}_2$ is the matrix of the predictors for the N_2 samples of the second instruments. The first $\mathbf{0}$ matrix is a matrix of zeroes with as many rows as $\mathbf{X}_1$ and as many columns as $\mathbf{X}_2$; the second $\mathbf{0}$ matrix is a matrix of zeroes with as many rows as $\mathbf{X}_2$ and as many columns as $\mathbf{X}_1$.

The joint regression model has generally an optimum complexity lightly greater than the separate regression models (one to two latent variables more used to explain the differences between the two instruments); its SEP is generally intermediate between those of the separate models, as in the case shown in Fig. 10. In this example the augmented matrix has been obtained from data sets UAB1 and UAB2, constituted by the spectra of

the same drug measured with two different instruments. The three calibration models (two models developed on the two instruments separately and the joint model) have been obtained by using the same number (12) of samples, selected by means of PC design on the separate PC plots for the two instruments. In the case of the joint regression model six samples were selected from the PC plot of the first instrument and six samples from the PC plot of the second one.

5. Conclusions

Multivariate calibration with biased regression techniques is a powerful tool for analytical chemistry, of possible use in many problems of pharmaceutical analysis, both in the case of direct analysis in complex matrices and of multicomponent analysis in simple systems.

Regression results can be improved by the use of techniques of elimination of non-informative predictors; however, much care is necessary in the refinement of the regression model and in the evaluation of its performances. Full-validation is strongly suggested, in spite of the very long time usually necessary.

The flexibility of the PLS algorithm also makes applications to unusual problems possible, as in the case of the joint regression model shown here.

As in all problems where chemometrics is required, it must be remembered that the tools of chemometrics can be used easily (a touch on the keyboard of the computer), but the abuse is very dangerous for science, as the abuse of drugs for humans.

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